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Real-Space Crystal Structure Solution. Crystal and Molecular Structure of Laminarabiose Octaacetate, $C_{28}H_{38}O_{19}$

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Abstract

The elucidation of a crystal structure on the basis of complete minimization of intramolecular and intermolecular energy of packing has been applied to laminarabiose octaacetate. [Crystal data: $M_r = 678{\cdot}6$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}379\ (2)$, $b = 22{\cdot}943\ (7)$, $c = 14{\cdot}599\ (4)$ Å, $Z = 4$, $V = 3476{\cdot}4$ Å^3, $D_m = 1{\cdot}30\ (1)$, $D_x = 1{\cdot}297$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 0·91 mm^{-1}, $F(000) = 1432$, room temperature, final $R = 0{\cdot}095$ for 1660 observed independent reflexions.] The two D-glucose residues have the $^4C_1$ pyranose conformation and are β-(1→3) linked. The conformational angles φ and ψ at the glycosidic linkage have the values −81·1 and 134·8° respectively. The present work establishes in an unambiguous manner the foundation of conformational analysis theory applied to the elucidation of crystal structures. It appears that intermolecular interactions in the crystal can be treated in good approximation with the intramolecular potential functions. When coupled with appropriate X-ray data, crystalline conformations may be deduced without highly refined potential functions. As compared to what is faced in polymer crystallography, where the number of packing parameters is reduced, finding a good starting point may represent the essential difficulty associated with the proposed methodology. Once a reasonable location has been found for the molecule, the minimization procedure allows one to handle a reasonable number of parameters and yet yields only a few possible structural models. At this stage, the best packing models have to be checked against X-ray structure amplitudes.

Introduction

The prediction of crystal structure on the basis of non-bonded potential energy has received relatively little attention (Williams, 1969; Coiro, Giglio & Quagliata, 1972; Simonetta, 1974; Dauber & Hagler, 1980). This method may be of special use in the case of small molecules (Zugenmaier & Sarko, 1972; Leser & Rabinovich, 1978) or for rigid molecules with few rotatable substituents (Williams, 1972; Ramachandran & Shamala, 1976) and in the area of polymer structure determination (Kitaigorodskii, 1973; Zugenmaier & Sarko, 1976; Smith & Arnott, 1978) where the lack of diffraction data makes it imperative to predict suitable structural models from the stereochemistry of the repeating units.

In the field of biological molecules, with the exclusion of globular proteins, it is becoming clear that, owing to either the poor quality or the dimensions of the single crystals which can be grown, only a small number of reflexions can be obtained experimentally. In this particular situation, neither conventional direct methods, nor the methods that have been developed for protein crystallography can be applied with success.

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Table 1. *Atomic positional parameters* ($\times 10^4$) *with e.s.d.'s in parentheses and equivalent isotropic thermal parameters* ($Å^2$)

$B_{eq} = \frac{4}{3}[(\beta_{11}/a^{*2}) + (\beta_{22}/b^{*2}) + (\beta_{33}/c^{*2})]$.

