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Note

X-ray crystallography and solution NMR spectroscopy characterization of heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)cyclomaltoheptaose ☆

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Abstract—Heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)cyclomaltoheptaose (**2**) has been characterized in aqueous solution by 1D and 2D NMR spectroscopy and in the solid state by X-ray crystallography. In methanol solution, the acetyl groups were found to interact with both inward and outward-pointing protons. This and the strong deshielding of the bridging carbons, relative to the nonacetylated precursor, indicate macrocyclic flexibility. In the crystalline state the macrocycle exists as a methanol complex. It exhibits elliptical distortion, all glucose residues been tilted with their primary side toward the cavity. The existing strain due to the congestion of 14 acetyl groups at the secondary site is relieved by two glucose rings acquiring the rarely observed skew-boat conformation, $^{0}S_{2}$, by the increased tilting of two glucose residues, as well as by minor variations of the torsion angles of the acetyl groups. The seven bromine atoms are quite accessible to nucleophiles.

Keywords: Heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)cyclomaltoheptaose; Structure; X-ray crystallography; Solution NMR spectroscopy; Skew-boat conformation

Cyclomaltoheptaose (β-cyclodextrin, β-CD) belongs to the family of cyclodextrins, which are cyclic oligosaccharides[1] able to bind a large variety of molecules in their cavity through molecular encapsulation. Chemical modification of the primary or secondary hydroxyl groups, often improves the inclusion ability or chiral selectivity and/or introduces catalytic activity. Perhalogenation of the primary hydroxyl groups[2,3] of β-cyclodextrin provides intermediates, such as heptakis(6-bromo-6-deoxy)cyclomaltoheptaose (**1**), useful for further chemical modifications,[4] which however, are soluble only in high boiling organic solvents (DMF, Me_2SO). Therefore, the analogues heptakis(2,3-di-*O*-methyl-6-bromo-6-deoxy)-[5] and heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)- (**2**)[6] and heptakis(2,3-di-*O*-acetyl-6-iodo-6-deoxy)cyclomaltoheptaose[7] have been synthesized, which are soluble in common organic solvents.

Persubstitution causes extensive distortion of the CD macrocycle. X-ray studies have shown that the distorted conformation of permethylated CDs[8] and peracylated CDs[9] results from a combination of the irregular tilting of the glucose units, as well as the conformation of the methoxy or acyl groups. In addition, change in the conformation of individual glucopyranose rings may contribute to the distortion, that is, in heptakis(2,3,6-tri-*O*-methyl)-β-CD·H_2O[10] one of the glucose units has the $^{1}C_{4}$ chair instead of the usual $^{4}C_{1}$ chair conformation, whereas in heptakis(2,3,6-tri-*O*-methyl)-β-CD/*m*-iodophenol complex[11] and in heptakis(2,3,6-tri-*O*-acetyl)- and heptakis(2,3,6-tri-*O*-propyl)-β-CD[9] one glucose unit adopts the $^{0}S_{2}$ skew-boat conformation.

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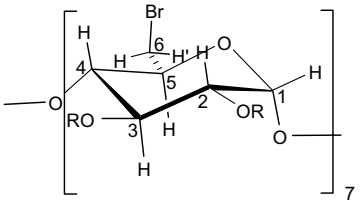
Moderate to severe macrocyclic distortion and existence of several conformations in solution have been demonstrated by NMR spectroscopy in various instances, that is, heptakis(2,3,6-tri-*O*-benzoyl)-β-CD exists in solution as a mixture of several C_1 conformers, even at low temperatures.[12] Frequently, the notion of 'cavity' space is of minimal significance in distorted macrocycles. However, even with shallow cavities, as in the case of heptakis(2,3,6-tri-*O*-methyl)-β-CD/(*S*)-(1,7-dioxaspiro[5.5]undecane) complex,[8] enantioselective complex formation has been observed. Heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)-β-cyclomaltoheptaose (**2**) provides a further interesting example of how derivatization affects the shape of the oligosaccharide.



