

Peracetylated  $\alpha$ -D-glucopyranosyl fluoride and peracetylated  $\alpha$ -maltosyl fluorideSimone Dedola,<sup>a</sup> David L. Hughes<sup>b\*</sup> and Robert A. Field<sup>a</sup><sup>a</sup>Department of Biological Chemistry, John Innes Centre, Colney Lane, Norwich NR4 7UH, England, and <sup>b</sup>School of Chemistry, University of East Anglia, Norwich NR4 7TJ, England

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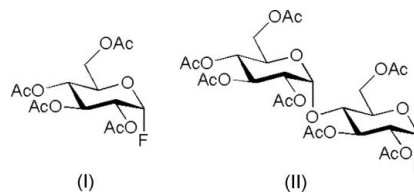
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The X-ray analyses of 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride, C<sub>14</sub>H<sub>19</sub>FO<sub>9</sub>, (I), and the corresponding maltose derivative 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride, C<sub>26</sub>H<sub>35</sub>FO<sub>17</sub>, (II), are reported. These add to the series of published  $\alpha$ -glycosyl halide structures; those of the peracetylated  $\alpha$ -glucosyl chloride [James & Hall (1969). *Acta Cryst.* **A25**, S196] and bromide [Takai, Watanabe, Hayashi & Watanabe (1976). *Bull. Fac. Eng. Hokkaido Univ.* **79**, 101–109] have been reported already. In our structures, which have been determined at 140 K, the glucopyranosyl ring appears in a regular <sup>4</sup>C<sub>1</sub> chair conformation with all the substituents, except for the anomeric fluoride (which adopts an axial orientation), in equatorial positions. The observed bond lengths are consistent with a strong anomeric effect, *viz.* the C1–O5 (carbohydrate numbering) bond lengths are 1.381 (2) and 1.381 (3) Å in (I) and (II), respectively, both significantly shorter than the C5–O5 bond lengths, *viz.* 1.448 (2) Å in (I) and 1.444 (3) Å in (II).

## Comment

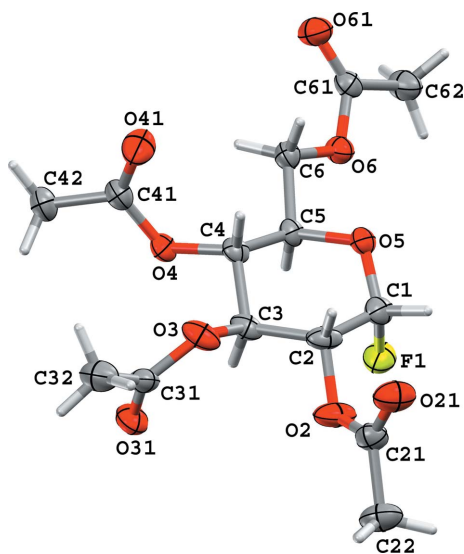
Glycosyl fluorides are widely used in carbohydrate chemistry and biochemistry. The F atom is comparable in size with a hydroxy group, hence the steric demand upon introduction of this group is quite small (O'Hagan 2008; Howard *et al.*, 1996). The popularity of glycosyl fluorides in chemical synthesis is due to their remarkable stability yet ease of chemospecific activation in performing glycosylation reactions. One notable advantage in using glycosyl fluorides as glycosyl donor is their high thermal stability compared with glycosyl chlorides, bromides or iodides. The utilization of carbohydrate fluorides as glycosyl donors originates from the work by Mukaiyama *et al.* (1981) on the synthesis of simple glucosides and disaccharides. Progress made in the utilization of glycosyl fluorides as donors in the synthesis of *O*- and *C*-glycosides has been

