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Crystal structures of glycolipids with odd and even numbered alkyl chains

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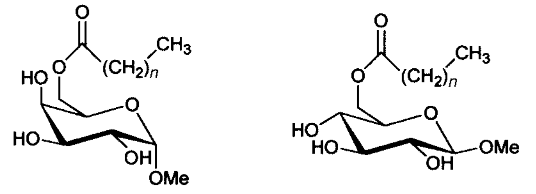
The effect of the alkyl chain on the thermal stability of crystals for a series of glycolipids, methyl 6-*O*-alkanoylglycopyranosides, was investigated using thermal analysis, X-ray structures and molecular mechanics. Glycolipids with two types of sugar moieties, α-galactopyranoside and β-glucopyranoside carrying an alkyl chain with various numbers of carbon atoms, 1–11, and 1–13, respectively, were used for the analyses. All the crystals have bilayer structures with interdigitated alkyl chains. The crystal packing is significantly affected by the sugar moieties but the same for individual sugar derivatives for a variety of alkyl chain lengths. Alkyl chains with an even number of carbon atoms in the α-galactoside derivatives have temperature factors (thermal parameters) which are higher than those for alkyl chains with an odd number of carbon atoms. Alkyl chains with an even number of carbon atoms in the β-glucosides have a disordered structure with two alternate conformations while the remaining derivatives have well ordered alkyl chains. The mean lengths of the hydrogen bonds in the β-glucosides with an even number of carbon atoms in the alkyl chain are longer than those with an odd number of carbon atoms, but a slight difference only is observed in the α-galactosides. The thermal stability of the α-galactosides with an odd number of carbon atoms in the alkyl chain is higher than that of α-galactosides with an even number of carbon atoms. On the other hand, the opposite behavior is observed for the β-glucosides. The difference in the melting points between β-glucosides with an odd and even number of carbon atoms in the alkyl chain is greater than the difference for the corresponding α-galactosides. The difference in the thermal stability is suggested to be related to the packing of the sugar moieties in the crystal based on molecular mechanics calculations.

Introduction

Some physico-chemical properties of amphiphiles are characteristically different between alkyl chains with an even and odd number of carbon atoms, denoted as E- and O-chain, respectively. The melting points, enthalpies and entropies of aliphatic hydrocarbons, alcohols, acids and glycerides systematically change between E- and O-chains.[1] The origin of such differences is ambiguously recognized as due to differences in steric effects in the crystal without detailed analysis of the meaning of the structure.

In spite of the importance of crystal structures when discussing and clarifying odd–even effects, the crystal structures of amphiphiles are limited in number since they do not always crystallize. Crystal structures have been reported for aliphatic acids[2] and their salts,[3] phospholipids,[4] anionic surfactants,[5–7] and glycolipids,[8–10] but studied less systematically to elucidate the effect of E- and O-chains except for some fatty acids and alcohols. For aliphatic acids, the odd–even effect is related to differences in the molecular arrangement of the hydrophilic moiety and packing of the alkyl chains in the sub-cell in the crystals,[11] which shows different arrangements between the derivatives with O- and E-chains. These results have suggested that the odd–even effect is caused by the whole crystal packing difference between the derivatives with E- and O-chains, rather than by the difference in the arrangement between the E- and O-chain moieties. In addition to this situation, crystals of fatty acids show polymorphism,[12] which makes it hard to clarify the origin of structural effects and the physico-chemical properties of the odd–even effect.



methyl 6-*O*-alkanoyl-α-D-galactopyranosides

methyl 6-*O*-alkanoyl-β-D-glucopyranosides

Scheme 1

We have been investigating the crystal structures of glycolipids, *e.g.*, methyl 6-*O*-alkanoylglycopyranosides (Scheme 1).[13–16] Amphiphiles with sugar moieties as hydrophilic groups have been used to solubilize and crystallize proteins. Some of these compounds showed a liquid crystalline state with hydrogen bonding between the sugar moieties,[9] while crystals of the glycolipids have a regular packing of layered sugar moieties linked by hydrogen bonds. Glycolipids with three types of sugar moieties, α- and β-glucopyranosides, and α-galactopyranosides were crystallized and their structures were determined for derivatives with a series of *O*-chains.[13–16] The derivatives of the α-galactosides have the highest thermal stability among the three glycolipids. These structures show the same type of alkyl chain packing for the glycosides having various O-chain lengths for each type of sugar moiety, but the crystal structures are significantly affected by the sugar moiety. Differences in crystal packing are specifically related to the hydrogen bonding geometry and linkages, such as the infinite and finite types found in the α-galactosides and the β-glucosides, respectively. The packing of the sugar moieties is only slightly affected by the length of the alkyl chain. The derivatives of the α-glucosides

Table 1 Compound numbering of the methyl acylglycosides

Molecule	No. of C atoms in alkyl chain
1 Methyl 6-*O*-acetyl-α-D-galactopyranoside[a]	1
2 Methyl 6-*O*-propanoyl-α-D-galactopyranoside	2
3 Methyl 6-*O*-butanoyl-α-D-galactopyranoside[a]	3
4 Methyl 6-*O*-pentanoyl-α-D-galactopyranoside	4
5 Methyl 6-*O*-hexanoyl-α-D-galactopyranoside[a]	5
6 Methyl 6-*O*-heptanoyl-α-D-galactopyranoside	6
7 Methyl 6-*O*-octanoyl-α-D-galactopyranoside[b]	7
8 Methyl 6-*O*-nonanoyl-α-D-galactopyranoside	8
9 Methyl 6-*O*-decanoyl-α-D-galactopyranoside[b]	9
10 Methyl 6-*O*-undecanoyl-α-D-galactopyranoside	10
11 Methyl 6-*O*-dodecanoyl-α-D-galactopyranoside[c]	11
12 Methyl 6-*O*-acetyl-β-D-glucopyranoside[d]	1
13 Methyl 6-*O*-propanoyl-β-D-glucopyranoside	2
14 Methyl 6-*O*-butanoyl-β-D-glucopyranoside[a]	3
15 Methyl 6-*O*-pentanoyl-β-D-glucopyranoside	4
16 Methyl 6-*O*-hexanoyl-β-D-glucopyranoside[a]	5
17 Methyl 6-*O*-heptanoyl-β-D-glucopyranoside	6
18 Methyl 6-*O*-octanoyl-β-D-glucopyranoside[e]	7
19 Methyl 6-*O*-nonanoyl-β-D-glucopyranoside	8
20 Methyl 6-*O*-decanoyl-β-D-glucopyranoside[e]	9
21 Methyl 6-*O*-undecanoyl-β-D-glucopyranoside	10
22 Methyl 6-*O*-dodecanoyl-β-D-glucopyranoside[c]	11
23 Methyl 6-*O*-tetradecanoyl-β-D-glucopyranoside[a]	13

Crystal structures reported in [a] ref. 16, [b] ref. 14, [c] ref. 15, [d] ref. 20 and [e] ref. 13.

have the lowest thermal stability among these three glycosides, because of the disordered packing of the sugar moieties. It is plausible that the origin of the odd–even effect is related to the change in the packing of the hydrophobic and hydrophilic moieties.

In this report, we describe the details of the odd–even effect of the β-glucosides and α-galactosides listed in Table 1, revealed by structures based on X-ray structures and thermal analyses. The definition of the O- and E-chains is in terms of the alkyl chain, excluding the acyl groups. Odd–even effects will be discussed in relation to the interaction of the hydrophobic and hydrophilic moieties in the crystal, which is evaluated by molecular mechanics calculations. We will also discuss the role of the hydrogen bonding between the sugar moieties in relation to the thermal stability of each type of glycolipid.

Experimental

Compounds of **2**, **4**, **6**, **8**, **10**, **13**, **15**, **17**, **19** and **21** (Table 1) were prepared by the reported method with lipase.[16] They were purified by silica gel column chromatography with chloroform–methanol (9:1, v/v) as the mobile phase and were recrystallized several times from acetone–methanol (1:1, v/v) for the α-galactosides and methanol–diethyl ether (5:95, v/v) for the β-glucosides, respectively, except for **15**, which did not crystallize. The solvent used for producing the crystals was used without drying.

