



# Quantitative and qualitative analyses of intermolecular interactions in neutral/deprotonated aspirin@ $\beta$ -CD inclusion complexes: QTAIM and NBO analyses

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## Abstract

Most of the researches in supramolecular chemistry area are focused on the conventional hydrogen bonds without taking into account unconventional intermolecular interactions. The nature and strength of the conventional and unconventional interactions in inclusion complexes formed between neutral aspirin (ASA) and its deprotonated form (ASA<sup>-</sup>) with  $\beta$ -cyclodextrin ( $\beta$ -CD) have been studied. It was conducted through combining atoms in molecules (AIM) theoretical criteria suggested by Koch and Popelier and natural bond orbital (NBO) analyses by means of dispersion-corrected density functional theory (DFT-D3) with the functional B3LYP using cc-pvdz basis set in the gas phase. We have found five intermolecular closed-shell interaction groups responsible for neutral ASA: $\beta$ -CD and deprotonated ASA<sup>-</sup>: $\beta$ -CD inclusion complexes stability: One is conventional O–H...O bond group. The four C–H...O, C–H...C, O–H...H–C and C–H...H–C groups are nonconventional. Also, with respect to the Koch and Popelier criteria, some of them present the properties of a hydrogen bond, while others do not. The non-covalent interaction energies are calculated using Espinosa approach. Finally, according to the AIM and NBO analyses, the topological parameters (electron density  $\rho_b$  and its Laplacian  $\nabla^2\rho_b$ ), estimated interaction energies ( $E_{int}$ ), and the stabilization energy  $E^{(2)}$  of both complexes were correlated with the intermolecular bond lengths.

**Keywords**  $\beta$ -Cyclodextrin · Aspirin · Inclusion complex · DFT-D3 · QTAIM · NBO

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## 1 Introduction

Understanding the nature of bonding interactions between the guest and the host molecules is of crucial importance in supramolecular and biological chemistry, particularly in inclusion complexes [1]. Usually, these molecules are held together by non-covalent interactions: electrostatics, van der Waals, hydrophobic interactions, hydrogen bonding, and charge transfer. All these interactions are contributed to the stability and conformational variability of these systems [2–4].

Aspirin (ASA) belongs to the family of the non-steroidal anti-inflammatory drugs (NSAIDs), and is one of the oldest and most popular drugs in the world [5, 6]. Besides the benefits of aspirin therapy as an analgesic, antiplatelet, anti-inflammatory, anti-pyretic, antithrombotic, and anticancer actions [7–10], this drug can cause severe and undesired side effects (upset or/and stomach bleeding, hematemesis, gastrointestinal ulcers, tinnitus, thrombocytopenia, agranulocytosis, and leucopenia) [11–15]. Several methods have been used to surmount these inconveniences such as a pro-drug