reported by Toshima (2000) and updated in the more recent review by Carmona *et al.* (2008). Interest in glycosyl fluorides has increased since Hayashi *et al.* (1984) developed a reliable and safe method for the preparation of these compounds by exposing suitably protected sugars to a 50–70% mixture of hydrogen fluoride in pyridine. The stability of glycosyl fluorides in their deprotected form also makes them important compounds for use as mechanistic probes in the elucidation of enzyme mechanisms and as reagents for enzymatic synthesis (reviewed by Williams & Withers, 2000). Extending our interest in the impact of fluorine substitution on carbohydrate biotransformations (Errey *et al.*, 2009) and the generation of amylose mimetics (Marmuse *et al.*, 2005; Nepogodiev *et al.*, 2007; Clé *et al.*, 2008), we had cause to investigate glucosyl fluorides. In this paper, we report the crystal structures of the 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride, (I), and the corresponding maltose derivative 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glucopyranosyl-(1 $\rightarrow$ 4)-2,3,6-tri-*O*-acetyl- $\alpha$ -D-glucopyranosyl fluoride, (II). The crystal structures obtained integrate with the published series of  $\alpha$ -glycosyl halide derivatives; X-ray structures of peracetylated  $\alpha$ -glucosyl chloride (James & Hall, 1969) and bromide (Takai *et al.*, 1976) have been reported previously and the members of this series show most clearly the anomeric effect, where the preference for the axial orientation of the halogen atom renders synthesis of the equatorial counterpart a synthetic challenge. Results from X-ray analyses typically allow direct evaluation of the impact of the anomeric effect on sugar structure.



The glucosyl unit in (I) (Fig. 1) adopts a <sup>4</sup>C<sub>1</sub> chair conformation. All bond lengths and angles conform with the values found in acetylated glucose. Values for the bond lengths which are affected by the anomeric effect, together with results from the X-ray crystal structures of other acetylated glucosyl halides, are summarized in Table 1. The conformational properties of pyranosyl halides have been explored by a number of theoretical studies using model compounds such as 2-fluorotetrahydropyran or 2-chlorotetrahydropyran. The theoretical approaches to generate three-dimensional structures rely on experimental data to generate the necessary set of parameters. In this context, good agreement was obtained by Tvaroska & Carver (1994) by comparison of their theoretical results with experimental ones obtained for the acetyl and benzoyl D-xylopyranose fluorides. To our knowledge, no crystal structure of anomeric aldohexosyl fluorides has been reported to date. The structural data reported herein are in agreement with the theoretical data obtained by Tvaroska & Carver (1994), supporting the theoretical methodology reported in their study.

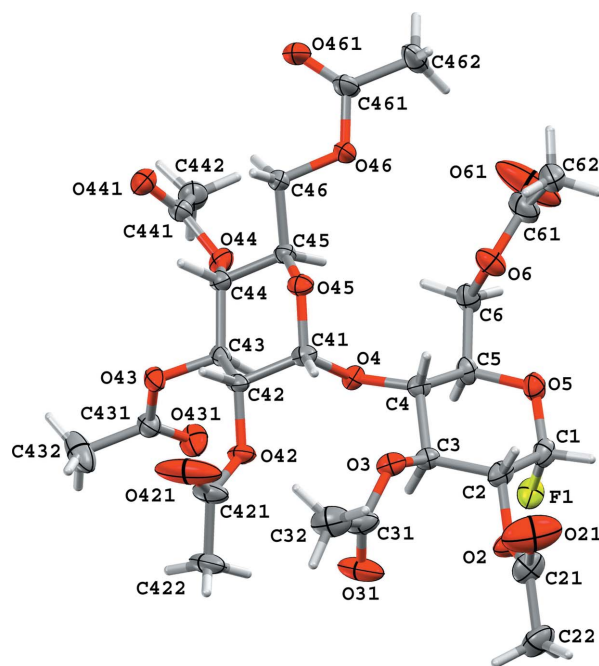
Influences on the bond lengths in a series of X-ray crystal structures of glycopyranosides have been examined by Briggs

**Figure 1**

The molecular structure of the fully acetylated glucosyl fluoride, (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as white rods. The methyl groups of three of the acetyl groups were refined as disordered in two distinct orientations; only one arrangement for each is shown here.

*et al.* (1984). They concluded that there is no correlation between the electronegativity of the substituent at the anomeric position and the C5—O5 bond length. Comparison of C5—O5 bond lengths in the series of halo-derivatives given in Table 1 shows a similar lack of correlation. The C1—O5 bonds in the fluoro- and chloroglucosides have similar values [1.381 (2) Å in the fluoride, (I), 1.383 Å in the chloride and 1.381 (3) Å in the maltosyl fluoride, (II)]; the same bond is shorter in the glucosyl bromide (1.346 Å). Comparing the sugar-ring bond lengths in these halides with those in pentaacetyl- $\alpha$ -D-glucopyranose (Jones *et al.*, 1982), it seems that the shortening of the C1—O5 bond is accompanied by a proportional lengthening of the C1—C2 and C3—C4 bonds. In contrast, the C2—C3, C4—C5 and C5—O5 bond lengths change little, with no apparent correlation with the C1—O5 bond lengths.

