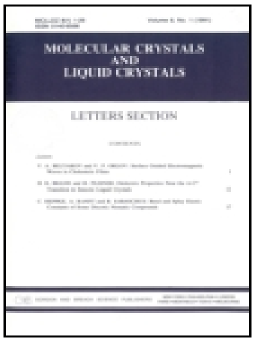

Molecular Crystals and Liquid Crystals

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Synthesis, Thermal Studies, Spectroscopy Characterization, and Crystal Structure of Nicotinamidium Oxamate

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Synthesis, Thermal Studies, Spectroscopy Characterization, and Crystal Structure of Nicotinamidium Oxamate

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The title compound has been synthesized by grinding in an agate mortar. Its structure was characterized by TGA-DSC studies, FT-IR, X-ray powder diffraction data, and single-crystal X-ray diffraction. This compound crystallize in the monoclinic system with space group $P2_1/c$, $Z = 4$, and unit cell parameters $a = 6.9834(4)$ Å, $b = 9.8771(6)$ Å, $c = 13.6740(8)$ Å, and $\beta = 103.861(1)°$. The salt, $C_6H_7N_2O^+ \cdot C_2H_2NO_3^-$, or NA^+:$OXAM^-$, is an ionic ensemble assisted by hydrogen bonds established between nicotinamidium cations and oxamate anions. The molecular structure and crystal packing are stabilized mainly by four intermolecular N–H···O hydrogen bonds, reinforced by two C–H···O hydrogen bonds and three intramolecular interactions. The two components thus construct a supramolecular assembly with a three-dimensional hydrogen bonded framework.

Keywords Hydrogen bonding; ionic ensemble; multicomponent crystal; X-ray crystal structure

1. Introduction

Pharmaceutical cocrystals are multiple component crystals in which at least one part is a solid at room temperature, and forms supramolecular synthons with a molecular or ionic active pharmaceutical ingredient (API) [1–4]. Pharmaceutical cocrystals are, therefore, crystalline molecular complexes containing therapeutically active molecules, usually in conjunction with molecules that do not have therapeutic value.

This type of molecular complex are attractive to pharmaceutical scientists because it can provide a number of crystalline states for a given API, in which the physical and chemical properties of the API such as solubility, stability and bioavailability are improved without affecting the chemical composition of API. Therefore, pharmaceutical cocrystallization plays a significant role in the development of new drugs [5–7].

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The main route to obtain good crystalline products, with API, has been the formation of salts, mainly through the groups of compounds classified as GRAS (generally regarded as safe) and approved by the FDA (food and drug administration) [8]. Salt formation is an acid-base reaction between the API and an acidic or basic substance, which is favored by the fact that most pharmaceutical compounds possess either acidic or basic functionality. Widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs [9].

Two good candidates for the pharmaceutical co-crystal formation are the pyridinecarboxamide compounds and the amino acids or carboxylic acids, due to their interesting hydrogen-bonding interactions.

Pyridinecarboxamides (picolinamide, nicotinamide, and isonicotinamide) are amide isomers which can be classified as GRAS compounds. In particular, nicotinamide (3-pyridinecarboxamide, niacinamide, and Vitamin B3) show important biological activity with a coenzyme called NAD (nicotinamide adenine dinucleotide) [10]. This coenzyme plays important roles in more than 200 amino acid and carbohydrate metabolic reactions [11]. Nicotinamide also have pharmaceutical importance since it is a vital molecule used in drugs to treat diabetes type 1 [12], and has demonstrated anti-inflammatory action that may help patients with skin diseases [13].

Nicotinamide is an excellent cocrystallizing compound. It has two hydrogen bonding groups suitable for the formation of an intermolecular synthon. The amide group has two hydrogen bond donors and two lone pairs on the carbonyl O atom. A second hydrogen bond acceptor is the lone pair on the N atom of the pyridine ring. This makes the molecule very versatile for a variety of hydrogen bonded interactions, especially in pharmaceutical co-crystals [14–21].

For the other hand, oxamic acid (OXAM) is an amino acid capable of generating infinite anionic aggregates through the complimentary hydrogen-bond functionalities of the carbonyl and amide functional groups [22]. The Cambridge Structural Database (CSD version 5.35, February 2014) [23] shows 220 cocrystals and salts having at least one amino acid component which making them reliable supramolecular agents [24].

