UDC 54.05+547.8+539.26+543.42+544.16

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SYNTHESIS, CRYSTAL STRUCTURE, HIRSCHFELD SURFACE ANALYSIS AND BIOLOGICAL ACTIVITY PREDICTION OF *N*-(DIMETHOXYPHOSPHORYL)-1-METHYLPYRIDINIUM-4-CARBOXIMIDATE

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N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate, a new carbacylamidophosphate-type compound, was synthesized and characterized by means of IR, ^{1}H and ^{31}P NMR and UV-Vis spectroscopies and X-ray analysis. The molecule of the synthesized compound has triclinic (P-1) symmetry, displays monomeric motif in crystal and crystalizes as solvate containing methanol molecule, which is connected to carbacylamidophosphate molecule through O(2)···H(5A)−O(5) hydrogen bond. Through π−π stacking interactions, the molecules of the synthesized compound are linked in the chain along the a crystallographic axis. Several other intermolecular bonds connect these chains along b and c crystallographic axes. The intermolecular interactions with H···H and O···H contacts prevail in the crystalline structure of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate, the contribution of planar stacking C···C contacts being equal to 4.1%. The synthesized compound was found to be well soluble in water. By using computer program PASS, we established that the synthesized substance is likely can exhibit 18 types of biological activity in experiment.

Keywords: carbacylamidophosphate, *N*-methylpyridinium, crystal structure, Hirschfeld surface, PASS.

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Introduction

Carbacylamidophosphates (CAPh) are known for their wide range of biological activity [1−3] as well as for acting as powerful chelating ligands [4]. General approaches to synthesis of carbacylamidophosphates are well established [4] and allow obtaining a variety of compounds with different substitutes. From the other side, quaternary nitrogen atoms in the sp^3 hybrid state (e.g., tetramethylammonium) or sp^2 state (N-methylpyridinium) do appear in molecules of biological interest. In particular, N-methylpyridinium is under investigation by scientists regarding its potential anti-carcinogenic properties [5], chemopreventive action [6], antioxidant capacity [7] and gastric-acid secretion inhibiting potential [8]. Thus, the synthesis and structure analysis of CAPh type compound with N-methylpyridinium substitute have been of interest in view of search for new drugs.

Herein we report synthesis, crystal structure, IR, NMR and UV absorption spectra as well as theoretical prediction of biological activity of new CAPh type compound of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate (Fig. 1).

Materials and methods

IR spectrum was recorded in the spectral range of 4000−400 cm^{-1} using a Perkin-Elmer Spectrum BX spectrometer on samples in the form of KBr

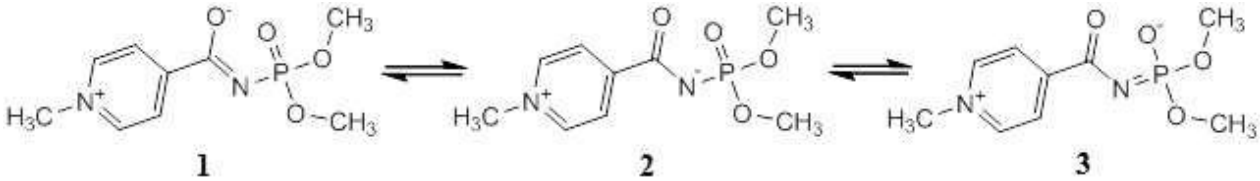


Fig. 1. Structural formula of possible tautomers for N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate

pellets.

^{1}H NMR and ^{31}P NMR spectra were obtained for the titled compound solution in DMSO-d6 on an AVANCE 400 Bruker NMR spectrometer at room temperature.

The absorption spectrum was recorded on KSVU-23 «LOMO» spectrometer.

X-ray diffraction data were collected on an «Xcalibur-3» diffractometer equipped with graphite-monochromated MoK_{α} radiation at 100 K. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX-2016 program [9]. Positions of the hydrogen atoms were located from electron density difference maps and refined by «riding» model with $U_{iso}=nU_{eq}$ of the carrier atom (n=1.5 for methyl groups and n=1.2 for other hydrogen atoms). Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Center, 11 Union Road, Cambridge, CB2 1EZ, UK (E-mail: deposit@ccdc.cam.ac.uk; fax: +44 1223 336033). CCDC number 2062594.