1 R = H
2 R = Ac

1. Solution studies

The ^{1}H NMR spectrum of **2**[12] is a first-order spectrum originating from an averaged macrocyclic structure of C_7 symmetry. Acyl substitution of **1**[13] is expected to result in increased chemical shift values of the ring protons, H-2 and H-3 by at most 0.5 ppm, as observed in linear oligo- or polysaccharides.[14a] Therefore, the substantial deshielding by 1.35 and 1.60 ppm observed for H-2 and H-3, respectively, must be the result of an additional change, namely that of macrocyclic conformation. In support of this is the observed significant shielding by 6.84 and 6.63 ppm, of the glucopyranose bridging carbons C-1 and C-4, respectively, compared to a ~1.5–2.0 ppm shielding of all other ring carbons. This indicates significant departure from the shape of **1**, as it has been documented that the chemical shift of the anomeric carbon systematically depends on the values of the glucosidic bond dihedral angles, φ and ψ.[14b] Increase (298–328 K) or decrease (298–268 K) of the sample temperature in methanol did not result in line broadening of the proton signals or significant changes of the chemical shifts. Dipolar interactions of the acetyl groups with their vicinal H-2 and H-3 and with H-1 at 278 K, but also with H-4 (outward pointing) and H-5 (inward pointing) at 308 K observed in the 2D ROESY spectrum indicate increased flexibility of the macrocycle and thus change of the interglucopyranose angles, as indicated above. Regarding the shape of the glucopyranose residues, no significant deviation from the chair conformation in solution could be detected, since the values of the coupling constants fall within the ranges previously observed for persubstituted CD derivatives.[12] Apparently, the exchange among conformationally distorted isomers, as those obtained in the solid state (see below), is fast in solution and signals due to a single type of glucose unit are observed.

2. Solid state studies

The numbering scheme for **2** in the crystalline state is given in Figure 1,[15] C*mn* and O*mn* denoting the *m*th atom within the *n*th glucosidic residue (G*n*). Table 1 gives the parameters describing the macrocycle's conformation. This is elliptically distorted with a major diameter O-46···O-42 = 10.42 Å, and a minor one O-41···O-44 = 7.95 Å. Further evidence of the distortion are the large differences in O-4*n*···O-4($n+1$) distances and the O-4($n-1$)···O-4*n*···O-4($n+1$) angles that depart from the C_7 symmetry of the native β-CD, as no intramolecular hydrogen bonds between the secondary

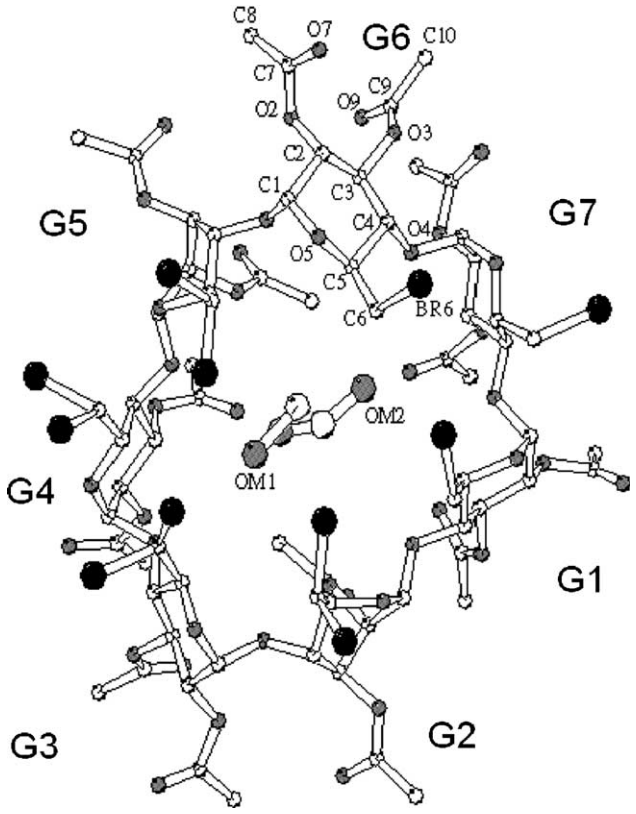


Figure 1. Diagram of **2** indicating the numbering scheme. The two methanol molecules inside the cavity are also shown; light gray denotes oxygen atoms, white carbon atoms, and black bromine atoms.

