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The nature of interactions in nicotinamide crystal

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ABSTRACT

In this study, we analyze the nature of intermolecular interactions in nicotinamide complexes appearing in conformations found in the crystal structure, including many-body effects. In doing so, we employ symmetry-adapted perturbation theory based on density functional theory description of monomers, and we perform the many-body variational–perturbational interaction energy decomposition. The principal finding of this study is that the stability of nicotinamide complexes is a complicated interplay of four (large in magnitude) interaction-energy components, i.e. induction, dispersion, electrostatic and exchange repulsion. However, the last two contributions cancel each other out to a large extent. In the case of considered three-body complexes, the nonadditivity effects are found to be not important. Based on the results of topological analysis of charge densities we characterized also the properties of short H ··· H contact and identified it as a weak noncovalent closed shell interaction.

1. Introduction

Nicotinamide (NAm) molecule appears to be very important precursor of many coenzymes responsible for redox processes in liver, brain and erythrocytes. Its physiological functions were recognized already in the mid-1930s, when Warburg and Christian isolated nicotinamide (NAm) from the hydrogen-transporting coenzymes NAD(H) and NADP(H), giving the first clue to its importance in metabolism [1]. About one decade later Elvehjem discovered its nutritional significance [2]. Since then NAm has been used successfully for the treatment of several deficiency conditions. One of the examples is the supplementation with NAm in the case of clinical depression. It has been shown that NAm enhances the effect of tryptophan in supporting of brain serotonin levels [3]. Nicotinamide was also found to protect high-risk children from progression of clinical insulin-dependent diabetes. It was assumed that the effect of nicotinamide involves the support of pancreatic cell function through the support of both NAD+ and DNA-protective enzyme poly(ADP-ribose) polymerase activity [4–6]. The study of Ieraci and Herrera on the ethanol-induced apoptotic neurodegeneration showed protective effect of NAm. Such properties of nicotinamide can be used to prevent the damage in fetal alcohol syndrome [7]. It is worth mentioning that nicotinamide exhibits ability to inhibit the oxidative damage. It was confirmed in the case of injury induced by reactive oxygen species whose presence can lead to oxidation of protein and lipid peroxidation. Interestingly, the protective effect was bigger than in the case of tocopherol and ascorbic acid [8]. Due to its particular importance, nicotinamide is the subject of many studies concerning its physico-chemical properties. The recent subject of interest is also the ability of nicotinamide to form co-crystals because of its well-known hydrogen-bonding moieties in the structure. The presence of two nitrogens of pyridine and amide enables to create reliable syntons with many active pharmaceutical ingredients [9–12]. Co-crystal can be defined as a crystalline structure composed of two or more different components in a stoichiometric composition stabilized by strong and directional hydrogen bonds, π–π stacking and electrostatic interactions [13]. Although co-crystals are known for a long time, it seems that their potential is not fully exploited. Due to the diversity of crystal forms, active pharmaceutical ingredients (AIP) and ability to improve their properties in clinical practice these are very attractive and challenging issues of pharmaceutical sciences. Indeed, co-crystal formation is an attractive route to modifications of physicochemical solid state properties such as stability, solubility and bioavailability without breaking or formation of covalent bonds [14–17]. It is proved that co-crystalization with nicotinamide can improve tableting behavior, dissolution performance and hygroscopic properties of drugs [18]. So far, several co-crystaline structures of nicotinamide with different AIPs have been determined. It is worth to mention here that in advance prediction if co-crystalization would be successful

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or not is still hardly possible [19]. Therefore, it is necessary to carry out plenty of experiments under many conditions with different techniques in order to propose active form of co-crystals.

