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Research paper

Complexation of nicotinic acid with first generation poly(amidoamine) dendrimers: A microscopic view from density functional theory

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ABSTRACT

This study explains some electronic and structural parameters of niacin (NA) encapsulation into PAMAM-G1 dendrimer using DFT calculations. Optimized structural geometries, interaction energies, NMR, NBO, and AIM analyses, in accordance with experiment, revealed that the stability of G1@NA complex can be attributed to the five intermolecular hydrogen bonds formed between the functional groups of G1 and NA. Because of nearing to the experimental results, all the calculations repeated again using a self-consistent reaction field (SCRF) and the polarizable continuum model (PCM) to address the implicit solvent effects and the obtained results were in line with the calculations in gas phase.

1. Introduction

In the pharmaceutical area, the key factors upon which the medical success of any drug is based are efficiency, toxicity, solubility, bioavailability, and biocompatibility. Based on recent studies, about 40% of newly developed active pharmaceutical ingredients (API) are not exploitable by the pharmaceutical industry because of low water solubility and, thus, bioavailability [1]. Therefore, the development of molecular-level drug carriers, which enhance water solubility of the drug while maintaining essential pharmacophoric features, has been of particular interest. Various nanocarrier systems such as liposomes, carbon nanotubes, polymeric micelles, and dendrimers have been utilized for this purpose.

Since their synthesis in 1985 [2], poly(amidoamine) (PAMAM) dendrimers have continuously aroused considerable attention in many different areas ranging from material science to medicine [3–5]. They are a class of synthetic, well-defined, hyper-branched nanostructure polymers consisting of three main architectural components: a central core from which dendritic arms emanate to form the interior layers, and the peripheral functional groups usually located at the surface of dendritic architecture [6]. Attractive features like biocompatibility [7], tunable solubility, ease of surface engineering [8], internal cavities [9], and the high functional group density at the chain ends with respect to typical linear polymers [10] make them promising candidates as nanocarriers for the encapsulation and delivery of poorly water-soluble drugs, which remains a major challenge in the pharmaceutical area. These polymers can interact with pharmaceutical compounds either in a covalent or non-covalent approach. Covalent interaction involves the binding of the drug molecule to the surface functional groups through a precisely chosen linker. Non-covalent interaction involves physical encapsulation of the drug molecules either in the internal cavities or on the surface [11].

Extensive experimental studies have been performed regarding the complexation of poorly water-soluble drugs with PAMAM dendrimers [12–14]. These studies have proposed several mechanisms to provide a mostly qualitative depiction of drug encapsulation into PAMAM dendrimers; however, they are not able to delineate the molecular-level description that can clarify both qualitative and quantitative information for such behavior. Furthermore, the experimental methods are very laborious, costly and require complicated instruments. In this regard, computational methods could supply valuable details into the nature of the forces behind the stabilization of the complex. Although considerable amount of Molecular Dynamics (MD) [15–18] and Coarse Grained (CG) [19,20] simulations along with molecular docking studies [21,22] have been performed to determine structural and dynamical aspects of drug-dendrimer complexation, investigations based on density functional theory (DFT) [23,24] have hardly ever reported the interaction mechanisms between drugs and PAMAM dendrimers.

Niacin, also known as vitamin B3 and nicotinic acid, is one of the essential dietary vitamins. Deficiency of niacin leads to Pellagra, and niacin has been widely used as a pharmacologic agent in

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the treatment of abnormalities in plasma lipid [25] and lipoprotein [26] metabolism, atherosclerotic cardiovascular disease [27], schizophrenia [28] and dyslipidemia [29]. In spite of its activity, nicotinic acid (NA) is not freely soluble in water at room temperature. Considering this, Yiyun and Tongwen [30] investigated the effect of PAMAM dendrimers on the aqueous solubility of NA at room temperature. Their study demonstrated that complexation of NA with PAMAM dendrimers can significantly promote solubility of the drug. Results revealed that different variables such as pH conditions, concentration, surface functional groups and generation of dendrimer affects the solubility of NA in the dendrimer solutions. Caballero et al. [31] evaluated association of niacin with PAMAM-G3 dendrimer using molecular dynamics simulations and found that NA prefers to interact with surface groups of PAMAM-G3 and stability of PAMAM-G3@NA complex can be attributed to electrostatic and van der Waals interactions between drug and monomers.

In spite of the medicinal relevance of PAMAM dendrimers a systematic quantum mechanical investigation on the mechanism of interaction between these nanostructures with drug molecules is still lacking. Given the aforementioned challenges and opportunities, we applied first principle computations for the first time to inspect the specifics of the encapsulation behavior of niacin to NH_2-terminated PAMAM-G1 dendrimers. First generation PAMAM dendrimers require a reasonable computational effort while provide the necessary accuracy. DFT calculations eliminate the trial and error experiments, and therefore decrease the cost of analysis. Furthermore, they provide a comprehensive insight on the changes of structural geometries, interaction energies, charge distribution and steric effects under encapsulation process.