Large crystals of **2**, **4**, **6**, **8**, **10**, **13**, **17**, **19** and **21** obtained from the solutions listed in Table 2 were cut into a suitable size for X-ray measurements.† Crystal data and the experimental details are summarized in Table 2. The positions of the carbon atoms of disordered even numbered alkyl chains of the glucosides were assigned from difference Fourier maps and included in the refinement using restraints for bond distances and angles. Hydrogen atoms of the hydroxy groups were added, and their positions were optimized by rotational search in the refinement

Table 2 Summary of experimental details of the X-ray analyses[a]

	2	**4**	**6**	**8**	**10**	**13**	**17**	**19**	**21**
Chemical formula	$C_{10}H_{18}O_7$	$C_{12}H_{22}O_7$	$C_{14}H_{26}O_7$	$C_{16}H_{30}O_7$	$C_{18}H_{34}O_7$	$C_{10}H_{18}O_7$	$C_{14}H_{26}O_7$	$C_{16}H_{30}O_7$	$C_{18}H_{34}O_7$
M	250.2	278.3	306.4	334.4	362.5	250.2	306.4	334.4	362.5
Solution	MeOH	MeOH	MeOH	MeOH	MeOH	Me_2CO	A–E[b]	A–E	A–E
Crystallization conditions	5 wt%, r.t.	10 wt%, r.t.	10 wt%, r.t.	10 wt%, r.t.	10 wt%, r.t.	10 wt%, 4 °C	5 wt%, 4 °C	5 wt%, 4 °C	5 wt%, 4 °C
a/Å	5.767(1)	5.770(1)	5.775(1)	5.768(1)	5.778(1)	7.932(1)	7.906(2)	7.922(1)	7.923(5)
b/Å	7.971(1)	7.973(1)	7.946(1)	7.903(1)	7.903(1)	7.100(1)	7.459(1)	7.449(1)	7.437(3)
c/Å	13.462(1)	15.451(1)	17.883(1)	20.113(1)	22.326(1)	10.984(1)	14.218(3)	15.815(1)	17.217(1)
β/°	91.473(1)	93.690(1)	97.146(1)	96.633(2)	92.830(1)	101.106(1)	102.627(1)	100.010(1)	92.626(1)
V/Å^3	618.6(1)	709.3(1)	814.3(1)	910.6(4)	1018.3(1)	607.1(1)	818.2(1)	919.0(1)	1013.5(1)
D_c/g cm^{-3}	1.343	1.303	1.249	1.220	1.182	1.369	1.244	1.208	1.188
μ/mm^{-1}	0.114	0.107	0.099	0.094	0.090	0.117	0.099	0.094	0.090
No. reflections measured	4521	5281	5483	5443	5603	9051	5483	5034	4339
No. reflections unique	3170	3321	3442	3714	3614	3060	3501	3269	2668
R_{int}	0.021	0.027	0.019	0.024	0.041	0.024	0.021	0.023	0.042
$R1$ $\{\lvert F_o\rvert > 4\sigma(\lvert F_o\rvert)\}$	0.043	0.053	0.044	0.052	0.053	0.038	0.045	0.050	0.051
$R1$ (all)	0.048	0.062	0.058	0.070	0.078	0.045	0.062	0.078	0.060
$wR2$ $\{\lvert F_o\rvert > 4\sigma(\lvert F_o\rvert)\}$	0.112	0.144	0.103	0.108	0.109	0.093	0.111	0.105	0.126
wR_2 (all)	0.115	0.150	0.125	0.134	0.140	0.098	0.123	0.132	0.132

[a] Details in common: monoclinic, space group $P2_1$, $Z = 2$, data collection at room temperature. [b] A–E = acetone–diethyl ether (1:9).

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† CCDC reference no. 188/207. See http://www.rsc.org/suppdata/p2/a9/a905624f for crystallographic files in .cif format.

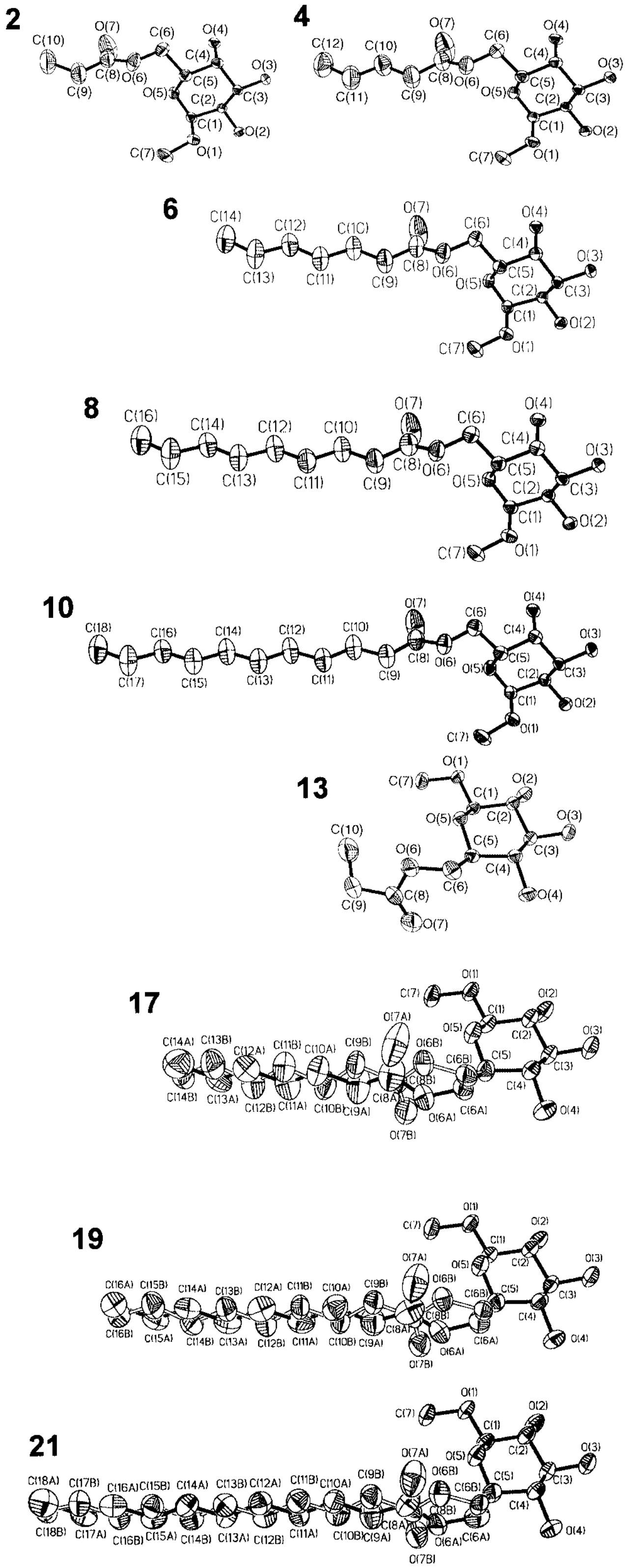
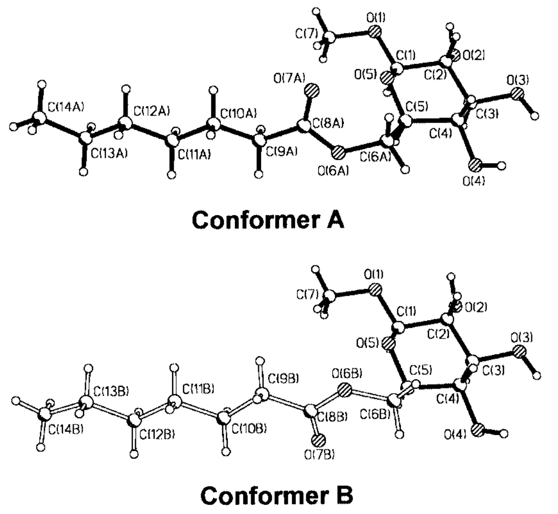


Fig. 1 Structures (ORTEP drawings) and atomic numbering of **2**, **4**, **6**, **8**, **10**, **13**, 17, **19** and **21**. Thermal ellipsoids are drawn at 50% probability.

with the restraint of an O–H bond length of 0.97 Å. The refinement converged at *R*-values of 0.043, 0.053, 0.044, 0.052, 0.053, 0.038, 0.045, 0.050 and 0.051 for **2**, **4**, **6**, **8**, **10**, **13**, **17**, **19** and **21**, respectively, for data with $F_o > 4\sigma(F_o)$.