	x	y	z	B_{eq}
O(1)	5278 (10)	2987 (6)	4855 (7)	2·87
O(2)	4907 (10)	1766 (6)	4429 (7)	3·12
O(3)	5033 (12)	1057 (6)	6030 (8)	3·30
O(4)	3010 (11)	1556 (6)	7362 (8)	3·75
O(5)	4497 (10)	2798 (6)	6296 (7)	3·26
O(6)	4489 (12)	2780 (7)	8246 (7)	3·96
OA(2)	6915 (10)	1409 (8)	4433 (11)	7·78
OA(3)	3247 (14)	469 (8)	6180 (11)	7·23
OA(4)	4352 (13)	1077 (9)	8333 (10)	7·88
OA(6)	3386 (24)	3147 (12)	9363 (14)	15·18
C(1)	4468 (17)	2574 (9)	5348 (11)	3·26
C(2)	5060 (15)	2008 (8)	5365 (10)	2·42
C(3)	4274 (15)	1610 (9)	5968 (10)	2·27
C(4)	4063 (14)	1852 (10)	6919 (11)	3·12
C(5)	3571 (16)	2444 (9)	6791 (11)	3·19
C(6)	3357 (18)	2812 (11)	7681 (13)	4·82
CA(2)	5845 (15)	1436 (10)	4049 (14)	4·90
CA(3)	4461 (25)	564 (15)	5960 (16)	4·41
CA(4)	3309 (21)	1171 (11)	8086 (12)	4·88
CA(6)	4385 (25)	3044 (16)	9020 (16)	10·04
CM(2)	5500 (19)	1183 (12)	3160 (12)	5·09
CM(3)	5330 (25)	18 (13)	5731 (18)	7·01
CM(4)	2060 (18)	842 (13)	8370 (16)	7·80
CM(6)	5665 (22)	2985 (14)	9606 (16)	7·96
O(1')	3647 (11)	4028 (6)	2305 (7)	4·01
O(2')	3464 (9)	3037 (5)	3400 (7)	2·68
O(4')	5346 (10)	4104 (6)	5819 (7)	5·37
O(5')	4719 (10)	4506 (6)	3455 (7)	4·04
O(6')	4969 (12)	5614 (6)	4444 (8)	3·31
OA(1')	2226 (19)	4820 (11)	2420 (13)	8·22
OA(2')	4794 (14)	2614 (7)	2342 (10)	6·54
OA(4')	7481 (17)	4092 (10)	5999 (10)	11·11
OA(6')	6748 (17)	6161 (10)	4264 (14)	9·29
C(1')	3770 (17)	4048 (9)	3293 (11)	3·09
C(2')	4380 (16)	3500 (11)	3547 (12)	3·89
C(3')	4609 (15)	3524 (8)	4603 (9)	2·27
C(4')	5473 (14)	4025 (8)	4829 (9)	2·13
C(5')	4869 (16)	4581 (8)	4410 (16)	2·83
C(6')	5784 (16)	5103 (10)	4595 (15)	3·64
CA(1')	2722 (26)	4466 (16)	1961 (19)	7·14
CA(2')	3781 (19)	2639 (10)	2751 (15)	4·70
CA(4')	6408 (23)	4102 (13)	6338 (13)	8·06
CA(6')	5557 (21)	6083 (12)	4338 (13)	4·98
CM(1')	2540 (24)	4304 (12)	939 (17)	8·76
CM(2')	2699 (17)	2173 (11)	2663 (17)	6·52
CM(4')	6058 (22)	4204 (11)	7353 (13)	6·04
CM(6')	4777 (34)	6671 (16)	4407 (19)	8·66

However, in most cases, the primary structures of these molecules are known, as well as the molecular geometry of the constituent units. This points towards the need for establishing a method that could be used to solve such crystalline structures (Ramachandran & Shamala, 1976). Along this line, a methodology with an associated computer program have been developed (Pérez, Sarko & Tran, 1985) and tested against known structures. The present work describes the application of the so-called 'real-space crystal structure solution' to the case of a medium-size organic chiral molecule (47 non-hydrogen atoms): laminarabiose octaacetate. This particular molecule was selected as a working example because, on the basis of a preliminary X-ray investigation, it was expected to exhibit a structural similarity to the previously determined parent disaccharide: *O*-methyl laminarabiose heptaacetate (Takeda, Kaiya, Yasuoka & Kasai, 1978).

Experimental

Samples of laminarabiose octaacetate [1,2,4,6-tetra-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose] were prepared by the conventional method of acetolysis. Crystals suitable for X-ray work were obtained by slow evaporation of an ethanolic solution. 25 reflexions used for measuring lattice parameters. D_m measured by flotation in a mixture of anhydrous CCl_4 and cyclohexane. CAD-4 diffractometer, ω–2θ scan mode, graphite-monochromatized Cu $K\alpha$ radiation, scan range $\Delta\omega = (0{\cdot}75 + 0{\cdot}35 \tan\theta)°$. 3149 independent reflexions up to $\theta = 65°$ ($0 < h < 11$; $0 < k < 26$; $0 < l < 16$); 1660 with $I > 2{\cdot}5\sigma(I)$. Three standard reflexions (1,0,11, 3,3,10, 940); 25% intensity decrease during data collection. Absorption ignored. Crystal dimensions $0{\cdot}20 \times 0{\cdot}20 \times 0{\cdot}10$ mm. Scattering factors from Cromer & Waber (1965) for C and O atoms and from Stewart, Davidson & Simpson (1965) for H atoms. Intensities corrected for Lorentz-polarization effects.

