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Structure redetermination of dextromethorphan hydrobromide monohydrate, $C_{18}H_{28}BrNO_2$ – localization of hydrogen atoms

<https://doi.org/10.1515/ncrs-2020-0528>

Received October 8, 2020; accepted November 29, 2020;

published online February 12, 2021

Abstract

$C_{18}H_{28}BrNO_2$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 7.0417(4)$ Å, $b = 9.1635(5)$ Å, $c = 27.3371(15)$ Å, $V = 1763.97(17)$ Å³, $Z = 4$, $R_{gt}(F) = 0.0275$, $wR_{ref}(F^2) = 0.0596$, $T = 200$ K.

CCDC no: 2047035

The molecular structure is shown in the Figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

The compound was obtained commercially (Lennon Limited). Crystals suitable for the diffraction study were

Table 1: Data collection and handling.

Crystal:	Colourless platelet
Size:	0.52 × 0.49 × 0.18 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	2.34 mm ⁻¹
Diffraction, scan mode:	Bruker APEX-II, φ and ω
θ_{max} , completeness:	28.3°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int} :	16,777, 4369, 0.029
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2 \sigma(I_{obs})$, 3771
$N(param)_{refined}$:	213
Programs:	Bruker [1, 2], SHELX [3], WinGX/ORTEP [4], Mercury [5], PLATON [6]

obtained upon recrystallization of the compound from warm acetonitrile.

Experimental details

Carbon-bound H atoms were placed in calculated positions (C–H 0.95 Å for aromatic carbon atoms, C–H 0.99 Å for methylene groups and C–H 1.00 Å for methine groups) and were included in the refinement in the riding model approximation, with $U(H)$ set to $1.2U_{eq}(C)$.

The H atoms of the methyl groups were allowed to rotate with a fixed angle around the C–C bond to best fit the experimental electron density (HFIX 137 in the SHELX program suite [3]), with $U(H)$ set to $1.5U_{eq}(C)$.

The H atoms of the water molecule as well as the nitrogen-bound H atom were located on a difference Fourier map and refined freely.

Comment

The effect of size and steric pretense of large ions on chemical and spectroscopic properties of compounds have been a focus of research for many decades. Among the many effects that can be attributed to the spatial

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	U _{iso} */U _{eq}
O1	0.6745 (2)	−0.10446 (17)	−0.03832 (6)	0.0253 (4)
N11	0.3967 (3)	0.0820 (2)	0.19631 (8)	0.0258 (4)
H711	0.336 (4)	0.156 (3)	0.2075 (10)	0.032 (8)*
C1	0.7232 (3)	0.0179 (3)	0.16452 (9)	0.0291 (6)
H1A	0.855963	0.045734	0.171890	0.035*
H1B	0.695332	−0.072823	0.182838	0.035*
C2	0.3952 (4)	−0.0202 (3)	0.23888 (10)	0.0407 (7)
H2A	0.264789	−0.031581	0.250831	0.061*
H2B	0.475027	0.019354	0.265072	0.061*
H2C	0.444642	−0.115398	0.228664	0.061*
C3	0.7810 (4)	−0.2208 (3)	−0.05989 (10)	0.0334 (6)
H3A	0.916357	−0.206953	−0.052912	0.050*
H3B	0.760930	−0.220967	−0.095363	0.050*
H3C	0.738816	−0.314107	−0.046172	0.050*
C11	0.5923 (3)	0.1380 (3)	0.18328 (8)	0.0235 (5)
H11	0.650488	0.180912	0.213385	0.028*
C12	0.5687 (3)	0.2590 (3)	0.14582 (8)	0.0224 (5)
H12	0.479292	0.332752	0.159836	0.027*
C13	0.7566 (3)	0.3369 (3)	0.13485 (10)	0.0307 (6)
H13A	0.809637	0.377013	0.165574	0.037*
H13B	0.848881	0.265851	0.121478	0.037*
C14	0.7276 (4)	0.4601 (3)	0.09823 (11)	0.0407 (7)
H14A	0.851901	0.504248	0.089987	0.049*
H14B	0.646998	0.536823	0.113053	0.049*
C15	0.6331 (4)	0.4031 (3)	0.05158 (9)	0.0367 (6)
H15A	0.606007	0.486004	0.029424	0.044*
H15B	0.721284	0.336086	0.034522	0.044*
C16	0.4502 (4)	0.3235 (3)	0.06292 (9)	0.0294 (6)
H16A	0.396046	0.285117	0.032082	0.035*
H16B	0.357926	0.393627	0.076845	0.035*
C17	0.4769 (3)	0.1967 (3)	0.09898 (8)	0.0220 (5)
C18	0.2809 (3)	0.1340 (3)	0.11293 (9)	0.0269 (5)
H18A	0.197737	0.214567	0.124000	0.032*
H18B	0.222088	0.089583	0.083602	0.032*
C19	0.2935 (4)	0.0199 (3)	0.15309 (10)	0.0291 (6)
H19A	0.164203	−0.010539	0.162978	0.035*
H19B	0.361814	−0.067131	0.140805	0.035*
C21	0.7079 (3)	−0.0143 (3)	0.11041 (9)	0.0228 (5)
C22	0.5985 (3)	0.0722 (2)	0.07872 (8)	0.0201 (5)
C23	0.5936 (3)	0.0362 (2)	0.02939 (8)	0.0215 (5)
H23	0.518950	0.093601	0.007743	0.026*
C24	0.6946 (3)	−0.0812 (2)	0.01095 (9)	0.0214 (5)
C25	0.8032 (3)	−0.1667 (3)	0.04196 (9)	0.0259 (5)
H25	0.872685	−0.247620	0.029671	0.031*
C26	0.8087 (3)	−0.1318 (3)	0.09145 (9)	0.0268 (5)
H26	0.883325	−0.189800	0.112876	0.032*
Br1	0.12707 (4)	0.63126 (3)	0.19641 (2)	0.04075 (9)
O90	0.1716 (4)	0.2931 (3)	0.23165 (10)	0.0535 (6)
H901	0.081 (5)	0.261 (4)	0.2473 (13)	0.050 (11)*
H902	0.147 (6)	0.369 (4)	0.2210 (14)	0.059 (12)*

