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Crystal structure of 1,2;5,6-di-*O*-isopropylidene-3-*O*-(phenylacetyl)-D-glucofuranose

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The synthesis and X-ray crystal structure of 1,2;5,6-di-*O*-isopropylidene-3-*O*-(phenylacetyl)-D-glucofuranose is reported. It crystallizes in the orthorhombic system with space group $P2_12_12_1$ (No. 19); $a = 9.9313(12)$ Å, $b = 10.0657(12)$ Å, $c = 20.343(2)$ Å, and $Z = 4$. The solid state structure is discussed in terms of the use of the title compound for further chemistry.

KEY WORDS: $C_{20}H_{26}O_7$; carbohydrate; ester.

Introduction

Abundant D-glucose has been used for many years as an affordable, optically pure starting material for organic synthesis[1] and many of its derivatives have become commercially available. One such compound, 1,2;5,6-di-*O*-isopropylidene-D-glucofuranose (commonly known as “diacetone glucose,” **1**, Scheme 1) has a singularly unprotected secondary hydroxyl group at C-3, which serves as a point for selective functionalization upon the D-glucose skeleton.

The present work is part of a project centered on the use of carbohydrates as building blocks for making chiral heterocycles and carbocycles, by applying carbenic and nitrenic reactions for construction of C—C bonds and C—N bonds, respectively. Accordingly, we have prepared diazoester and acyl azide derivatives of **1** and then studied their decomposition chemistry.[2] Herein we focus specifically on the synthesis and structure of 1,2;5,6-di-*O*-isopropylidene-3-*O*-(phenylacetyl)-D-glucofuranose, **2**, and the implications of the solid state structure on further chemistry.

Experimental

Synthesis

In order to attach a carbene precursor, O-3 of compound **1** was coupled with phenylacetic acid using the common dicyclohexylcarbodiimide/*N*,*N*-dimethylaminopyridine (DCC/DMAP) protocol to afford the ester **2** as a colorless solid in 90% yield. NMR spectra of **2** were obtained using a VARIAN GEMINI 2000 spectrometer, at 400 MHz for ^{1}H and 100 MHz for ^{13}C: ^{1}H NMR ($CDCl_3$)δ 1.25 (s, 3H), 1.28 (s, 3H), 1.38 (s, 3H), 1.5 (s, 3H), 3.6 (s, 2H), 3.95 (dd, 1H, $J = 5.3, 8.6$ Hz), 3.99 (d, 1H, $J = 5.9, 8.6$ Hz), 4.08 (ddd, 1H, $J = 5.3, 5.9, 8.1$ Hz), 4.18 (dd, 1H, $J = 2.9, 8.1$ Hz), 4.42 (d, 1H, $J = 3.8$ Hz), 5.27 (d, 1H, $J = 2.9$ Hz), 5.81 (d, 1H, $J = 3.7$ Hz), 7.25–7.55 (m, 5H). ^{13}C NMR ($CDCl_3$)δ 25.2, 26.2, 26.8, 26.9, 41.4,

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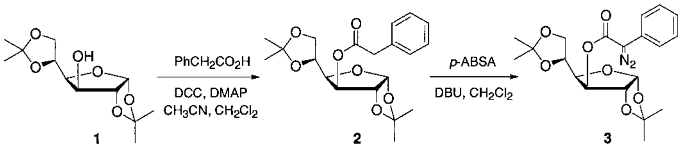

Scheme 1.

67.2, 72.2, 76.3, 79.8, 83.1, 104.9, 109.2, 112.2, 127.1, 128.5 (double intensity), 129.0 (double intensity), 133.2, 169.8. MS: Calculated: 378.42. Found (APCI, positive mode): 379.27 (M+H$^+$).

