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Crystal structure of *p*-[*N*-methyl(diethoxyphosphonyl)-(4-dimethylaminophenyl)]toluidine – a potential cytotoxic agent

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The structure of an α-aminophosphonic acid diester, *p*-[*N*-methyl(diethoxyphosphonyl)-(4-dimethylaminophenyl)]toluidine, was determined by single-crystal X-ray diffraction. The compound is a racemic mixture and crystallizes as colourless prisms in a centrosymmetric manner in the monoclinic crystal system, space group $P2_1/c$, with two molecules in the asymmetric unit. One of the ethyl groups in one of the non-equivalent molecules exhibits a disorder. The bond lengths and angles, as well as the conformations of the two molecules, are comparable. Two intermolecular hydrogen bonds of the type N-H···O connect the non-equivalent molecules into dimers, and stabilize the crystal structure.

Keywords: single crystal X-ray diffraction analysis, aminophosphonic acid diesters, N-H…O hydrogen bonding.

INTRODUCTION

α-Aminophosphonic acid derivatives have attracted continuous interest owing to their pronounced biological activities. These compounds have been shown to serve as inhibitors of GABA receptors, inhibitors of various proteolytic enzymes like synthase, HIV protease, thrombin and serine proteases, and as inhibitors of bone resorption [1-4]. Aminophosphonates have been found to act as peptide mimics, antibiotics, antiviral and antitumor agents [5, 6]. They have been used as diagnostic imaging agents and contrast agents for magnetic resonance imaging [7].

The broad spectrum of pharmacological applications and utility of the aminophosphonic acid derivatives has stimulated extensive studies on various aspects of their chemistry and biochemistry and much attention has been paid to the investigation of their synthesis, structural and spectral characteristics, biological properties and relationship between structure and activity [8-10]. The biological activity of these compounds depends on their structural parameters and on the absolute configuration of the stereogenic α-carbon atom to phosphorus [11, 12]. Single-crystal X-ray analysis provides important information on the geometric parameters and the stereochemistry of the α-aminophosphonic acid derivatives; these studies establish the feasibility of hydrogen bonding that is essential for the interaction of the molecules with the biological systems [10, 13, 14]. Here we report the crystal structure of the α-aminophosphonic acid diester *p*-[*N*-methyl(diethoxyphosphonyl)-(4-dimethylaminophenyl)]toluidine. The compound showed prominent cytotoxicity against the multi-drug-resistant cancer cell line HL-60/Dox [15].

EXPERIMENTAL

The title compound, $C_{20}H_{29}N_2O_3P$, was synthesized and tested *in vitro* for cytotoxicity against a panel of cell lines representative for some important types of human leukemia including the multi-drug-resistant model HL-60/Dox [15].

X-ray crystallography: A crystal of the title compound was mounted on a glass capillary and all data were collected at room temperature on an Oxford diffraction Supernova diffractometer using Mo-Kα radiation (λ = 0.71013 Å) from a micro-focus source. The determination of cell parameters, data integration, scaling and absorption correction were carried out using the CrysalisPro [16]. The structures were solved with ShelxS-2013 and refined using full-matrix least-squares on F^2 with the ShelxL-2013 package [17]. The N hydrogen atoms were positioned from difference Fourier map while all other hydrogen atoms were placed at idealized positions. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using the riding model.

ORTEP [18] drawing diagram of the molecular structures of the two molecules is shown in Fig.1.

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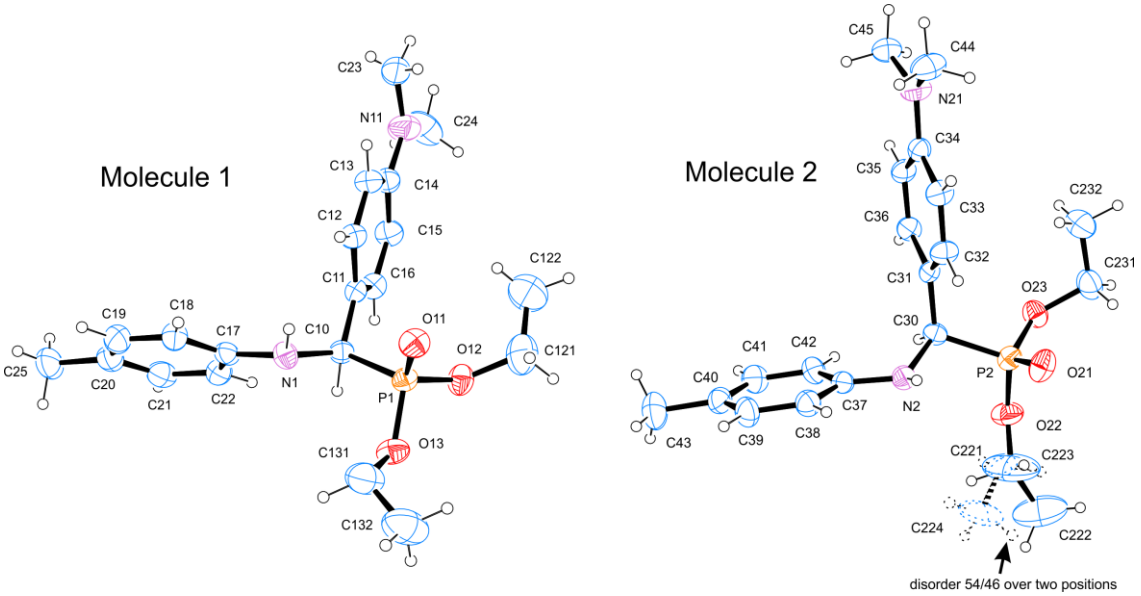