In the maltosyl fluoride structure, (II), both pyranose rings adopt a  ${}^4C_1$  chair conformation (Fig. 2). It is interesting to observe in (II) the orientation of the contiguous pyranose rings, which is described by the torsion angles around the glycosidic bonds, C4—O4 and O4—C41, denoted as conformational angles  $\Psi$  and  $\Phi$  [in (II),  $\Psi = \text{H4—C4—O4—C41} = -29^\circ$  and  $\Phi = \text{C4—O4—C41—H41} = -32^\circ$ ], and by the valence angle  $\tau = \text{C4—O4—C41}$ , which is 116.66 (14)° in (II). All these values are in good agreement with those in  $\beta$ -maltoseoctaacetate (Brisse *et al.*, 1982) and -octapropanoate (Johnson *et al.*, 2007) and conform closely with those in other maltose derivatives discussed by Johnson *et al.* (2007) in respect of having short chains containing an  $\alpha$ -(1 $\rightarrow$ 4) inter-sugar glycosidic linkage, and are therefore useful as models to study starch structure. The twist of the nonreducing sugar ring is defined by the virtual torsion angle O44—C44...C41—O4; this has a value of  $-4.8$  (3)° in compound (II), which, if inserted in an amylose chain of starch (see, for example,

**Figure 2**

The molecular structure of the fully acetylated maltosyl fluoride, (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as white rods.

Takahashi & Nishikawa, 2003), would add to the bias of successive residues, forming a left-handed helix (French & Johnson, 2007).

Intermolecular interactions in crystals of both (I) and (II) are principally through weak hydrogen bonds. In (I), there are five contacts (four C—H...O and one C—H...F) in which the H...F/O distance is less than 2.55 Å. In (II), there are six interactions (five C—H...O and one C—H...F). In all these contacts, the angles subtended at the H atoms (in calculated sites) are greater than 137° and most are greater than 150°.

## Experimental

The title compounds, (I) and (II), were both obtained as single  $\alpha$ -anomers (as judged by  ${}^1\text{H}$  NMR spectroscopy). They were prepared following known procedures (Juennemann *et al.*, 1993), exposing the peracetylated glucose or maltose to a 70% mixture of hydrogen fluoride in pyridine in a Teflon bottle. The resulting products were purified by crystallization from a mixture of ethyl acetate and hexane (ratio *ca* 4:1). Crystals suitable for X-ray diffraction were obtained as colourless blocks in both cases by slow recrystallization from the same solvent system.

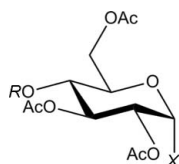
## Compound (I)

### Crystal data

$\text{C}_{14}\text{H}_{19}\text{FO}_9$	$V = 857.06$ (3) Å <sup>3</sup>
$M_r = 350.29$	$Z = 2$
Monoclinic, $P2_1$	Mo $K\alpha$ radiation
$a = 5.35502$ (11) Å	$\mu = 0.12$ mm <sup>-1</sup>
$b = 7.96182$ (14) Å	$T = 140$ K
$c = 20.1151$ (5) Å	$0.55 \times 0.31 \times 0.11$ mm
$\beta = 92.061$ (2)°	

**Table 1**

Selected bond lengths (Å), including those affected by the anomeric effect, in glycosyl halide derivatives and pentaacetyl- $\alpha$ -D-glucopyranose.



