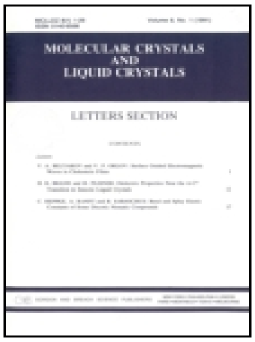
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N-Carbamoyl-Piperidine-4-Carboxylic Acid: An X-ray and Density Functional Tight-Binding Studies

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The compound N-carbamoyl-piperidine-4-carbocylic acid was synthesized and characterized by FT-IR and NMR spectra. Its molecular structure was solved by single crystal X-ray diffraction and compared with DFTB (density-functional tight-binding) theoretical calculations in the solid state. In the title compound, $C_7H_{12}N_2O_3$*, the piperidine ring adopts a chair conformation. The mean plane between the carboxylate and the ureid groups make a dihedral angle of 35.3(3)°. The structure is stabilized by intermolecular O–H···O, N–H···O and C–H···O hydrogen bonds in a three-dimensional network.*

Keywords Crystal structure; DFTB calculation; hydrogen bonds; *N*-carbamoyl

1. Introduction

N-carbamoyl amino acid compounds have attracted interest in biochemistry and metabolic process because of their application as starting point in the synthetic route to *N*-carboxyanhydride compounds, which are well-known precursors of peptides [1,2]. These compounds can display pharmaceutical and biological activity with a variety of applications. For example, *N*-carbamoyl-glycine causes sedative and anticonvulsant effects [3], *N*-carbamoyl-β-alanine has antidiabetic properties [4], *N*-carbamoyl-methionine is used in insulin analogues design [5], and *N*-carbamoyl-γ-aminobutyric acid is a weak GABA antagonist [6]. Additionally, the *N*-carbamoyl molecules containing ureido and acid groups are susceptible to form excellent supramolecular architectures through hydrogen bonds, which play a key role in molecular recognition and crystal engineering [7]. Studies of such interactions are also of current interest because of their applications in drug and pharmaceuticals design [8–11].

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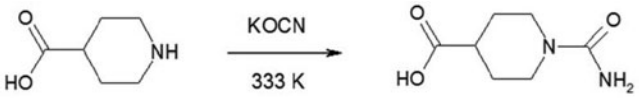
We are currently investigating the energetic character and arrangement of hydrogen-bonding patterns in structurally related amino acids. In particular, the structures of the isomers 2-piperidinecarboxylic acid (pipecolic), 3-piperidinecarboxylic acid (nipecotic) and 4-piperidinecarboxylic acid (isonipecotic) have been assessed by means of ab initio density-functional and semi-empirical calculations [12–14].

Continuing these investigations, and as part of ongoing studies on *N*-carbamoyl α-amino acids and hydantoin derivatives [15–18], in this work we report the crystal structure of a new compound, also namely *N*-carbamoyl-isonipecitoc acid (I).

2. Experimental

2.1. Synthesis

500 mg (3.4 mmol) of 4-piperidinecarboxylic acid was dissolved in 20 ml of water and the solution was acidified with concentrated HCl (37% v/v). Then, 826 mg (10.2 mmol) of potassium thiocyanate (KOCN) was added to this solution. The mixture was warmed up, with agitation, to 333 K, during 4 hr. The resultant solution was cooled at room temperature until the precipitation of a white solid. Crystals of (I) suitable for X-ray analysis were obtained by slow evaporation of an ethanol solution at room temperature (Scheme 1).



Scheme 1. Synthesis of *N*-carbamoyl-piperidine-4-carboxylic acid (I).

2.2. Spectral Studies

The synthesized compound was characterized by spectroscopic data. The Fourier transform infrared spectroscopy (FT-IR) absorption spectrum was obtained as KBr pellet using a Perkin-Elmer 1600 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 model spectrometer in DMSO-d_6 solution.

FT-IR: 3404 (t, O—H), 3226 cm^{-1} (t, C—N), 1716 cm^{-1} (t, C=O), 1668 cm^{-1} (t, C—O), 1453 cm^{-1} (t, C—N).

^{1}H-NMR (400 MHz, DMSO d$_6$): δ 11.0 (s, 1H; OH), 6.0 (s, 2H; NH$_2$), 3.39 (m, 2H; H4a,H6a), 3.29 (m, 2H; H4b,H6b), 2.37 (m, 1H; H2), 1,86 (m, 2H; H3a,H5a), 1.61 (m, 2H; H3b,H5b).