Fig. 1. *ORTEP* view and numbering scheme of the two molecules present in the asymmetric units of the title compound. H-atoms are presented with spheres of arbitrary size.

A summary of the fundamental crystal and refinement parameters is provided in Tables 1 and 2.

Table 1. Most relevant crystal data and refinement indicators

$C_{20}H_{29}N_2O_3P$	$F(000)$ = 1616
M_r = 376.42	D_x = 1.169 Mg m^{-3}
Monoclinic, $P2_1/c$	Melting point: 101-102 ºC
Hall symbol: -P 2ybc	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 18.1979 (12) Å	Cell parameters from 1277 reflections
b = 11.3948 (7) Å	θ = 3.0–27.0°
c = 22.3224 (13) Å	μ = 0.15 mm^{-1}
β = 112.506 (8)°	T = 290 K
V = 4276.3 (5) Å^3	Prism, colourless
Z = 8	0.23 × 0.21 × 0.15 mm

SuperNova, Dual, Cu at zero, Atlas diffractometer	7385 independent reflections
Radiation source: SuperNova (Mo) X-ray Source	3300 reflections with $I > 2\sigma(I)$
Mirror monochromator	R_{int} = 0.103
Detector resolution: 10.3974 pixels mm^{-1}	θ_{max} = 27.0°, θ_{min} = 3.0°
ω scans	h = −18 21
Absorption correction: multi-scan CrysAlisPro, Agilent Technologies,	k = −14 12
T_{min} = 0.978, T_{max} = 1.000 15622 measured reflections	l = −28 25

Refinement on F^2	Primary atom site location: direct
Least-squares matrix: full	Secondary atom site location: from difference Fourier
$R[F^2 > 2\sigma(F^2)]$ = 0.079	Hydrogen site location: mixed
$wR(F^2)$ = 0.188	H-atom parameters constrained
S (GOF) = 0.99	$w = 1/[\sigma^2(F_o^2) + (0.0605P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$
7385 reflections	$(\Delta/\sigma)_{max} < 0.001$
490 parameters	$\Delta\rho_{max}$ = 0.35 e Å^{-3}
0 restraints	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
0 constraints	Extinction correction: none

Table 2. Hydrogen bond geometry (Å and º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*N*1···O21	0.95	2.12	3.049 (5)	168
N2—H1*N*2···O11	0.88	2.04	2.924 (4)	174

Crystallographic data (excluding structure factors) for the structural analysis were deposited at the Cambridge Crystallographic Data Centre, CCDC No 984798. A copy of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk, or www.ccdc.cam.ac.uk.

RESULTS AND DISCUSSION

The single-crystal X-ray study showed that the title compound crystallizes in a centrosymmetric manner (SG $P2_1/c$, No 14) with two molecules in the asymmetric unit. The bond lengths and angles of the two molecules are comparable. The aromatic ring systems present in the molecules are essentially planar. The values of the angle between the mean planes of the aromatic rings are comparable (86.19 and 81.32º for molecules 1 and 2, respectively). One of the ethyl groups in molecule 2 (O22, C221 and C222) exhibits a disorder over two positions, the major one being 54%. The values of the ADP of the second ethyl group (O23, C231 and C232) do not suggest a similar disorder over two positions.

The superposition of the two independent molecules of the title compound (Fig. 2) shows a slight rotation (~3-4º) of the 4-dimethylaminophenyl and toluidine moieties around the C-C and C-N bonds, respectively.

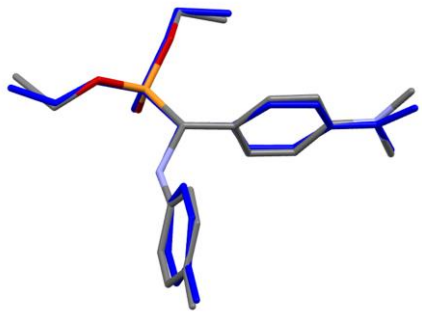

Fig. 2. Overlay of the two independent molecules present in the ASU.

The ethyl moieties are also slightly misaligned but this can be explained by their relative freedom of movement (expressed also as a disorder for O22, C221 and C222).

