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Cholesterol as a Versatile Platform for Chiral Recognition

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Key Words: chiral recognition; supramolecular; cholesterol; boronic acid; crown ether

Abstract: The cholesterol moiety is the perfect host. The environment it creates changes to accomodate each new guest. Cholesteric liquid crystals change colour. Cholesteric gels have different phase transition temperatures. Cholesteric LB films change the area they cover.

Introduction

Chiral recognition is at the heart of all natural processes. Unlike Nature, systems able to directly convert chiral interactions into readable outputs are scarce, artificial systems have traditionally relied on the indirect measurement of chiral recognition, employing such methods as association constants, membrane transport rates, etc.[1]

Since cholesterol easily forms supramolecular aggregates, it offered itself as a versatile platform on which to build devices capable of molecular recognition, through environmental amplification. With our work we have shown that the cholesterol can be employed in supramolecular systems such as: Liquid Crystals[2-5], Gels[6] and LB films.[7,8]

From the knowledge we gleaned a general design strategy can be proposed from which cholesteric systems capable of detecting any chiral species can be devised. The essentials of such a device are few; the main requirement is that the recognition site be rigidly linked to a cholesterol moiety (Figure 1). In our work we have successfully employed two recognition sites one a "crown" (chiral cation detection) and the other a "boronic acid" (chiral diol detection).

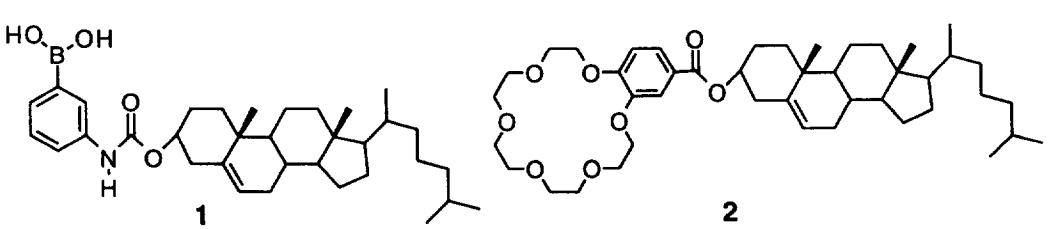

Figure 1. Structures of cholesteric "boronic acid" and "crown"

Liquid Crystal Systems

Differentiation by colour should be the magnum opus of chiral discrimination. Sadly, the number of approaches to chiral detection using colour are few; to our knowledge Kaneda et al.[9] and our group are the only groups with functional approaches. Kaneda employs chiral azophenolic acerands in which chiral point interactions can be directly "read" by a colour change. Our method is somewhat different and employs a chiral environment as outlined in the introduction. The use of cholesterol as a chiral environment is not a new idea. Many people have studied and attempted to control chiral reactions in liquid crystals,[10-12] but control of chiral reactions in the cholesteric chiral medium has met with only mediocre success.[12] With our approach, we do not try to control the guest but allow the guest to control the chirality of its environment.

Our first foray into this realm of environmental amplification employed a cholesteric crown ether (**2**). When chiral ammonium ions (particularly, those of α-amino acid esters) are added to a ternary blend of cholesterol chloride, cholesterol nanoate, and steroidal crown ether, the helical pitch of the mixed cholesteric liquid crystal is altered resulting in a visible colour change. The direction of the induced shift is indicative of the absolute configuration of the added ammonium ions.[4]

With saccharides and the cholesterol boronic acid similar doping experiments to those carried out with the crowned cholesterol produced similar colour changes.[13] The interaction of boronic acid with saccarides produces a cyclic boronate ester, this covalent linkage allows us to isolate the complexes. Once the complexes are isolated the opportunity exists to examine structure activity relationships. Such an opportunity was not available with ammonium ions.

Solvent extraction of saccharides was carried out at 25 °C using solid-liquid ($CDCl_3$) extraction. As much by serendipity as by design the cholesterol boronic acid was a much more efficient saccharide extractor than the boronic acid previously used;[14] complete extraction was observed for all monosaccharides. Selection within the saccharides similar to that previously observed was seen in the rate of extraction, the less favorable saccharides taking longer to be completely extracted. However, after 48 h all the saccharides investigated were completely extracted

Characterisation of the extracted saccharides could be achieved employing just ^1H NMR ($CDCl_3$). The molar ratio of the extracted species could be conveniently estimated by the integral intensities of selected proton resonances of the monosaccharide versus either the phenyl or the alkenyl protons of compound **1**. In the case of the D-fucose complex the anomeric proton of the monosaccharide at δ 5.9 ppm and the alkenyl proton of compound **1** at δ 5.4 ppm were employed. In general all the saccharides form a 1:2 complex with compound **1**. Two main structural classes exist for the extracted monosaccharides, either, two five membered rings are formed (1,2-3,4 complex), or, a five and a six membered ring are formed (1,2-4,6 and 2,3-4,6 complexes: Figure 2).