^{13}C-NMR (100 MHz, DMSO d$_6$): δ 180.0 (C1), 156.5 (C7), 43.8 (C4,C6), 41.0 (C2), 28.2 (C3,C5).

2.3. X-ray Data Collection and Structure Determination

Colorless laminar crystal (0.39 × 0.20 × 0.18 mm) was used for data collection. Diffraction data were collected at 298(2) K by ω-scan technique on a Rigaku AFC7S Mercury diffractometer [19] equipped with graphite monochromatized MoKα radiation ($\lambda = 0.71073$ Å). The data were corrected for Lorentz-polarization and absorption effects [19]. Three standard reflections were monitored every 100 reflections (intensity decay: none). The structure

Table 1. Crystal data, data collection and structure refinement

Chemical formula	$C_7H_{12}N_2O_3$	CCDC	1029614
Formula weight	172.19	Radiation (MoKα)	$\lambda = 0.71073$ Å
Crystal system	Orthorhombic	θ range (°)	2.4–28.1
Space group	Pbca (N°61)	*hkl* range	−11, 11; −11, 12; −22, 22
a (Å)	9.939(2)	Reflections Unique	1706
b (Å)	9.431(2)	Rint	0.094
c (Å)	17.293(3)	With $I > 2\sigma(I)$	941
V (Å^3)	1621.0(5)	Refinement method	Full-matrix least-squares on F^2
Z	8	Number of parameters	123
dx (g cm^{-3})	1.411	$R(F^2)$ [$I > 2\sigma(I)$]	0.0675
$F(000)$	736	wR(F^2) [$I > 2\sigma(I)$]	0.1665
μ (mm^{-1})	0.111	Goodness of fit on F^2	1.09
Crystal size (mm)	0.39 × 0.20 × 0.18	Max/min $\Delta\rho$ (e Å^{-3})	0.18/−0.20

was solved by direct methods using the SHELXS program [20] and refined by a full-matrix least-squares calculation on F^2 using SHELXL [20].

All H atoms were placed at calculated positions and treated using the riding model, with C—H distances of 0.97–0.98 Å, N-H distances of 0.86 Å and O-H distances of 0.82 Å. The Uiso (H) parameters were fixed at 1.2Ueq (C, N, O). All geometrical calculations were done using the program Platon [21]. Table 1 summarizes the crystal data, intensity data collection and refinement details for the title compound.

2.4. Solid-State Density Functional Tight-Binding Calculations

Theoretical investigation of hydrogen bonds in the crystal was performed using the Density Functional Tight-Binding (DFTB) approximation [22, 23]. The bases set are eigenfunctions from Density Functional Theory/Local Density Approximation (DFT/LDA) calculations of a single atom in a confined potential [24]. Self-consistent periodic DFTB calculations for

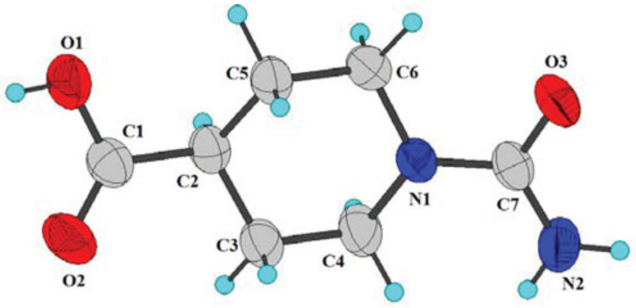


Figure 1. The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown with an arbitrary radius.

Table 2. Comparison of selected geometric data for (I) (Å, °) from X-ray data (DRX) and calculated (DFTB)

	DRX	DFTB	MOGUL	Δ(DRX/DFTB)	Δ(DRX/MOGUL)
O1-C1	1.322(4)	1.358	1.32(2)	−0.035	0.002
O2-C1	1.204(4)	1.229	1.22(2)	−0.023	−0.016
O3-C7	1.252(4)	1.277	1.26(2)	−0.025	−0.008
N1-C7	1.358(4)	1.378	1.35(2)	−0.020	0.008
N2-C7	1.347(4)	1.364	1.35(2)	−0.017	−0.003
O2-C1-O1	122.6(3)	121.188	123.4(8)	1.312	−0.8
O2-C1-C2	124.0(3)	123.663	124.4(8)	0.337	−0.4
O1-C1-C2	113.4(3)	115.057	112.1(8)	−1.657	1.3
N2-C7-N1	118.7(3)	120.009	117.5(8)	−1.309	1.2
O3-C7-N1	120.8(3)	119.331	120.3(8)	1.469	0.5
O3-C7-N2	120.4(3)	120.622	122.2(8)	−0.022	−1.8