Calorimetry

A Seiko DSC220 differential scanning calorimeter was used for thermal analysis. The samples were crystallized from the same solution as used in the preparation of the crystals for X-ray analysis. The DSC curves were measured at the scan rate of 2.0 °C min^{-1}. The enthalpy at melting was estimated by integration of the DSC peak, and the entropy was calculated from the enthalpy and melting point. The enthalpy at the melting point was estimated by integration of the DSC peak, and the entropy was calculated by eqn. (1):



Conformer A

Conformer B

Fig. 2 Two conformers in the structure of **18**.

$$\Delta S = -\Delta H / T_{\mathrm{mp}} \qquad (1)$$

where ΔS, ΔH and T_{mp} are the entropy and enthalpy of melting and the melting point, respectively.

Molecular mechanics calculations

The internal and external potential energies of a glycolipid molecule in the crystal were calculated using the program CHARMm[17] with the original parameters for sugar residues for each type of sugar moiety and default values for the acyl chain. The adequacy of the default values of atomic charge, an important parameter for this calculation, was evaluated and used for the revised potential-energy surface for molecular mechanics studies of carbohydrates without an extra term for consideration of hydrogen bonding.[18] The external potentials were estimated for molecules produced within a 10 Å distance. The cutoff distances for the van der Waals and electrostatic potential were set to 10 Å in a switching function.

Results

Molecular structures

The molecular structures and atom labelling for **2**, **4**, **6**, **8**, **10**, **13**, **17**, **19** and **21** are shown in Fig. 1. All of the crystals were anhydrous. The pyranoside rings have a $^4C_1$ conformation. The β-glucosides with E-chains, **17**, **19** and **21**, have a disordered structure with two alternate conformations (denoted by A and B) of the alkyl chain moiety as shown in Fig. 2, in contrast with an ordered structure for the β-glucosides with O-chains and the α-galactosides with E- and O-chains. The conformational parameters of the ester moieties are listed in Table 3. The torsion angles of the alkyl chain differ by 2–7°, 1–7°, 7–12° and −1 to 9° for *α*[C(4)–C(5)–C(6)–O(6)], *β*[O(5)–C(5)–C(6)–O(6)], *γ*[C(5)–C(6)–O(6)–C(8)], and *δ*[C(6)–O(6)–C(8)–C(9)], respectively, between the O- and E-chain of the α-galactosides. The conformation of the O-chains of the β-glucosides is the same as those of conformer B of the E-chains of the β-glucosides. The A and B conformers of the alkyl chains in the β-glucosides are related by a pseudo two-fold symmetry axis through the midpoints of the C–C bonds. The alkyl chains of all the α-galactosides and two conformers

Table 3 The torsion angle of the connecting domain between pyranoside and alkyl chain moieties

	α-Galactoside					β-Glucoside							
						Conformer A				Conformer B			
	α	*β*	*γ*	*δ*		*α*	*β*	*γ*	*δ*	*α*	*β*	*γ*	*δ*
1[a]	−60	179	−179	177	**12**[a]	161	42	72	−177	—	—	—	—
2	−166	73	−121	−180	**13**	177	57	82	−175	—	—	—	—
3[a]	−170	68	−139	−179	**14**[a]	158	41	69	−179	—	—	—	—
4	−165	73	−122	−178	**15**	—	—	—	—	—	—	—	—
5[a]	−170	70	−132	179	**16**[a]	160	43	69	179	—	—	—	—
6	−165	75	−121	−176	**17**	−163	71	−107	172	160	45	62	−178
7[b]	−169	71	−131	180	**18**[d]	158	42	69	179	—	—	—	—
8	−164	75	−121	−176	**19**	−161	71	−109	171	159	43	63	−179
9[b]	−168	71	−129	178	**20**[d]	158	40	70	179	—	—	—	—
10	−164	75	−120	−175	**21**	−164	67	−104	173	158	42	64	−178
11[c]	−167	74	−131	176	**22**[c]	158	39	70	180	—	—	—	—
					23[a]	158	39	69	179	—	—	—	—

Data from [a] ref. 16, [b] ref. 14, [c] ref. 15 and [d] ref. 13.

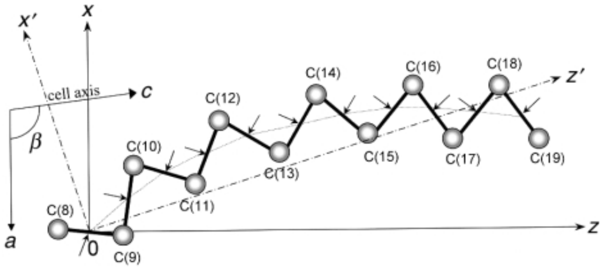


Fig. 3 Schematic drawing of a bent alkyl chain; *x* and *z* axes are in the Cartesian system. The origin is defined at the midpoint of the C(8)–C(9) bond. The arrows indicate the midpoints of each C–C bond. The *z'* axis corresponds to the least-squares line through the midpoints on the *x*–*z* plane for all derivatives of the α-galactosides and β-glucosides.

of the E-chains of the β-glucosides have all-*trans* conformations except for **13** which is obviously different from those of **17**, **19** and **21** in the torsion angles of *α*, *β*, *γ* and *δ* listed in Table 3. The alkyl chains are bent and curved as schematically shown in Fig. 3. The degree of bending in each derivative is illustrated in Figs. 4 and 5, for the α-galactosides and the β-glucosides, respectively. The bending tendency is different between the E-chains of the α-galactosides and the O-chains of the β-glucosides. The B conformer of the E-chain of the β-glucosides curves like the O-chain. The thermal parameters of the sugar moieties are smaller than those of the alkyl chain moieties. The E-chains in the α-galactosides have smaller thermal parameters than those of the O-chains. The thermal parameters in the sugar moieties of the α-galactosides with E-chains are nearly the same as those with O-chains while for the β-glucosides, the O-chain derivatives have smaller thermal parameters than those of the E-chain derivatives, **17**, **19** and **21**.

Crystal structures

The crystal structures of **2**, **4**, **6**, **8**, **10**, **13**, **17**, **19** and **21** are shown in Fig. 6 for the α-galactosides and in Fig. 7 for the β-glucosides. The crystals have bilayer structures with interdigitated alkyl chains. The sugar moieties are linked by hydrogen bonding between the layers. There is no hydrogen bonding between the sugar moieties within a layer. The crystals consist of hydrophilic layers of sugar moieties and hydrophobic layers of alkyl chains. The thickness of these layers is affected by the inclination of the alkyl chain and the packing of the sugar moieties, as shown in Table 4. The area occupied by a hydrophilic group is estimated in the *ab* plane. The cross sectional areas of the alkyl chain are estimated from eqn. (2),[4]

$$S \cos \varphi = 2\Sigma \qquad (2)$$

where *S* is the area occupied by the hydrophilic group in a layer and the angle *φ* is formed by the line normal to the *ab* plane and the least squares line through the midpoints of the C–C bonds. The values of *S*, *φ* and *Σ* are listed in Table 4. The cross-sections of the E-chains of the β-glucosides were calculated for each disordered structure. The mean *S* values of the E-chain of the α-galactosides are 0.4 Å^2 larger than those of the O-chain, while those of the E-chain of the β-glucosides are 1.2 Å^2 larger than those for the previous or next molecular number of O-chain derivatives. The inclinations of the alkyl chains of the α-galactosides are slightly different for the derivatives with O- and E-chains, 47° and 50–51°, respectively, which are longer than the alkyl chain with six carbon atoms. The cross-sections of the β-glucosides are also only slightly different among alkyl chains of various lengths, in spite of the relatively large difference, 1.5–1.2 Å^2, between the occupied area of the layer of the O- and E-chains, causing a larger inclination of the O-chains than that of the E-chains, because of the longer hydrogen bonding lengths between the sugar moieties as discussed below.

The packing categories defined by Vand[11] are distorted types of $O_\perp$, $O_\parallel$ and $O_\parallel$, $O_\parallel$ for the O- and E-chains of the α-galactosides and β-glucosides, respectively.