Crystal structure determination

Upon crystallization by slow evaporation of a 50:50% by volume ethyl acetate and hexane solvent mixture, compound **2** was collected as colorless crystals that were suitable for analysis by X-ray diffraction. X-ray data were collected on a Bruker SMART APEX 4k CCD Single Crystal Diffractometer equipped with a normal focus, 2.4 kW sealed tube X-ray source (graphite monochromatized Mo K$_\alpha$ radiation, $\lambda = 0.71073$ Å) operating at 50 kV and 40 mA. The diffraction data were obtained by collection of

Table 1. Crystal Data Summary and Refinement Results for **2**

Structural formula	$C_{20}H_{26}O_7$
CCDC deposit no.	201732
Formula weight	378.41
Color/shape	Colorless/rectangular prism
Crystal size, mm	0.48 × 0.24 × 0.18
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (No. 19)
Unit cell dimensions	
	$a = 9.9313(12)$ Å
	$b = 10.0657(12)$ Å
	$c = 20.343(2)$ Å
	$V = 2033.6(4)$ Å
Z	4
ρ_{calc}, g/cm^3	1.236
Temperature, K	298(2)
λ(Mo Kα), Å	0.71073
μ, mm^{-1}	0.093
θ Range for data collection (deg)	2.00–28.27
Limiting indices	$-12 \leq h \geq 12, -12 \leq k \geq 12, -26 \leq l \geq 25$
No. of reflections collected	17652
No. of independent reflections	4711 (R_{int} = 0.0230)
No. of parameters	324
Refinement method	Full-matrix least squares on F^2
Hydrogen atom positions	Mixed independent and constrained refinement
Final R indices [$I > 2\sigma(I)$]	$R_1(F)^a = 0.0637$, $wR_2(F^2)^b = 0.1612$
Final R indices (all data)	$R_1(F)^a = 0.0754$, $wR_2(F^2)^b = 0.1696$
Goodness-of-fit on F^2	1.157
Absolute structure parameter	$-0.6(12)$
Largest diff. Peak and hole	0.289 and -0.188 e Å^{-3}

[a] $R_1(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ with $F_o > 4.0\sigma(F)$.

[b] $wR_2(F^2) = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$ with $F_o > 4.0\sigma(F)$, and $w^{-1} = \sigma^2(F_o)^2 + (W\cdot P)^2 + T\cdot P$, where $P = (\mathrm{Max}(F_o^2, 0) + 2F_c^2)/3$, $W = 0.0945$, and $T = 0.12$.

606 frames at each of three φ settings, 0°, 120°, and 240°, using a scan width of 0.3° in ω. At the end of the data collection, 50 initial frames were recollected to monitor crystal decay. The exposure time was 10 s/frame.

The initial unit cell parameters were determined in Bruker's SMART[3] program from 999 reflections, which were harvested from 380 frames for a minimum threshold of $I/\sigma \geq 5.0$. These parameters were then used to integrate all the data in Bruker's SAINT[4] program, where global refinement of the unit cell parameters was also performed to give the final values utilized in the subsequent structural analysis. Prior to structure solution and refinement, the data files written by SAINT were processed through SADABS[5] for correction of errors due to absorption by the glass capillary, crystal decay, and other effects.

The structure was solved via direct methods using the SHELXS[6] program, and refined via full-matrix least squares against F^2 on all data using SHELXL.[6] Structure plots that appear in this paper were obtained from the program SHELXP.[6] Positions for all non-hydrogen atoms were refined anisotropically. This was followed by isotropic refinement of all hydrogen positions, except for those on the four methyl groups in the molecular unit. For two of these methyl-carbons, hydrogen positions were not assigned (discussed later), while for the other two [i.e. C(11) and C(12)], the hydrogen atoms were refined using a riding model. The absolute structure could not be determined reliably because of the absence of significant anomalous scatterers in the sample, although it was taken to be correct on the basis of the NMR data. Refinement data are summarized in Table 1 and atomic coordinates and equivalent isotropic displacement parameters are listed in Table 2.

Table 2. Atomic Coordinates (10^4) and Equivalent Isotropic Displacement Parameters (10^3 Å^2) for **2**

