Chemistry of Natural Compounds, Vol. 42, No. 3, 2006

STRUCTURES OF DEOXYPEGANINE SALTS

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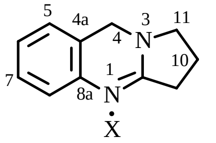
UDC 548.737

The structures of deoxypeganine (DOP) hydrochloride and oxalate were solved by x-ray structure analysis. An infinite chain along the crystallographic c axis was formed in the crystal structure of DOP oxalate. A molecular framework consisting of Cl anions and DOP cation protonated at N1 was found in the structure of unhydrated DOP hydrochloride. The molecular packing of the "host" (DOP cation) was pseudoisostructural in the studied ion-molecular crystals but differed from other known DOP salts. The "guest" molecules (acid anions) in the studied and known DOP salts formed different intermolecular contacts.

Key words: quinazolines, deoxypeganine hydrochloride and oxalate, host—guest complexes, x-ray structure analysis.

The alkaloid deoxypeganine (DOP) has been isolated from *Peganum harmala* [1] and prepared synthetically by reduction of deoxyvasicinone with zinc in dilute H_2SO_4 or HCl [2-4]. It is a highly active anticholinesterase and is used in medicine as the hydrochloride dihydrate (**1**) [5]. We previously studied the structure of **1** and found long-chain complexes in the crystals that involved water molecules, Cl ions, and DOP [6] and were characteristic of polymethylene homologs of quinazoline alkaloids [7, 8]. However, the complex formed in crystalline DOP (**2**) had a framework nature [9, 10].



1 - 4

1: X = $HCl \cdot 2H_2O$ [6]
2: X = $2HCl \cdot ZnCl_2$ [9, 10]
3: X = HCl
4: X = $C_2H_2O_4$

Therefore, it seemed interesting to investigate the crystal structures of unhydrated DOP hydrochloride (**3**) and DOP oxalate (**4**) so that they could be compared with known structures of **1** and **2** with respect to formation of inter- and intramolecular H-bonds (the nature of salt formation) in ion-molecular crystals of DOP. Furthermore, whereas only one DOP molecule is protonated in DOP hydrochloride, the hydrogens from one or both hydroxyls of oxalic acid (**5**) can participate in the protonation. Thus, one carboxylic H can do the protonation and form a DOP salt with N1 while the free carboxylic H can form intermolecular H-bonds with another molecule of **5**. The resolution of these issues is certainly of theoretical interest.

Our goal was to prepare the corresponding DOP salts and study their single crystals using x-ray structure analysis (XSA).

Figure 1 shows a portion of the packing that demonstrates the nature of salt formation and the numbering of key atoms in the structures of **3** and **4**. It can be seen the anions in **4** (residues of **5**) bind molecules of the cations into a long chain along the *c* axis. Experimental determination of the positions of the H atoms on N1 and in **5** enabled the path of formation of the intermolecular H-bonds in the crystal to be followed (Fig. 1). The intermolecular contacts in **4** showed that the DOP cation protonated on N1 was H-bonded to **5** with an Os2...N1 distance of 2.739 Å; N1–H...Os2, 1.88; and an N1–H...Os2 angle of 178°. Anions transformed by a glide plane along the *c* axis were also related by a strong H-bond with Os1...Os4 = 2.497 Å; Os4–H...Os1, 1.53; and an Os4–H...Os1 angle of 169°. This results in an infinite ribbon along the crystallographic *c* axis with a repeat unit corresponding to the links in the chain. The thickness of the ribbon is determined by the constant *a* = 6.825(1) Å because the planar DOP cations and **5** anions are situated in the 0yz plane.

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TABLE 1. Bond Lengths (r, Å) and Angles (ω, °) in **3** and **4**

