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ORIGINAL RESEARCH

Platinum precursor of anticancer drug: a structure fixed by long intermolecular N–H···I and C–H···I hydrogen bonds

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Abstract The title compound **1**, *cis*-[diiodo(1*R*,2*R*)-1, 2-diaminocyclohexane-κ*N*,κ*N*′]platinum(II), a precursor of a novel platinum-based anticancer complex, was synthesized. High purity (>99%) was determined by HPLC–UV/VIS and its structure was characterized by LC–ESI–MS, FT-IR and X-ray single-crystal diffraction. The molecules of the title compound interact via N–H···I and C–H···I intermolecular (ultra)-long hydrogen–iodine (acceptor) bonds (distances up to 3.1 Å). The crystal structure of the title compound **1** was compared to the structure calculated on the basis of density function theory (DFT). The calculated and measured data varied by a maximum of 0.09 Å in bond lengths and the maximum deviation between the compared angles were less than 2°. Experimentally measured bond lengths in the crystal were observed to be reduced when compared to the theoretical calculation. This was caused by both steric requirements of individual structural units and the presence of hydrogen bonds in real sample, which were confirmed by FT-IR (new bands as well as the band shifts to lower wavelengths).

Systematic name: *cis*-[diiodo(1*R*,2*R*)-1,2-diaminocyclohexane-κ*N*,κ*N*′]platinum(II), Other name: *cis*-[Pt($C_6H_{14}N_2$)I_2] or *cis*-[Pt(DACH)I_2].

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Keywords Cytostatics · DFT · Intermolecular long hydrogen bond · Platinum-based anticancer complex · Single crystal/structure

Introduction

The search for novel anticancer therapeutics is one of the main streams in the present pharmaceutical research. Platinum complexes belong to the oldest but still intensively studied group of cytostatics. Some of the novel structures are based on platinum 1*R*,2*R*-1,2-diaminocyclohexane (=DACH) carrier ligand and various leaving groups bound to the central platinum atom (e.g. Oxaliplatin, AP5346, precursor *cis*-[Pt(DACH)(NO_3)$_2$]) [1, 2]. There are several synthetic ways used for the preparation of DACH–platinum-based complexes. One of the interesting ways is the synthesis (Fig. 1) starting from *cis*-[Pt(DACH)halogene$_2$] [1, 3]. The presented work was dedicated to the topics of the preparation and structural characterization of the platinum complex *cis*-[diiodo(1*R*,2*R*)-1,2-diaminocyclohexane-κ*N*,κ*N*′]platinum(II)], which represents one of the alternatives for the preparation of DACH-platinum-based complexes.

Compared to other halogenated precursors (e.g. *cis*-[Pt(DACH)Cl_2] or *cis*-[Pt(DACH)Br_2]), the prepared iodine analogue *cis*-[Pt(DACH)I_2] has the advantage that the by-product AgI exhibits lower water solubility compared to AgCl or AgBr and it could be separated by an ordinary filtration (solubility of AgI = 2.6×10^{-6} g dm^3 at 25 °C, AgBr 1.4×10^{-4} g dm^3 at 25 °C, AgCl 1.9×10^{-3} g dm^3 at 25 °C [4]). Therefore, the compound *cis*-[Pt(DACH)I_2] can be favourably used for a reaction with a silver salt of a relevant ligand (e.g. $AgNO_3$, Ag_2SO_4 and silver dicarboxylates, e.g. silver oxalate) [5]. The elimination of the residue

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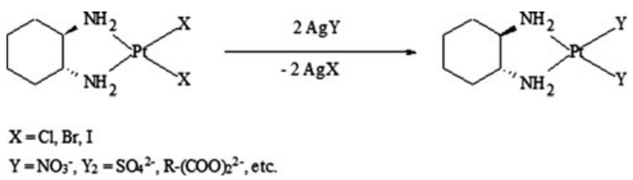
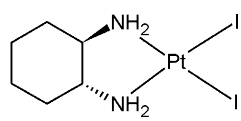


Fig. 1 Scheme of DACH–platinum complexes synthesis starting from *cis*-[Pt(DACH)halogene$_2$]