From the interest in studying the formation of multicomponent crystals containing amino acids, amines, amides and carboxylic acids [25, 26], we report here the structure of the ionic ensemble formed between a pyridinecarboxamide, nicotinamide (NA), and an amino acid, OXAM, and its hydrogen-bonding patterns analysis.

2. Experimental

2.1. Synthesis

The multicomponent compound was prepared by mixing nicotinamide (0.0366 g) and OXAM (0.0267 g) in a 1:1 molar ratio. The reagents were ground in an agate pestle and mortar and dissolved in methanol (5 mL). Colorless crystals of **1** suitable for X-ray diffraction analysis were grown by slow evaporation.

2.2. Thermal Analysis

Melting point was determined on an Electrothermal Model 9100 apparatus. Thermal analysis of NA^+:$OXAM^-$ was performed in a Perkin-Elmer TGA7 coupled with a DSC console. Sample was heated from 25 to 400°C at a rate of 10°C min^{-1}, under a nitrogen flux of

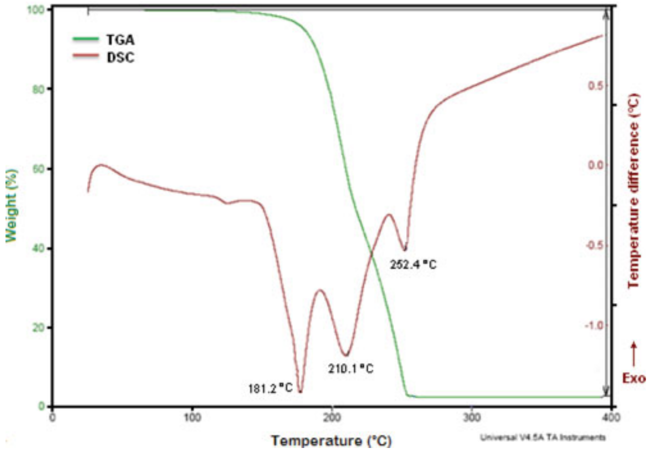


Figure 1. TGA and DSC for NA$^+$:OXAM$^-$.

100 mL min^{-1} (Fig. 1). A sharp endothermic peak observed at 181.2°C corresponds to the compound melts, which was further confirmed by melting point analysis (180-182 °C). At a temperature 210.1°C, one sharper endothermic peak occurred corresponding to traces of OXAM (m.p. 210°C). No traces of pure nicotinamide (m.p. of 128°C) were found. The sample decomposed completely at 252.4 °C.

2.3. FT-IR Spectrum

The FT-IR spectrum for the title compound was recorded on a Perkin Elmer 1600 spectrometer employing a KBr disc, in the region from 400 to 4000 cm^{-1} (Fig. 2). The bands at 3302 and 3204 cm^{-1} are typical of the NH group, from both components. The bands at 1646 and 1720 cm^{-1} may be assigned to the carbonyl group (C = O) of carboxylic acid and amide groups, respectively. Furthermore, symmetric (1520 cm^{-1}) and asymmetric (1464 cm^{-1}) tension bands of COO$^-$ group, indicates that the OXAM is in anionic form. Likewise, there

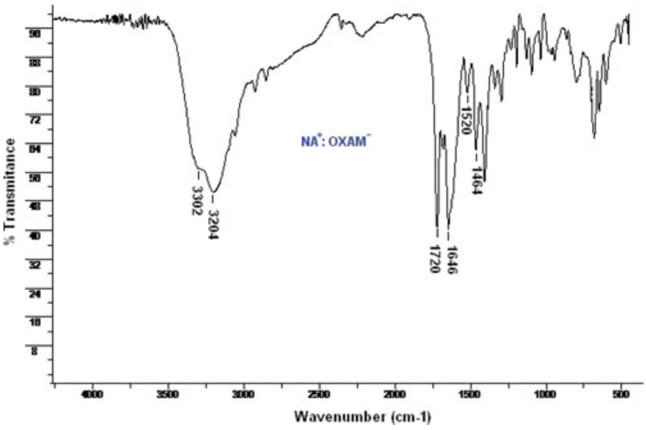


Figure 2. FT-IR spectrum for NA$^+$:OXAM$^-$.