X	R	C5—O5	O5—C1	C1—X	C1—C2	C2—C3	C3—C4	C4—C5
Br <sup>a</sup>	Ac	1.458 (14)	1.347 (15)	2.002 <sup>f</sup>	1.572 (16) <sup>g</sup>	1.531 (16) <sup>g</sup>	1.600 (16) <sup>g</sup>	1.500 (16) <sup>g</sup>
Cl <sup>b</sup>	Ac	1.445 <sup>f</sup>	1.383 <sup>f</sup>	1.777 <sup>f</sup>				
F <sup>c</sup>	Ac	1.4477 (18)	1.381 (2)	1.3981 (19)	1.514 (3)	1.512 (2)	1.515 (2)	1.516 (2)
F <sup>d</sup>	(Ac) <sub>4</sub> Glc	1.444 (3)	1.381 (3)	1.393 (3)	1.513 (4)	1.527 (4)	1.532 (3)	1.529 (4)
OGly <sup>d</sup>	(Ac) <sub>4</sub> Glc	1.433 (3)	1.420 (3)	1.409 (3)	1.514 (4)	1.517 (4)	1.514 (3)	1.532 (4)
OAc <sup>e</sup>	Ac	1.422 (4)	1.403 (4)	1.431 (4)	1.507 (4)	1.524 (4)	1.504 (4)	1.534 (4)

Notes: (a) Takai *et al.* (1976); (b) James & Hall (1969); (c) this work, compound (I); (d) this work, compound (II); (e) Jones *et al.* (1982); (f) s.u. values are not available; (g) s.u. values are taken from a mean value.

### Data collection

Oxford Xcalibur 3 CCD area-detector diffractometer  
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)  
 $T_{\min} = 0.970$ ,  $T_{\max} = 1.033$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.033$   
 $wR(F^2) = 0.073$   
 $S = 1.02$   
2677 reflections  
224 parameters  
1 restraint  
H-atom parameters constrained  
 $\Delta\rho_{\max} = 0.22 \text{ e } \text{\AA}^{-3}$   
 $\Delta\rho_{\min} = -0.14 \text{ e } \text{\AA}^{-3}$

### Compound (II)

#### Crystal data

$\text{C}_{26}\text{H}_{35}\text{FO}_{17}$   
 $M_r = 638.54$   
Monoclinic,  $P2_1$   
 $a = 5.63832 (9) \text{ \AA}$   
 $b = 18.2908 (3) \text{ \AA}$   
 $c = 14.8144 (2) \text{ \AA}$   
 $\beta = 94.4966 (15)^\circ$   
 $V = 1523.09 (4) \text{ \AA}^3$   
 $Z = 2$   
Mo  $K\alpha$  radiation  
 $\mu = 0.12 \text{ mm}^{-1}$   
 $T = 140 \text{ K}$   
 $0.42 \times 0.37 \times 0.14 \text{ mm}$

### Data collection

Oxford Xcalibur 3 CCD area-detector diffractometer  
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)  
 $T_{\min} = 0.923$ ,  $T_{\max} = 1.070$

### Refinement

$R[F^2 > 2\sigma(F^2)] = 0.048$   
 $wR(F^2) = 0.117$   
 $S = 1.07$   
4545 reflections  
404 parameters  
1 restraint  
H-atom parameters constrained  
 $\Delta\rho_{\max} = 0.70 \text{ e } \text{\AA}^{-3}$   
 $\Delta\rho_{\min} = -0.46 \text{ e } \text{\AA}^{-3}$

Since the anomalous scattering does not allow definitive determination of the absolute configurations in either of these compounds, the intensities of Friedel pairs were merged (using the MERG 3 command in *SHELXL97*; Sheldrick, 2008). The configurations were

already established since these compounds were prepared from  $\alpha$ -D-glucose and  $\alpha$ -D-maltose.

All H atoms were included in idealized positions, with C—H = 0.96–0.98 Å and  $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$  for methyl groups or  $1.2U_{\text{eq}}(\text{C})$  otherwise. The methyl groups were refined as rigid groups rotating about the C—Me bond. In compound (I), three of the methyl groups showed disorder over alternative orientations, all of which were included as idealized methyl groups with two positions rotated by  $60^\circ$  from each other. These were allowed to rotate about the C—Me bond, and the site-occupation factors of the two orientations refined to 0.25 (3):0.75 (3), 0.39 (2):0.61 (2) and 0.22 (2):0.78 (2) for the H atoms at C22, C42 and C62, respectively.

For both compounds, data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPII* (Johnson, 1976) and *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3170). Services for accessing these data are described at the back of the journal.

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