Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl19

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Version of record first published: 24 Sep 2006

To cite this article: Philip Bault, Paul Gode, Gerard Goethals, John Goodby, Julie Haley, Stephen Kelly, Georg Mehl, Gino Ronco & Pierre Villa (1999): Synthesis and Mesomorphism of Four Series of 6-Z-n-Alkyl-α-D-Galactopyranoses, Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals, 332:1, 391-398

To link to this article: http://dx.doi.org/10.1080/10587259908023783

Mol. Cryst. Liq. Cryst., 1999, Vol. 332, pp. 391-398
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Synthesis and Mesomorphism of Four Series of 6-Z-*n*-Alkyl-α-D-Galactopyranoses

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Three homologous series of 6-Z-*n*-alkyl-α-D-galactopyranoses, where Z represents either a carboxy group (OCO), a sulphur atom (S) or an oxypropylthio group (OC_3H_6S) have been synthesised starting from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in either two or three steps. The synthesis of the fourth series of 6-*O*-*n*-alkyl-α-D-galactopyranoses (Z = O) has already been reported. The length of the terminal aliphatic chains has been varied systematically and the effect on the thermotropic liquid crystal transition temperatures prepared. An enantiotropic smectic A* phase was found for all of the homologues studied. The order of efficiency of the linking group Z in favouring liquid crystal formation for the same homologues of the 6-Z-*n*-alkyl-α-D-galactopyranoses is S ≈ OCO > O > OC_3H_6S.