Biological activity prediction for the titled compound was performed using computer program PASS (Prediction of Activity Spectra for Substances) version 9.1, which predicts 3750 kinds of biological activity with the average prediction accuracy of about 95% [10].

Results and discussion

Synthesis and spectral characterization

N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate was obtained in two stages (Scheme 1). The known [4], but rarely used for CAPhs synthesis approach by using azide as precursor was applied to obtain the target compound.

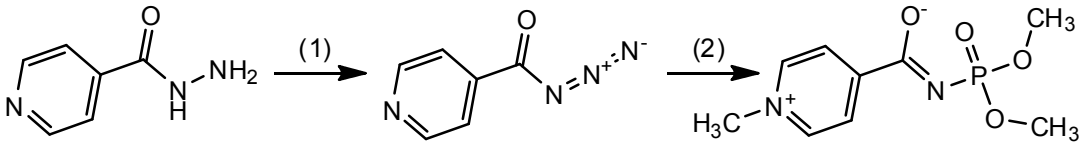
Stage (1): to a stirred at 0^0C mixture of 1.37 g (0.01 mol) of 4-pyridinecarboxylic acid hydrazide in 13 mL of water, 7 mL of diethyl ether and 12 mL of 1 N hydrochloric acid, the solution of 0.78 g (0.011 mol) of sodium nitrite in 5 mL of water was added dropwise. After complete addition, the mixture was stirred for 45 minutes. Then the mixture was carefully treated by 5.04 g (0.06 mol) of solid $NaHCO_3$ and extracted with three 100 mL portions of diethyl ether. The extracts were combined, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure to the volume ≈20 mL and the obtained azide was used in the next stage without further purification.

Stage (2): to the well stirred and cooled to -5^0C solution of 4-pyridinecarboxylic acid azide in diethyl ether, the solution of 1.24 g (0.01 mol) of $P(OCH_3)_3$ in 10 mL of dry CH_2Cl_2 was added dropwise during 30 min. The extrusion of nitrogen was very intensive. The mixture was stirred at the room temperature overnight and the resulting solid was filtered off, washed twice by 20 mL of diethyl ether and dried on air. The yield of the target yellowish product was 2.1 g (86%). The obtained compound is well soluble in methanol and water, soluble in 2-propanol under heating and insoluble in acetone and benzene.

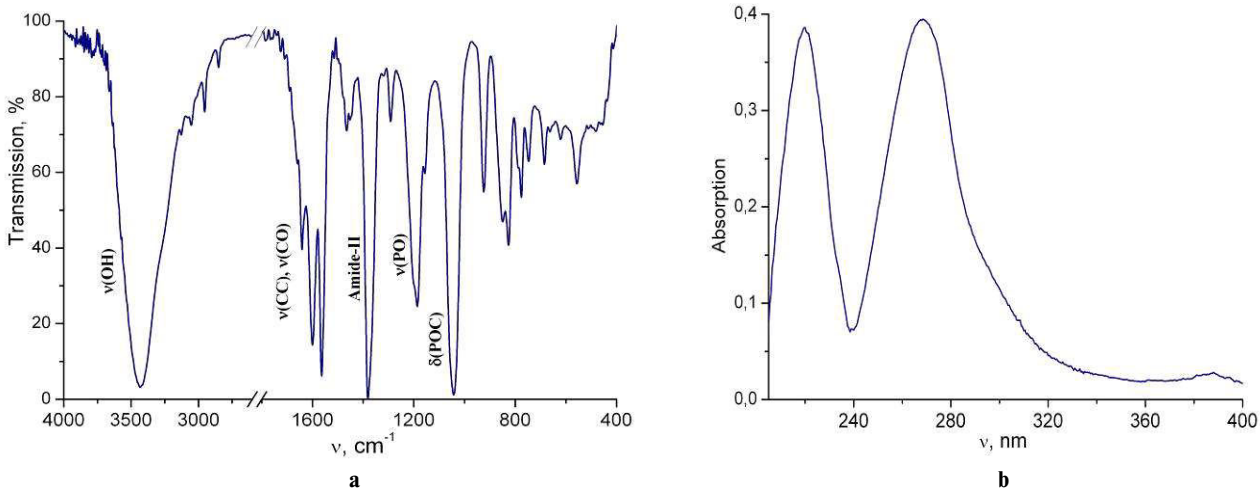
Spectral characteristics of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate: ^{1}H NMR (DMSO-d6): C−H 3.36 (s, 3H), 3.49 (d, 6H), 4.34 (s, 3H), 8.31 (d, 2H), 8.91 (d, 2H) ppm; ^{31}P NMR (DMSO-d6): 12.99 ppm; IR (KBr pellet, cm^{-1}): 3430vs (ν(OH)), 3126w, 2952w, 2849w, 1640m, 1598s, 1565vs, 1452w, 1381vs, 1292w, 1187s, 1043vs, 925m, 849m, 824m, 776m, 745w, 684w, 619w, 554m (Fig. 2,a). UV-Vis abs. (H_2O, max, nm): 220, 268 (Fig. 2,b).