The structure was solved using the computer program *CRYSP* (Pérez, Sarko & Tran, 1985) and was refined using a full-matrix least-squares refinement with *ORFLS* (Busing, Martin & Levy, 1962). All H positional parameters were calculated and included in the refinement with isotropic temperature factors. The final R values for all observed and measured reflexions were 0·095 and 0·102 respectively. Quantity minimized: $\sum w(F_o - F_c)^2$, each reflexion being assigned a weight $w = 1/\sigma^2(F)$ derived from $\sigma(I)$. At the end of the refinement, $S = 5{\cdot}2$, $\Delta/\sigma < 0{\cdot}40$. A final electron density map showed no significant residual density, the extreme fluctuations being $-0{\cdot}20$, $+0{\cdot}30$ e $Å^{-3}$. The final atomic coordinates are listed in Table 1.* Computer drawings have been obtained with the program *PITMOS* (Dheu & Pérez, 1981).

Real-space structure determination

Principle

The principle of real-space structure determination is to vary the conformation geometry both of the molecule and of its symmetry-related close neighbours in such a manner that all conformational (intramolecular) and packing (intermolecular) features of the structure are optimized relative to the imposed constraints and/or available experimental data. Basically, the procedure to accomplish this requires the movement of atoms within the constraints provided by some predetermined set of

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, Tables 2 and 3 and tables of the energy parameters and of the results of the different trials have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39956 (17pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

stereochemical criteria. The type of the function that is minimized is:

$$Y=\sum_{i=1}^{l}\left(\frac{r_i-r_{oi}}{\mathrm{SD}_i^r}\right)^2+\sum_{i=1}^{m}\left(\frac{\theta_i-\theta_{oi}}{\mathrm{SD}_i^\theta}\right)^2+\sum_{i=1}^{n}\left(\frac{\varphi_i-\varphi_{oi}}{\mathrm{SD}_i^\varphi}\right)^2+\frac{1}{W^2}\sum_{\substack{i=1\\j=1}}^{N}w_{ij}(d_{ij}-d_{oij})^2.$$

In this function, r_i, θ_i and φ_i are, respectively, the bond lengths, bond angles and conformational angles for the l, m and n corresponding variables in the molecule, with r_{oi}, θ_{oi}, φ_{oi} and SD_i^r, SD_i^θ, SD_i^φ the corresponding best (or average) values and their standard deviations. The first three terms represent the intramolecular potential energy. The fourth term approximates non-bonded repulsions, with d_{ij} the equilibrium distance, w_{ij} the weight of that contact in the summation, and W the overall weight of the non-bonded term in the function Y. The summation is over all N non-bonded distances taken pairwise. The table listing the energy parameters used in this work has been deposited.*

In order to keep the refinement process mathematically as simple as possible, the constraint optimization of Box (1965) is used. In this method a multidimensional space can be searched for a minimum of a function of n independent variables, which are subject to m constraints where the lower and upper constraints are either constants or functions of the variables.

Strategy

Crystallographic investigations of oligosaccharide structures have led to the conclusion that separation into rigid entities (bond lengths, bond angles and sugar-ring conformation and flexible components, *i.e.* the glycosidic torsion angles and the rotatable substituents) is valid. The laminarabiose octaacetate molecule was generated using a mean geometry for the β-D acetate glucose units (Pérez & Brisse, 1978). The numbering of the atoms shown in Fig. 1 proceeds from the non-reducing end (unprimed atoms) to the reducing end (primed atoms). The atoms in the acetate group have been labelled C*A*, C*M* and O*A*. These abbreviations stand for the carbonyl C, the methyl C and the carbonyl O respectively. On Fig. 1 are also shown and labelled the conformational parameters that were considered.