Fig. 2 Chemical structure of the title compound **1**



silver salt from the prepared Pt-complex represents one of the crucial problems of the existing Pt-based cytostatics technologies. The utilization of *cis*-[diiodo(1*R*,2*R*)-1,2-diaminocyclohexane-$\kappa N,\kappa N'$]platinum(II)] as the precursor thus represents an interesting alternative for a dramatic reduction of the potential content of residual silver salts. In this article, high yield (>98.5%), high purity (>99%) synthesis and structure characterization of *cis*-[diiodo(1*R*,2*R*)-1,2-diaminocyclohexane-$N,\kappa N'$]platinum(II)] is presented (Fig. 2—compound (I)).

Experimental

Synthesis of *cis*-[Pt(DACH)I$_2$]

The title compound **1** was prepared using the following procedure: an aqueous solution of $K_2[PtCl_4]$ (0.33 mol dm^{-3}, 88 mL) was mixed with aqueous solution of KI (6.98 mol dm^{-3}, 29 mL). Mixture was stirred for 30 min, and then aqueous solution of DACH tartrate (1.61 mol dm^{-3}, 20 mL) was added. The pH value of the reaction mixture was adjusted with potassium hydroxide. The reaction mixture was stirred in the absence of light at 45 °C for 8 h. Subsequently, the product was removed from the suspension by filtration through sintered glass filter, and dried in vacuum oven. The resulting yellow powder, crude *cis*-[Pt(DACH)I$_2$], was obtained in a yield 98.5%. Yellow single crystals of *cis*-[Pt(DACH)I$_2$] for XRD single-crystal analysis were obtained from the acetonitrile suspension of *cis*-[Pt(DACH)I$_2$] (0.17 mol dm^{-3}, 10 mL) by a filtration through an ultra-filter (pore size 0.22 μm; Sigma–Aldrich) and then by a spontaneous precipitation from solution.

Physical techniques and materials

All reagents and solvents for synthesis were commercially available and used without further purification. The infrared spectrum was recorded on FT-IR spectrometer Nicolet 740 equipped with microscope Continuum (Thermo Scientific, USA). A ProStar HPLC system equipped with a ProStar 210 dual pump, degasser and Varian 410 autosampler (Varian, USA) with a Hypercarb Thermo (100 × 2.1 mm × 5 μm) column connected to Hypercarb Thermo pre-column (Thermo Electron Corporation, USA) was used. A mobile phase consisting of a 70:30 (v/v) acetonitrile:water mixture adjusted to pH 11 with triethylamine was used for isocratic elution at a flow rate of 250 μL min^{-1}. The sample injection volume was 20 μL. The LC system was directly coupled alternatively to ProStar 320 UV/Vis detector (Varian, USA) or a Varian 1200L triple quadrupole mass spectrometer (Varian, USA) equipped with an electrospray ion source operated in the positive ion mode (ESI$^+$). The data processing was realized using the Varian MS Workstation program (System Control, *Version 6.9.1*; Varian, USA).

X-ray data collection and structure determination

Crystallographic measurements were done with four circle CCD diffractometer Geminy of Oxford Diffraction, Ltd., with graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The crystal structure was solved by charge-flipping method using program Superflip [6] and refined with the Jana2006 program package [7] by full-matrix least squares technique on F^2. The molecular structure plots were prepared using the ORTEP III [8]. Supramolecular interactions were viewed in Mercury [9]. Crystallographic data and details of the data collection and structure refinements are listed in Table 1. Selected bond distances and angles are listed in Table 2.

Computational details

Density functional theory (DFT) calculations with B3LYP functional were performed using Gaussian 03W program [10]. Geometry of *cis*-[Pt(DACH)I$_2$] was optimized using 6-31G(d,p) for C, H, N and lanl2dz basis sets Pt, I. Vibrational frequencies were then calculated with the same basis sets. Selected bond distances and angles are listed in Table 2.