The packing of the terminal methyl groups of the alkyl chains in each derivative is shown in Fig. 8. The terminal carbon atoms of the O-chains of the α-galactosides are in close contact with carbonyl oxygen atoms. The closest contact of 3.496 Å for **20** is shorter than the closest contact of 3.579 Å in **19**. There are no significant close contacts between the β-glucosides in the O- and E- chains but the interatomic distance between the terminal carbon atom and a C(7) atom of the O-chain derivative is slightly shorter than that of the E-chain derivative. The alkyl chains of the α-galactosides are bent by the repulsive contact between the terminal carbon atom and the adjacent oxygen atom. The terminal carbon atom of the E-chains of the β-glucosides is pushed away by the adjacent methyl group of the sugar moiety, and the chain is bent. The O-chains of the β-glucosides are bent by the adjacent C(5) atom at the second carbon atom from the end of the chain.

Packing of sugar moieties and hydrogen bondings

Molecules having the same sugar moiety and various O- and E-chain lengths have similar packing as shown in Figs. 6 and 7. Hydrogen bonding between adjacent sugar moieties is identified by O···O and O···H–O distances of <3.5 Å and 2.3 Å, respectively.

Continuous hydrogen bonding linkages, ···O(2)–H(O2)···O(3)–H(O3)···O(4)–H(O4)···O(2)–H(O2)··· and O(4)–H(O4)···O(3)–H(O3)···O(2)–H(O2)···O(5) are observed in crystals of the α-galactosides and the β-glucosides,

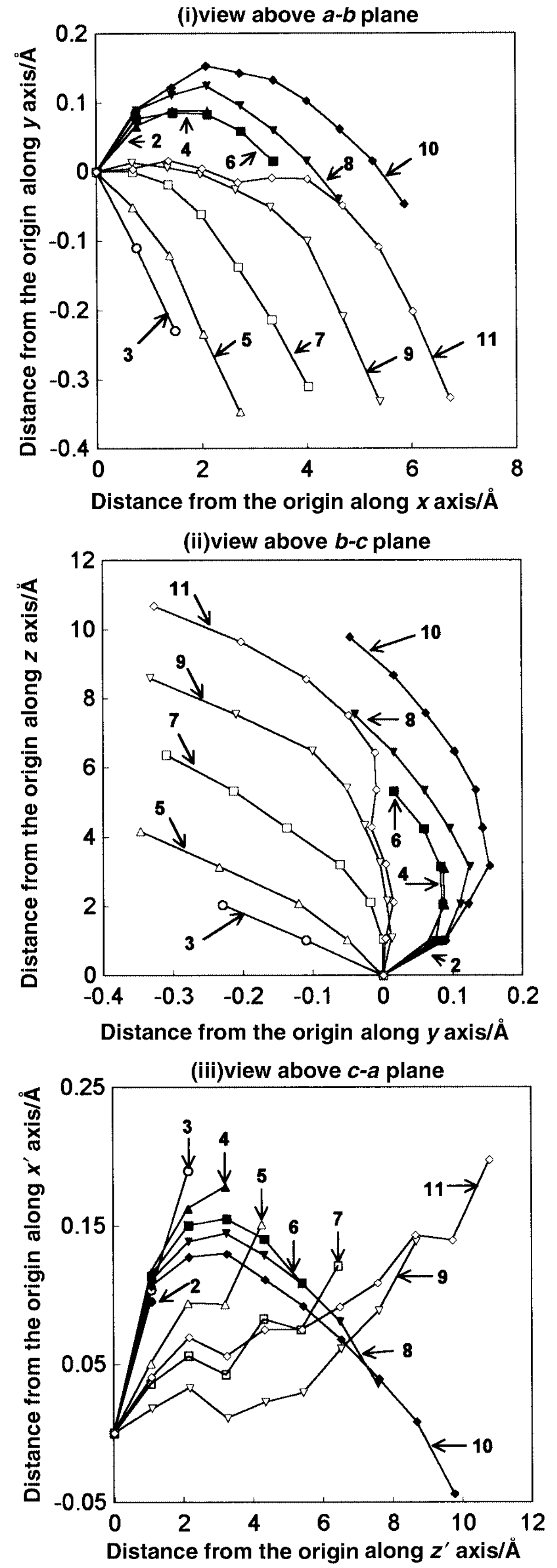


Fig. 4 Bending of the alkyl chain of the α-galactosides. The coordinates of the midpoints of the C–C bonds in the alkyl chain are defined in Fig. 3.

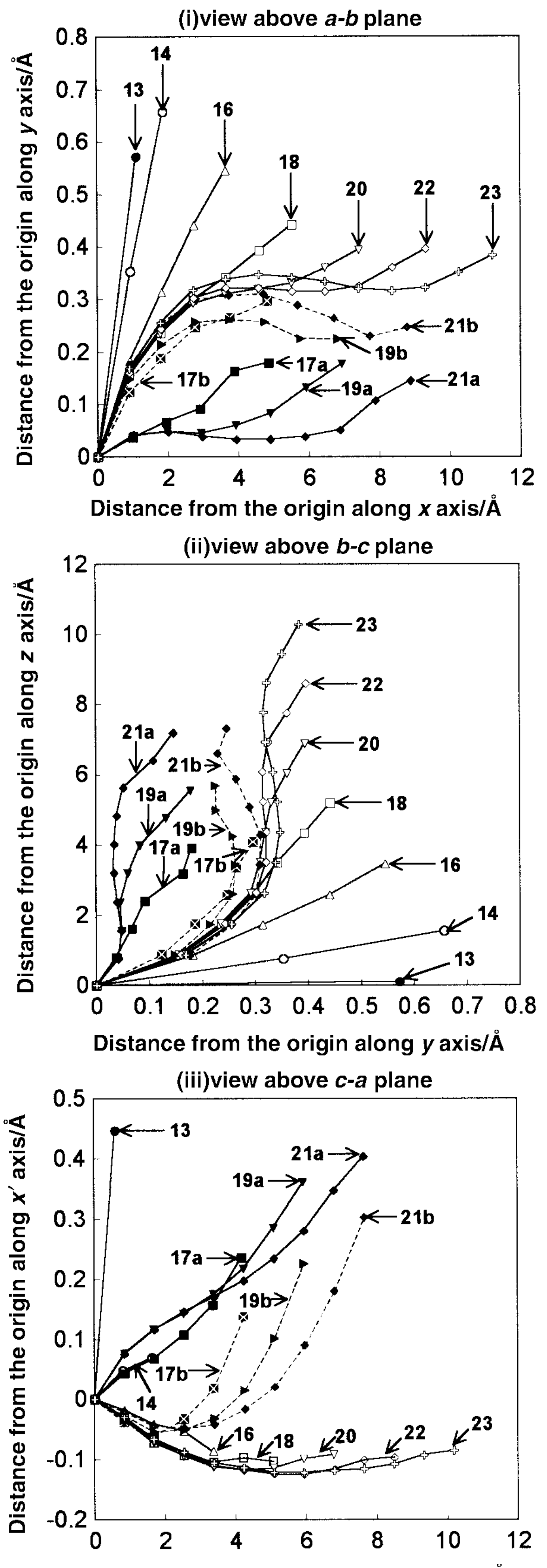


Fig. 5 Bending of the alkyl chain of the β-glucosides. The coordinates of the midpoints of the C–C bonds in the alkyl chain are defined in Fig. 3. The arrows denote the direction of the bending of the alkyl chain.

respectively. The linkage is infinite and finite for the α-galactosides and the β-glucosides, respectively. This linkage is commonly observed in the derivatives for each sugar moiety regardless of the the alkyl chain length. The α-galactosides and β-glucosides with E- and O-chains also have infinite and finite hydrogen bonding chains, respectively, as well as those previously reported for derivatives with O-chains,[16] and hydro-