The relative orientation of contiguous pyranosides is customarily described by the torsion angles around the glycosidic bonds C(1)–O(1) and O(1)–C(3′) and are denoted as the conformational angles φ[O(5)–C(1)–O(1)–C(3′)] and ψ[C(1)–O(1)–C(3′)–C(4′)]. The potential energy was calculated by including the partitioned contributions arising from the non-bonded energies and torsion energies about the glycosidic torsional angles φ and ψ. The van der Waals interactions between non-bonded atoms were evaluated using the 6–12 potential functions with the parameters proposed by Scott & Scheraga (1966). Each methyl group was treated as a spherical domain of fixed size. An intrinsic torsional potential with a threefold barrier of 3·8 kJ mol^{-1} was assigned to φ and ψ rotations. The energy map computed as a function of the rotation about φ and ψ angles at intervals of 5° is given in Fig. 2. With respect to the relative energy minimum, iso-energy contours were drawn by interpolation of energy. The 12 kcal mol^{-1} (50 kJ mol^{-1}) contour was selected as the outer limit. In the case of acetylated carbohydrates, the orientation of the primary acetate group at C(6) has been shown to be an important factor in the establishment of the preferred conformations around φ and ψ (Pérez & Brisse, 1978). In order to study the influence of the relative orientation of the primary acetate groups on the allowed conformations of laminarabiose octaacetate, an energy map was computed for the deoxy analogue, *i.e.* with the primary acetate group at C(6) and C(6′) removed. It was found that the surface so obtained encompasses an area identical with that defined by the 12 kcal mol^{-1} contour of laminarabiose octaacetate. From this it can be concluded that in the case of peracetyl-

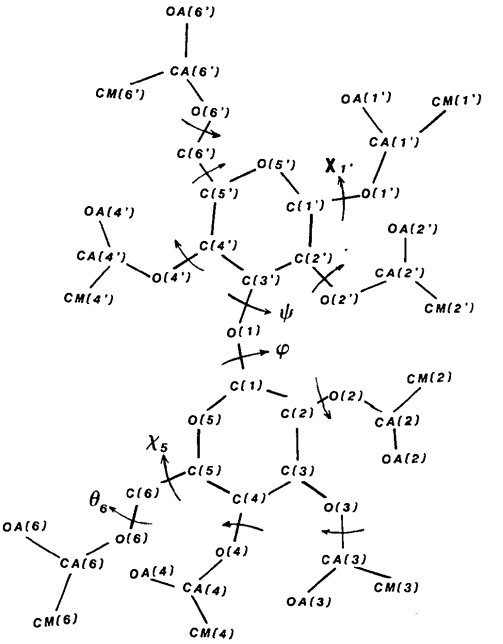

Fig. 1. Numbering of the atoms in laminarabiose octaacetate, along with the parameters that define the conformational flexibility of the molecule.

* See deposition footnote.

ated D-glucose residues linked β-(1→3) the orientation of the substituent at C(6) and C(6′) does not have any major influence on the energetically allowed conformational space.

The conformation of the primary acetate substituent at C(6) is described by the torsion angles O(5)–C(5)–C(6)–O(6) and C(5)–C(6)–O(6)–C*A*(6), referred to as $\chi(5)$, $\theta(6)$, $\chi(5')$ and $\theta(6')$ in the unprimed and primed residues respectively. The two-dimensional conformational spaces available for acetoxymethyl groups in carbohydrates, along with a comparison with the experimental data from crystal structures of acetylated carbohydrates, have been reported (Pérez, St. Pierre & Marchessault, 1976). The different stable conformers and their possible variations are depicted schematically in Fig. 3. The secondary acetate groups are arranged in such a way that the carbonyl O nearly eclipses the axial H atom at the corresponding ring C atoms; only small variations of about 10° are expected to occur.