Results and discussion

Purity and structure determination—HPLC–ESI–MS and HPLC/UV

The LC–MS method was used for *cis*-[Pt(DACH)I$_2$] purity determination. The sample *cis*-[Pt(DACH)I$_2$] contained one major substance with retention time 8.49 min (Fig. 3) and several minorities with individual content lower than 0.1% (some of the impurities was lower than 0.5%; HPLC–UV as

Table 1 Crystallographic and structure refinement for compound **1**

Empirical formula	$C_6H_{14}I_2N_2Pt$
Formula weight	563.1
Crystal system, space group	Monoclinic, *C*2
T (K)	120
a (Å)	14.026 (5)
b (Å)	7.4813 (10)
c (Å)	11.4872 (12)
β (°)	98.074 (17)
V ($Å^3$)	1193.4 (5)
Z	4
μ (mm^{-1})	16.885
Crystal size (mm)	0.1340 × 0.0459 × 0.0295
T_{min}	0.605
T_{max}	0.765
Measured reflections	3877
Independent reflections	2077
Reflections with $I > 3\sigma(I)$	1712
Parameters	107
R_{int}	0.023
S	1.04
$R[F^2 > 3\sigma(F^2)]$	0.025
$wR(F^2)$	0.064
$\Delta\rho_{max}$ (e $Å^{-3}$)	1.49
$\Delta\rho_{min}$ (e $Å^{-3}$)	−0.91

well HPLC–ESI–MS)—Fig. 3a. In the ESI-spectrum of *cis*-[Pt(DACH)I_2], one cluster of peaks was detected with the most abundant one at $m/z = 564.4$ Da (Fig. 3b, detail of the cluster Fig. 3c). The relative intensity of peaks present in the cluster (Fig. 3c) corresponds to the isotopic distribution of substance with molecular formula $C_6H_{14}I_2N_2Pt$ (Fig. 3c). For structure elucidation also the MS/MS experiment was performed. The MS/MS spectrum is depicted in the Fig. 3d where the presence of two iodide atoms was confirmed ($\Delta m/z = 127$ Da).

Crystal structure—XRD

The title compound **1** crystallizes in the monoclinic space group *C*2. The molecular structure and atom numbering scheme are given in Fig. 4. The molecule of *cis*-[Pt(DACH)I_2] is formed by one cyclohexane ring, a five-membered diamine ring, a central Pt atom and two iodium atoms bound to Pt. The bond distances and angles are in a good agreement with those reported in similar Pt–I organometallic compounds [11–14]. The molecule is approximately planar with cyclohexane ring having chair conformation. The Pt–I distance of app. 2.60 Å is the same as in other DACH Pt–I published complexes, as well as the Pt–N distance of app. 2.03 Å. The C1–C2 bond 1.473 Å is slightly shorter than similar bonds in a *cis*-[Pt(CH_3CN)$_2$(DACH)](NO3)$_2$.(H_2O) (1.521 and 1.495 Å [13]) and *cis*-[Pt(DACH)Br_2 (1.52 Å [14]).

Table 2 Selected bond lengths (Å) and angles (°) optimized at the DFT/6-31G (d, p) (C, H, N) and lanl2dz (Pt, I) level of theory and compared to experimental values (XRD)

Bond/angle (Å/°)	Calculated DFT/ 6-31G (d,p) lanl2dz	Experimental XRD
Pt1–N1	2.12967	2.09678
Pt1–N2	2.12971	2.03592
Pt1–I1	2.67741	2.60485
Pt1–I2	2.67739	2.60690
N1–C1	1.49111	1.49338
N2–C2	1.49113	1.52227
C1–C2	1.54068	1.47057
C2–C3	1.53425	1.53682
C3–C4	1.53799	1.51889
C4–C5	1.53601	1.49746
C5–C6	1.53799	1.53799
C1–C6	1.53425	1.55662
I1–Pt1–I2	96.4	95.9
N1–Pt1–N2	81.9	83.8
N1–Pt1–I1	90.8	89.4
N2–Pt1–I2	90.8	90.9
Pt1–N1–C1	109.2	107.2
Pt1–N2–C2	109.2	109.0

The absolute structure was tested by introducing (adding) twinning and refining volume fractions. The inversion was used as a merohedral twinning operation. In this case, the volume fraction of the inversion twin is the Flack parameter [15]. This parameter refined to a final value of 0.024 (5), which confirms that the above configuration is the correct absolute structure.