Table 1. Conformation of the macrocycle

	D^a (Å)	φ^b (deg)	d^c (Å)	C-4*n*–O-4*n*–C-1($n+1$) (deg)	$D_3{}^d$ (Å)	Tilt angles[e] (deg)
G1	4.76(3)	151.6(6)	−0.29(6)	116(2)	3.67(3)	16.5(7)
G2	3.99(3)	105.9(6)	−1.27(2)	123(2)	4.32(3)	27.4(8)
G3	4.44(3)	122.1(6)	−0.03(1)	120(2)	4.51(3)	39.0(6)
G4	4.75(3)	142.8(6)	0.19(1)	119(2)	3.87(3)	16.2(6)
G5	4.12(3)	107.4(6)	−1.34(3)	115(2)	4.15(3)	28(2)
G6	4.31(2)	134.2(6)	−0.37(1)	114(2)	4.62(3)	60(1)
G7	4.27(3)	114.6(5)	0.49(1)	120(2)	3.97(2)	15.3(7)

[a]O-4$n\cdots$O-4($n+1$) distances.
[b]O-4($n-1$)$\cdots$O-4$n\cdots$O-4($n+1$) angles.
[c]Deviations (Å) from the least-squares optimum plane of the five O-4*n* atoms.
[d]Intramolecular distances between atoms O-3$n\cdots$O-2($n+1$).
[e]Tilt angles between the optimum O-4*n* plane and the mean planes through atoms O-4($n-1$), C-1*n*, C-4*n*, O-4*n* (with esds in parentheses).

hydroxyl groups O-3*n* and O-2($n+1$) exist in this molecule. As Table 1 shows, the O-3$n\cdots$O-2($n+1$) distances in **2** exceed the corresponding values of native β-CD, which are close to 2.8 Å.

The glucose puckering parameters (Q) of glucose residues G2 and G5 (0.696 and 0.764, respectively) differ from those of the other five glucose units (range 0.501–0.586) (Table 2). The above Q values in combination with the θ values of 86.43 and 84.80 for residues G2 and G5, respectively, indicate[16,17] that residues G2 and G5 adopt the skew-boat (twist) conformation, ${}^0S_2$ (Fig. 2) in contrast to the rest that retain the regular ${}^4C_1$ conformation.

The mean plane of the O-4 atoms in Table 1 was defined by the five glucose residues that have the regular ${}^4C_1$ conformation. Nonetheless, the deviations from the O-4*n* least-squares plane are large and the subsequent calculation of the tilt angles is only indicative of the degree of tilting of every glucose unit. All glucose residues are tilted with their primary side toward the cavity. At the primary hydroxyl side the C–Br bonds exhibit a variety of conformations: In four residues, G2, G3, G4,

Table 2. Conformation of the glucose units

	Q	θ (deg)	φ (deg)	Φ (deg)	Ψ (deg)	O-5*n*–C-5*n*–C-6*n*–BR*n* (deg)	C-1*n*–C-2*n*–O-2*n*–C-7*n* (deg)	C-2*n*–C-3*n*–O-3*n*–C-9*n* (deg)
G1	0.573	6.23	−33.24	100(2)	123(2)	75(2)	93(3)	−107(3)
G2	0.696	86.43	−39.68	104(3)	127(3)	77(3) −54(3)	130(3)	−132(3)
G3	0.501	10.09	72.74	83(3)	113(3)	−70(3) 65(7)	135(3)	−96(3)
G4	0.535	5.93	−155.31	96(3)	151(2)	−68(3) 29(6)	89(4)	−121(3)
G5	0.764	84.80	−35.05	105(3)	146(2)	66(4) −52(4)	146(3)	−107(3)
G6	0.565	5.72	8.51	82(3)	97(3)	−65(3)	124(4)	−98(3)
G7	0.586	9.12	139.40	104(3)	157(2)	−62(2)	86(3)	−126(3)

Φ = O-5($n+1$)–C-1($n+1$)–O-4(n)–C-4(n), Ψ = C-1($n+1$)–O-4(n)–C-4(n)–C-3(n).