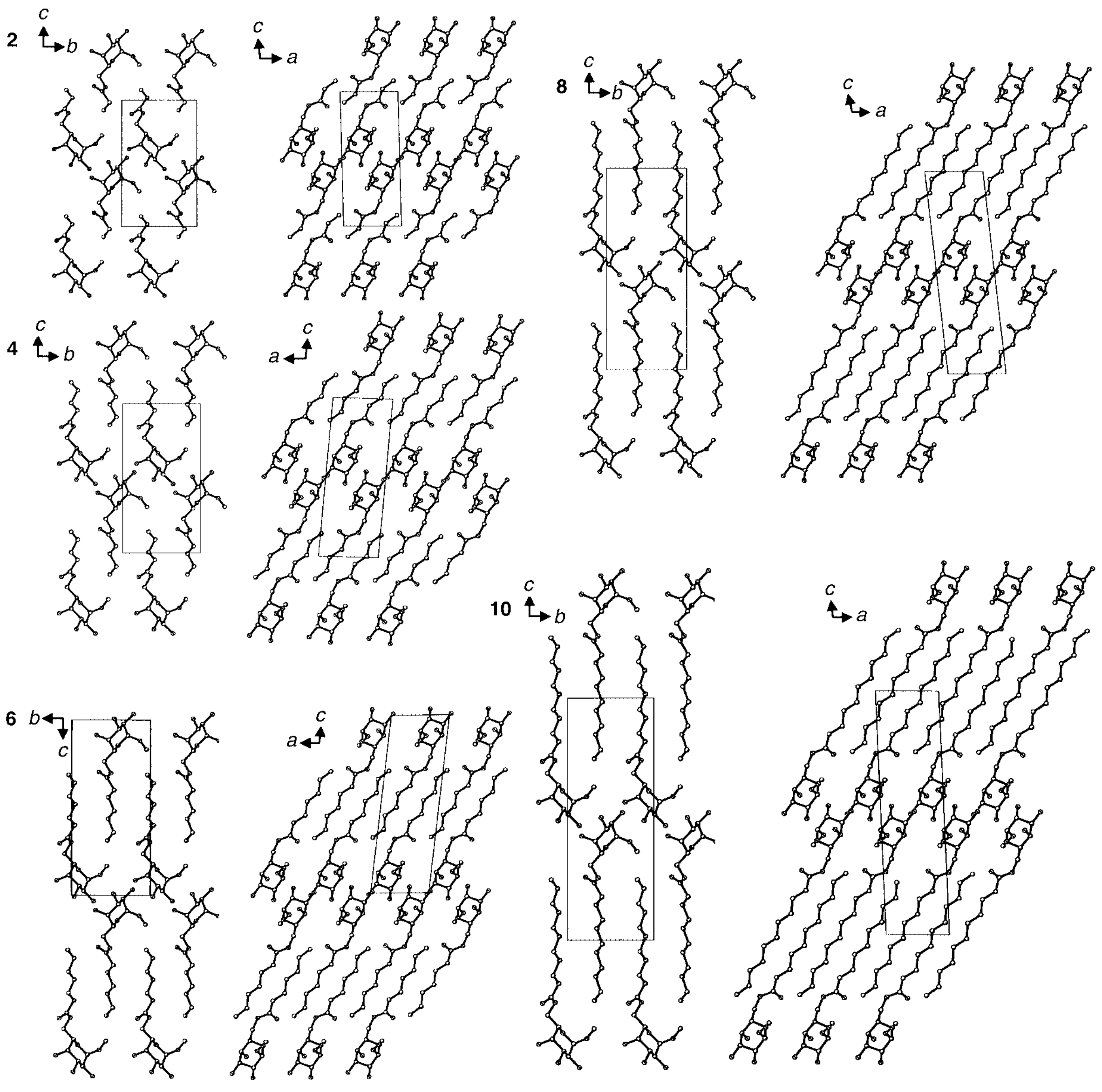


Fig. 6 Crystal structures of the α-galactosides, **2**, **4**, **6**, **8** and **10** projected on the *ac* and *bc* planes.

gen bonding distances are shown in Fig. 9. The mean hydrogen bonding distances of the α-galactosides shown in Table 5 are 0.1 Å shorter than those of the β-glucosides. The distance between H(O2) and O(5) is longer than those of the other hydrogen bondings and show a difference of 0.07 Å between the β-glucosides with O- and E-chains. The hydrogen bonding distances of the β-glucosides with E-chains are longer than those with O-chains. The mean hydrogen bonding distances of the α-galactosides are the same for the O- and E-chain derivatives.

Calorimetry

Melting points, enthalpies and entropies are plotted in Fig. 10. The α-galactosides have melting points higher than the β-glucosides. The melting points of the α-galactosides monotonically decrease with an increase in the alkyl chain length, but those of the β-glucosides decrease in the range C_1–C_8 and then increase. The α-galactosides with E-chains have higher melting points than those with O-chains in a given range of chain length. The melting points of β-glucosides with O-chains are higher than those with E-chains and the lowest melting point is observed for **17** with an alkyl chain which consists of six carbon atoms. The difference in the melting points of the β-glucosides with O- and E-chains is significantly larger than those of the α-galactosides.

Molecular mechanics calculations

The external and internal energies of the molecules were estimated by molecular mechanics. The values of internal energy calculated using the X-ray coordinates are significantly large because of the deviation of the bond length parameters from the ideal values. Since the difference in the bond length and angle terms between the molecule minimized in the crystalline state and that in a vacuum is nearly zero, the internal energy originates from the dihedral term in the sugar ring. The internal energy values calculated from the dihedral terms of a molecule except for those of the sugar moieties are listed in Table 6.

The external potential energy between the molecules in the crystal is treated in terms of the van der Waals force with Lennard-Jones potential (LJP) and the electrostatic potential (ESP). Hydrogen bonding energy is also included in these two potentials.

The interaction energy between the sugar and acyl moieties is calculated in order to evaluate their contribution to the crystal packing. The external energies of the sugar moieties, E_{sugar}, are calculated without the O(6) atom which is included in the calculation of the external energies of the acyl moieties. E_{acyl} was estimated by subtracting the external energy of the sugar from the total energy, E_{total}. These terms were calculated for the LJP and ESP, which are $E_{\text{acyl, LJP}}$, $E_{\text{total, LJP}}$ and $E_{\text{sugar, LJP}}$, and

