

Co-crystallization with Nicotinamide in Two Conformations Lowers Energy but Expands Volume

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Received 31 January 2014; accepted 18 February 2014

Published online 14 March 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23929

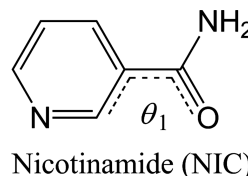
ABSTRACT: A dispersion-corrected density functional theory method has been used to study the formation energies and volumes of cocrystals. For four cocrystals of nicotinamide (NIC) and (*R*)-mandelic acid, a broad agreement is found between experimental and computed values. We report that cocrystals containing NIC are anomalous as their formation generally decreases energy but expands volume. In this respect, the formation of NIC cocrystals is in contrast to most physical processes, but similar to water freezing. As in the case of water freezing, the cocrystallization with NIC leads to stronger hydrogen bonds and looser molecular packing, a combination that is likely responsible for the anticorrelation between energy and volume. NIC has two conformers 4 kJ/mol apart in energy and both can form cocrystals, with the resulting structures having comparable formation energies and volumes. These results are relevant for understanding the nature of cocrystallization and why NIC is a prolific cocrystal former. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 103:2896–2903, 2014

Keywords: cocrystal; nicotinamide; thermodynamics; structure-property relationship; molecular modeling; lattice energy calculation; crystal engineering; hydrogen bonding; molecular packing

INTRODUCTION

The cocrystallization of multiple chemical components is an important phenomenon in science and technology. Cocrystals have received recent attention as an approach to engineering pharmaceutical solids^{1–4} and other molecular materials.⁵ Despite this growing interest, however, the nature of cocrystallization remains inadequately understood. Many have studied the discovery and structures of cocrystals, whereas less is known about their thermodynamics and structure–property relations. It is unclear why some molecules [e.g., nicotinamide (NIC)]^{6–9} are prolific cocrystallizers and to what extent this tendency can be linked to molecular attributes (e.g., conformational flexibility and ability to form hydrogen bonds). The formation of racemic compounds—a special class of cocrystals containing the opposite enantiomers—is typically associated with energy decrease and volume reduction in reference to their components,^{10,11} but it is unknown whether the same holds for cocrystallization in general. Answering these questions helps advance the science of cocrystals.

Zhang et al.¹² reported recently that the cocrystallization of NIC (Scheme 1) with (*R*)-mandelic acid (RMA) is anomalous in that it lowers energy but expands volume, in contrast to most physical processes, but analogous to water freezing. Their conclusion relied on the experimental formation energies of several NIC–RMA cocrystals and the formation volumes from crystallographic data. They observed that the expansion of volume upon cocrystallization correlates with the formation of shorter and stronger hydrogen bonds. In a nearly concurrent report, Chan et al.¹³ demonstrated the ability to calculate *ab initio* the formation energies of cocrystals. They applied a dispersion-corrected



Scheme 1. Structure of nicotinamide (NIC). θ_1 indicates the main torsion angle.

density functional theory (DFT-D) method to calculate the lattice energies of cocrystals relative to their components. They found that the formation energies are generally negative for known cocrystals containing NIC and the isomers of NIC, verifying that the formation of these cocrystals is energetically favored.

The present work builds on the two aforementioned studies to further understand the cocrystallization of NIC and its ability to form many cocrystals. For the cocrystals of NIC and RMA, we verify that the computed formation properties are in broad agreement with the experimental values. The combined results from experiment and theory strengthen the previous conclusion that the cocrystallization of NIC with a second component generally lowers energy but expands volume. We also report that NIC, a flexible molecule, can form cocrystals of comparable stability using two different conformers whose energies are 4 kJ/mol apart. These results are relevant for understanding the formation of organic cocrystals and why NIC is a prolific cofomer.

METHODS

The formation property of a cocrystal A_mB_n is the change of some property of interest (e.g., enthalpy and volume) associated

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Journal of Pharmaceutical Sciences, Vol. 103, 2896–2903 (2014)
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with the following reaction:



where A and B are the crystals of component A (NIC) and component B (coformer), respectively. The value of a formation property depends on the definition of one mole of molecules in the cocrystal but is unambiguous if calculated per unit mass. With details given elsewhere,⁹ Eq. (2) is used to determine the formation enthalpy via calorimetry:

$$\Delta H_f = \Delta H_{m(\text{A+B})}(T_S \rightarrow T_L) - \Delta H_{m\text{AB}}(T_S \rightarrow T_L) \quad (2)$$

where T_S is a temperature at which the cocrystal and the physical mixture of component crystals are solid and at which ΔH_f is evaluated, T_L is a temperature at which the cocrystal and the physical mixture are both melted to the same liquid, and $\Delta H_{m(\text{A+B})}(T_S \rightarrow T_L)$ and $\Delta H_{m\text{AB}}(T_S \rightarrow T_L)$ are the corresponding enthalpies of melting (properly scaled to reflect the stoichiometry of the cocrystal). For our systems under ambient conditions, ΔH_f is approximately the same as the formation energy ΔE_f because the difference $\Delta H_f - \Delta E_f = P\Delta V_f$ is small at 1 bar. For example, the typical formation volume of a NIC cocrystal is $\Delta V_f = +20 \text{ cm}^3/\text{kg}^{12}$; at $P = 1 \text{ bar}$, $P\Delta V_f = 2 \text{ mJ/g}$, which is much smaller than the typical magnitude of ΔH_f ($\sim 20 \text{ J/g}$).¹² From here on, we shall not distinguish ΔH_f and ΔE_f and use ΔE_f only.