(I) were performed using the DFTB+ program [23], with the mio-0–1 set of parameters. The following input parameters were used: DFT/LDA potentials [23], Broyden mixer in the selfconsistent part and conjugate gradient relaxation iterative optimizations of the wavefunctions. The Monkhorst–Pack scheme [25], using the Supercell–Folding routine contain in the program DFTB+. A posteriori dispersion corrections for the van der Waals interactions were applied [26, 27]. The structure was evaluated and compared with the structure obtained from X-ray diffraction.

3. Results and Discussion

Figure 1 shows the molecular structure and the atom labeling scheme of (I). This compound crystallizes in a neutral form, unlike the amino acid parent 4-piperidinecarboxylic acid [12], with the piperidine ring in a chair conformation. All bond distances and angles are normal [28].

The dihedral angle between the carboxylate and the ureid groups is 35.3(3)°. This value differs from the observed in the four *N*-carbamoyl of amino acids reported in the Cambridge Structural Database, CSD version 5.35 update May 2014 [28]: *N*-carbamoyl-L-proline [15], *N*-carbamoyl-DL-proline [16], *N*-carbamoyl–L-asparagine [29] and *N*-carbamoyl-DL-aspartic acid [30], which have intercepting angles of 79.08(9)°, 86.62(8)°, 155.0(3)° and 164.2(5)°, respectively.

Table 3. Hydrogen bonds geometry (Å, °). (D-donor; A-acceptor; H-hydrogen).

D–H···A	D–H	H···A	D···A	D–H···A
O1–H1···O3$^{(i)}$	0.90(3)	1.74(3)	2.639(3)	177(3)
N2–H2A···O3$^{(ii)}$	0.85(4)	2.37(4)	3.187(4)	163(3)
N2–H2B···O2$^{(iii)}$	0.95(4)	2.02(4)	2.960(4)	175(3)
C4–H4A···O3$^{(ii)}$	0.990	2.510	3.329(4)	140.0

Note. Symmetry codes: (i) 3/2−*x*, −*y*, 1/2+*z*, (ii) 1/2+*x*, 1/2−*y*, 1−*z*, (iii) *x*, 1/2−*y*, −1/2+*z*.

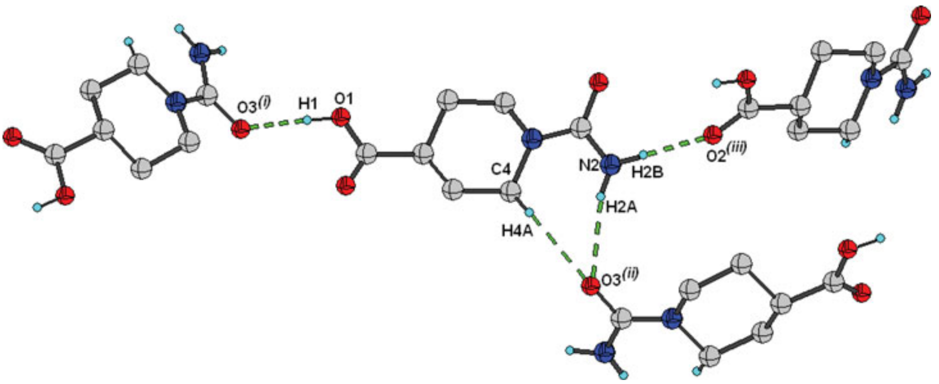


Figure 2. A portion of the crystal packing shows all hydrogen bonds formed (O–H···O, N–H···O, C–H···O) in (I).