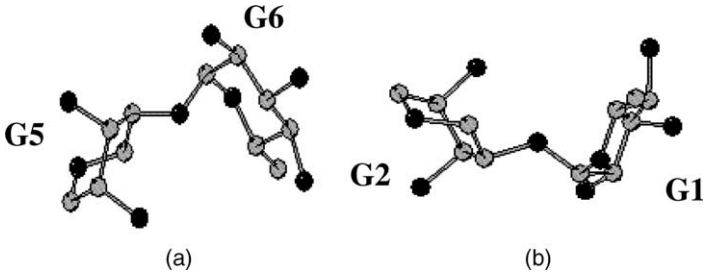


Figure 2. The glucose residues in conformation ${}^0S_2$, are shown, G5 (a) and G2 (b); gray denotes carbon atoms, black, oxygen atoms.

G5, the Br atom is disordered, with major occupancies 88%, 88%, 92%, and 57%, respectively. The Br atoms point inward [(+)-*gauche* with respect to the C-5–O-5 bonds] in two of these major conformations, G2 (88%) and G5 (57%), whereas in the other two, G3 and G4, outwards ((−)-*gauche*). Of the remaining nondisordered Br atoms, one is directed toward the cavity (G1) and two outwards, G6 and G7 (Table 2). Although many bromine atoms are pointing inward, they are quite exposed and the primary site is not closed (Fig. 1).

At the secondary hydroxyl side, the acetyl groups' conformations are in accord with other acetylated β-cyclodextrins but they do not show as much variation as in heptakis(2,3,6-tri-*O*-acetyl)-β-CD.[9] For all residues but G2 and G5, the C-2*n*–O-2*n* and C-3*n*–O-3*n* bonds are equatorial, whereas in residues G2 and G5, which have the $^0S_2$ conformation the O-2 and O-3 oxygen atoms are in a pseudo-axial position. In the former the acetyl groups on the O-2*n* atoms are directed away from the cavity and on the O-3*n* toward the cavity, whereas in the $^0S_2$ conformation the acetyl groups on the O-2 atoms point toward the cavity and those on the O-3 atoms point outside. The methyl moiety of all acetyl groups is found *trans* with respect to the C-2–O-2 or C-3–O-3 bonds. Overall, the strain due to the accumulation of the acetyl groups at the secondary hydroxyl side of **2** is relieved: (i) by the two glucose rings with the rarely observed conformation $^0S_2$ because the C-2–O-2 and C-3–O-3 bonds point to opposite directions, (ii) by the high tilting of residues G3 and especially G6 positioned at the one end of the long diameter of the elliptic cavity, because the corresponding acetate groups get out of the way of those on adjacent glucose units.

The numerous intermolecular interactions between methanol molecules and **2** contribute to the stabilization of the cavity and its periphery (Table 3a). The conformations of the acetate groups are stabilized by a number of C–H···O hydrogen bonds, common in carbohydrate crystal structures, intra- and some intermolecularly (Table 3b). The latter are two direct hydrogen bonds in the *bc* plane between adjacent cyclodextrins, made possible by the increased tilting of the specific residue or the torsion angles of the acetate groups. Finally, C–H···O contacts are observed between adjacent glucose residues (Table 3c).

The molecules are stacked head-to-tail along the *a*-axis (Fig. 3) forming infinite columns arranged in a parallel fashion. Methanol molecules are entrapped in the macrocycle's cavity in two partially occupied positions, M1 and M2, the latter exhibiting disorder of the hydroxyl group over two positions. Methanol molecules, M3–M7, are found in the space between macrocycles along the *a*-axis. The inside and outside methanol molecules communicate via H-bonds M1···M4···M3 as shown in Figure 3 and Table 3a. The solvent molecules are also in close contacts with bromine atoms at the primary side of the macrocycles and keto oxygen atoms at the secondary side of adjacent macrocycles, as shown in Table 3a. Thus, methanol molecules act as mediators in connecting the macrocycles in the columns mentioned above.