The knowledge about the non-covalent forces that cause the stabilization of a molecular crystals is one of the most important and useful elements in crystal engineering, especially in control of the stoichiometry and composition of co-crystals [20–22]. This forms the basis for the present study, which reports on the results of quantum-chemical calculations of the intermolecular interactions in nicotinamide crystals, including many-body effects. The structures were taken from Cambridge Crystal Structure Database (CSD). In doing so, we aim at providing a better understanding of the nature of binding forces in the molecular crystal to elucidate what might further contribute to the development of a strategy to predict and design the pharmaceutically relevant properties of co-crystals involving nicotinamide. Additionally, we have investigated the hydrogen bonds by means of periodic DFT calculations and atoms in molecule (AIM) theory.

2. Computational methods

2.1. DFT-SAPT calculations

In the present study, the components of the intermolecular interaction energy were obtained within the DFT-SAPT framework, which combines Kohn–Sham formulation of density functional theory (DFT) and symmetry-adapted intermolecular perturbation theory, as implemented in the MOLPRO package [23]. In this approach the total intermolecular interaction energy E_{int} is determined as a sum of first-order electrostatic energy $E_{\mathrm{el}}^{(1)}$, second-order induction $E_{\mathrm{ind}}^{(2)}$, dispersion $E_{\mathrm{disp}}^{(2)}$ and the exchange counterparts $E_{\mathrm{exch}}^{(1)}$, $E_{\mathrm{exch\text{-}ind}}^{(2)}$, $E_{\mathrm{exch\text{-}disp}}^{(2)}$, respectively:

$$E_{\mathrm{int}} = E_{\mathrm{el}}^{(1)} + E_{\mathrm{exch}}^{(1)} + E_{\mathrm{ind}}^{(2)} + E_{\mathrm{exch\text{-}ind}}^{(2)} + E_{\mathrm{disp}}^{(2)} + E_{\mathrm{exch\text{-}disp}}^{(2)} \quad (1)$$

The intramolecular charge-transfer contribution is included in $E_{\mathrm{ind}}^{(2)}$, while the exchange terms describe the repulsive effects of electron exchange between subsystems [24]. We estimated also the δ(HF) correction:

$$\delta(\mathrm{HF}) = E_{\mathrm{int}}^{\mathrm{HF}} - E_{\mathrm{el}}^{(1)}(\mathrm{HF}) - E_{\mathrm{exch}}^{(1)}(\mathrm{HF}) - E_{\mathrm{ind}}^{(2)}(\mathrm{HF}) + E_{\mathrm{exch\text{-}ind}}^{(2)}(\mathrm{HF}) \quad (2)$$

This contribution provides an estimation of higher-order induction and exchange-induction effects, that might be of particular importance for hydrogen-bonded stabilized systems. All DFT-SAPT calculations were performed assuming LPBE0AC exchange-correlation potential with a hybrid xc kernel containing 25% of exact exchange and a 75% contribution of the adiabatic local density approximation (ALDA) and with the aid of Dunning's correlation consistent aug-cc-pVDZ set (used as an atomic basis set), and the cc-pVTZ basis set which was used as the density-fitting basis [24]. In order to achieve the accuracy and to correct the wrong asymptotic behaviour of the xc potential we included the Δxc for the bulk potential which is the difference between the HOMO energy obtained from DFT calculation and the (negative) ionisation potential of the monomer (IP): The data were obtained for two sets of structures, containing two and three molecules of nicotinamide, respectively. In the latter case, trimers were described in terms of pairwise interactions.

2.2. Variational–perturbational scheme

The variational–perturbational scheme was applied in order to estimate the importance of nonadditivity of interactions in the case of nicotinamide complexes in orientations appearing in the crystal structure. In this approach the total intermolecular energy and all of its components are basis set superposition error free due to the counterpoise correction. At the MP2 level of theory, the total intermolecular interaction energy of a 3-body complex can be decomposed in the following way [25,26]:

$$\Delta E^{\mathrm{MP2}} = \Delta E^{\mathrm{HF}} + \epsilon_{\mathrm{el,r}}^{(12)} + \epsilon_{\mathrm{disp}}^{(20)} + \Delta E_{\mathrm{exch\text{-}del,2}}^{(2)} + \Delta E_{\mathrm{exch\text{-}del,3}}^{(2)} \quad (3)$$