Crystal structure

A single crystal suitable for X-ray diffraction studies was obtained during slow evaporation of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate solution in methanol. In the form of crystal, the titled compound was found to be a solvate, which contain a methanol molecule and displays monomeric motif in crystal (Fig. 3). A molecule of methanol is connected with CAPh compound by the hydrogen bond O(5)−H(5A)···O(2). The O(2)···O(5) distance is 2.727 Å, the H(5A)···O(2) distance is equal to 1.888 Å and the angle O(5)−H(5A)···O(2) is 176.43^0. An oxygen atom of the methanol molecule also participates in creating weak intermolecular O(5)···H(2)−C(2) interactions with another neighboring CAPh molecule The bonds length in the C(O)NP(O) structural fragment of the titled compound are given in Table 1. The P=O bond length in N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate is comparable with that in CAPh type compounds, while C=O bond is slightly longer and



Scheme 1. Synthesis rout for N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate



a b

Fig. 2. IR transmission (a) and UV-Vis absorption (b) spectra of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate

P−N and C−N bonds are slightly shorter as compared with reported CAPhs (Table 1). Thus, the tautomer form 1 (Fig. 1) can be assumed for the obtained compound. The C=O and P=O groups are located in synclinal position, the O(2)−P(1)−N(2)−C(C7) torsion angle is equal to 51.94⁰ and the pseudo-torsion angle O(2)−P(1)−C(7)−O(1) is 37.95⁰. The O(1)−C(7)−N(2)−P(1) torsion angle is 6.79⁰. The −C(1)−C(7)(O(1))N(2)− unit is planar, the sum of the angles around C(7) atom is equal to 360⁰.

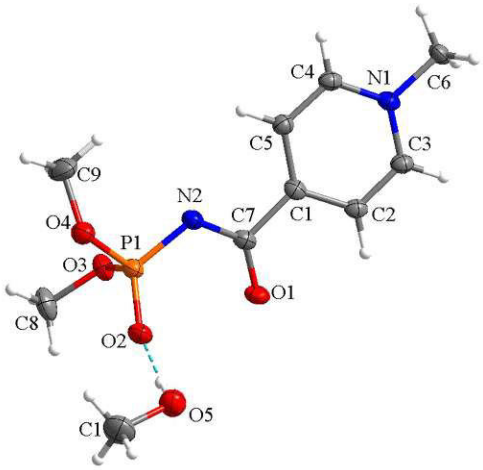


Fig. 3. The molecular structure of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate showing displacement ellipsoids drawn at the 50% probability level

The carbonyl bond is co-planar to the aromatic heterocycle (the O(1)−C(7)−C(1)−C(2) torsion angle is 13.62⁰). The length of C1−C7 bond in N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate is equal to 1.515(3) Å and is commensurable with C−C(O) bond length in CAPhs with aryl derivatives in the carbonyl group. The phosphorus atom environment has a distorted tetrahedral configuration.

