Thermotropic liquid-crystalline properties of some novel hexuronic acid derivatives bearing a single or two alkyl chains

Xavier Auvray,*[a] Bernard Labulle,[a] Claude Petipas,[a] Jean-Noël Bertho,[b] Thierry Benvegnu[b] and Daniel Plusquellec*[b]

[a]*Laboratoire des Fluides Granulaires et Supramoleculaires, associe au CNRS, Universite de Rouen, Faculte des Sciences, BP 118, 76821 Mont Saint Aignan Cedex, France*

[b]*Laboratoire de Syntheses et Activations de Biomolecules, associe au CNRS, Ecole Nationale Superieure de Chimie, Avenue du General Leclerc, F-35700 Rennes, France*

We have recently developed a new method for *O*-glycosidation of totally *O*-unprotected aldoses and uronic acids. Either pyranosides or the corresponding furanosidic isomers are thus obtained in one step from natural carbohydrates. This paper is concerned with the thermotropic liquid-crystalline phases of alkyl β-D-galacto-(or gluco)-furanosiduronic acids bearing a saturated alkyl chain at the anomeric position and of some dialkylated derivatives. Phase identifications and measurements of phase transition data were carried out by differential scanning calorimetry (DSC), polarizing optical microscopy and small angle X-ray diffraction studies. Uronic derivatives have quite crystalline structures; upon heating, these compounds exhibit a smectic A* transformation.

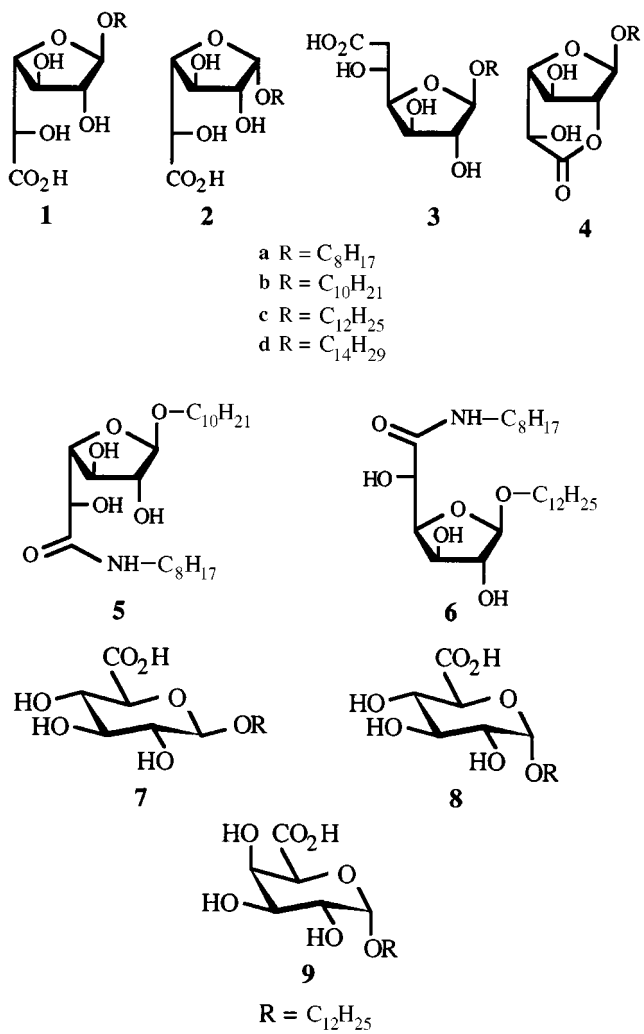
The synthetic potential of carbohydrates has, over the last decade, provided a wide range of structurally homogeneous amphiphilic materials which have found applications, *e.g.* as surfactants for the extraction and the purification of membrane proteins [1,2] or as thermotropic and lyotropic liquid crystals.[3–5]

The mesogenic nature of several amphiphilic glycosyl derivatives has already been demonstrated.[3,6] On heating, these compounds can exhibit a thermotropic liquid crystalline behaviour with a succession of crystal–crystal, crystal–liquid crystal and liquid crystal–isotropic liquid transformations. For some compounds, transition points may differ on heating and cooling and with the number of cycles. The thermotropic liquid-crystalline mesomorphism of monoalkyl glycopyranosides has been shown by Goodby to exhibit smectic A* phases.[4] However, dialkylated systems have recently been characterised as being discotic columnar in type.[7]