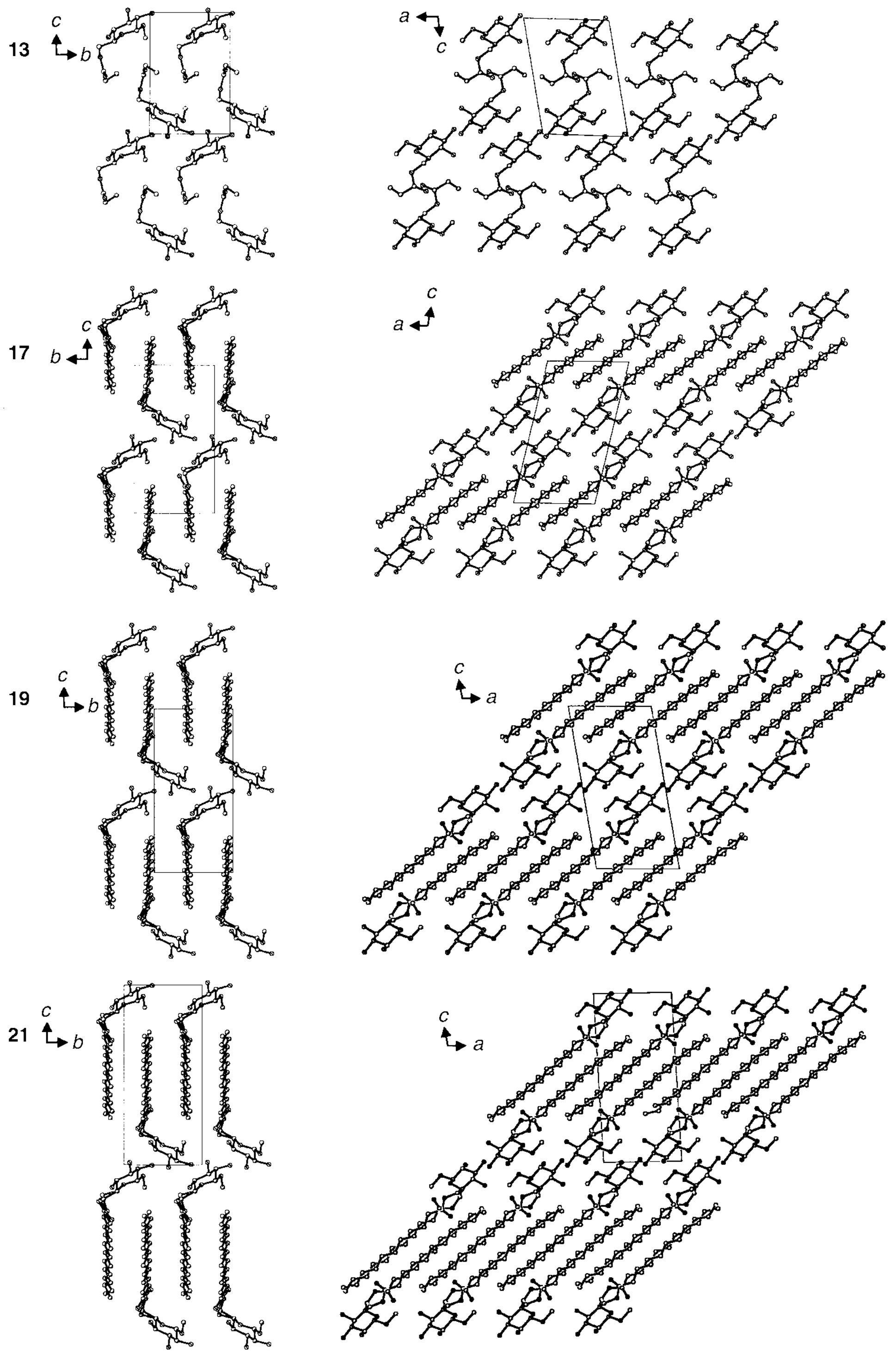


Fig. 7 Crystal structures of the β-glucosides, **13**, **17**, **19** and **21** projected on the *ac* and *bc* planes.

$E_{\text{acyl, ESP}}$, $E_{\text{total, ESP}}$ and $E_{\text{sugar, ESP}}$, respectively. The $E_{\text{acyl, ESP}}$ values are not reasonable for some structures because the disordered structures of the β-glucosides with E-chains and those with O-chains have large atomic temperature factors suggesting that the average atomic position deviates from the minimum energy position. The values of $E_{\text{sugar, ESP}}$, $E_{\text{sugar, LJP}}$ and $E_{\text{acyl, LJP}}$ are shown in Fig. 11.

The $E_{\text{sugar, ESP}}$ values of the α-galactosides are lower than those of the β-glucosides. $E_{\text{sugar, ESP}}$ of the O-chain *α*-galactosides is *ca.* 10–19 kJ mol^{-1} lower in energy than that of E-chain derivatives. The $E_{\text{sugar, LJP}}$ values of the β-glucosides are lower than those of the α-galactosides though the difference between the derivatives with O- and E-chains is slight. The packing of the sugar moieties of the α-galactosides is more stabilized than that of the β-glucosides, because the total external energy of the α-galactosides is lower than that of the β-glucosides, which is shown by the difference of the ESP between the α-galactosides and the β-glucosides being larger than those of LJP for the sugar moieties.

The LJP values of a methylene group in the alkyl chains were calculated from the least-squares line in the plot of the alkyl chain length *vs.* $E_{\text{acyl,LJP}}$ as listed in Table 7. The intercept of the least-squares line indicates the sum of LJP values of the terminal methyl and the carbonyl group in the crystal which are also listed in Table 7. The LJP values of the methylene group of the O-chains in the α-galactosides are the highest while the A conformer of the E-chains of the β-glucosides has the lowest value. The α-galactosides have higher LJP values than the β-glucosides. The repulsion of the terminal methyl and carbonyl group of the odd-numbered galactosides

Table 4 Structural parameters for crystal packing for **2**–**13**

		No. of C atoms in alkyl chain	Occupied area of layer, S/Å^2	Cross-section of alkyl chain, Σ/Å^2	Inclination of alkyl chain, φ/°
2		2	46.0	20.9	25
3[a]		3	46.4	19.4	33
4		4	46.0	19.1	34
5[a]		5	46.4	19.4	33
6		6	45.9	19.5	32
7[b]		7	46.3	19.6	32
8		8	45.6	19.5	31
9[b]		9	46.1	19.6	32
10		10	45.7	19.6	31
11[c]		11	46.0	19.5	32
13		2	56.3	28.0	85.3
14[a]		3	57.9	18.2	51
16[a]		5	57.4	18.3	50
17	A	6	59.0	18.5	51
	B			19.1	50
18[d]		7	57.2	19.5	47
19	A	8	59.0	18.5	51
	B			19.0	50
20[d]		9	56.8	19.3	47
21	A	10	58.9	18.7	51
	B			18.9	50
22[c]		11	56.8	19.3	47
23[a]		13	56.7	19.1	47

Data from [a] ref. 16, [b] ref. 14, [c] ref. 15 and [d] ref. 13.

Table 5 Average hydrogen bonding distances for the α-galactosides and β-glucosides

Hydrogen bonding linkage C(A)–O(B)–H(C)···O(D)	Alkyl chain	Distance/Å Δ(B···D)	Δ(C···D)
α-Galactosides			
C(2)–O(2)–H(O2)···O(3)	Odd	2.76(2)	1.81(2)
	Even	2.75(1)	1.81(1)
C(3)–O(3)–H(O3)···O(4)	Odd	2.83(2)	1.91(2)
	Even	2.82(1)	1.89(1)
C(4)–O(4)–H(O4)···O(2)	Odd	2.76(3)	1.83(3)
	Even	2.76(1)	1.84(1)
Mean value	Odd	2.78(4)	1.85(5)
	Even	2.78(3)	1.85(3)
	Odd and even	2.78(4)	1.85(4)
β-Glucosides			
C(4)–O(4)–H(O4)···O(3)	Odd	2.79(1)	1.89(1)
	Even[a]	2.84(3)	1.94(1)
C(3)–O(3)–H(O3)···O(2)	Odd	2.85(1)	1.93(1)
	Even[a]	2.90(1)	1.97(1)
C(2)–O(2)–H(O2)···O(5)	Odd	2.92(1)	1.98(1)
	Even[a]	3.00(1)	2.05(2)
Mean value	Odd	2.85(5)	1.93(4)
	Even	2.90(7)	1.98(5)
	Odd and even	2.87(5)	1.94(5)

[a] Mean values calculated for molecules **18**, **20** and **22**.

Table 6 Internal energy values for derivatives **1**–**23**

α-Galactoside	Internal energy/ kJ mol^{-1}	β-Glucoside	Internal energy/ kJ mol^{-1}
1	3.39	**13**	3.19
2	1.08	**14**	2.84
3	1.67	**17**	3.40
4	1.37	**18**	1.86 (A) 3.86 (B)
5	2.17	**19**	3.50
6	1.64	**20**	2.08 (A) 3.86 (B)
7	2.39	**21**	3.58
8	1.72	**22**	2.08 (A) 3.93 (B)
9	2.03	**23**	3.61
10	1.72	**24**	3.63
11	2.37		
12	2.37		

Table 7 Values of the Lennard-Jones potentials

	Alkyl chain		Lennard-Jones potential/kJ mol^{-1} –CH$_2$–	CH_3, C=O
α-Galactoside	Odd		−6.0(2)	−28.5
	Even		−6.4(2)	−31.9
β-Glucoside	Odd		−6.7(2)	−33.6
	Even	(conformer A)	−7.2(3)	−33.4
	Even	(conformer B)	−7.1(1)	−32.6

is shown by higher LJP values than for the even-numbered derivatives.

Discussion

The present crystal structures of the alkanoyl glycosides suggest that the odd–even effect is caused by the difference in the fitting of the terminal methyl groups with adjacent molecules between the E- and O-chains. This effect is observed as a change in the alkyl chain packing and hydrogen bonding distances between the hydrophilic moieties. The calorimetric study of the β-glucosides shows a more prominent difference in thermal stability between the E- and O-chain derivatives than in the α-galactosides. The odd–even effect is examined in detail below in which the mechanism of the effect is discussed and related to the thermal stability of the crystals.