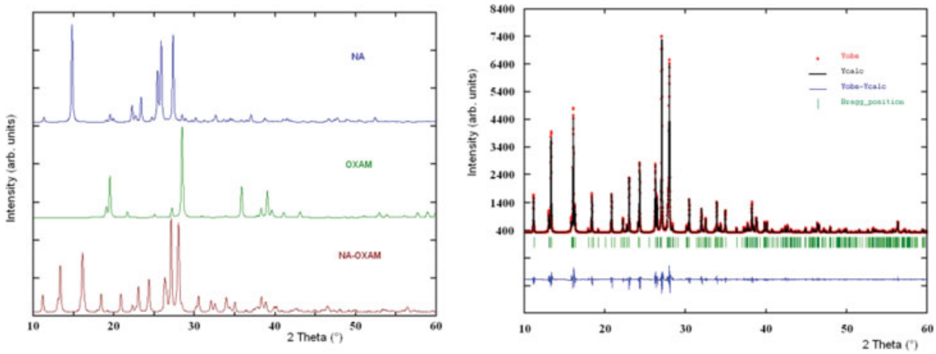


Figure 3. (**a**) X-ray powder diffraction patterns for NA, OXAM and NA^+:$OXAM^-$. (**b**) Le Bail fit of the powder diffraction data for NA^+:$OXAM^-$.

is a widening in the region of 3400–3100 cm^{-1} due possibly to the formation of hydrogen bonds.

2.4. X-ray Powder Diffraction

The X-ray powder diffraction patterns for NA, OXAM and NA^+:$OXAM^-$ were collected at room temperature in a Phillips PW-1250 goniometer using monocromatized Cu$K\alpha$ radiation. A small quantity of each compound was ground mechanically in an agate mortar and pestle and mounted on a flat holder covered with a thin layer of grease. The samples were scanned from 10° to 60° 2θ, with a step size of 0.02° and counting time of 10s. Silicon was used as an external standard. X-ray powder patterns showed in Fig. 3a evidences the formation of a new compound.

For the multicomponent NA^+:$OXAM^-$ powder pattern, the 20 first measured reflections were completely indexed using the program Dicvlo04 [27], which gave a unique solution in an orthorhombic cell with parameters $a = 6.99$ Å, $b = 9.85$ Å, $c = 13.69$ Å, and $\beta = 103.7°$ in a P-type cell. In order to confirm the unit cell parameters, a Le Bail

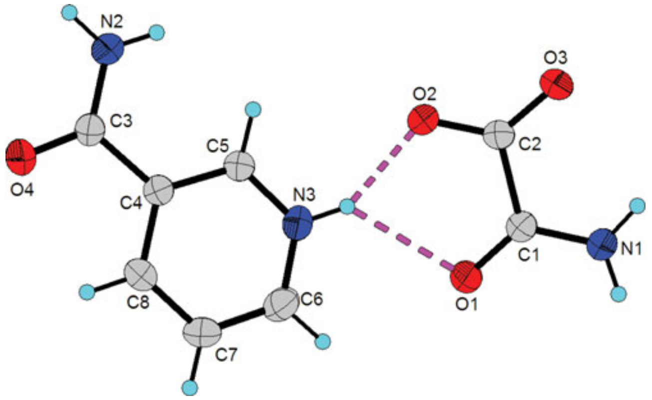


Figure 4. The molecular structure of 1, showing the atomic numbering scheme. Displacement ellipsoids are drawn at 50% probability level. H atoms are shown as spheres of arbitrary radii.

Table 1. Crystal data, data collection, and structure refinement.

Chemical formula	$C_6H_7N_2O^+ \cdot C_2H_2NO_3^-$	CCDC	892975
Formula weight	211.18	Radiation (MoKα)	$\lambda = 0.71073$ Å
Crystal system	Monoclinic	θ range (°)	2.6–29.5
Space group	$P2_1/c$	*hkl* range	$-7 \leq h \leq 9$; $-13 \leq k \leq 13$; $-18 \leq l \leq 18$
a (Å)	6.9834(4)	Reflections	
b (Å)	9.8771(6)	Collected	14159
c (Å)	13.6740(8)	Unique (Rint)	2385 (0.016)
β (°)	103.861(1)	With $I > 2\sigma(I)$	2180
V (Å^3)	915.71(9)	Refinement method	Full-matrix least-squares on F^2
Z	4	Number of parameters	136
dx (g cm^{-3})	1.532	$R(F^2)$ $[I > 2\sigma(I)]$	0.0433
F(000)	440	$wR(F^2)$ $[I > 2\sigma(I)]$	0.1313
μ (mm^{-1})	0.125	Goodness of fit on F^2	1.04
Crystal size (mm)	0.6 × 0.5 × 0.5	Max/min $\Delta\rho$ (e Å^{-3})	0.35/-0.28

Table 2. Selected geometrical parameters (Å, °).