In some instances, glycolipids that exhibit thermotropic properties may also generate lyotropic properties and hence materials, described as amphitropic, may display rich polymorphism as a function of water concentration.[3,6,8]

The synthesis of alkyl glycosides usually requires time-consuming methodologies, *i.e.* protection of the glycosyl donor, activation, coupling and deprotection.[9] Moreover, they appear to be inappropriate for the synthesis of glycofuranosidic compounds. We recently developed a new method for *O*-glycosidation of totally *O*-unprotected aldoses and uronic acids. Either pyranosides or the corresponding furanosidic isomers are thus obtained in one step from natural carbohydrates.[10] This method allowed us to investigate the liquid crystalline properties of a new family of amphiphilic compounds derived from uronic acids.

This paper is concerned with the thermotropic liquid-crystalline phases of alkyl D-galacto-(or gluco)-furanosiduronic acids **1**–**9** bearing a saturated alkyl chain at the anomeric position and of some dialkylated derivatives. Phase identifications and measurements of phase transition data were carried out by differential scanning calorimetry (DSC), polarizing optical microscopy and small angle X-ray diffraction studies on powdered samples.



Experimental

Synthesis of materials

Alkyl D-galactofuranosiduronic acids 1a–d and 2c. Alkyl D-galactofuranosiduronic acids **1a–d** and **2c** were synthesized by direct glycosidation of totally *O*-unprotected D-galacturonic acid (20 mmol) with fatty alcohols (40 mmol) in heterogeneous media using tetrahydrofuran (40 ml) as a solvent, ferric chloride (60 mmol) as a promoter and calcium chloride (40 mmol) as an additive. Reactions were carried out under a nitrogen

atmosphere at room temperature for 48–72 h.[10] After work-up, D-galactofuranosiduronic acids were obtained in 50–80% overall yields with a high β-stereoselectivity (typically $\alpha:\beta \approx 1:9$). The β-anomers crystallized out of diethyl ether–light petroleum mixtures thus affording pure compounds **1a–d**.

The structure of these compounds was deduced from ^1H and ^{13}C NMR data. The data clearly indicated the furanosic form and the stereochemistry of the anomeric carbon. Selected data for compound **1b**: mp 92–93 °C, $[\alpha]_D^{20}$ −65 (*c* 1, MeOH); δ_H [400 MHz, $(CD_3)_2SO + D_2O$; *J* values in Hz]: 3.78 (dd, 1H, J_{2-3} 5.2, H-2), 3.95 (dd, 1H, J_{2-3} 5.2, J_{3-4} 7.7, H-3), 4.02 (dd, 1H, J_{4-5} 2.2, H-4), 4.09 (d, 1H, H-5), 4.72 (d, 1H, J_{1-2} 2.7, H-1); δ_C (100 MHz, CD_3OD): 71.09 (C-5), 78.73 (C-3), 83.93 (C-2), 85.66 (C-4), 110.10 (C-1) and 173.16 (C-6).

Compound **2c** was recovered from the mother liquor, purified by column chromatography and crystallized from diethyl ether. Selected data for compound **2c**: mp 102–104 °C; δ_C (22.5 MHz, CD_3OD): 72.20 (C-5), 76.15 (C-3), 79.46 (C-2), 85.12 (C-4), 103.46 (C-1) and 176.16 (C-6).

Decyl and dodecyl β-D-glucofuranosiduronic acids 3b–c. Compounds **3b–c** were synthesized in two steps from commercially available D-glucofuranurono-6,3-lactone ('D-glucurone'). The coupling of D-glucurone with decanol or dodecanol (2 equiv.) was performed in refluxing tetrahydrofuran (THF) for 2 h in the presence of $BF_3 \cdot OEt_2$ (2 equiv.). The β-lactonic glucoside was easily purified by silica gel column chromatography (eluent, diethyl ether and then diethyl ether–methanol, 9:1) and saponified (2.5 mol dm^{-3} NaOH in water–acetone, 15 min at room temp. and then HCl) into crystalline decyl or dodecyl β-D-glucofuranosiduronic acid (72% overall yield) which was recrystallized from diethyl ether–methanol.