Calorimetric results and the molecular mechanics calculations reveal the relationship between the melting enthalpy and packing energy. The difference in the melting enthalpy between the E- and O-chain derivatives reflects the packing energy of the sugar moieties. The calculated packing energy and enthalpy of the α-galactosides are lower than those of the β-glucosides with the same alkyl chain length. Since sugar moieties of the α-galactosides have nearly the same packing energy, independent of either E- or O-chain, the difference in the packing energy reflects the difference in the enthalpy of the alkyl groups

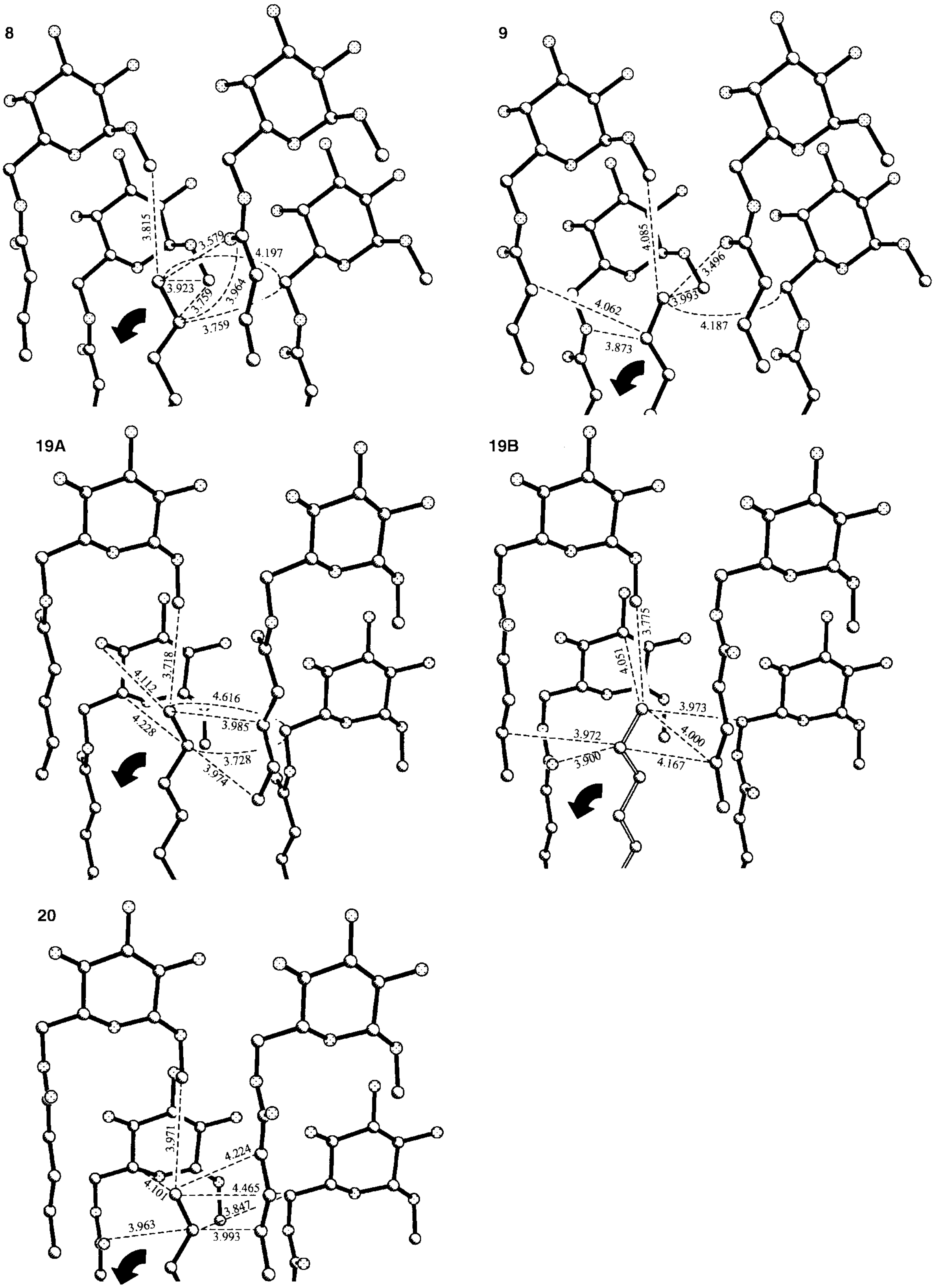


Fig. 8 Molecular arrangement around the end of the alkyl chain and contact distances for the α-galactosides (**8** and **9**) and the β-glucosides (**19** and **20**); **19A** and **19B** show conformers A and B, respectively.

between the E- and O-chains. As a result, the enthalpy values of the O-chain in the α-galactosides are higher than those of the E-chain. As the E- and O-chains of the β-glucosides have nearly the same values of packing energy, the difference in the enthalpy between these glycosides is ascribed to the different packing energies of the sugar moieties between E- and O-chain derivatives. Thus the packing energy estimated using molecular mechanics for the crystal structure is related to the enthalpy values and the relationship between the calorimetric enthalpy and the crystal structures is explained in terms of the packing energy.

The structural characteristics of odd–even effects can be classified in terms of sugar moieties. The odd–even effect of the α-galactosides is caused by the steric hindrance between a terminal methyl group and adjacent molecules, and is observed as the difference in the mean values of the thermal parameters and

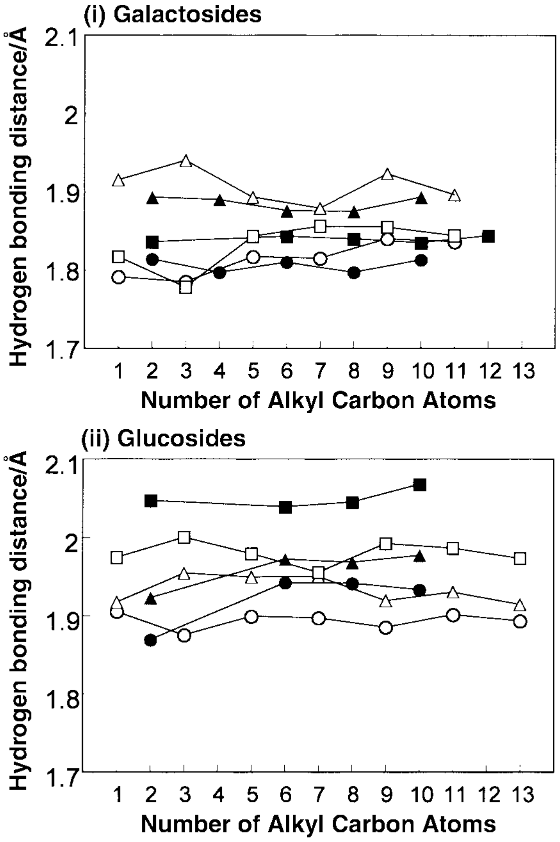


Fig. 9 Distances between hydrogen atoms and the oxygen atoms in the hydrogen bonding linkage; galactosides with O-chain: (○) H(O2)···O(3), (△) H(O3)···O(4), (□) H(O4)···O(2), E-chain galactosides: (●) H(O2)···O(3), (▲) H(O3)···O(4), (■) H(O4)···O(2), O-chain glucosides: (○) H(O4)···O(3), (△) (O3)···(2), (□) H(O2)···O(5), E-chain glucosides: (●) H(O4)···O(3), (▲) H(O3)···O(2), (■) H(O2)···O(5).