C1-O1	1.234(1)	C1-N1	1.322(2)
C2-O2	1.252(2)	C2-O3	1.239(2)
C3-O4	1.231(2)	C3-N2	1.327(2)
C1-C2-O2	115.5(1)	N1-C1-O1	124.8(1)
N2-C3-O4	123.3(1)	C5-N3-C6	122.6(1)
C3-C4-C5-N3	179.9(1)	N2-C3-C4-C5	1.8(2)

Table 3. Hydrogen bonds geometry (Å, °).

D–H···A	D–H	H···A	D···A	D–H···A	Symmetry codes
N1—H1A···O1$^{(i)}$	0.86	2.12	2.979 (1)	175	$^{(i)}$ $2-x, -y, -z$
N1—H1B···O2$^{(ii)}$	0.86	2.23	3.028 (1)	153	$^{(ii)}$ $2-x, -\frac{1}{2}+y, \frac{1}{2}-z$
N2—H2A···O4$^{(iii)}$	0.86	2.10	2.945 (2)	169	$^{(iii)}$ $1-x, 2-y, -z$
N2—H2B···O3$^{(iv)}$	0.86	2.08	2.927 (2)	167	$^{(iv)}$ $2-x, \frac{1}{2}+y, \frac{1}{2}$-$z$
C5—H5···O3$^{(iv)}$	0.93	2.21	3.112 (2)	164	$^{(iv)}$ $2-x, \frac{1}{2}+y, \frac{1}{2}-z$
C7—H7···O4$^{(v)}$	0.93	2.28	3.180 (2)	162	$^{(v)}$ $1-x, -\frac{1}{2}+y, -\frac{1}{2}-z$
Intramolecular HB					
N3—H3···O1	0.86	2.270	2.923 (1)	132	—
N3—H3···O2	0.86	1.860	2.614 (1)	146	—
N1—H1B···O3	0.86	2.360	2.704 (2)	104	—

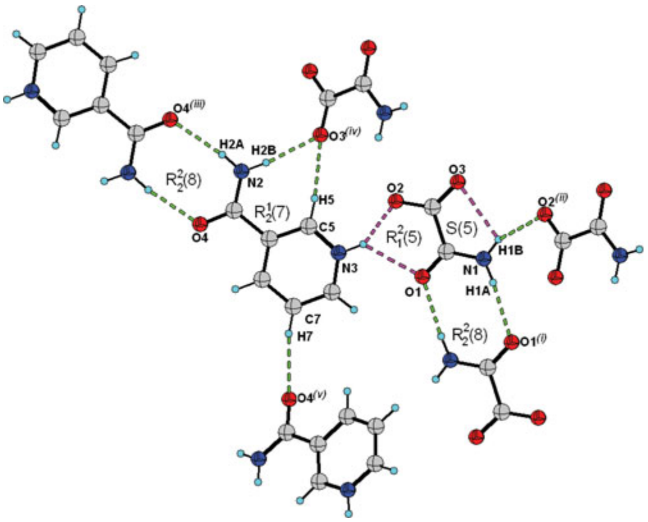


Figure 5. A portion of the crystal packing shows all intermolecular (N–H···O, C–H···O) and intramolecular hydrogen bonds formed in NA^+:$OXAM^-$.

refinement [28] of the whole diffraction pattern without structural was carried out using the Fullprof program [29]. Figure 3b shows a very good fit between the observed and calculated patterns.

2.5. *X-ray Single-crystal Crystallography*

Colorless block crystal of the title compound with dimensions 0.6 × 0.5 × 0.5 mm was used for data collection. Diffraction data were collected at 296(2) K by ω-scan technique on a Bruker SMART APEX II CCD diffractometer [30] equipped with Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å). The data were corrected for Lorentz-polarization and absorption effects

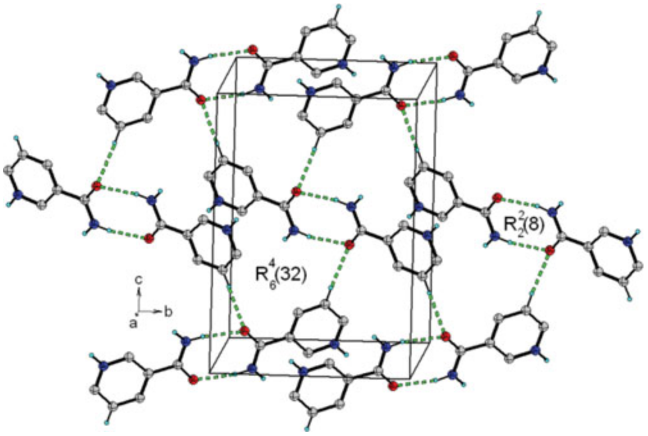


Figure 6. Packing of the homomeric NA^+ interactions shows the cyclic structures with graph-set motifs $R^2{}_2(8)$ and $R^4{}_6(32)$.