Compound **3b**: mp 93–94 °C; $[\alpha]_D^{20}$ −50.7 (*c* 0.85, MeOH); δ_C (22.5 MHz, CD_3OD) (selected data): 71.98 (C-5), 78.11 (C-3), 82.11 (C-2), 84.28 (C-4), 110.31 (C-1) and 176.54 (C-6).

Compound **3c**: mp 99–100 °C; $[\alpha]_D^{20}$ −46.2 (*c* 0.87, MeOH); δ_C (22.5 MHz, CD_3OD) (selected data): 72.09 (C-5), 78.24 (C-3), 82.25 (C-2), 84.36 (C-4), 110.45 (C-1) and 176.57 (C-6).

Uronamides 5 and 6. Compound **5**. A mixture containing 7.5 mmol of pyridine and 7.5 mmol of furanoside **1b** in 25 ml of THF was added to a solution of triphosgene (0.74 g, 2.5 mmol) in 25 ml of dichloromethane at −15 °C. After 30 min, a solution of triethylamine (8.2 mmol) in dichloromethane was added at 5 °C. The mixture was then stirred at room temp. for 20 h and concentrated to yield (decyl β-D-galactofuranosid)-urono-6,2-lactone **4b** which was used in the next step without any further purification.

The lactone **4b** was then treated with octylamine (7.5 mmol) in a mixture of diisopropyl ether and methanol (4:1, v/v). The mixture was stirred at room temp. for 5 h, diluted with diisopropyl ether (20 ml) and washed with aqueous HCl and then water and concentrated. Recrystallization from diethyl ether–heptane afforded compound **5** (67% yield) as a colourless crystalline solid: mp 72–74 °C, $[\alpha]_D^{20}$ −70.7 (*c* 0.66, $CHCl_3$); δ_C (22.5 MHz, $CDCl_3$): 14.10 (CH_3), 22.68, 26.10, 26.88, 29.35, 29.51, 29.64, 31.89 (CH_2), 39.45 (CH_2-NH), 68.03 (CH_2-O), 71.57 (C-5), 78.35 (C-3), 79.46 (C-2), 85.98 (C-4), 107.74 (C-1) and 171.91 (C-6).

Compound **6** was synthesized as described above from (dodecyl β-D-glucofuranosid)urono-3,6-lactone and was recrystallized from diethyl ether (yield 95%) as a crystalline solid: mp 79 °C, $[\alpha]_D^{20}$ −42.2 (*c* 1.02, THF); δ_C (22.5 MHz, $CDCl_3$): 14.10 (CH_3), 22.68, 26.12, 26.99, 29.29, 29.40, 29.53, 29.70, 31.87, 31.95 (CH_2), 39.53 (CH_2-NH), 68.89 (CH_2-O), 70.60 (C-5), 76.94 (C-3), 80.35 (C-2), 82.49 (C-4), 108.49 (C-1), 172.28 (C-6).

Differential scanning calorimetry

Differential scanning calorimetry was used to determine the phase transition temperatures that were otherwise confirmed by X-ray diffraction and polarizing optical microscopy and to calculate enthalpies of transition. Differential scanning thermograms (scan rate 2 °C min^{-1}) were obtained using a Mettler DSC TA 3000 system operating on TC10A software.

Optical microscopy

The microscopic examinations were carried out using a Jenapol polarizing microscope fitted with a Mettler hot plate. The textures of the phases were observed by dissolution of the crystals as the temperature was increased.

X-Ray diffraction

The phases were studied in a small angle X-ray scattering apparatus with a linear localizing detector using Cu-Kα1 radiation (λ 1.54 A). With this geometry, the range of scattering vectors **s** was:

$$5 \times 10^{-3} \text{Å}^{-1} < |\mathbf{s}| < 0.12 \text{ Å}^{-1} \quad (1)$$

as given by eqn. (1) with $|\mathbf{s}| = 2\theta/\lambda$, 2θ being the angle between incident and scattered beam. This scattering vector range corresponds to the following *d*-spacing range: $200 > d > 8.3$ A.

The sample was placed in a 1 mm thick cell with Mylar windows, which could be heated from 15 to 100 °C in 0.1 °C increments. A conventional X-ray diffraction apparatus was also employed with the beam focused on a film. This enabled observation of the disordered state of hydrocarbon chains, which is characterized by a diffuse ring of radius 0.238 A^{-1} (4.2 A), similar to that observed with liquid hydrocarbons.