Table 3. Close contacts

X···Y	Distance (Å) X···Y	Angle (deg) X···Y–C
a. Between solvent molecules as well as of solvent molecules with the macrocycle		
OM1···OM4A	2.927	
···BR5A	2.930	119.20
···BR2A	3.099	105.91
···BR3B	3.329	81.56
···C-63	3.528	87.84
OM2B···C-66	3.381	87.42
···C-85	3.460	127.39
OM3···OM4A	2.626	
···O-91	3.065	123.77
···O-72	3.242	115.92
OM4A···BR5A	2.333	114.56
···BR2A	3.175	148.49
OM4B···O-93[a]	3.141	143.19
CM4···BR5B	2.326	148.55
···BR3B	2.429	143.48
···BR2B	3.405	123.06
OM6···O-94[a]	2.828	128.13
···O-97[a]	2.936	123.20

b. Among acetate groups intra and intermolecularly			
O···H–C	Distance (Å) O···C	Angle (deg)	
		C–O···C	O···C–C
O-71···C-84[b]	3.545	122.20	88.35
O-91···C-107	3.582	139.64	84.19
O-72···C-86[c]	3.267	128.62	108.61
···C-101	3.355	138.34	74.98
O-92···C-83	3.282	163.71	106.19
O-93···C-84	3.485	92.67	85.45
O-96···C-87	3.090	111.15	80.67
O-77···C-106	3.282	111.47	73.09
O-97···C-85	3.271	130.16	162.18

c. Between C-6n–H6n···O-5(n + 1)			
O-5···H–C-6	Distance (Å) O···C	Angle (deg)	
		C-5–O-5 ···C-6($n-1$)	O-5···C-6 -($n-1$)– C($n-1$)
O-51···C-67	3.141	119.13	87.64
O-52···C-61	3.292	152.43	95.61
O-53···C-62	3.583	84.05	83.96
O-54···C-63	3.461	96.43	88.09
O-55···C-64	3.016	89.77	96.08
O-56···C-65	3.336	80.16	83.65

[a] $x-1, y, z$.
[b] $x, y, z+1$.
[c] $x, y-1, z$.

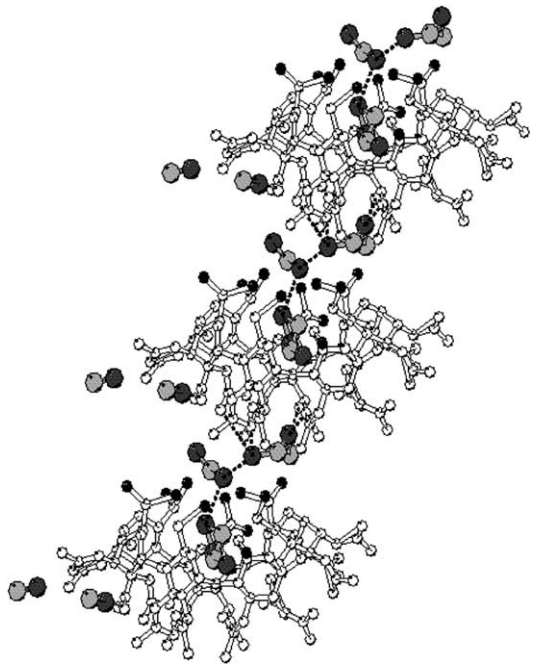


Figure 3. Alignment of molecules of **2** along the *a*-axis. H-bonds between methanol M1 (inside the cavity) and M4 (between CD molecules), as well as between M4 and M3, are shown by dashed lines. Close interactions of M3 and M6 with acetate groups of an adjacent macrocycle are also shown by dashed lines.

In conclusion, we have shown by both solution and crystal structure that the title β-CD derivative demonstrates high flexibility of the acetyl groups and the macrocyclic skeleton. The detailed structure in the crystal shows that the width of the primary side is reduced by the inward pointing bromine atoms of residues G2 and G5, which are in the $^0S_2$ conformation and by residue G6, which shows a very high tilting angle. The strain due to the accumulation of acetyl groups at the secondary hydroxyl side is relieved in **2** by the two glucose rings in $^0S_2$ conformation as well as by the high tilting of residues G3 and especially G6. Minor variations of the torsion angles of acetyl groups contribute further to their accommodation at the secondary side. In heptakis(2,3,6-tri-*O*-acetyl)-β-CD only one residue is in the $^0S_2$ conformation and wider variations in the tilting angles of glucose rings and the torsion angles of the acetate groups are observed. These variations might contribute also to the stabilization of the 'empty' cavity of the latter compound. The solvent molecules in the cavity of **2** may help it not to collapse. The fact that the solvent has a stabilizing effect is also observed in the structure of heptakis(2,3-di-*O*-methyl-6-bromo-deoxy)-β-CD,[5] where entrapped acetone stabilizes the cavity. Therefore, it is apparent that the persubstituted cyclodextrin systems possess high versatility in the way they stabilize themselves and the existence of a guest (solvent) in the cavity increases this versatility and contributes to stabilization.