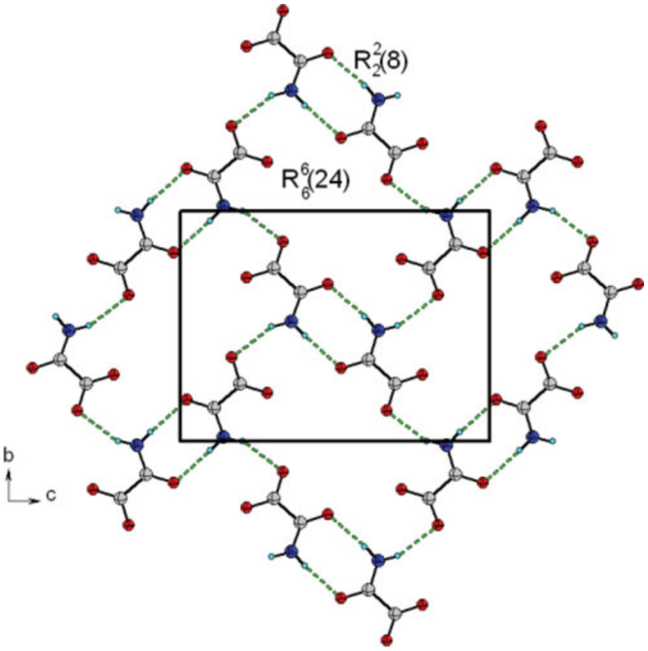


Figure 7. Packing of the homomeric OXAM$^-$ molecules shows the cyclic structures with graph-set motifs R$^2{}_2$(8) and R$^6{}_6$(24) in the *bc* plane.

[31]. The structure was solved by direct methods using the SHELXS program [32] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [32]. All H atoms were placed at calculated positions and treated using a riding model, with C-H distances 0.96–0.98 Å and Uiso(H) = 1.2Ueq(C)], N-H 0.86 Å, and Uiso(H) = 1.2Ueq(N)]. Figure 4 shows the molecular structure and the atom-labeling scheme of NA$^+$:OXAM$^-$. Table 1 shows the crystallographic data and structure refinement parameters and Table 2 shows

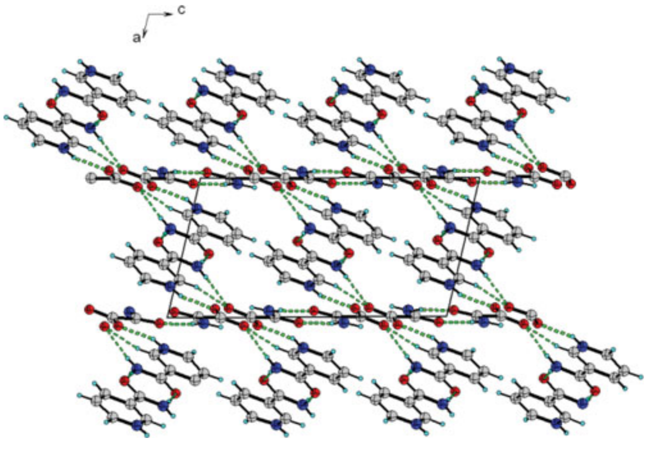


Figure 8. Packing of the three-dimensional hydrogen bond network in NA$^+$:OXAM$^-$.

selected geometrical parameters for NA$^+$:OXAM$^-$. All figures were performed using the Diamond software [33].