where $\epsilon_{\mathrm{disp}}^{(20)}$ is the second order dispersion interaction; $\epsilon_{\mathrm{el,r}}^{(12)}$ describes the electron correlation correction to the first order electrostatic interaction and the remaining electron correlation effects are encompassed in the $\Delta E_{\mathrm{ex}}^{(2)}$ term. ΔE^{HF} is the intermolecular interaction energy at the HF level of theory:

$$\Delta E^{\mathrm{HF}} = \epsilon_{\mathrm{el}}^{(10)} + \epsilon_{\mathrm{exch,2}}^{\mathrm{HL}} + \epsilon_{\mathrm{exch,3}}^{\mathrm{HL}} + \Delta E_{\mathrm{del,2}}^{\mathrm{HF}} + \Delta E_{\mathrm{del,3}}^{\mathrm{HF}} \quad (4)$$

$\epsilon_{\mathrm{el}}^{(10)}$ is the electrostatic interactions of unperturbed monomer charge densities; $\Delta E_{\mathrm{ex}}^{\mathrm{HL}}$ stands for the associated exchange repulsion and ΔE_{del} is the delocalization component. Moreover variational–perturbational scheme was applied in order to estimate the 2-body interactions in the considered crystal. All calculations of the decomposition of intermolecular interaction energy at the MP2/aug-cc-pVDZ level of theory were performed using the modified version of the GAMESS US package [27–31].

2.3. Atoms in molecules method

In the present study, the topological properties of electron density in the considered complexes were assigned using the Quantum Theory of Atoms in Molecules (QTAIM) of Bader [32,33].

We estimated the properties of bond critical points (BCPs) localized at the bond path linking the interacting species, especially the electronic density at BCP, $\rho(\mathbf{r}_{\mathrm{BCP}})$, and its Laplacian, $\nabla^2\rho(\mathbf{r}_{\mathrm{BCP}})$. It is known that negative values of $\nabla^2\rho(\mathbf{r}_{\mathrm{BCP}})$ imply concentration of electronic charge in the intermolecular region and its magnitude yields the information about the strength of interactions of considered systems. The positive values of Laplacian, in turn, correspond to the reduction of electronic charge in the intermolecular region.

The local kinetic $G(\mathbf{r}_{\mathrm{BCP}})$, potential $V(\mathbf{r}_{\mathrm{BCP}})$ and total $H(\mathbf{r}_{\mathrm{BCP}})$ energy densities, estimated at the bond critical point can be also useful in analysis of the weak intermolecular interactions. The electronic energy density of the local charge distribution may be calculated as the sum of the local kinetic and potential energy densities:

$$H(\mathbf{r}_{\mathrm{BCP}}) = G(\mathbf{r}_{\mathrm{BCP}}) + V(\mathbf{r}_{\mathrm{BCP}}) \quad (5)$$

The AIM calculations were performed using the AIM2000 program [34].

2.4. Solid state DFT calculation

Optimization, atom positions and the unit cell parameters of NAm were performed using the CRYSTAL09 software package [35] using density functional theory and based on the linear combination of atomic orbitals (LCAO) method. In this work we tested four functionals, namely local density approximation (LDA), PBE, developed for solids PBEsol and B3LYP hybrid functional with the 6-311G(d,p) basis set obtained from the EMSL basis-set library [36,37]. Grimme's approach was used to include long-range dispersion contributions to the DFT total energy and gradients at the B3LYP level of theory. Van der Waals radii and atomic coefficients were taken from [38] and [39] for B3LYP-D and B3LYP-D* respectively. We applied isotropic shrinking factors of 4 and 4 for the Monkhorst–Pack and Gilat k-point net, respectively. Values of 8, 8, 8, 8 and 16 were employed as truncation criteria for the bielectronic integrals. An energy convergence criterion of 10^{-9} a.u. was used in