Results and Discussion

Thermotropic behaviour of alkyl D-glycofuranosiduronic acids

Differential scanning calorimetry. The temperatures and enthalpy data for the first heating cycles of alkyl β-D-galactofuranosiduronic acids **1a–d** are given in Table 1. In order to determine potential correlations between stereochemistry and mesomorphic properties, these results are compared with the data for dodecyl α-D-galactofuranosiduronic acid **2c** and those of alkyl β-D-glucofuranosiduronic acids **3b–c**. It should be noted that in all the thermograms, the peaks for various transitions were found to be sharp, indicating the high purity of materials.

The data indicate that the transition temperatures presented in Table 1 for octyl, decyl, dodecyl and tetradecyl homologues **1a–d** increased as a function of the alkyl chain length and that clarification temperatures increased more rapidly than melting temperatures (T_{sm}) thus displaying more important mesophase areas in the case of long chain compounds.

Interestingly, the α-anomer **2c** melts to the liquid crystal state and then to the isotropic liquid at about the same temperature as its β-anomer **1c**. Furthermore, the galactosides **1b–c** display a higher clearing point than their glucosiduronic epimers **3b–c**. The clearing point enthalpies for all compounds are relatively small in comparison with their melting enthalpies and the measured values are of a similar magnitude to those found in conventional liquid systems which exhibit smectic to isotropic liquid transitions.[3–8]

The results for the dodecyl and tetradecyl compounds **1c** and **1d** are a little different from those of the octyl and decyl homologues **1a** and **1b** insofar as a crystal-to-crystal transition occurred at respectively 41 and 57 °C probably due to dislocation of lipophilic chains. Furthermore, after the first heating cycle, only a clarification phenomenon was observed when the temperature was increased again.

These results also allow a comparison between pyranose

Table 1 Transition temperatures, enthalpy values (in brackets) for (alkyl D-glycofuranosid)uronic acids and for dialkyluronic derivatives, long-d_s spacing of the crystal phase, d_{sm} spacing of liquid-crystal phase and l_s the extended chain length

product[a]		crystal-to-crystal transition/°C (ΔH/J g^{-1})	melting point/°C (ΔH/J g^{-1})	clearing point/°C (ΔH/J g^{-1})	l_s/Å
1a	R = $CH_3(CH_2)_7$	—	86	100	11.6
	d_s = 20.4 Å d_{sm} = 26.0 Å		(89.17)	(2.52)	
1b	R = $CH_3(CH_2)_9$	—	91	136	14.2
	d_s = 22.9 Å d_{sm} = 29.6 Å		(103.11)	(3.36)	
1c	R = $CH_3(CH_2)_{11}$	41	95	143	
	d_s = 25.9 Å d_{sm} = 32.9 Å	(10.54)	(105.09)	(3.45)	16.7
1d	R = $CH_3(CH_2)_{13}$	57	99	145	
		(20.25)	(111.75)	(3.46)	
2c	R = $CH_3(CH_2)_{11}$	—	96	145	
			(117.91)	(3.21)	
3b	R = $CH_3(CH_2)_9$	—	89	104	
	d_s = 22.5 Å d_{sm} = 27.4 Å		(133.21)	(2.82)	
3c	R = $CH_3(CH_2)_{11}$		92	120	
5	d_s = 33.9 Å d_{sm} = 31.75 Å	57	72	88	
		(23.93)	(90.92)	(14.29)	
6	—	55	75		
		(50.96)	(93.71)	—	
7			83	173	(lit.[11])
8			65	173	(lit.[11])
9			85	170	(lit.[10,12])
			(57.86)		

[a]Estimated lengths of extended molecules (l_{max}/Å): **1a**: 16.1; **1b**: 18.7; **1c**: 21.2; **1d**: 23.7; **5**: 32.3.

and furanose systems. The dodecyl D-glucopyranosiduronic acids **7** and **8** have been previously described by Vill *et al.*[11] whereas dodecyl α-D-galactopyranosiduronic acid **9** was obtained in this laboratory.[10,12] From the transition temperatures of dodecyl compounds **1c**, **2c**, **3c**, **7**, **8** and **9** it can be seen that the furanosiduronic compounds **1c**–**3c** display much lower clearing temperatures than the corresponding pyranoses **7**–**9**. However, the melting temperatures are closer in value except for the α-D-glucopyranoside **8**.