Through π−π stacking, P(1)=O(2)···H(6A)', P(1)−O(3)···H(6C)'' and C(7)=O(1)···N(1)'' interactions, the molecules of the title compound are linked in the chain along a axis (Fig. 4). Along c axis, the CAPh molecules form a chain by being connected through P(1)−O(40)···H8A interactions between the phosphoryl group methylate substitutes of neighboring molecules (Fig. 5). Both C=O and

Table 1

Selected bonds length for N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate and some CAPh type compounds

Bond type	Bond length	Bond length (data from literature), Å			
		HL^1[11]	HL^2[11]	HL^3[12]	HL^4[13]
P(1)–O(2)	1.477(2)	1.478(1)	1.475(4)	1.453(2)	1.461(4)
P(1)–N(2)	1.623(2)	1.684(2)	1.671(5)	1.643(3)	1.667(5)
N(2)–C(7)	1.324(3)	1.373(2)	1.376(8)	1.388(4)	1.393(7)
C(7)–O(1)	1.252(2)	1.216(2)	1.211(7)	1.209(4)	1.219(6)
C(7)–C(1)	1.515(3)	–	–	–	–
P(1)–O(3)	1.5897(16)	–	–	–	–
P(1)–O(4)	1.5840(16)	–	–	–	–

P=O groups participate in connecting of CAPh molecules along b axis and create C(7)=O(1)···H(4)', C(7)=O(1)···H(6B)' and P(1)=O)···H(4)' intermolecular contacts (Fig. 6).

Hirshfeld surface analysis and fingerprint plots

The intermolecular interactions for the titled compound were also visualized by Hirshfeld surface analysis, which has been known as an effective tool for exploring intermolecular interactions and packing modes in molecular crystals, as they provide a visual picture of intermolecular interactions and of molecular shapes in a crystalline environment [14]. Using *CrystalExplorer17* program, the Hirshfeld surface mapped over d_{norm} and selected two-dimensional fingerprint plots for the title compound were created (Fig. 7).

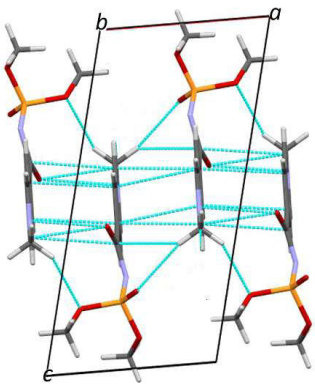


Fig. 4. A section of a chain along the a axis formed by short intermolecular contacts and π–π interactions (shown as blue dotted lines). The methanol molecules are omitted

The dark red spots on the d_{norm} surface arise as a result of the short interatomic contacts, i.e., strong hydrogen bonds, while the intermolecular interactions appear as light-red spots. The light red spots on the d_{norm} surface obtained for the title compound are located near the oxygen atoms of PO and CO groups and the nitrogen and carbon atoms of N'-methylpyridinium fragment of the molecule and can be attributed to the O···H and π–π stacking contacts, respectively. A single dark red spot appears from the hydrogen bond between the CAPh compound and a methanol molecule, which was discussed above in the previous section.

The two-dimensional fingerprint plots show distances from the Hirshfeld surface to the nearest exterior atom (d_e plots) and from interior atom to the surface (d_i plots), specify atom···atom contacts

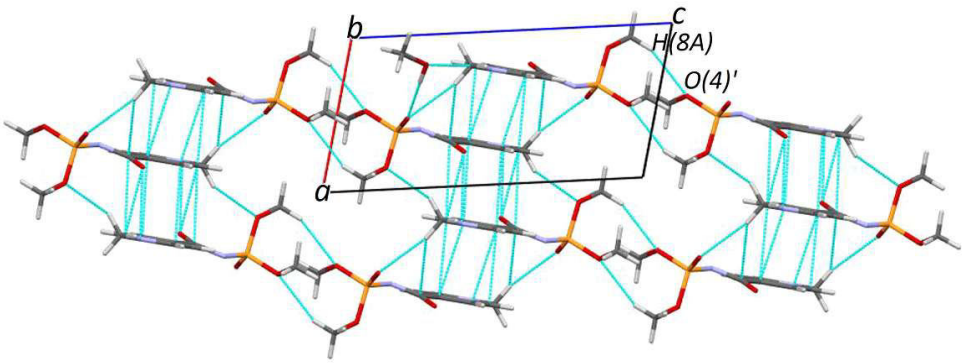


Fig. 5. The crystal packing of the title compound viewed along the c axis. The methanol molecules are omitted