Supramolecular arrangement and bonding

Crystal structure is held together by a system of H-bonds, all of them having iodium atom as an acceptor (Table 3). The are two systems of supramolecular interactions: one formed by N–H···I interactions linking neighbouring molecules into a chain along *a* axis, and one formed by C–H···I and N–H···I interactions linking layers of chains stacked along *b* axis. The distance between layers is exactly a half of the *b* parameter, i.e. 3.74 Å. The first system is formed by two parallel chains of hydrogen bonds linking an N atom of the diamino group with the I atom of neighbouring molecule and take the form I2···N2 ···N1···I1 and vice versa (N2···I2 ···I1···N1) as shown in Fig. 5. The layers of chains are held together by four hydrogen bonds C2–H1C2···I1, C1–H1C1 ···I2, N1–H1N1···I2, N2–H1N2 ···I1 depicted in Fig. 6. Only H–I distances up to 3.1 A

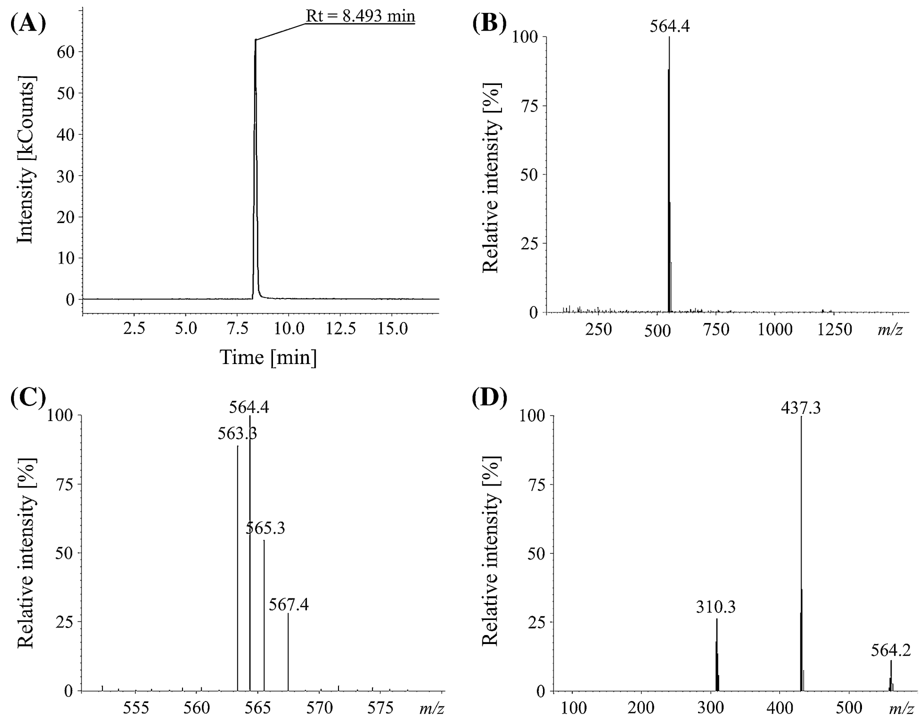


Fig. 3 HPLC-MS analysis of *cis*-[Pt(DACH)I_2] (HPLC (**a**); ESI^+-spectrum (**b**); ESI^+-spectrum, cluster detail (**c**); ESI^+-MS/MS spectrum (**d**)

were considered and included and are given in Table 2. Structures with similar H···I contact between 3.1 and 3.2 Å have been reported [11, 12]. The anisotropic refinement of the N2 atom resulted in the displacement parameters not being definite positive, thus this atom was refined with isotropic ADPs.

Theoretical study—DFT calculation

The theoretical calculation was used for an optimization of a structure of prepared substance (proposed as square planar Pt^{II} and 1*R*,2*R* isomer of DACH). First, the proposed structure was optimized, followed by the comparison of the experimentally obtained structure data with the calculated ones. The results show a good agreement between the two (the largest deviation in bond lengths is 0.09 Å and in angles 2°). When the optimization in the program Gaussian was carried out with data from single-crystal analysis, it led to the same results as the optimization of theoretically proposed structure.