To calculate the formation energy of a cocrystal by DFT-D, Eq. (3) is used¹³

$$\Delta E_f = E_{cc} - (mE_A + nE_B) \quad (3)$$

where E_{cc} , E_A , and E_B are the energies of the cocrystal, the component crystal A, and the component crystal B, respectively. Each calculated energy is the total energy of the crystal, including intramolecular and intermolecular contributions. To calculate the energy of a crystal, its experimental crystal structure is optimized to minimize its lattice energy, within the constraints of the experimental space group symmetry, by varying the lattice parameters and the nuclear positions using the GRACE package.¹⁴ GRACE provides an efficient algorithm for optimizing the coordinates and lattice parameters of molecular crystals. Lattice energies and gradients are provided by a solid-state DFT method with corrections for dispersive interactions (the DFT-D method).¹⁵ GRACE uses the VASP program¹⁶ to calculate the lattice energy and its gradients. The dispersive correction is provided by a damped molecular mechanical potential.^{15,17} The DFT calculations use projector-augmented wave potentials¹⁸ to describe the interaction between ions and electrons together with the PW91 exchange–correlation functional.¹⁹ A plane wave basis set cutoff energy of 520 eV was used and Brillouin zone integrations were performed on a k-point grid with a spacing of less than 0.07 \AA^{-1} . The electronic wave function convergence on total energy was set to $5 \times 10^{-7} \text{ kcal/mol}$ of atoms for structure optimizations. With these settings, lattice energy differences between crystal packings of a given molecule are typically converged to within 0.01–0.02 kcal/mol. Minimizations were considered complete when energies were converged to better than $2.5 \times 10^{-4} \text{ kcal/mol}$, atomic displacements to $3 \times 10^{-3} \text{ \AA}$, and maximum atomic forces to $0.7 \text{ kcal}/(\text{\AA} \text{ mol})$. For relaxed cell calculations, the stresses were

converged to within 0.1 GPa. It is worth noting that the DFT-D model is parameterized to yield the structures and energies of crystals at low temperatures.¹⁵

A cocrystal's formation volume is calculated using Eq. (4):¹²

$$\Delta V_f = V_{cc} - [m/(m+n)V_A + n/(m+n)V_B] \quad (4)$$

where V_{cc} , V_A , and V_B are the volumes of one molecule in the cocrystal, the component crystal A, and the component crystal B, respectively. The volume of one molecule in a crystal is calculated from crystallographic data using $V = V_{\text{cell}}/Z$, where V_{cell} is the volume of the unit cell and Z the number of molecules therein. One “molecule” (one formula unit) in a cocrystal A_mB_n consists of $m/(m+n)$ of A and $n/(m+n)$ of B. The value of V thus obtained is the volume occupied by one molecule in a crystal *including void space*. In cases where the structure of a cocrystal is solved at a significantly different temperature than those of the component crystals, temperature corrections are made using procedures described previously.¹²

Cocrystals containing NIC were retrieved from the Cambridge Structural Database (CSD)²⁰ under the following constraints: 3D atomic coordinates determined, $R \leq -0.1$, no errors, not polymeric, no ions, and organics only. Structures solved from powder patterns were excluded, as well as those of clathrates, hydrates, and cocrystals with more than two components. To calculate ΔV_f , the data on component B (coformer) were retrieved with the same criteria.

RESULTS AND DISCUSSION

Comparison of Experimental and Calculated Formation Properties of NIC Cocrystals

The DFT-D model has been applied to study four experimentally characterized cocrystals of NIC and RMA. The two components can cocrystallize in the ratios of 4:1, 1:1 (two polymorphs), and 1:2; we designate these cocrystals as N_4R , NR Form 1, NR Form 2, and NR_2 . The availability of multiple NIC–RMA cocrystals allows a critical test of the agreement between experiment and theory, with cancellation of systematic errors, much like the availability of many polymorphs in studying structure–property relations.²¹ Table 1 summarizes the optimized unit-cell parameters and their deviations from the experimental structures. With the exception of NR Form 2, the optimization of all crystals converged to structures closely matching the experimental structures. In the case of NR Form 2, the minimization led to a larger-than-expected change of the experimental crystal structure, with an expansion of 6.6% along the *a*-axis and a contraction of 7.2% along the *c*-axis.

To assess the results obtained for NR Form 2, its crystal structure was reoptimized using three alternative approaches. In the first, a preliminary optimization was performed in which the unit cell was fixed but the molecular coordinates were allowed to vary, before simultaneously optimizing the molecular coordinates and lattice parameters. The resulting structure deviated from experiment in a similar way to that reported in Table 1. In the second approach, the crystal structure was optimized without any consideration of symmetry. The initial atomic coordinates from experiment were subject to small random displacements to remove any memory of the space group symmetry. The subsequent optimization converged to a structure that was higher in energy than that found previously. A

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