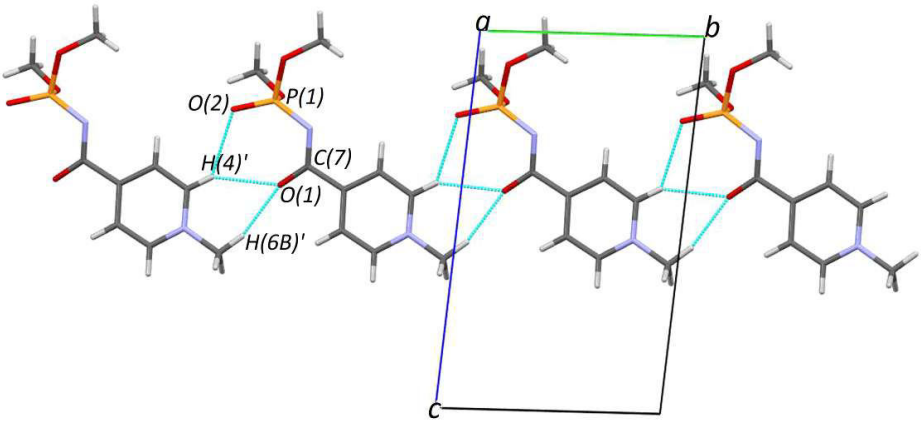


Fig. 6. A section of a chain along the b axis formed by short intermolecular interactions (shown as blue dotted lines). The methanol molecules are omitted