trans-Six membered rings are less stable than the five membered ring.[15] From Figure 2 it can be seen that this chiaroscuro analysis falls short of describing the actual situation. Some systems that could have formed perfectly good five membered rings opt for the six membered ring alternative. Why do these systems prefer the six membered ring? With galactose and talose the ring is a cis rather than trans six membered one, and it is known from decalin that the cis fused six membered ring system is conformationally flexible whereas the trans system is fixed. This conformational lability may provide enough advantageous entropic energy to tip the balance in favor of the six membered ring. With allose and mannose a trans six membered ring is formed, but this may not be an inherent preference for the six membered ring but rather a preference for the 2,3 five membered ring over the 1,2 five membered ring. In a 1:2 complex once the 2,3 five ring has been formed the only choice remaining is the formation of a trans six membered ring.

The induced shifts produced by the extracted monosaccharides in a cholesteryl chloride, nanoate composite liquid crystal[16] are given in Table 1.

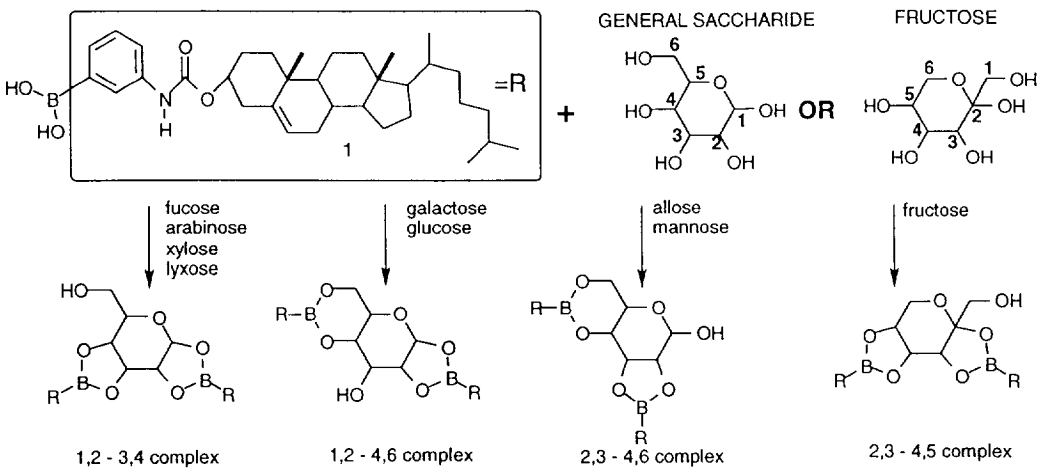

Figure 2. Structures of 2:1 complexes (**1**/monosaccharide)

Table 1. Shifts in the reflectance maxima caused by added 2:1 complex: **1**/saccharide

Group	2:1 Complex **1**/saccharide	Induced shift[a] relative to compound **1**	
		mol% 2.4[b]	*mol% 1.2*[c]
	D-fucose		*123±13*
	L-arabinose		*27±8*
I	L-fucose	*-164±12*	*-95±6*
	D-arabinose	*-82±10*	*-45±6*
	D-fructose	*-37±11*	*-23±11*
	D-glucose	*91±10*	*42±12*
	D-allose	*69±10*	*19±10*
II	D-xylose		*34±15*
	L-glucose	*-71±10*	*-61±6*
	D-mannose	*-3±10*	*5±6*
	D-galactose	*-44±10*	*-33±11*
III	L-galactose	*-17±10*	*-21±7*
	D-talose	*3±11*	
Blank	2-deoxy-D-galactose	*6±15*	

[a]Shifts are the average of five repeats, errors given are the maximum deviation from the mean. [b]At 2.4mol% compound **1** has a base reflectance of 625±10. [c]At 1.2mol% compound **1** has a base reflectance of 650±6.

Analysis of Figure 2 and Table 1 shows that saccharides with similar structural features induce shifts in the same sense (Figure 3). Within the saccharides extracted three such structure/shift group relationships exist, the first group includes saccharides with two (*cis*) five membered boronate ester rings (Group I), when the first ring (following normal saccharide numbering) is down with respect to the saccharide plane and the second is up a red shift is induced (D-fucose, L-arabinose). Conversely, when the first ring is up and the second is down, a blue shift is induced (D-fructose, D-arabinose, L-fucose). The next structure/shift sub-group contains saccharides with one cis five membered ring and either a *trans* five or a *trans* six membered *trans* ring (Group II). When the first ring (*cis* five membered) is down a red shift is induced (D-glucose, D-allose, D-xylose),

and conversely when this ring is up a blue or no shift is induced (L-glucose, D-mannose). The final structure/shift group is the most anomalous; the saccharide contains both a *cis* five membered ring and *cis* six membered ring (Group III). When the first ring is either up or down a blue shift is induced (D-galactose, L-galactose), D-tallose induces no shift. This anomalous behaviour may be a result of the conformational lability of the *cis* six membered ring, or, as explained below the behaviour may not be anomalous if a threshold must be overcome before a shift in the pitch occurs.