2. Theoretical methods

All geometry optimizations and energy calculations were performed based on density functional theory (DFT) using the M06-2X functional [32] in conjunction with 6-31G(d) basis set as implemented in GAMESS software package [33]. M06-2X is a hybrid meta exchange correlation functional with double the amount of nonlocal exchange (2X), which is parameterized only for nonmetals. This functional is recommended greatly for the study of main-group thermochemistry and kinetics, noncovalent interactions, and electronic excitation energies to valence and Rydberg states.

The vibrational frequency calculations were performed at the same level to verify that all of the optimized structures correspond to minima on the potential energy surface and to find the zero point energy (ZPE) corrections scaled according to recommended correction factors.

We used the following definition as the enthalpy change under encapsulation of NA into PAMAM-G1 at T = 298 K and P = 1 atm

$$\Delta H = [(H + ZPE)_{complex}] - [(H + ZPE)_{G1}] - [(H + ZPE)_{NA}] \quad (1)$$

where $H_{complex}$, H_{G1}, and H_{NA} are sum of electronic and thermal enthalpies of G1@NA complex, PAMAM-G1, and NA molecule, respectively, as obtained from the vibrational frequency calculations. It is well-known that a negative value of ΔH corresponds to an exothermic process. Gibbs free energy changes (ΔG) of the complexation process and the binding energy, $E_{binding}$, between NA and G1 dendrimer were also calculated using corresponding data at the same conditions.

Moreover, implicit solvent effects were addressed through a self-consistent reaction field (SCRF) employing the polarizable continuum model (PCM) considering the dielectric constant of water ($\varepsilon = 78.36$). In PCM, the solute part is implicitly located inside a cavity surrounded by the solvent part represented as a structureless material characterized by its dielectric constant and solvent radius. Potentiometric (acid–base) titrations of NH_2-terminated PAMAM dendrimers at physiological pH revealed that all primary amines located at the periphery are protonated. Therefore, to mimic the experimental conditions representing NH_2-terminated PAMAM-G1 dendrimers at physiological pH, all primary amines (located at the periphery) are protonated. The pK_a value for the NA molecule is reported to be 4.75, and therefore NA exists as nicotinate at neutral pH.

To perform chemical shielding (CS) calculations, the gauge-including atomic orbital (GIAO) approach [34] was employed at the M06-2X/6-311+G(d) level of theory. The chemical shift isotropy (σ_{iso}) and anisotropy ($\Delta\sigma$) parameters were calculated applying principal components ($\sigma_{11} \leqslant \sigma_{22} \leqslant \sigma_{33}$) of the chemical shift tensor, as follows

$$\sigma_{iso}\ (\text{ppm}) = \frac{\sigma_{11} + \sigma_{22} + \sigma_{33}}{3} \quad (2)$$

$$\Delta\sigma\ (\text{ppm}) = \sigma_{33} - \left(\frac{\sigma_{11} + \sigma_{22}}{2}\right) \quad (3)$$

Natural bond orbital (NBO) [35] analysis was performed at the M06-2X/6-311++G(d,p) level as a means to get a clear insight of the charge distributions and steric effects. Moreover, GaussSum program [36] was employed to obtain density of state (DOS) results. The HOMO-LUMO energy gap (E_g) is defined as

$$E_g = E_{LUMO} - E_{HOMO} \quad (4)$$

In DOS graphs, E_{LUMO} and E_{HOMO} refer to the energy of lowest unoccupied molecular orbital and highest occupied molecular orbital, respectively.

To explore the electron density and bonding characteristics of G1@NA complex, the Bader's quantum theory of atoms in molecules (QTAIM) [37] was employed. According to this theory, upon chemical bond formation between two neighboring atoms a bond critical point (BCP) appears between them. The characteristics of the BCPs are very important for determination of electron density (ρ_C) and its corresponding Laplacian ($\nabla^2\rho_C$), and therefore describing the nature of atom-atom interactions in the investigated system. The Laplacian of electron density is the second derivative of a scalar function, and represents information about the tendency of electron density to concentrate or deplete. The total electronic energy density at BCP (H_C) elucidates the energetic properties of BCPs, and is the sum of local kinetic energy density (G_C) and local potential energy density (V_C) at BCP.

$$H_C = G_C + V_C \quad (5)$$

It is also known from the Virial theorem that there is a relation between the Laplacian of the electron density at BCP and its other characteristics.

$$(1/4)\nabla^2\rho_C = 2G_C + V_C \quad (6)$$

A negative value of the Laplacian indicates the concentration of the electron density among the nuclei of interacting atoms and one may assume a shared interaction such as covalent bonds and lone pairs. A positive Laplacian value of the electron density at corresponding BCP shows the depletion of electron density as in ionic, van der Waals, and hydrogen bonds interactions. However, sometimes $\nabla^2\rho_C > 0$ but the total electronic energy density, H_C, is negative and such a situation is attributed to the partially covalent interaction. The AIM analysis was performed at M06-2X/6-31G (d) level of theory using AIM2000 package of software [38].