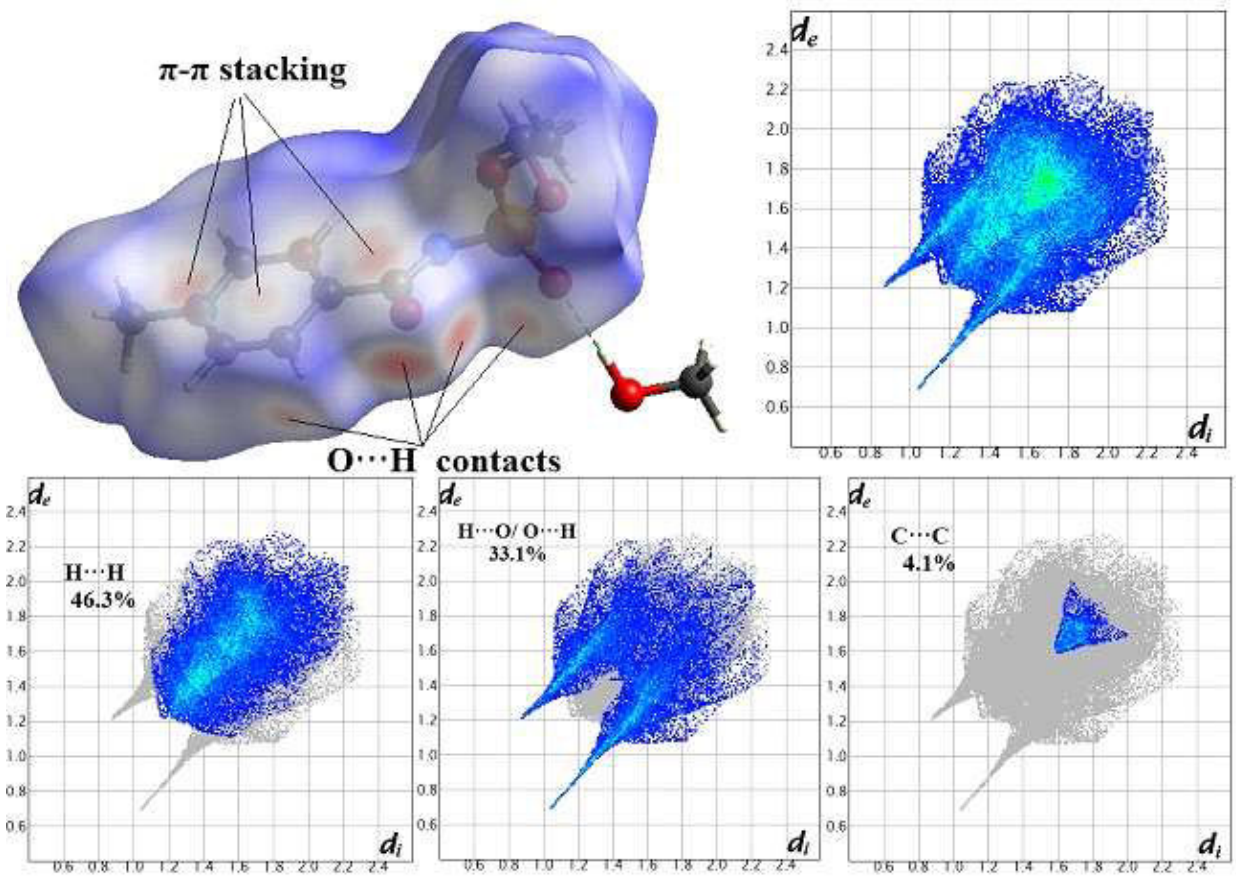


Fig. 7. The Hirshfeld surface mapped over d_{norm} and selected two-dimensional fingerprint plots for the title compound

in a crystal and provide a quantitative idea of the types of intermolecular contacts experienced by molecules. The analysis of the obtained fingerprint plots shows that the H···H contacts have major contribution to the Hirshfeld surface (46.3%). The closest H···H contact occurs at $d_i=d_e$~1.2 Å. The second largest contribution comes from H···O/O···H contacts (33.1%). The H···C/C···H and H···/N···H interactions' contribution to the Hirshfeld surface are 8.1% and 4.2%, respectively. Participation in a planar stacking arrangement of the molecules (π−π stacking) shows up as a region near the centre of the plot in the vicinity of (d_i, d_e) 1.6−1.90 Å. The contribution of C···C contacts to the Hirshfeld surface is equal to 4.4%.

PASS analysis

The predicted activity spectrum obtained by PASS program is presented by the list of activities with the probabilities «to be active» (Pa) and «to be inactive» (Pi) calculated for each activity (Table 2). The list is arranged in descending order of Pa−Pi; therefore, more probable activities are at the top of the list. Only activities with Pa>Pi are considered as probable for a particular compound [10]. If Pa is higher than 0.5, it means that the substance is likely to exhibit the activity in experiment [15].

Based on the structural data of the titled compound, presented as MOL-file, the theoretical prediction of the compound biological activity was conducted by computer program PASS. The program has given a list of 619 entries with Pa>Pi and from which there are 18 entries with Pa higher than 0.5 (Table 2). No entries with Pa significantly higher than 0.7 was found for N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate which indicates low chance for it to be the analogue of a known pharmaceutical agent.

Conclusions

A new carbacylamidophosphate type compound, *N*-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate, was synthesized.

It was found that the molecule of *N*-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate displays monomeric motif in crystal and crystalizes as solvate containing methanol molecule, which is connected to carbacylamidophosphate molecule through O(2)···H(5A)−O(5) hydrogen bond. Through π−π stacking and several other intermolecular bonds

Table 2

Predicted biological activity spectrum for N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate (only activities predicted with Pa>0.5 are shown)

No.	Pa	Pi	Activity
1	0.712	0.026	Glutamate-5-semialdehyde dehydrogenase inhibitor
2	0.714	0.050	CDP-glycerol glycerophosphotransferase inhibitor
3	0.638	0.036	Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor
4	0.608	0.013	Antineoplastic (non-Hodgkin's lymphoma)
5	0.591	0.049	Pseudolysin inhibitor
6	0.604	0.069	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
7	0.577	0.048	Nicotinic alpha4beta4 receptor agonist
8	0.597	0.069	CYP2H substrate
9	0.538	0.016	Alcohol dehydrogenase (acceptor) inhibitor
10	0.542	0.038	Oxygen scavenger
11	0.509	0.005	Antineoplastic (pancreatic cancer)
12	0.552	0.055	Ribulose-phosphate 3-epimerase inhibitor
13	0.508	0.012	Antitoxic
14	0.528	0.044	Beta-adrenergic receptor kinase inhibitor
15	0.528	0.044	G-protein-coupled receptor kinase inhibitor
16	0.582	0.104	Aspulvinone dimethylallyltransferase inhibitor
17	0.501	0.083	Sugar-phosphatase inhibitor
18	0.557	0.144	Phobic disorders treatment

the molecules of *N*-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate are linked in the chains along a, b and c crystallographic axis.