Keywords: liquid crystal carbohydrates; galactopyranose; linkages

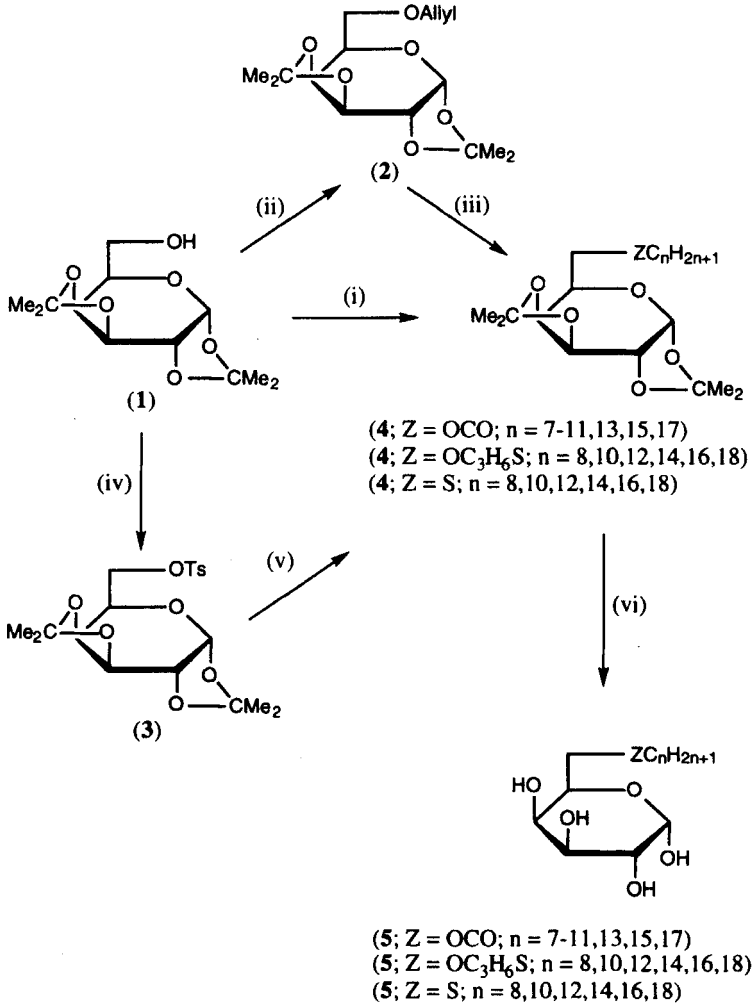
INTRODUCTION

Chemically simple carbohydrate derivatives which exhibit thermotropic liquid crystalline properties in the pure state, or lyotropic properties as suspensions or emulsions with solvents (especially water), are of increasing interest for a number of reasons. Mixtures of monosaccharides, oligosaccharides and polysaccharides, such as alkyl polyglycosides (APGs), have significant practical applications as non-ionic, surfactants, which are non-toxic, biocompatible and biodegradable as well as being easily prepared in a high

overall yield from a diverse, renewable and natural resource. They are used as cheap components of detergents for laundry and dishwashing applications (in tens of thousands of tons p.a.)[1-3]. More expensive, monodisperse monosaccharides, such as alkyl glycosides, are commercially available as mild solvents for membrane proteins, which can be solvated, extracted, then separated and reconstituted in a non-denatured form[4, 5]. They are also used as components of liposomes and vesicles in high-value-added drug-release formulations[6, 7] as well as exhibiting promising antiviral and antibacterial activity themselves[8-10]. Perfluorinated carbohydrate derivatives have also been used as artificial blood[11]. Most of these practical applications of carbohydrates involve aqueous solutions, suspensions, emulsions or gels. Since the solubility, surface tension, critical micelle concentration, lyotropic phase formation, aqueous gel formation, etc., are all dependent on the hydrophilic-lipophilic balance (HLB)[12], i.e., on the chain length of the alkyl/acyl substituent for a given carbohydrate headgroup, it is important to synthesise homologous series for systematic investigations of their physical and biological properties.

A number of recent studies of a diverse variety of substituted carbohydrates have shown that the main molecular factors determining the type of thermotropic and lyotropic mesophases observed for liquid crystalline carbohydrate derivatives are the configuration of the hydrophilic (carbohydrate) part of the molecule, the number and length of the hydrophobic substituents, such as alkyl chains characteristic of liquid crystalline carbohydrate derivatives, and the degree and strength of hydrogen bonding with neighbouring molecules[13-19]. However, the dependence of mesomorphic behaviour on the nature of the linkage between the hydrophilic and hydrophobic parts of liquid crystalline carbohydrates has been studied to a much lesser extent, although it has been reported recently[14,15] that some thio-ether and ester derivatives of D,L-xylitol, which is an open-chain polyol, exhibit higher clearing points than those sugars with oxygen in place of the sulphur atom or carboxy group. Many homologues of these xylitol derivatives were found to be soluble in water and were also reported to exhibit interesting lyotropic behaviour.

Most thermal data for liquid crystalline carbohydrate derivatives to be found in the literature are for glucose, perhaps due to its ready availability and cheapness. However, recent investigations of the physical properties of other carbohydrates, such as galactose [16-19] in the pure state as well as components of aqueous suspensions and emulsions with lyotropic liquid crystalline properties [20], indicate that they may exhibit a more advantageous property spectrum compared to that of analogous glucose derivatives. It has also been reported that substituted sugars in the pyranose form with axial hydroxy groups, such as galactose, exhibit higher clearing points than those sugars, such as glucose, with only equatorial hydroxy groups with the same substituents, such as alkyl chains[16-19]. Therefore, we report here the synthesis of three short homologous series of related 6-Z-*n*-alkyl-α-D-galactopyranoses. The nature of the linkage between the lipophilic and hydrophilic parts of the molecule has been varied in order to determine the effect of the nature of this linkage on the macroscopic liquid crystalline properties of these carbohydrates.