Purity and structure determination—FT-IR

The FT-IR analysis of *cis*-[Pt(DACH)I_2] was carried out by direct measurement of the prepared substance (Fig. 7a) as well as by theoretical calculations on the DFT level of theory (Fig. 7b). FT-IR (microscope inlet, bands in cm^{-1}) was evaluated and interpreted as follows: 3258, 3184 *as* resp. *s* stretching vibration of N–H primary amines; 2926, 2852 *as* resp. *s* stretching vibration of C–H aliphatic bonds; 1658, 1632 deformation vibration of Alk-N–H bonds; 1449, 1465 deformation vibration of C–H aliphatic bonds. Absorptions bands in the region 1200–1000 cm^{-1} correspond to skeletal vibrations in the molecule. Infrared spectrum also confirms that the starting compound DACH tartrate is not present in product crystals, because of specific DACH tartrate bands absent in the *cis*-[Pt(DACH)I_2] FTIR spectrum. The analysis of the starting compound (DACH tartrate) also confirmed the presence of bands corresponding to N–H primary amines in crystals of product. The band with the wave number 3359 cm^{-1} does not correspond to free-N–H groups and is a result of the presence of a long N–H···I hydrogen bond in the molecule.

FT-IR calculated spectrum on DFT level of theory and its comparison with the experimental one could be interpreted as follows: Shifts of individual bands towards lower

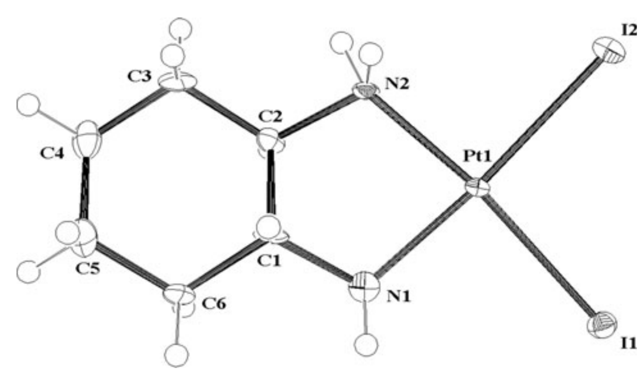


Fig. 4 Ortep drawing of **1** showing atom numbering

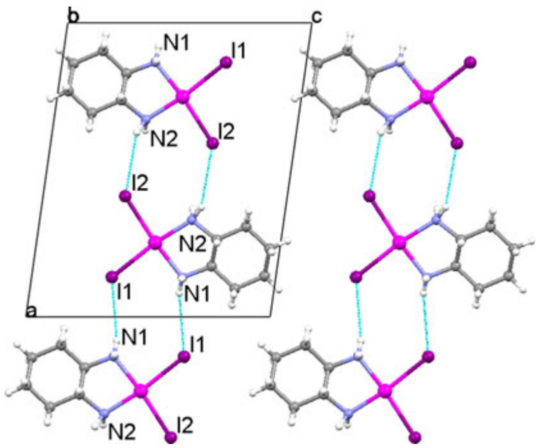


Fig. 5 N–H···I hydrogen bonds linking neighbouring molecules into a chain parallel to *a* axis. View down the *a* axis

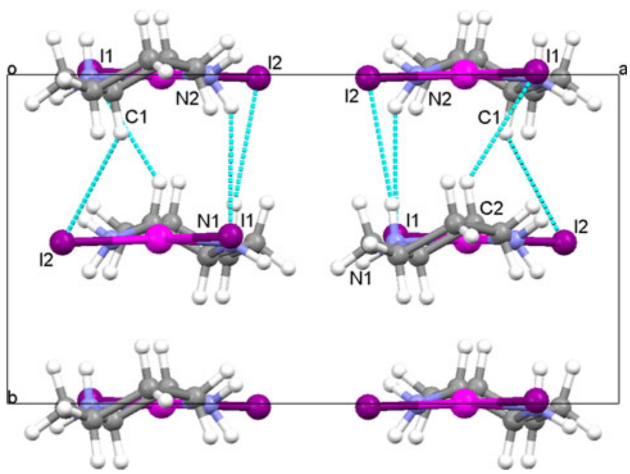


Fig. 6 C–H···I and N–H···I hydrogen bonds linking layers of chains stacked along *b* axis. Hydrogens not participating in hydrogen bonding have been omitted for clarity. View down the *c* axis