Thermal optical microscopy. Compounds **1a**–**c** display the same behaviour as a function of temperature. At (T_{sm} −30 °C), bright points first appear in the finest crystals and then the surface state of crystals is modified; on further heating the texture changes and crystals progressively lose their faceted shape and become translucent when the temperature increases. At (T_{sm} −3 or −5 °C), crystals become pasty; they are inclined to deformation and they lie down on the microscope glass plates. In this case, the textures observed between crossed polarizers are neither oily streaks nor fans. The characteristic textures of a smectic A* phase appear only after T_{sm} when the sample becomes fluid.

X-Ray diffraction studies of compounds 1a–c and 3b. At room temperature, the diffraction patterns of the three galacturonic compounds **1a**–**c** exhibit fine and intense peaks in the small-angle range which are characteristic of quite crystalline sheet-like structures [as shown in Fig. 1(*a*) for compound **1b**]. As expected, an increase in the chain length leads to an increase in the interlamellar distance d_s (Table 1). The increment per two CH_2 amounts to 2.5 Å, corresponding to the variation of an extended chain length according to Tanford's equation[13] (Table 1). Alkyl chains appear therefore to be extended and interdigitated, practically perpendicular to bilayers. The width of the carbohydrate layer is therefore *ca.* 9 Å. Upon heating a novel peak appears progressively at small angles as shown in Fig. 1(*b*) for compound **1b**. The intensity of this peak increases with temperature while the interlamellar spacing increases [Fig. 1(*b*)–(*c*)]. At 91 °C the diffraction pattern for the latter compound exhibits a single peak [Fig. 2(*d*)] corresponding to a layer spacing d_{sm} of 29.6 Å (to be compared with d_s = 22.9 Å at room temperature) characteristic of a smectic A* lamellar mesophase. The relationship between d_{sm} and the estimated length of the extended molecule (Table 1) allows us to propose for the mesophases a head-to-head bilayer model in which alkyl chains are dislocated with no interdigitization. This phase which appears at 30–35 °C before T_{sm} can be induced by a superficial melting, corresponding to superficial crystal hydration. In this system, a gradual chain melting can be observed as in some phospholipids.[14] Surprisingly, the crystal-to-crystal transition which occurred at 41 °C for the dodecyl compound **1c** (Table 1) did not appear within the diffraction patterns.

We next considered the X-ray results of the glucuronic mesogen **3b** and found that the results were similar to those for the galacturonic epimer **1b**.

All acidic compounds therefore exhibit thermotropic mesophase formation. A fluid smectic A* liquid crystalline phase appears in all cases between the crystal and the isotropic liquid whatever the alkyl chain length, the configuration of the anomeric carbon and the *gluco*/*galacto* configuration. Since hydrogen bonding is involved in stabilization of both crystalline structures and liquid crystalline phases,[15] one can envisage mesophases in which the lamellar structures are stabilized *inter alia* by strong hydrogen bonding of the carboxylic groups through dimerization of layers or linkages between neighbouring carboxylic groups in a single layer. The results obtained therefore allow comparison to be made between uronic derivatives and their neutral counterparts. The alkyl glycopyrano- and furano-sides have been previously reported[4,16] to exhibit analogous thermotropic properties. The comparison of published results with the present data demonstrates that the uronic derivatives exhibit higher transition temperatures than the analogous neutral derivatives, as might be expected.