(i) $C_nH_{2n+1}COCl$/TEA/Toluene
(ii) $BrCH_2CH{=}CH_2$/KOH/Toluene/Me_2SO
(iii) HSC_nH_{2n+1}/Toluene
(iv) TsCl/TEA/Toluene
(v) HSC_nH_{2n+1}/KOH/Toluene/Me_2SO
(vi) CF_3CO_2H/H_2O

SYNTHESIS

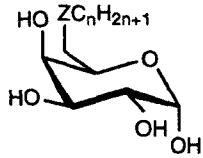
The 6-Z-*n*-alkyl derivatives of D-galactose (**5**) were prepared following the general synthetic pathways depicted in Scheme 1. The starting material 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**), was prepared by method of Régnault[21]. The esters (**5**; Z = OCO; n = 7-11,13,15,17) were obtained by reaction of the diacetal (**1**) with various acid chlorides in the presence of triethylamine to yield the protected intermediates (**4**; Z = OCO; n = 7-11,13,15,17). The deacetylation conditions with trifluoroacetic acid were chosen to produce the α configuration for the 6-*O*-*n*-acyl-α-D-galactopyranoses (**5**; Z = OCO; n = 7-11,13,15,17). The thioethers (**5**; Z = S; n = 8,10,12,14,16,18) were synthesised by tosylation of the diacetal substrate (**1**) to yield the protected tosylate (**3**) followed by reaction with HSC_nH_{2n+1} in the presence of potassium hydroxide to give the protected diacetals (**4**; Z = S; n = 7-11,13,15,17). Deacetalisation with CF_3CO_2H gave the 6-*S*-*n*-alkyl-6-thio-α-D-galactopyranoses (**5**; Z = S; n = 8,10,12,14,16,18) in the α configuration as above. The protected thioethers (**4**; Z= OC_3H_6S; n = 8,10,12,14,16,18) were obtained by reaction of the allylic intermediate (**2**), prepared by base-catalysed alkylation of (**1**) with allyl bromide, with various thiols in toluene at 80°C. Deacetalisation with CF_3CO_2H gave the 6-*O*-(propylene-[3'-*S*-*n*-alkyl])-α-D-galactopyranoses (**5**; Z= OC_3H_6S; n = 8,12,16,18) as above.

RESULTS AND DISCUSSION

The liquid crystal transition temperatures of the 6-*O*-*n*-acyl-α-D-galactopyranoses (**5**; Z = OCO; n = 7-1,13,15,17) are collated in Table 1 and plotted against the number (n) of methylene units in the terminal chain in figure 1. T_{SmA^*I} increases from low values for short alkyl chains, but then reaches a maximum before decreasing gradually as the chain becomes longer. The melting point (T_m) shows a certain degree of alternation and a general tendency to increase with increasing chain length, although the differences for the absolute values of T_m are generally small. Therefore, a broad SmA* phase is observed for all of the homologues of the 6-*O*-*n*-acyl-α-D-galactopyranoses (**5**; Z = OCO; n = 7-11,13,15,17).

The 6-*S*-*n*-alkyl-6-thio-α-D-galactopyranoses (**5**; Z = S; n = 8,10,12,14,16,18) exhibit T_m and T_{SmA^*I}, see Table 1. Therefore a broad SmA* phase is observed for most homologues. T_m is almost independent of chain length, whereas T_{SmA^*I} increases from low values for short alkyl chain lengths, reaches a maximum and then decreases gradually as the chain becomes longer. The 6-*S*-*n*-alkyl-6-thio-α-D-galactopyranoses (**5**; Z = S; n = 8,10,12,14,16,18) possess clearing points at higher temperatures and melting points at lower temperatures than those of the corresponding 6-*O*-*n*-alkyl-α-D-galactopyranoses, but lower than those of the corresponding homologues of the 6-*O*-*n*-acyl-α-D-galactopyranoses. This is probably attributable to a higher degree of molecular polarisability of the esters and thioethers.