Bond	r (**3**)	r (**4**)	Angle	ω (**3**)	ω (**4**)
N(1)-C(2)	1.314 (3)	1.316 (8)	C(2)-N(1)-C(8a)	120.92 (15)	120.9 (6)
N(1)-C(8a)	1.413 (3)	1.418 (8)	N(3)-C(2)-N(1)	122.88 (17)	122.7 (6)
C(2)-N(3)	1.307 (2)	1.307 (8)	N(3)-C(2)-C(9)	111.96 (17)	112.4 (7)
C(2)-C(9)	1.488 (3)	1.485 (9)	N(1)-C(2)-C(9)	125.16 (16)	124.9 (7)
N(3)-C(11)	1.464 (3)	1.469 (8)	C(2)-N(3)-C(11)	113.40 (16)	112.1 (6)
N(3)-C(4)	1.466 (3)	1.444 (8)	C(2)-N(3)-C(4)	124.88 (16)	125.2 (6)
C(4)-C(4a)	1.503 (3)	1.504 (9)	C(11)-N(3)-C(4)	121.72 (15)	122.5 (6)
C(4a)-C(5)	1.386 (3)	1.384 (8)	N(3)-C(4)-C(4a)	110.79 (15)	110.4 (6)
C(4a)-C(8a)	1.389 (3)	1.399 (9)	C(5)-C(4a)-C(8a)	118.64 (18)	117.6 (7)
C(5)-C(6)	1.381 (3)	1.357 (10)	C(5)-C(4a)-C(4)	120.03 (17)	120.3 (7)
C(6)-C(7)	1.383 (3)	1.376 (10)	C(8a)-C(4a)-C(4)	121.33 (17)	122.0 (6)
C(7)-C(8)	1.388 (3)	1.376 (9)	C(6)-C(5)-C(4a)	121.1 (2)	121.9 (7)
C(8)-C(8a)	1.389 (3)	1.387 (8)	C(7)-C(6)-C(5)	119.63 (19)	119.5 (7)
C(9)-C(10)	1.525 (3)	1.528 (11)	C(6)-C(7)-C(8)	120.5 (2)	120.5 (7)
C(10)-C(11)	1.530 (3)	1.518 (11)	C(8a)-C(8)-C(7)	119.17 (18)	119.6 (7)
Cs1-Os2		1.226 (7)	C(8)-C(8a)-C(4a)	120.97 (18)	120.8 (6)
Cs1-Os1		1.244 (8)	C(8)-C(8a)-N(1)	119.84 (17)	121.1 (6)
Cs1-Cs2		1.534 (8)	C(4a)-C(8a)-N(1)	119.19 (17)	118.2 (6)
Cs2-Os3		1.194 (7)	C(2)-C(9)-C(10)	103.78 (16)	102.3 (7)
Cs2-Os4		1.280 (8)	C(9)-C(10)-C(11)	106.32 (16)	105.5 (6)
			N(3)-C(11)-C(10)	103.93 (17)	103.6 (6)
			Os2-Cs1-Os1		127.4 (6)
			Os2-Cs1-Cs2		117.6 (7)
			Os1-Cs1-Cs2		115.0 (6)
			Os3-Cs2-Os4		124.8 (6)
			Os3-Cs2-Cs1		121.0 (7)
			Os4-Cs2-Cs1		114.0 (6)

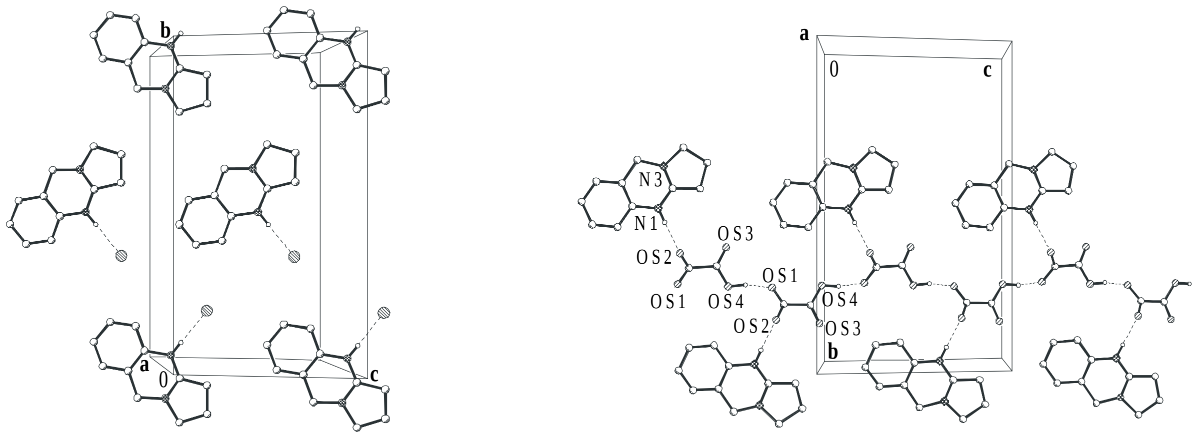


Fig. 1. Crystal packing of **3** and **4** (projection along 0yz, H atoms forming intermolecular bonds are shown).