To begin the structure determination, the conformation of a single isolated molecule of laminarabiose octaacetate was examined. Since the model was derived from a closely related molecule, the first two terms of Y were not used, and all the bond distances (r's) and angles (θ's) were kept constant. Also, the conformation of the secondary acetate groups was assumed, and the primary acetate groups were given one of the possible stable conformations. Only the two variables φ and ψ had to be varied. A disaccharide conformation dictated by $\varphi = -84{\cdot}0°$ and $\psi = 128{\cdot}8°$ was found, in agreement both with the low-energy region of the calculated (φ, ψ) map in Fig. 2, and with the conformation found in *O*-methyl laminarabiose heptaacetate (Takeda *et al.*, 1978).

The packing analysis was then started by including three rotational parameters R_x, R_y, R_z and three translational parameters T_x, T_y and T_z. The starting values of these parameters were selected on the basis of the orientation and location found in *O*-methyl laminarabiose heptaacetate. At a very early stage of the work, it became clear that the conformational parameters $\chi(5)$ and $\theta(6)$ involved with the primary acetate group at C(6) were playing a major role in establishing the packing features. Moreover, among the four stable conformers shown in Fig. 3, the one designated as GT 75 could be discarded since high values of the calculated energy were consistently found. Therefore, three starting models having different conformations at C(6), respectively GG 180, GG 120 and GT 180, were considered, and submitted to packing-energy minimization. Several parameters were considered. A table describing the results of these several trials, along with some conditions that were set upon their variations, has been deposited.* Each starting model converged toward a packing position within the unit cell. At this stage, the viability of these different structural models was tested against structure factor calculation. Only 100 reflexions in the low-resolution region were considered. The three following values for the agreement factor R were found:

$R = 0{\cdot}393$ (GT 180, $Y = 431{\cdot}0$)
$R = 0{\cdot}338$ (GG 120, $Y = 425{\cdot}0$)
$R = 0{\cdot}279$ (GG 180, $Y = 372{\cdot}0$).

This indicates that the model corresponding to the lowest packing energy also corresponds to the lowest R value. When the 1660 observed reflexions were included the R value calculated for the best model ($Y = 372{\cdot}0$) increased to 0·33. The refinement of the structure then proceeded smoothly as indicated in *Experimental.*

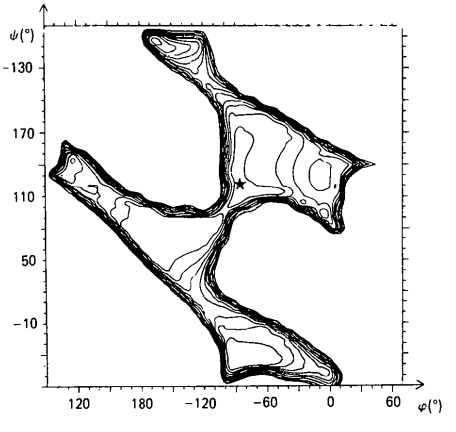

Fig. 2. Energy diagram computed for laminarabiose octaacetate. Contours were drawn by interpolation of energies computed at 5° in φ and ψ. Relative iso-energy contours are drawn at intervals of 1 kcal mol^{-1} (4·2 kJ mol^{-1}), with respect to the calculated absolute minimum (*).

* See deposition footnote.

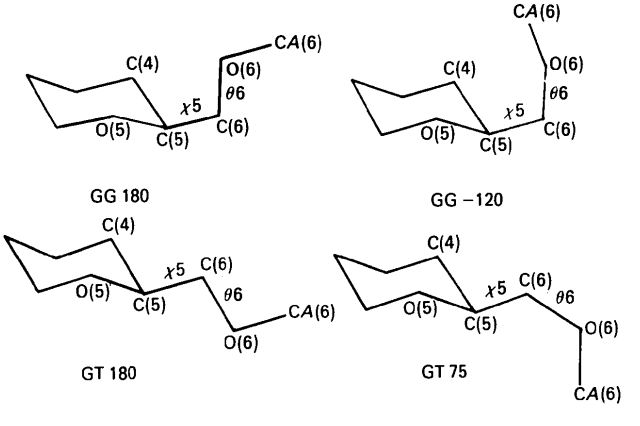

Fig. 3. Schematic of the different stable conformations for the primary acetate group in *gluco* carbohydrates.