requirements of counterions have been the glass transition temperature in ionomers [7], surfactant modifying properties [8], the charge transfer in radical ions [9] and

polymer-modified electrodes [10] as well as the structural and vibrational spectroscopic behaviour of DNA building blocks [11]. Furthermore, the benefit of choosing the adequate size of counterions to crystallize ionic compounds has been confirmed and reviewed on many occasions [12]. In continuation of our interest in metrical features of large cations [13–15] the structure of the title compound has been determined. While the latter has been reported previously [16], no hydrogen positions were determined which precludes discussions of inter- and intramolecular interactions. The molecular and crystal structures of tetrachlorido cuprate and cobaltate salts are known [17], as are the crystal and molecular structures of the neutral parent opioid dextromethorphan [18, 19]. The latter has found use as cough medication and has received renewed attention as potential remedy for several symptoms of Alzheimer's disease [20].

The structure solution shows the presence of the polycyclic morphinan scaffold consisting of a central 2-aza-decalin system that features an *ortho*-methylene methoxyphenyl moiety bridging the latter via one of the annealing carbon atoms as well as one of the intracyclic nitrogen-bonded carbon atoms. A methyl group completes the coordination environment of the tertiary amine-type pnictogen atom. The latter is further protonated to produce the pertaining ammonium cation whose charge is balanced by the presence of a bromide anion. The asymmetric unit contains an additional water molecule. C–N bond lengths span a range of 1.494(3)–1.512(3) Å with the shortest bond established towards the exocyclic carbon atom. These values are in good agreement with the ones found for other tertiary ammonium compounds whose metrical parameters have been deposited with the Cambridge Structural Database [21]. A conformational analysis of the six-membered rings [22, 23] performed with *PLATON* [6] shows the two 2-aza-decalin rings to adopt ⁴C₁ conformations (^{C17}C_{N11} and ^{C15}C_{C12}, respectively) while the bridging six-membered ring is present halfway in between ³H₂ and ³E (^{C12}H_{C11} and ^{C12}E, respectively) conformations. The least-squares planes as defined by the non-hydrogen atoms of the two separate six-membered rings of the 2-aza-decalin scaffold enclose angles of 74.59(12)° and 81.61(12)° with the corresponding least-squares plane as defined by the six-membered ring of the bridging motif as well as 7.33(13)° with one another. The plane of the aromatic moiety intersects at angles of 80.05(12)° and 87.08(11)° with the former two planes as well as 5.48(11)° with the latter plane. All three stereocenters are present in (*S*) configuration. The Flack parameter refined to 0.004(4) using 1407 quotients [24].

In the crystal, classical hydrogen bonds of the O–H...Br as well as the N–H...O type are observed next

to C—H...O contacts whose range falls by more than 0.1 Å below the sum of van-der-Waals radii of the atoms participating in them. While the oxygen atom of the water molecule exclusively acts as acceptor for the N—H...O hydrogen bonds the C—H...O contacts invariably employ the oxygen atom of the methoxy group as acceptor. The latter contacts are supported by one of the aromatic hydrogen atoms in *ortho*-position to the methoxy group as well as one hydrogen atom of the methylene group next to the bridgehead carbon atom in the all-carba ring of the 2-aza-decalin building block. In terms of graph-set analysis [25], the descriptor for these contacts is $DDDC_1^1(4)C_1^1(7)$ at the unitary level. In total, the entities of the asymmetric unit are connected to a three-dimensional network. The aromatic systems show no signs of stacking.

Author contribution: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: The corresponding author thanks the National Research Foundation for financial support.

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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