There are numerous intermolecular interactions in the crystalline structure of *N*-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate; the interactions with H···H and O···H contacts prevail; the contribution of planar stacking C···C contacts is equal to 4.1%.

The theoretical prediction of biological activity and good solubility of *N*-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate in water make it worth examining its biological activity.

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СИНТЕЗ, КРИСТАЛІЧНА СТРУКТУРА, АНАЛІЗ ПОВЕРХНІ ХІРШФЕЛЬДА ТА ПРОГНОЗ БІОЛОГІЧНОЇ АКТИВНОСТІ *N*-(ДИМЕТОКСИФОСФОРИЛ)-1-МЕТИЛПІРИДИНІЙ-4-КАРБОКСИМІДАТУ

В.О. Труш, Н.С. Каряка, І.С. Коновалова, С.В. Шишкіна, В.М. Амірханов

Новий карбациламідофосфат – *N*-(диметоксифосфорил)-1-метилпіридиній-4-карбоксимідат – був синтезований і охарактеризований методами ІЧ, ^{1}H та ^{31}P ЯМР і УФ абсорбційної спектроскопії та рентгеноструктурного аналізу. Молекула одержаної сполуки має триклінну (P-1) симетрію, є мономером у кристалі і кристалізується як сольват, що містить молекулу метанолу, яка з'єднана з карбациламідофосфатом водневим зв'язком O(2)···H(5A)–O(5). Через π–π стекінгові взаємодії молекули одержаної сполуки з'єднуються в ланцюг уздовж кристалографічної осі a. Кілька інших міжмолекулярних зв'язків з'єднують ці ланцюги уздовж кристалографічних осей b та c. Серед міжмолекулярних зв'язків в кристалічній структурі *N*-(диметоксифосфорил)-1- метилпіридиній-4-карбоксимідату домінують H···H та O···H взаємодії, а внесок планарних стекінгових взаємодій C···C складає 4,1%. Знайдено, що одержана сполука добре розчиняється у воді. З використанням комп'ютерної програми PASS було встановлено, що одержана сполука з великою ймовірністю може проявляти в експерименті 18 типів біологічної активності.

Ключові слова: карбациламідофосфат, *N*-метилпіридиній, кристалічна структура, поверхня Хіршфельда, PASS.

SYNTHESIS, CRYSTAL STRUCTURE, HIRSCHFELD SURFACE ANALYSIS AND BIOLOGICAL ACTIVITY PREDICTION OF N-(DIMETHOXYPHOSPHORYL)-1-METHYLPYRIDINIUM-4-CARBOXIMIDATE

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N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate, a new carbacylamidophosphate-type compound, was synthesized and characterized by means of IR, ^{1}H and ^{31}P NMR and UV-Vis spectroscopies and X-ray analysis. The molecule of the synthesized compound has triclinic (P-1) symmetry, displays monomeric motif in crystal and crystalizes as solvate containing methanol molecule, which is connected to carbacylamidophosphate molecule through O(2)···H(5A)–O(5) hydrogen bond. Through π–π stacking interactions, the molecules of the synthesized compound are linked in the chain along the a crystallographic axis. Several other intermolecular bonds connect these chains along b and c crystallographic axes. The intermolecular interactions with H···H and O···H contacts prevail in the crystalline structure of N-(dimethoxyphosphoryl)-1-methylpyridinium-4-carboximidate, the contribution of planar stacking C···C contacts being equal to 4.1%. The synthesized compound was found to be well soluble in water. By using computer program PASS, we established that the synthesized substance is likely can exhibit 18 types of biological activity in experiment.

Keywords: carbacylamidophosphate; *N*-methylpyridinium; crystal structure; Hirschfeld surface; PASS.

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