3. Results and Discussion

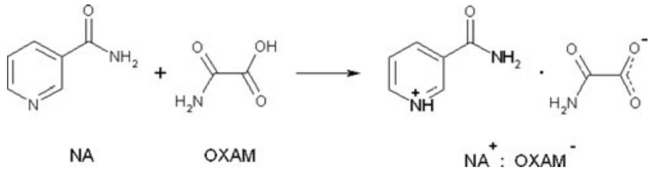
A search in the Cambridge Structural Database (version 5.35, February 2014) [23] shows 70 adducts containing nicotinamide; 54 cocrystals and 16 salts. In contrast, only seven adduct containing OXAM were found, all salts. In this work, the multicomponent compound NA$^+$:OXAM$^-$ is a salt. The asymmetric unit consists of one NA$^+$ ion with a positive charge residing on atom N3 and an OXAM$^-$ anion acting as an oxamate ion [for the carboxylate group, C2-O2 and C2-O3 are 1.252 (2) and 1.239 (2) Å, respectively].

The nicotinamidium (NA$^+$) plane is twisted by 17.38 (5)° from the oxamate (OXAM$^-$) plane. Meanwhile, NA$^+$ cation is essentially flat with a maximal deviations of 0.026 (1) Å in N2 and −0.032 (4) Å in O4, and OXAM$^-$ is lightly twisted by 6.84 (9)° between the acid and amide groups. The nicotinamide molecule adopts a *syn* conformation with the heterocyclic N and amide N on same sides of the molecule [torsion angle N2-C3-C4-C5 = 1.8 (2) Å].

A new search in the Cambridge Structural Database (version 5.33, August 2012) [23] revealed that in the 70 nicotinamide adducts found, the nicotinamide molecule displays both *syn* (38 structures) and *anti* (31 structures) conformations. Only in the cocrystal nicotinamide succinic acid (2/1) both conformations are present in the same structure [16].

This salt NA$^+$:OXAM$^-$ is an ionic ensemble assisted by hydrogen bonds. The nicotinamide moiety (NA) has a protonated ring N atom (NA$^+$ or 3-pyridinecarboxamidium), while the amino acid moiety (OXAM) has a negative charge on the carboxylate amide group (OXAM$^-$ or oxamate) (see Scheme 1).

The molecular structure and crystal packing are stabilized mainly by four intermolecular N–H···O hydrogen bonds, reinforced by two C–H···O hydrogen bonds and three intramolecular interactions (Table 3). The intramolecular N1–H1B···O3 gives rigidity to the oxamate molecule with graph-set motif S(5) [34, 35], while the intramolecular interactions, N3–H3···O1 and N3–H3···O2 produces a bifurcated hydrogen bond that connect both molecules in the asymmetric unit, forming a five member ring with graph-set motif $R^2_1(5)$, see Fig. 5. This graph-set is also found in the six adducts containing OXAM with 1:1 stoichiometry, found in the CSD database: KUQVOI, MOSSOD, TOYLIC, TYUO, TOYMAV, and TOYMEZ [23].



Scheme 1. Synthesis of 3-pyridinecarboxamidium oxamate.

The four intermolecular N–H···O hydrogen bonds act as follows: N1—H1A···O1 ($2-x$, $-y$, $-z$) connect two oxamate molecules forming a cycle with a typical $R^2_2(8)$ amide-amide sinthon. N1—H1B···O2 ($2-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$) connect the oxamate ion with a new oxamate molecule. N2—H2A···O4 ($1-x$, $2-y$, $-z$) connect two nicotinamide cation molecules forming a $R^2_2(8)$ amide-amide sinthon, and N2—H2B···O3 (2-x, $\frac{1}{2}+y$, $\frac{1}{2}$-z) connect the same nicotinamide cation molecule with a new oxamate anion. This last interaction is reinforced by a non-conventional C5—H5···O3 (2-x, $\frac{1}{2}$+y, $\frac{1}{2}$-z) hydrogen bond forming a new cycle structure described by the graph-set motif $R^1_2(7)$. Another C7—H7···O4 (1-x, -$\frac{1}{2}$+y, -$\frac{1}{2}$-z) hydrogen bond connect that nicotinamide molecules with a new amide. All these interactions are shows in Fig. 5.

Figure 6 shows how the homomeric nicotinamide cation forms amide-amide dimers with graph-set motif $R^2_2(8)$ and a cycle formed by six NA^+ molecules with graph-set motif $R^4_6(32)$.

On the other hand, Fig. 7 shows how the $OXAM^-$ molecules are joined forming cyclic structures with graph-set motifs $R^2_2(8)$ and $R^6_6(24)$. This graph-set arrangement is only found in the structure of TOYMID [22]. The combinations of all interactions produce an intricate three-dimensional hydrogen bond network as shown in Fig. 8.

Funding

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Supplementary Data

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (Deposition No. CCDC-892975). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk/products/csd/request/ (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam. ac.uk).

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