wave numbers compared to measured ones are caused by H-bridges in the real structure which were not considered in calculations. Strong bands with wave number 1131 and 1057 cm^{-1} correspond to vibrations in the DACH part of the structure and weaker intensity of these bands in the experimentally measured crystal is caused by the H-bonds in the molecule which could considerably reduce skeletal vibrations in the real sample.

Conclusions

A new precursor *cis*-[diiodo(1*R*,2*R*)-1,2-diaminocyclohexane-κ*N*,κ*N′*]platinum(II) of platinum-based anticancer complexes was synthesized and its structure successfully characterized. Supramolecular organisation of its structure was determined. The molecules of *cis*-[diiodo(1*R*,2*R*)-1,2-diaminocyclohexane-κ*N*,κ*N′*]platinum(II) interact via N–H···I and C–H···I intermolecular (ultra)-long hydrogen–iodine (acceptor) bonds (distances up to 3.1 Å). This fact was proved experimentally as well as theoretically. The calculated and measured data varied by a maximum of 0.09 Å and the maximum difference between the compared angles were less than 2°. Experimentally measured bond lengths in the crystal were observed to be reduced when compared to the theoretical calculation. This is caused by both steric requirements of individual structural units and the presence of hydrogen bonds in real samples, which were experimentally confirmed by FT-IR (new bands as well as the band shift to lower wavelengths) as well as X-ray single-crystal diffraction analysis.

Table 3 Hydrogen-bond geometry (Å, °)

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
C2–H1C2···I1	0.96	3.02	3.785(10)	137.10
C1–H1C1···I2	0.96	2.99	3.737(11)	135.48
N1–H1N1···I2	0.87(4)	2.97(4)	3.822(19)	168(12)
N1–H2N1···I1	0.87(9)	3.07(7)	3.748(10)	136(9)
N2–H1N2···I1	0.87(11)	3.00(10)	3.74(2)	144(10)
N2–H2N2···I2	0.87(12)	3.10(11)	3.748(9)	133(9)

Only interactions with H–I distances up to 3.1 Å are considered and included

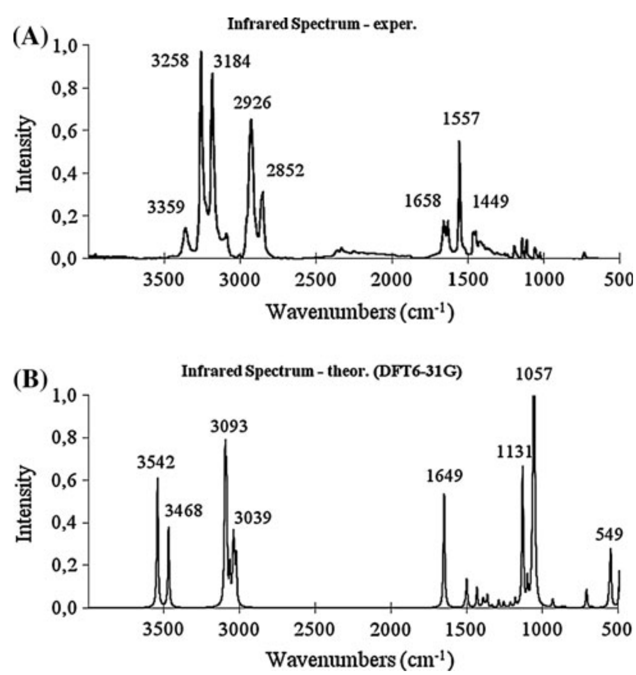


Fig. 7 FTIR spectra of *cis*-[Pt(DACH)I_2]: experimentally measured (**a**); theoretically calculated DFT (**b**)

Supplementary data

Crystallographic data (excluding structure factors) for the structure reported in this article has been deposited with the Cambridge Crystallographic Center, CCDC No. 739030.

Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

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