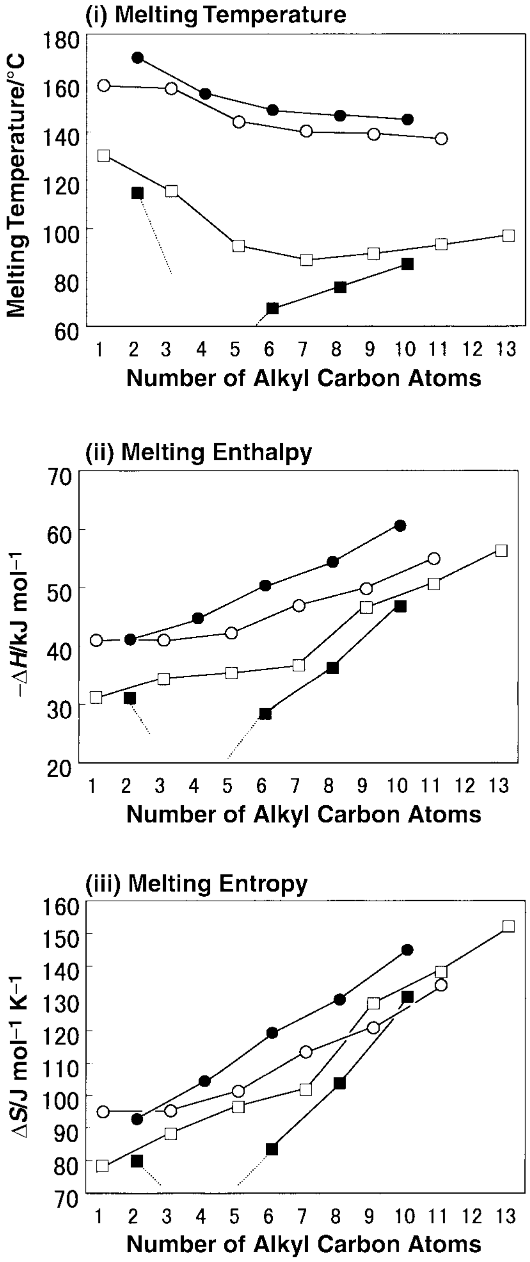


Fig. 10 Plot of melting points (i), melting enthalpies (ii), and melting entropies (iii) of each glycoside *vs.* the number of alkyl carbon atoms; (●) and (○): the E- and O-chain galactosides, respectively, (■) and (□): E- and O-chain glucosides, respectively.

Vand's packing types between the E- and O-chains. Since there is no significant difference in hydrogen bond distances between the E- and O-chain crystals, the odd–even effect is considered to be small for the packing of hydrophilic moieties and dominant for the alkyl chain packing.

In the crystal structure of the β-glucosides, the odd–even effects are observed as the disorder in the alkyl chain and the difference in the hydrogen bonding length for sugars packing between the E- and O-chain derivatives. The absence of significant close contact between the E-chain and adjacent molecules with both conformations assists the formation of disordered structures. The odd–even effects in the sugar packing of the β-glucosides, **17**, **19** and **21** are observed as the difference in the hydrogen bonding lengths. The relatively long distance of the hydrogen bonding in the E-chain β-glucosides is caused by the close contact of the terminal methyl group which pushes away the adjacent sugar moiety.

Comparison of the packing energy of the sugar moiety indicates that in the α-galactosides crystals the hydrogen bonds are stronger than in the β-glucosides. The β-glucosides form a hydrogen bonding linkage between the hydroxy group and the less polarized ring oxygen whereas the α-galactosides have no such hydrogen bond. The relatively long distance between the hydroxy group and the ring oxygen indicates only a weak hydrogen bond. In addition, the hydrogen bonding linkage in the β-glucoside crystals is terminated at O(5), whereas an infinite hydrogen bonding chain is observed in the α-galactosides. *Ab initio* calculations also indicate that the long chain of hydrogen bonding is energetically more favorable than a simple hydrogen bonding linkage.[19,20] From these results, it is concluded that the packings of the α-galactosides are more stable than those of the β-glucosides. The α-galactosides, which have a stable sugar packing, are less affected in their structure by the difference between the E- and O-chains than the β-glucosides.

There are no obvious changes in the sugar packing between the E- and O-chain derivatives. In the arrangement of the sugar moieties of the α-galactosides and β-glucosides, the mode of packing and hydrogen bonding is not affected by the alkyl chain length. Additionally, the mode of the hydrogen bonding linkage of the β-glucosides is the same as that found in crystals of methyl 6-*O*-acetyl-β-D-glucopyranoside[21] and methyl β-D-glucopyranoside hemihydrate.[22] Thus, the mode of the hydrogen bonding is largely conserved and scarcely affected by the packing of substituents attached to the sugar moieties. One reason for the importance of the arrangement of the sugar moieties in determining the crystal packing is the hydrogen bonding between the sugar moieties, which is stronger than the van der Waals force between the alkyl chains. The mode of the hydrogen bonding linkage does not change between the crystals of the E- and O-chain derivatives but the hydrogen bonding length is affected. A slight change in the hydrogen bonding

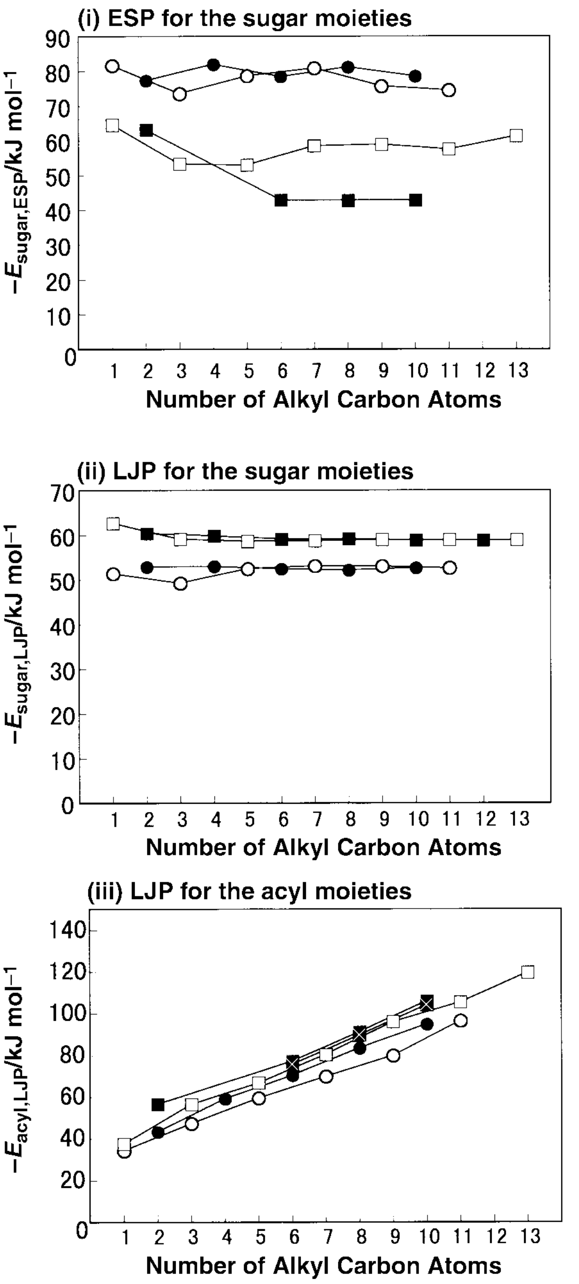


Fig. 11 Calculated intermolecular potential energies in the crystalline state; (●) and (○): galactosides with E- and O-chains, respectively, (■) and (□): glucosides with E- and O-chains, respectively.

distance considerably affects the thermal stability of the crystal because the hydrogen bonding energy dominates in entire crystal packing energy.

The packing energy of the alkyl chains reveals that the packing energy of the O-chain of the galactoside is higher than that of the corresponding E-chain while the packing energy of the E-chains of the β-glucosides is nearly the same as that of the O-chains. This difference in the galactosides is related to the loose packing of the O-chains as suggested by their larger thermal parameters relative to E-chains. The differences in the structure and thermal stability between the E- and O-chains are smaller than those caused by the difference between the sugar moieties.

Conclusion

The difference in the thermal stability between crystals of E- and O-chain derivatives is ascribed to differences in hydrogen bonding contacts. The E-chain derivatives of β-glucosides have a finite hydrogen bonding chain including the bond, O(5)···H–O, and the mean length of the hydrogen bonds is the longest in the alkanoyl glucosides. In addition, the hydrogen bonding energy of the E-chain α-galactoside is nearly the same as that of the O-chain derivatives, but that of the β-glucoside is 34 and 20 kJ mol^{-1} higher than those of E- and O-chain derivatives of the α-galactoside, respectively. The reason for the lowest stability of the E-chain β-glucosides is related to the weak hydrogen bonding. It is concluded that the difference in the hydrogen bonding energy causes a greater difference in the thermal stability of the β-glucosides between the E- and O-chain derivatives than in the α-galactosides.

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