Description of the structure

The bond distances and angles in the molecules are given in Tables 2 and 3 respectively.* It should be noted that, owing to the relative paucity of the number of observed reflections, the accuracy of the structural parameters obtained in this work is not high. Incidentally, a comparable feature was observed in the case of *O*-methyl laminarabiose heptaacetate (Takeda *et al.*, 1978). All bond distances and angles conform to the tabulated values for oligosaccharides (Arnott & Scott, 1972). The torsion angles about the various skeletal bonds of the pyranose rings are given in Table 4. The ring conformation found in this structure is similar to that found in other peracetylated glucose residues (Pérez & Brisse, 1978).

As in other carbohydrate acetates, the secondary acetate groups are so arranged that the carbonyl O nearly eclipses the axial H atom at the corresponding ring C atom. As discussed above, the orientation of the primary acetate substituent at C(6) and C(6′) falls in the range of stable conformers (Pérez *et al.*, 1976). Interestingly, the major conformational differences between the structures of *O*-methyl laminarabiose heptaacetate and the corresponding octaacetate molecule occur at the primary acetate group at C(6). This conformational change does not alter the overall shape of the molecule but does influence some of the packing features. In Fig. 4, the location of each molecule with respect to its unit cell is shown in a superimposed manner. From this, packing differences are easily detectable. This obviously explains why our preliminary assumption about a possible isomorphism between the two crystal structures turned out to be wrong. Indeed, the two structures are different.

In the field of oligosaccharide structures, a knowledge of the stable conformations about the glycosidic linkage, *i.e.* the torsional angles φ and ψ, is of interest. From this, extrapolation to the conformation of the parent polysaccharide may be envisaged. In Table 4, the stable conformations found for β-(1→3)-linked glucose residues are reported. It is clear that for both acetylated disaccharides the glycosidic conformations compare well (−81·1, 134·8°) and (−83·5, 128·1°). However, noticeable differences are observed when these values are compared to those obtained for laminarabiose (Takeda, Yasuoka & Kasai, 1977): −93·6, 77·7°. In agreement with an earlier observation (Pérez & Marchessault, 1978), φ angles vary very little, whereas ψ extends over a wider range. In laminarabiose there is an intramolecular hydrogen bond between O(4′) and O(5) (2·786 Å), whereas in the acetylated disaccharides only non-bonded interactions are predominant.

The packing of the molecules in the unit cell is shown in Fig. 5. The molecules are held in the crystal

Table 4. *Torsion angles* (°)(*e.s.d.'s* 1·5°)

Torsion angles about the glycosidic bond		
O(5)–C(1)–O(1)–C(3′)	−81·1	
C(1)–O(1)–C(3′)–C(4′)	134·8	
Endocyclic torsion angles	Unprimed residue	Primed residue
O(5)–C(1)–C(2)–C(3)	62·3	66·1
C(1)–C(2)–C(3)–C(4)	−54·4	−60·5
C(2)–C(3)–C(4)–C(5)	51·2	54·1
C(3)–C(4)–C(5)–O(5)	−60·4	−57·6
C(4)–C(5)–O(5)–C(1)	71·4	65·9
C(5)–O(5)–C(1)–C(2)	−70·6	−70·5
Exocyclic torsion angles		
O(1)–C(1)–C(2)–O(2)	−74·1	−70·1
O(2)–C(2)–C(3)–O(3)	73·0	67·6/O(1)
O(3)–C(3)–C(4)–O(4)	−80·7	−78·6/O(1)
O(4)–C(4)–C(5)–C(6)	67·9	71·4