Having in mind the similarity (bond lengths and angles and also the superposition of the molecules) one should expect similar hydrogen bonding interactions. Indeed, two intermolecular N-H···O hydrogen bonds (Table 2 and Fig. 3) stabilize the molecular geometry of the two non-equivalent molecules.

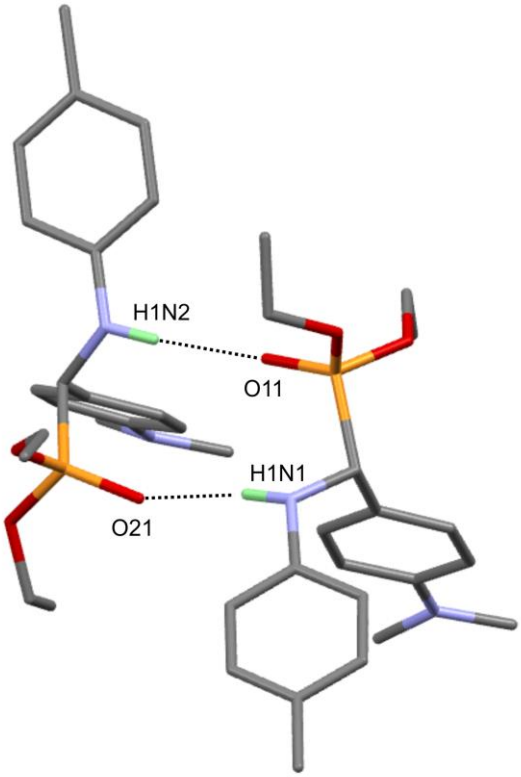

Fig. 3. Observed hydrogen bonding interactions in the title compound

Such type of hydrogen bonding interaction has also been observed in earlier reported crystal structures of two racemic anthracene-containing α-aminophosphonic acid diesters (dimethyl and diethyl) [19, 20], where both molecules form "inversion" dimers linked by pairs of N-H···O hydrogen bonds.

Similarly to those compounds, the title compound crystallizes as a racemate. The three-dimensional packing (Fig. 4) also reveals that the crystal packing is governed by the hydrogen bonding interactions and thus the phosphonic and toluidine fragments are oriented toward each other producing hydrogen bonded dimers, while the 4-dimethylaminophenyl and ethyl moieties are oriented to minimize additional steric contacts.

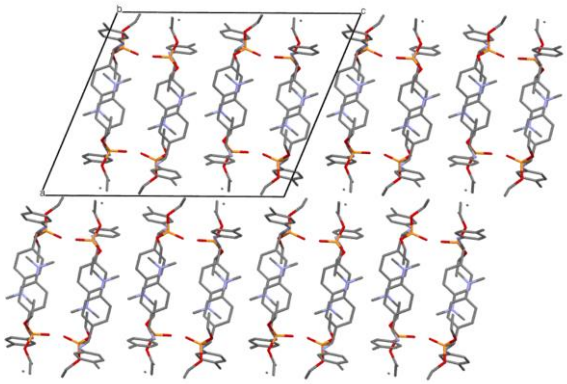

Fig. 4. Three-dimensional packing of the molecules of the title compound.

CONCLUSION

The compound *p*-[*N*-methyl (diethoxy-phosphonyl)-(4-dimethylaminophenyl)] toluidine, exhibiting prominent cytotoxicity against a human leukemic multi-drug-resistant cell line, was characterized by single-crystal X-ray analysis. This revealed that the crystals are monoclinic, space group $P2_1/c$, with two molecules in the asymmetric unit. Important information on the structural parameters (bond lengths, bond angles and torsion angles, as well as intermolecular N-H···O hydrogen bonding) was obtained and a positional disorder of one of the ethyl groups was found. The obtained structural data of the compound could be useful in the further studies of its cytotoxicity mode of action.

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КРИСТАЛНА СТРУКТУРА НА p-[N-МЕТИЛ(ДИЕТОКСИФОСФОНИЛ)-(4-ДИМЕТИЛАМИНОФЕНИЛ)]ТОЛУИДИН– ПОТЕНЦИАЛЕН ЦИТОТОКСИЧЕН АГЕНТ

И. Крайчева[*1], Б. Л. Шивачев[2], Р. П. Николова[2], А. Богомилова[1], И. Цачева[1], Е. Воденичарова[1], К. Троев[1]

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(Резюме)

Структурата на диестер на *α*-аминофосфонова киселина, *p*-[*N*-метил(диетоксифосфонил)-4(-диметиламинофенил)]толуидин, беше определена чрез монокристален рентгено-дифракционен анализ. Съединението представлява рацемат и кристализира центросиметрично като безцветни призми от моноклинната система, в пространствена група $P2_1/c$, с две молекули в асиметричната клетка. Едната от етилните групи в една от нееквивалентните молекули показва безпорядък. Дължините на връзките и валентните ъгли, както и конформациите на двете молекули, са близки. Две междумолекулни водородни връзки от типа N-H···O стабилизират структурата, свързвайки нееквивалентните молекули в димери.