Table 2 shows selected geometrical data for (I) compared with those obtained from solid-state DFTB calculations and with averages values calculated with Mogul1.6 [31] in searches based on the related structural fragments found on the CSD database [28]. Table 3 shows how the molecular structure of (I) obtained from X-ray diffraction data agrees very well with the solid state DFTB calculations, with the average deviation for bond distances being 0.024 Å and for bond angles 1.02°. The correctness of the geometry of the refined molecule is also confirmed when it is compared with the Mogul1.6 average distances and

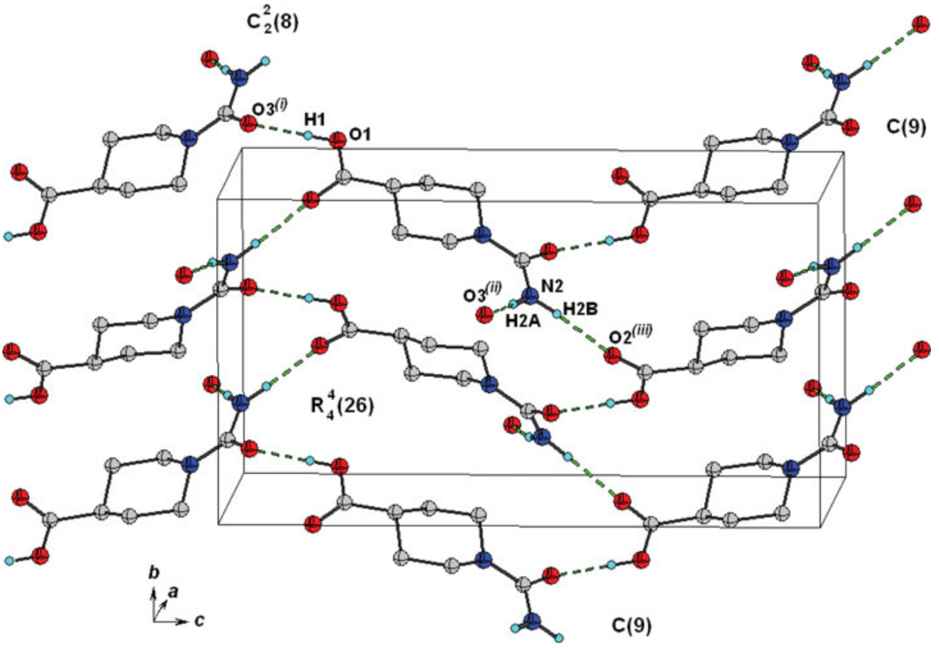


Figure 3. A partial packing view of (I). Hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding have been omitted for clarity. [symmetry codes: (i) 3/2−*x*, −*y*, 1/2+*z*; (ii) 1/2+*x*, 1/2−*y*, 1−*z*; (iii) *x*, 1/2−*y*, *z*−1/2]

angles. For bond distances, the average deviation is 0.007 Å and for bond angles, the average deviation is 1.0°.

The structure of (I) is built up from self-assembly of molecules via O–H···O, N–H···O and C–H···O hydrogen-bonding interactions (Fig. 2 and Table 3). The interactions O1–H1···O3 ($^3/_2-x$, $-y$, $1/2-z$) and N2–H2A···O2 ($1/2+x$, $1/2-y$, $1-z$) form infinite chains which run along the ***c*** axis with graph-set notation C(9) [32,33] and along the ***b*** axis with graph-set $C^2_2(8)$ (Fig. 2). Together, these hydrogen-bond patterns produces a 26-atom macrocycle described by $R^4_4(26)$. The infinite chains are connected by the N2–H2B···O2 (x, $1/2-y$, $z-1/2$) interactions, which generates infinite chains, graph-set C(9), along the ***a*** axis, and a 24-atom macrocycle with graph-set $R^4_4(24)$. The network is reinforced by the intermolecular C4–H4···O3 (x, $1/2-y$, $z-1/2$) interaction. All these interactions are shows in Fig. 3. The union of all interactions generates a three-dimensional network.

4. Conclusions

The title compound was synthesized by a reaction of isonipecotic acid and potassium thiocyanate. The structure was unambiguously assigned by X-ray diffraction studies. The FT-IR and NMR results were consistent with the structural results. DFTB theoretical calculations allowed us to confirm the experimental solution. The structure of (I) is built up from self-assembly of molecules via O–H···O, N–H···O and C–H···O hydrogen-bonding interactions, forming a three-dimensional network.

Acknowledgments

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Supplementary Data

Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (CCDC-1029614). These data can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223336033; e-mail: deposit@ccdc.cam.ac.uk.

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