	x	y	z	U_{eq} [a]
O(1)	−9144(2)	−8017(2)	−2420(1)	68(1)
O(2)	−7603(2)	−8821(2)	−3124(1)	58(1)
O(3)	−4838(2)	−8137(2)	−2040(1)	54(1)
O(4)	−7611(2)	−8326(2)	−1578(1)	62(1)
O(5)	−5348(2)	−11060(2)	−1276(1)	72(1)
O(6A)	−6220(20)	−11215(17)	−241(12)	83(3)
O(6B)	−6480(20)	−11587(18)	−345(12)	83(3)
O(7)	−3266(2)	−9445(3)	−2484(1)	91(1)
C(1)	−7894(2)	−7623(3)	−2158(1)	54(1)
C(2)	−6857(2)	−8048(2)	−2671(1)	50(1)
C(3)	−5908(2)	−8957(2)	−2297(1)	47(1)
C(4)	−6791(2)	−9438(3)	−1745(1)	52(1)
C(5)	−6097(3)	−9906(3)	−1126(1)	59(1)
C(6)	−7038(4)	−10376(5)	−584(2)	79(1)
C(7)	−5362(3)	−11885(3)	−709(1)	72(1)
C(8A)	−3980(30)	−11600(40)	−253(8)	130(6)
C(8B)	−4140(20)	−11910(40)	−450(7)	130(6)
C(9A)	−5353(15)	−13378(11)	−917(7)	113(3)
C(9B)	−6102(16)	−13129(13)	−945(8)	113(3)
C(10)	−8970(2)	−8407(3)	−3090(1)	61(1)
C(11)	−9854(3)	−9585(4)	−3237(2)	95(1)
C(12)	−9210(4)	−7218(4)	−3528(2)	90(1)
C(13)	−3557(2)	−8487(3)	−2181(1)	54(1)
C(14)	−2583(3)	−7532(3)	−1869(2)	63(1)
C(15)	−2324(2)	−7893(2)	−1161(1)	57(1)
C(16)	−3209(3)	−7546(3)	−669(2)	73(1)
C(17)	−2975(4)	−7919(4)	−24(2)	83(1)
C(18)	−1843(4)	−8626(4)	128(2)	81(1)
C(19)	−969(4)	−8981(4)	−349(2)	80(1)
C(20)	−1186(3)	−8622(3)	−998(2)	69(1)

[a] U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Results and discussion

The ^{1}H NMR spectrum of **2** contained all of the expected signals including 1-H doublets for H(2) and H(3) [attached to carbons C(2) and C(3), respectively], which is a feature often seen in derivatives of **1**. Despite these protons being vicinal they do not couple; a consequence of the ~90° dihedral angle that is reinforced by the crystal structure of **2**, shown in Fig. 1, in which this relationship is clearly seen in the solid state.

The major feature of note during the course of the refinement was the observation of relatively high equivalent isotropic atomic displacement parameters at the O(6), C(8), and C(9) positions. Each of these atoms had large enough anisotropic displacement along one direction such that they could be split between two positions (0.502, 0.537, and 0.787 Å apart, respectively), presumably reflecting the greater flexibility of the dioxolane ring

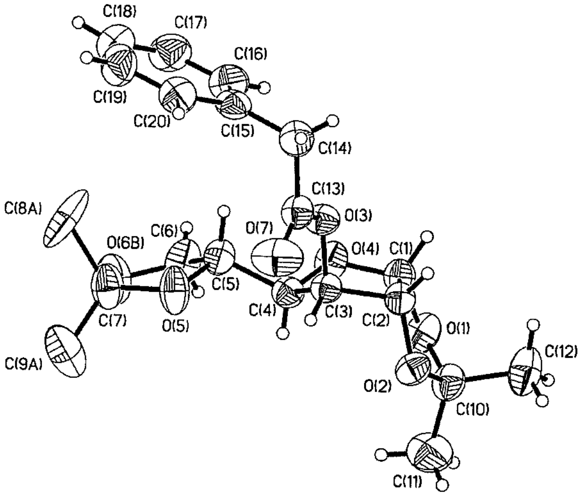

Fig. 1. Molecular structure of **2**, with displacement ellipsoids at the 40% probability level. Hydrogen atoms are drawn as circles with an abritrary radius. Only one of the split-atom pairs at each of the O(6), C(8), and C(9) positions are shown for clarity.

on which they are located relative to the one attached at C(1) and C(2). The split positions are labeled as O(6A) and O(6B), C(8A) and C(8B), and C(9A) and C(9B) in Table 2. Because of the disorder, the six hydrogen atoms connected to the C(8) and C(9) methyl carbons were not assigned.

The crystal structure results embodied in Fig. 1 illustrates nicely the thinking behind the use of derivatives of **1** in our initial studies of diazo decomposition on carbohydrate platforms. The carbene (or carbenoid) that would form at the alpha-carbon of the phenacyl group (C(14) in Fig. 1) would have three major C—H insertion pathways open to it; either into the C(1)—H(1) bond, the C(2)—H(2) bond, or the C(5)—H(5) bond. In this case the preference was for five-membered ring formation via insertion into the C(2)—H(2) bond.[2]

Acknowledgments

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