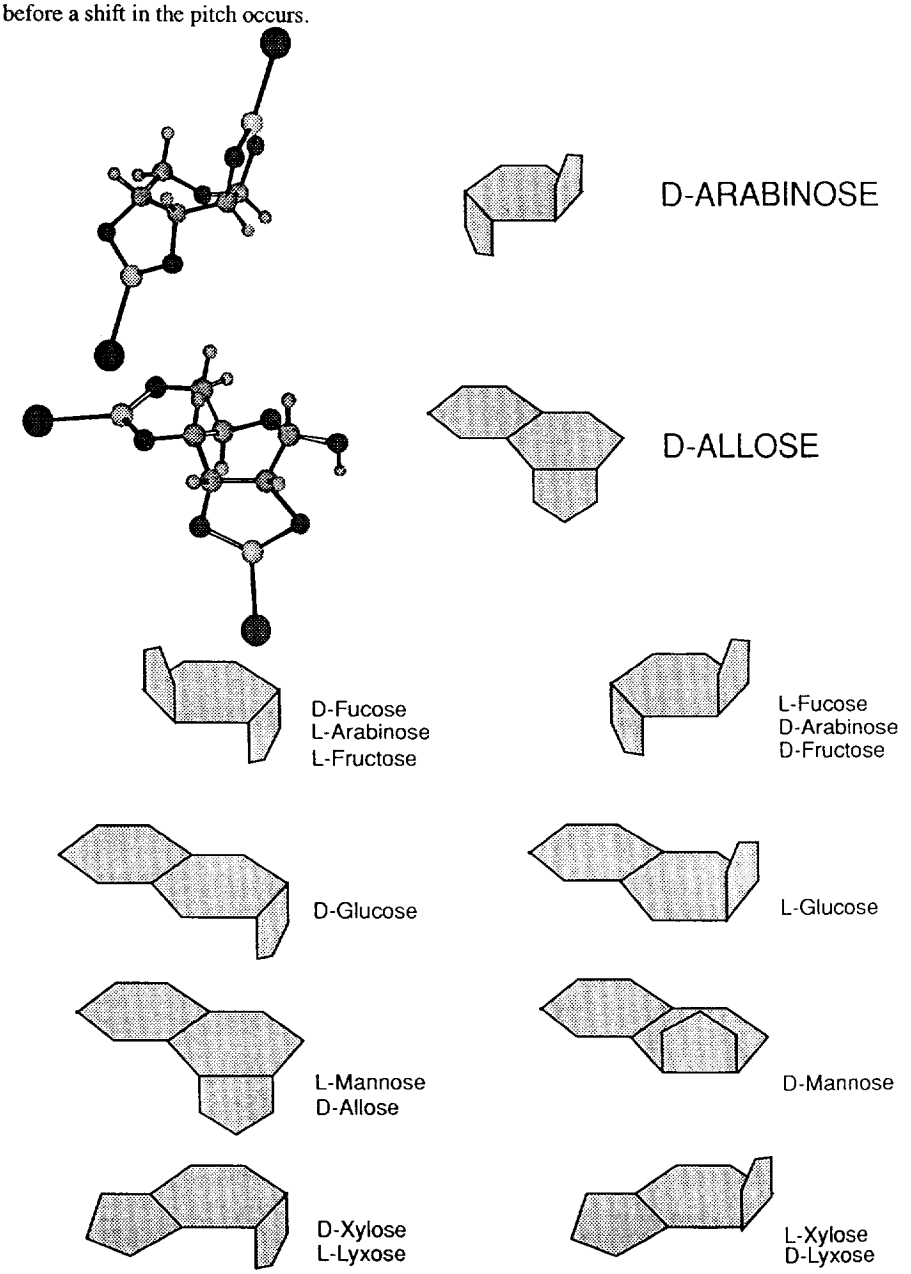

Figure 3. Cartoon representation of 2:1 complex, with two calculated structures for comparison.

From the above qualitative structural analysis and the result that the 1:1 complex of 2-deoxy-D-galactose causes no shift, the spatial disposition of two cholesteryl boronic acid moieties is the driving force for the change in the cholesteric pitch. Structural analysis of the complexes utilising a molecular orbital calculation[17-19] reveals a quantitative relationship between the magnitude and direction of the induced shift and the angle between the phenyl planes of the two boronic acid moieties (Figure 4). For the correlation depicted in Figure 4, one apparent anomaly needs to be clarified. Why are blue shift additives "effective" at all angles, but those compounds inducing a red shift have a threshold value of about 40° (D-fructose)? This can be easily explained by the inherent twist of the support liquid crystal; complexes that add to this inherent twist cause blue shifts, and those that subtract cause red shifts, with D-fructose (40°) acting as the effective zero or threshold.