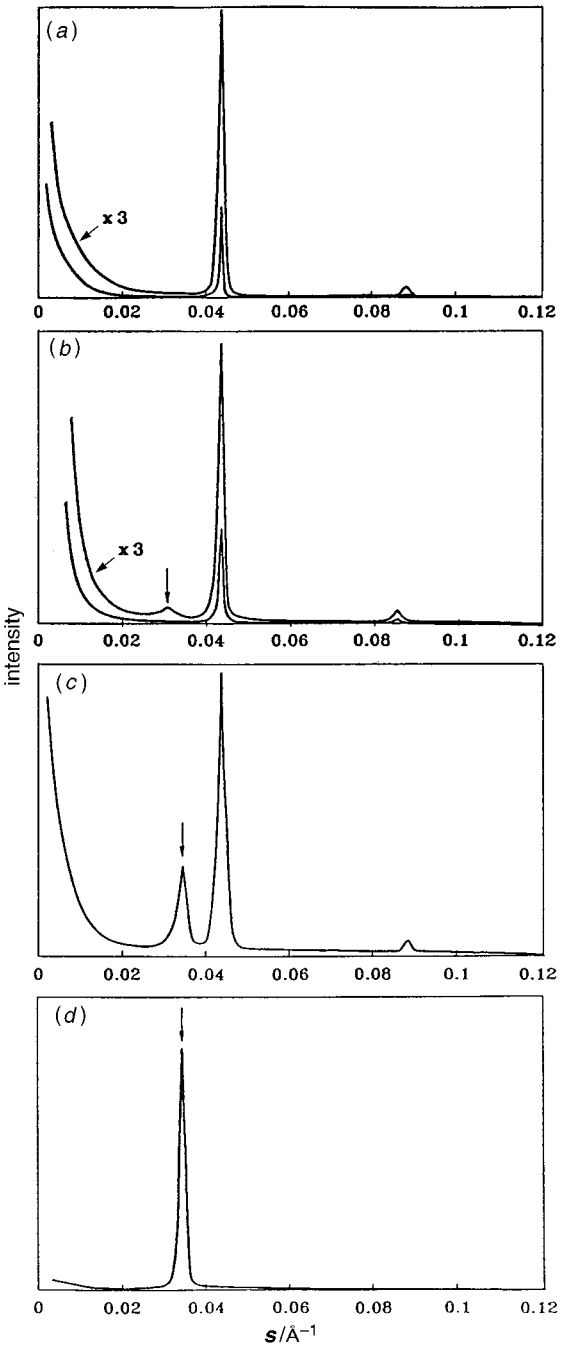


Fig. 1 X-Ray diffraction diagrams for compound **1b** during heating; (*a*) 20, (*b*) 65, (*c*) 82 and (*d*) 91 °C

Similar comparisons can also be made between the thermotropic properties of furanosiduronic compounds **1c**–**3c** and their pyranosiduronic isomers **7**–**9**. It clearly appears from the data that (*i*) the furanosiduronic compounds **1c**–**3c** display much lower clearing temperatures than the pyranoses **7**–**9** and (*ii*) the melting temperatures are closer in value except for the glucopyranoside **8**. The pyranosidic compounds thus exhibit much broader mesophase domains than their furanosidic isomers. These results therefore show that the flexibility of the furanose ring and the availability of both hydroxy and carboxy groups for hydrogen bonding with neighbouring molecules markedly affect the stability of mesophases.

Thermotropic behaviour of dialkylated furanoside uronic derivatives 5 and 6

The temperature and enthalpy data derived from the differential scanning calorimetry thermograms for the first heating cycles of compounds **5** and **6** are given in Table 1. The glucuronic derivative **6** displays two high enthalpy crystal-to-crystal and melting transitions but no evidence of liquid-crystal formation was obtained upon heating. Conversely, the galacturonic derivative **5** exhibits a solid state transition at 57 °C and two melting and clearing transitions respectively at 72 and 88 °C. The latter transitions were also detected by X-ray diffraction experiments and thermal polarisation microscopy but no evidence for a crystal-to-crystal transition could be found. The 33.9 A spacing of the crystalline phase compared with the estimated length of the extended molecule (Table 1) suggests a non-interdigitizing molecular packing in which the hydrophobic tails are fully extended. The 31.7 Å parameter of the mesophase and the birefringent texture observed under the microscope are therefore compatible with a monolayer packing in which the hydrophobic tails are separated from each other with respect to the galactosyl moiety. Such supramolecular structures have been previously proposed by Thiem and coworkers for frustrated glycosides.[17] This model allows therefore comparison to be made between the galactosyl compound **5** and its *gluco* epimer **6** which does not exhibit any mesophase upon heating. In contrast to **5**, compound **6** bears two alkyl chains on the same side of the carbohydrate moiety determining on obtuse angle. Such a kind of structure may therefore be related to alkyl 6-*O*-acyl-α-D-glycopyranosides which have been shown previously[8] to exhibit unstable mesophases due to a low freedom of movement.

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