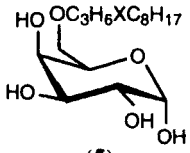
TABLE 1. Transition temperatures (°C) for the 6-Z-*n*-alkyl-α-D-galactopyranoses (**5**)



Compound	Cr		SmA*		I
(**5**; Z = OCO; n = 7)	•	85	•	133	•
(**5**; Z = OCO; n = 8)	•	90	•	155	•
(**5**; Z = OCO; n = 9)	•	87	•	175	•
(**5**; Z = OCO; n = 10)	•	115	•	181	•
(**5**; Z = OCO; n = 11)	•	94	•	182	•
(**5**; Z = OCO; n = 13)	•	117	•	184	•
(**5**; Z = OCO; n = 15)	•	118	•	182	•
(**5**; Z = OCO; n = 17)	•	114	•	181	•
(**5**; Z = S; n = 8)	•	98	•	173	•
(**5**; Z = S; n = 10)	•	104	•	191	•
(**5**; Z = S; n = 12)	•	109	•	185	•
(**5**; Z = S; n = 14)	•	100	•	183	•
(**5**; Z = S; n = 16)	•	103	•	181	•
(**5**; Z = S; n = 18)	•	114	•	177	•
(**5**; Z = OC_3H_6S; n = 8)	•	95	•	156	•
(**5**; Z = OC_3H_6S; n = 10)	•	101	•	166	•
(**5**; Z = OC_3H_6S; n = 12)	•	99	•	165	•
(**5**; Z = OC_3H_6S; n = 14)	•	109	•	163	•
(**5**; Z = OC_3H_6S; n = 16)	•	90	•	162	•
(**5**; Z = OC_3H_6S; n = 18)	•	104	•	154	•
(**5**; Z = O; n = 8)	•	113	•	169	•
(**5**; Z = O; n = 10)	•	117	•	172	•
(**5**; Z = O; n = 12)	•	119	•	171	•
(**5**; Z = O; n = 14)	•	114	•	169	•
(**5**; Z = O; n = 16)	•	121	•	167	•
(**5**; Z = O; n = 18)	•	119	•	164	•

The liquid crystal transition temperatures of the 6-*O*-(propylene-[3'-*S*-*n*-alkyl])-α-D-galactopyranoses (**5**; Z= OC_3H_6S; n = 8,12,16,18) also recorded in Table 1 are significantly lower than those of the corresponding esters, ethers or thioethers (**5**; Z = OCO, O, S). This may be due to intermolecular dipole-dipole interactions attributable to non-conjugated heteroatoms, although there may also be purity considerations. This is shown more clearly by the thermal data collated in table 2 where it can be seen that the replacement of a methylene group in the middle of a chain of the 6-*O*-dodecyl-α-D-galactopyranose (**5**; Z= O; n = 12) by a sulfur atom to produce the 6-*O*-(propylene-[3'-*S*-*n*-octyl])-α-D-galactopyranose (**5**; Z= OC_3H_6S; n = 8) leads to a lower clearing point for the latter. This may have parallels with similar behaviour found for non-amphiphilic liquid crystals and is not well understood[22].

TABLE 2. Transition temperatures (°) for the 6-*O* -(propylene-[3'-*S*-octyl])-α-D-galactopyranose (**5**; Z = OC_3H_6S; n = 8) and the 6-*O*-dodecyl-α-D-galactopyranose (**5**; Z = O; n = 12)[19]



(**5**)

Compound	X	Cr		SmA*		I
(**5**; Z = OC_3H_6S; n = 8)	S	•	95	•	156	•
(**5**; Z = O; n = 12)	CH_2	•	119	•	171	•

Therefore, the order of efficiency of the linking group Z in favouring liquid crystal formation for the same homologues of the 6-*O*-*n*-acyl-α-D-galactopyranoses (Z = OCO), 6-*S*-*n*-alkyl-6-thio-α-D-galactopyranoses (Z = S), 6-*O*-*n*-alkyl-α-D-galactopyranoses (Z = O) and 6-*O*-(propylene-[3'-*S*-*n*-alkyl])-α-D-galactopyranoses (OC_3H_6S), is the following:

$$S \approx OCO > O > OC_3H_6S$$

This correlates well with the order of polarisability of the linking unit Z for the first three members of the series (except for the 6-*O*-(propylene-[3'-*S*-*n*-alkyl])-α-D-galactopyranoses, where the presence of a sulfur atom in the middle of a chain gives rise to a lower clearing point).