3. Experimental

3.1. General methods

Heptakis(6-bromo-6-deoxy)cyclomaltoheptaose (**1**)[13] and heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)cyclomaltoheptaose (**2**)[6] were synthesized using literature methods. The NMR spectra were acquired on a Bruker DRX Avance 500 MHz in MeOH-d_4 or Me_2SO, as indicated. The 2D spectra were acquired using the pulse sequences provided in the software's library employing gradient selection, except for the ROESY spectra, which were run with phase cycling using 350 ms spinlock time at 30 dB.

3.2. Crystal structure determination

Colorless crystals were formed after evaporation of a saturated MeOH solution of **2** over a period of 5 days. The chosen single crystal was sealed into a glass capillary with mother liquor. Diffraction data were collected at room temperature on a Syntex diffractometer upgraded by Crystal Logic,[18] with graphite monochromated Cu Kα radiation ($\lambda = 1.5418$ Å) generated by a Rigaku rotating anode. Crystal data are given in Table 4. Intensities for 4558 unique reflections were collected by the θ–2θ scan method. The data were corrected for absorption and Lorentz and polarization effects. The structure was solved using the molecular replacement method.[19] A glucopyranose ring with a regular $^4C_1$ chair conformation[20] was used as the starting model, which revealed 5.5 glucose units. Subsequent Fourier difference maps completed the whole molecule and gave also the positions of the solvent non-H atoms. The refinement of the structure proceeded by F^2 full matrix least squares using the program

Table 4. Crystal data and structure refinement

Molecular formula	$C_{70}H_{91}O_{42}Br_7 \cdot 2.59CH_3OH$
Formula weight	2163.80
Temperature	293 K
Radiation/wavelength	1.5418 Å
Space group	*P*1
a, α	12.705(8), 96.490(13)
b, β	17.843(9), 101.627(14)
c, γ	14.823(9), 128.169(14)
Volume/*Z*	2461(2) Å^3/1
Density (calculated)	1.460 Mg/m^3
2θ range for data collection	6.40°–99.88°
Index ranges	$-12 \leqslant h \leqslant 12$, $-17 \leqslant k \leqslant 11$, $-13 \leqslant l \leqslant 14$
Reflections collected/observed	4558/2695
Solution method	Molecular replacement
Refinement method	Full matrix least squares on F^2
Data/restraints/parameters	4558/22/680
Goodness-of-fit on F^2	1.056
Final *R* indices [$F_0 > 4\sigma(F_0)$]	$R_1 = 0.0836$, $wR_2 = 0.1948$
R indices (all data)	$R_1 = 0.1568$, $wR_2 = 0.2459$
Largest diff. peak and hole	0.45 and −0.39 e Å^{-3}

SHELX97[21] up to an $R_1 = 0.0836$, $wR_2 = 0.1948$, goodness-of-fit = 1.056 for $F_0 > 4\sigma(F_0)$ (Table 4). The C-6*n* atoms, most of the Br atoms and some atoms of the acyl chains were treated anisotropically. Hydrogen atoms at idealized positions were placed at the host in a riding mode ($U_H = 1.3U_C$). MeOH molecules (structure occupation factors between 0.26 and 0.46) were found inside the CD cavity and between host molecules. Specifically, the total sum of the occupancies of the solvent molecules is 2.59(3) distributed over seven positions. In two of them, OM2 and OM4, oxygen atoms are found disordered over two positions. During the refinement the sum of the occupations of these two positions was restrained to the occupancy of the CM2 and CM4 atoms, respectively.

Crystals of the same unit cell, shape, and color as the above were also obtained from an aqueous solution of the substance. However, we failed to collect data, despite our insistent attempts, because the crystals decayed beyond acceptable limits upon X-ray irradiation. Full crystallographic details have been deposited with the Cambridge Crystallographic Data center. These data may be obtained, on request, from CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; deposition number 228790.

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