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Water-Encapsulated Ni(II) Salphen-Type Host Complexes: Experimental and Theoretical Analysis of Potentially Bioactive Quasi-Isostructural Polymorphs

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In this study, we report the formation of two quasi-isostructural polymorphs (α and β) of a Ni(II) salphen-type Schiff base complex using solvent evaporation technique. The polymorphs are inclusion compounds with guest water molecules exhibiting similar spectroscopic and thermal characteristics. Single crystal XRD (X-ray Diffraction) analyses reveal the subtle differences in packing and supramolecular interactions which are quantified using Hirshfeld and 2D finger print analyses. Electrostatic potential analysis shows significant difference in potential distribution in the two molecules. The compositional analysis of the frontier orbitals and differences among the atomic charge distribution of the polymorphs are established using DFT (Density Functional Theory) calculations. Apart from highlighting the strength of encapsulation, DFT study substantiates the formation of inclusion compounds through single point energy calculations. Effects of inherent differences in the polymorphs on potential biological activity are probed using *in silico* molecular docking with B-DNA and Human Serum Albumin (HSA). The α form shows superior bioactivity while β form excels in water encapsulation.

Introduction

Complexes from ligand systems obtained by [2 + 1] condensation of o-vanillin or its derivatives with a diamine are interesting due to the presence of two different cavities. The smaller N_2O_2 and larger O_4 cavities serve as a platform for structural tuning. Apart from the expected transition metal coordination, the outer O_4 cavity is of great importance as it can coordinate to larger lanthanide ions[1–3] and also act as a host cavity for guest molecules.[4] In the latter case, these are dubbed as inclusion compounds due to the presence of host-guest interactions. These inclusion compounds with water guest molecules are considered as potential precursors for the synthesis of pharmaceutically important, rarely reported inorganic cocrystals.[5,6]

On the other hand, polymorphs are increasingly employed nowadays mainly in pharmaceutical industry due to their difference in biological activity which may have its origin from the anisotropy in the electronic/noncovalent character.[7,8] The phenomenon of polymorphism refers to the occurrence of different crystal structures of the same compound[9,10] while isostructurality indicates the presence of different compounds with the same structure.[11] Quasi-isostructurality refers to the existence of similar packing and intermolecular interactions[12,13] but to a lower degree so that it cannot be classified as 3D (D = Dimensional), 2D, 1D or even 0D isostructurality.[14] In this scenario, it is important to consider the contribution of Ni(II) salphen-type (salphen = *N,N'*-bis(salicylidene)-1,2-phenylenediamine) complexes which have shown interesting spectroscopic and electrochemical features[15,16] and above all promising biological activity.[17–19] Among the myriad of biological applications known for these metal complexes, the one that stands out the most is their use as metallodrugs which is further evidenced by the greater binding affinity of Ni(II) complexes with G-quadruplex DNA when compared to similar metal complexes.[20] For the development of any drug, it is important to monitor drug-DNA interactions since DNA is the main molecular target[21] and this study should be equally complemented by drug-protein interactions. Investigations involving drug-protein interactions especilaly with Human Serum Albumin (HSA) are more frequently probed now since they are in abundance in blood plasma and play a decisive role in pharmacokinetic behavior of drugs.[22]

When compared to organic counterparts, the contributions of inorganic polymorphic systems are relatively less explored and literature reports on such systems are hard to find.[23–26] Eventhough there are number of reports on similar complexes[27] and investigations on water mediated suparmolecular structures, none of them discuss the relevance of polymorphic forms.[28] In this context, we believe that the work reported here consisting of the theoretical/experimental investigations of two quasi-isostructural polymorphic Ni(II) salphen-type complexes and their implications on potential bioactivity is first of its kind. These polymorphs are indistinguishable from routine spectroscopic analyses but a deep structural and

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