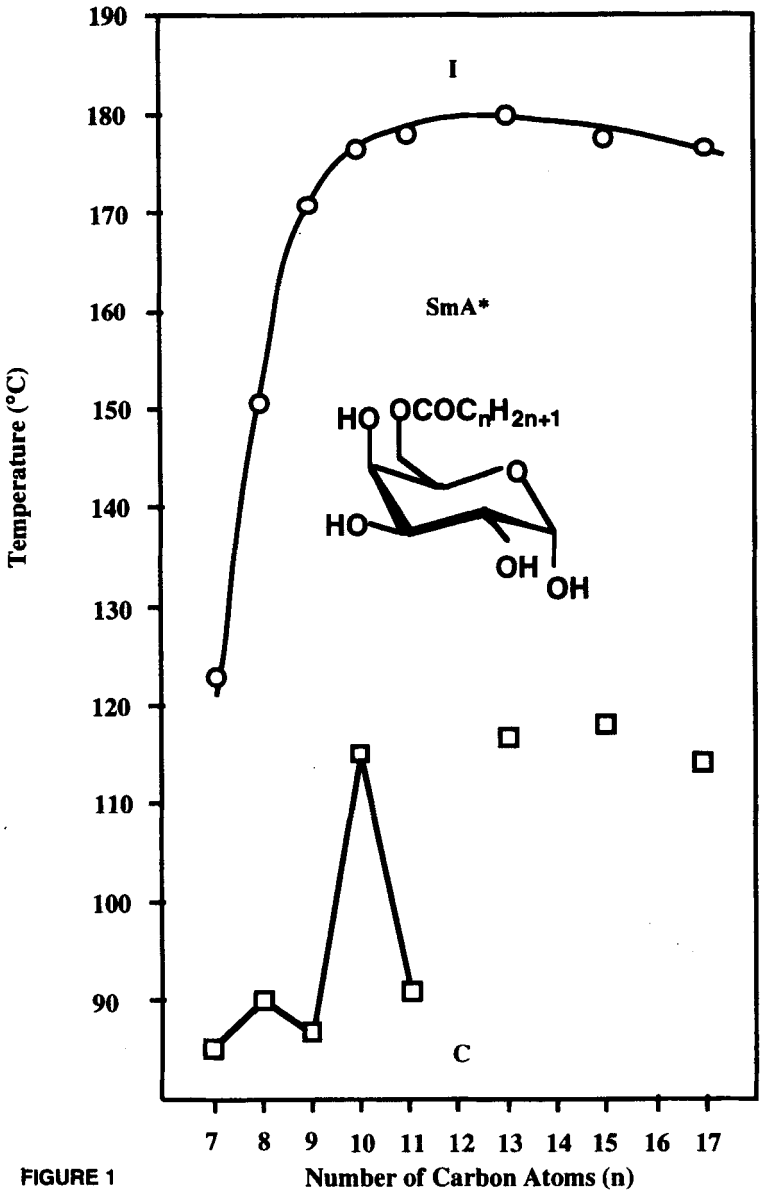


FIGURE 1

Acknowledgments
We gratefully acknowledge the EPSRC for support of an Advanced Fellowship (SMK). We would also like to thank the co-sponsored Alliance Programme of the British Council and the Ministère des Affaires Etrangères, Direction de la Cooperation Scientifiques et Techniques for financial support for this research work. Mrs. J. Welsh and C. Kennedy (CHN) are also thanked for their technical assistance.

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