Torsion angles for the β-D-(1→3) linkage

	Laminarabiose 8-OAc (this work)	Laminarabiose 7-OAc (Takeda *et al.*, 1978)	Laminarabiose (Takeda *et al.*, 1977)
O(5)–C(1)–O(1)–C(3′)	−81·1	−83·5	−93·6
C(1)–O(1)–C(3′)–C(4′)	134·8	128·1	77·7
O(5)–C(5)–C(6)–O(6)	−71·3	−69·5	
C(4)–C(5)–C(6)–O(6)	49·0	52·7	
C(5)–C(6)–O(6)–C*A*(6)	−176·5	−126·7	
O(5′)–C(5′)–C(6′)–O(6′)	77·7	81·9	
C(4′)–C(5′)–C(6′)–O(6′)	−162·7	−157·5	
C(5′)–C(6′)–O(6′)–C*A*(6′)	−163·6	−160·9	

* See deposition footnote.

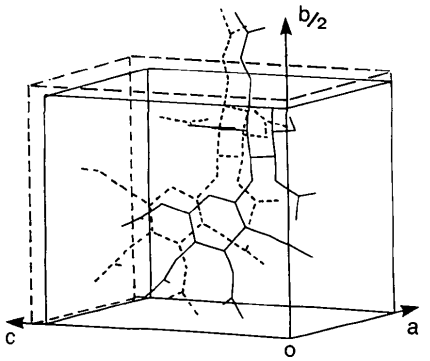

Fig. 4. Comparison between the crystal structure of *O*-methyl laminarabiose heptaacetate (solid lines) and laminarabiose octaacetate (dashed lines).

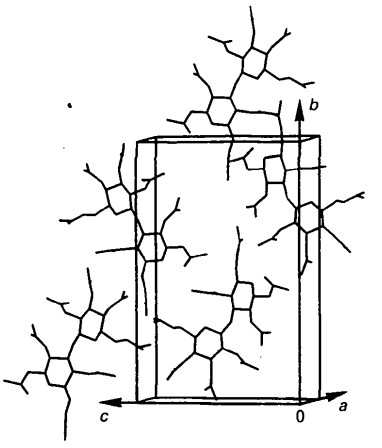

Fig. 5. Molecular packing of laminarabiose octaacetate.

by van der Waals forces only; no short non-bonded distances are observed.

The authors thank Professor A. Sarko for providing the initial version of the *CRYSP* program. The data collection was performed within the 'Groupe Grenoblois de Diffractométrie'.

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Use of the Multiwire Area Detector Diffractometer as a National Resource for Protein Crystallography

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Abstract

After many years of development, a high-speed data-collection system for protein crystallography using multiwire area detectors called Mark II has been dedicated as a national resource at the University of California, San Diego. Protein crystallographers can apply for time and come to this resource to collect data. During the last twelve months, this system has been used to collect more than 5 million intensity measurements in 17 different projects. The quality of the data was excellent with data reproducibility around 6% in intensity. The data were of such quality that many groups with good heavy-atom derivatives were able to have the protein structure solved within two months after the data collection.

The Mark II system which can collect data at 100 times the rate of a standard diffractometer consists mainly of a rotating-anode X-ray generator (Elliot GS6) with a graphite monochromator and two multiwire X-ray area detectors (Cork, Hamlin, Vernon, Xuong & Perez-Mendez, 1975). The crystal is oriented by a three-circle goniostat and can be cooled to 243 K by a dry nitrogen cooling device. The whole system is controlled by a VAX 11/750 computer. This computer not only controls the orientation of the crystal but also analyzes the data from the area detectors to extract right away the integrated intensity of the recorded reflections as the data are being collected. Both the hardware and software of the Mark II have been described in detail elsewhere (Cork *et al.*, 1975; Hamlin, 1982; Xuong, Freer, Hamlin, Nielsen & Vernon, 1978; Howard, Nielsen & Xuong, 1985). We have now published a method or strategy on how to set up the data-collection runs depending on the space group and cell dimensions of the protein crystal (Xuong, Nielsen, Hamlin & Anderson, 1985). The system is kept in running condition by a small crew consisting of one physicist, one electronic technician and one computer programmer. The first-time user is helped by 'in-house' protein crystallographers but can learn to operate the system in a day or two.

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