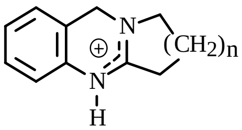
The planar cation and Cl anions in **3** lie in the 0yz plane, like in **4**. For this reason, the packing of the molecular complexes in the structures of **3** and **4** were similar (pseudoisomorphous crystal structures). This was confirmed by the closeness of the unit-cell constants and the same space groups for **3** and **4** (see Table 3 and Fig. 1). However, the nature of the intermolecular interactions in the crystals of **3** and **4** were different. The Cl anions in the crystal structure of **3** were bonded to DOP cations through a Cl...H–N H-bond with Cl...N1 = 3.04 Å; Cl...H, 2.18; and a Cl...H–N angle of 174.8°. These molecular complexes (frameworks) in **3** were situated at van-der-Waals distances.

TABLE 2. Lengths (Å) of C2=N1 and C2–N3 Bonds in Polymethylenequinazoline and -quinazol-4-one Salts

Compound	C2=N1	C2-N3
	Quinazolines	
DOP*$2H_2O$*HCl (**1**) [6]	1.324 (5)	1.287 (6)
DOP*2HCl*$ZnCl_2$ (**2**) [9]	1.320 (6)	1.285 (6)
	1.292 (6)	1.306 (6)
DOP*2HCl*$ZnCl_2$ (**2**) [10]	1.313	1.299
	1.353	1.311
DOP*HCl (**3**)	1.314 (3)	1.307 (2)
DOP*$C_2H_2O_4$ (**4**)	1.316 (8)	1.307 (8)
2,3-Tetramethylene-3,4-dihydroquinazoline*$2H_2O$*HCl [8]	1.33 (1)	1.31 (1)
2,3-Pentamethylene-3,4-dihydroquinazoline*$2H_2O$*HCl [7]	1.30 (1)	1.33 (1)
2,3-Pentamethylene-3,4-dihydroquinazoline*HCl*$ZnCl_2$ [13]	1.321 (4)	1.304 (4)
2,3-Pentamethylene-3,4-dihydroquinazoline*HCl*$ZnCl_2$ [13]	1.337 (10)	1.324 (10)
	1.336 (10)	1.335 (11)
Average	1.328 (6)	1.311 (6)
	Quinazol-4-ones	
Deoxyvasicinone*HCl [12]	1.303 (7)	1.326 (8)
Deoxyvasicinone*HCl*$CoCl_2$ [14]	1.35 (1)	1.34 (1)
Deoxyvasicinone*HCl*$ZnCl_2$ [15]	1.312 (5)	1.335 (5)
	1.317 (5)	1.330 (5)
2,3-Pentamethylene-3,4-dihydroquinazol-4-one*NO_3 [16]	1.311 (4)	1.340 (4)
2,3-Pentamethylene-3,4-dihydroquinazol-4-one*HCl*$CuCl_2$*$1.5H_2O$ [17]	1.307 (5)	1.346 (3)
Average	1.310 (4)	1.335 (5)

The protonated DOP in **3** and **4** was generally planar within ±0.023 and ±0.032 Å, respectively. The five-membered rings adopted a flattened C11 envelope conformation. The carboxylates in dibasic **5** of **4** are twisted at an angle of 50.8°. Only one carboxylate of dibasic **5** that protonates N1 was involved in salt formation. As a result, the hydroxyls resonated and their bond lengths were 1.245(8) and 1.227(8) Å (Table 1), respectively, in this part of the anion (Os1–Cs1–Os2). On the other hand, these distances in the other carboxylic group (Os3–Cs2–Os4) were different [1.195(8) and 1.283(8) Å, respectively]. They were close to the normal values for double and single carboxylic bonds, respectively, that are involved in various conjugated molecular systems [11].

The lengths of the N1=C2 [1.314(3) and 1.316(8) Å] and C2–N3 [1.307(2) and 1.307(8) Å] bonds of the cationic heterocycle in **3** and **4** were practically indistinguishable within 3σ because of the portonation of N1 in DOP. This indicated that the acquired positive charge was redistributed around the –N1–C2–N3 pyrimidine ring. As a result, the formally different C–N chemical bonds became equivalent. Furthermore, a tendency was observed to shorten the length of the formally single C2–N3 bond as compared with the formally double N1=C2 bond. Such delocalization of the positive charge can be illustrated as follows:



Protonation of N3 in the hydrochloride and in the salt of **5** was excluded by steric considerations although it is known that a more basic N3 in bicyclic quinazoline derivatives is protonated.

Therefore, it seemed interesting to check the tendencies for other quinazoline alkaloid salts. For this, we investigated six- and seven-membered analogs of DOP, i.e., 2,3-tetra- and 2,3-pentamethylene-3,4-dihydroquinazolines. Table 2 gives the N1–C2 and C2–N3 bond lengths in salts of tricyclic quinazolines from XSA (CCDC). According to Table 2, the N1–C2 bond in quinazoline salts was in general longer than the C2–N3 bond. This was clearly seen in structures with more accurately determined bond lengths. They averaged 1.328(6) and 1.311(6) Å, respectively.

TABLE 3. Principal Crystallographic Parameters and X-ray Structural Data for **3** and **4**

Parameter	**3**	**4**
Molecular formula	$C_{11}H_{12}N_2$*HCl	$C_{11}H_{12}N_2$*$C_2H_2O_4$
MW/g·mol^{-1}	208.68	262.26
Space group	$P2_1/c$, Z = 4	$P2_1/c$, Z = 4
a, Å	7.127 (5)	6.825 (1)
b, Å	16.463 (12)	17.508 (4)
c, Å	9.234 (8)	10.337 (2)
α	90	90
β	110.18 (6)	99.70 (3)
γ	90	90
V, Å^3	1016.9 (14)	1217.6 (4)
ρ, g/cm^3	1.363	1.431
Crystal size, mm	1.00×0.75×0.60	0.90×0.35×0.20
2θ scanning range	2.5≤θ≤26.0°	2.3≤θ≤27.5°
μ_{exp}, cm^{-1}	0.335	0.108
Number of reflections	1992	2003
Number of reflections $I > 2\sigma(I)$	1727	1141
R1 (I>2σ (I) and total)	0.0421 (0.0514)	0.1250 (0.1953)
wR2	0.1194 (0.1098)	0.1623 (0.1878)
GOOF	1.132	1.200
Difference electron-density peaks	0.197 and -0.271 e. Å^3	0.282 and -0.227 e. Å^3

However, on going to salts of tri- and pentamethylene-3,4-dihydroquinazol-4-ones, this tendency was not observed, although it was noted that the N1=C2 and C2–N3 bonds were averaged upon protonation of N1 when compared with those obsesrved in the alkaloid bases {for them, these bonds were 1.280(6) and 1.360(6) Å [12], respectively}. Also, the N1–C2 bond was shorter than C2–N3 with averages of 1.310(4) and 1.335(5) Å, respectively.

Such differences in the behavior of C–N bonds in quinazoline and quinazolone alkaloids and their homologs and salts are explained by the presence of an amide carbonyl in the molecules. Therefore, the carbonyl, attracting the unshared electron pair of N3, decreases the basicity of the N, preventing the redistribution of the positive charge from protonated N1.

Thus, crystal structures of unhydrated DOP hydrochloride and DOP oxalate (**3** and **4**) were pseudoisomorphous with respect to the molecular packing of the host (DOP cation) but differed from previously studied DOP salts (**1** and **2**). The guest molecules (acid residues) in the studied and known DOP salts (crystals of **1-4**) form different types of intermolecular contacts.

It was found that the N1–C2 and C2–N3 bonds were averaged in the salts. However, the C2–N3 bond became shorter than the N1–C2 bond on going from quinazolone to quinazoline derivatives.

EXPERIMENTAL

Preparation of Single Crystals of DOP Salts. Unhydrated DOP hydrochloride (**3**) was prepared by treating an ethanol solution of DOP hydrochloride dihydrate with a saturated aqueous solution of *β*-cyclodextrin. Single crystals of **3** were prepared by slow evaporation at room temperature of this solution.

DOP oxalate (**4**) was prepared by dissolving DOP and crystalline oxalic acid in acetone in a 1:1 molar ratio. Slow evaporation of the solution at room temperature produced single crystals of **4** suitable for XSA.

X-ray Structure Analysis. Single crystals were transparent elongated prisms. Unit-cell constants and intensities of reflections were measured on a STOE Stadi-4 four-circle diffractometer (ω/2ω-scanning) using Mo Kα-radiation (graphite monochromator). Absorption corrections were not applied. Table 3 lists the principal crystallographic data and the experimental conditions for the XSA.

The structures were solved by direct methods using the SHELXS-97 programs and refined by full-matrix isotropic-anisotropic least-squares methods using the SHELXL-97 programs. Positions of H atoms were found geometrically and refined with fixed isotropic thermal factors $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for other atoms and U_{eq} are the equivalent isotropic thermal parameters of the corresponding C atoms. H atoms of the hydroxyls of the solvates in **4** were found from a difference electron-density synthesis and were refined isotropically.

Data from the XSA were deposited as CIF files in the Cambridge Crystallographic Data Center (Nos. CCDC 273915 and CCDC 273916).

ACKNOWLEDGMENT

The work was supported financially by the Basic Research Foundation of the Academy of Sciences of the Republic of Uzbekistan (Contract N99-04).

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