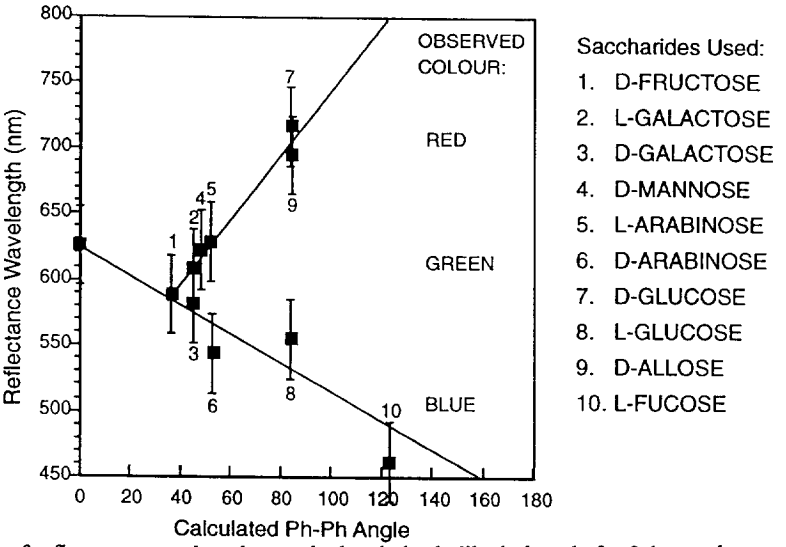

Figure 4. Plots of reflectance wavelength *vs.* calculated ph-ph dihedral angle for 2:1 complex.

Gel System

Recently a new class of cholesterol-based gels, held together by weak hydrogen bonding or van-der-Waals interactions were reported.[20-22] Our interest was sparked, since we have previously studied cholesterol derivatives bearing crown ether, azobenzene or boronic acid moieties.[2,5,23-27] Our continuing theme is the development of signal-responsive chemistry; employing molecular transducers capable of translating host-guest interactions into readable outputs. Gelation has provided us with a new medium in which to explore such interactions. We met with an early success; the sol-gel phase transition temperature (T_{gel}) can be controlled by both metal cations and photo isomerization of the azobenzene moiety.[26]

As mentioned in the preceeding section cholesterol-bound saccharides have a dramatic influence on the pitch length in mixed cholesteric liquid crystals.[5] Addition of 2 or 3 mol% of the 2:1 saccharide complex to a composite liquid crystal membrane alters the pitch in a direction relative to the absolute configuration of the complexed saccharide. This change could be read-out by eye as a colour change in the liquid crystal.

The gelation test was carried out as follows: the complexes (0-5 wt%) were mixed with solvent in a septum-capped test tube and the mixture was heated until the solid was dissolved. The solution was cooled to room temperature (G in Table 1 denotes that a gel is formed at this stage). In the case that a gel was not formed at room temperature, the solution was cooled in a refrigerator (at -6 °C) for one day (Gc in Table 1 denotes that a gel was formed at this stage). The results are summarized in Table 2.

Inspection of Table 2 reveals an interesting general trend: optical pairs of saccharides lie at different points along a path of increasing molecular interaction; the path from solution to crystallinity. From our previous work

with composite liquid crystal membranes red shift complexes increase the pitch and blue shift complexes decrease the pitch of the liquid crystal membrane. Obviously factors that work to increase the pitch act to reduce molecular interaction, likewise a decrease in pitch can be correlated with an increase in molecular cohesion. With carbon tetrachloride as solvent: L-lyxose (gel), D-lyxose (insoluble); D-xylose (gel), L-xylose (insoluble); L-mannose (gel), D-mannose (insoluble); D-glucose (solution) and L-glucose (recystalizes). For the chiral pairs of complexes the former are predicted to have weak cohesion from the liquid crystal work (red shift), and the latter strong intermolecular cohesion (blue shift). This prediction clearly holds under this set of conditions, and from further inspection of Table 2 it can be seen that this is a general trend for all solvents.

Table 2. Results of the gelation tests carried out with monosaccharide complexes[a]

Solvent	Lyxose		Xylose		Mannose		Glucose		Galactose	
	D-Blue[b]	L-Red[b]	D-Red[b]	L-Blue[b]	D-Blue[b]	L-Red[b]	D-Red[b]	L-Blue[b]	D-Blue[b]	L-Red[b]
Hexane	SW	SW	I	I	I	I	I	I	I	I
Benzene	G	G	G	G	S	R	S	I	G	G
Toluene	G	G	G	G	I	G	S	I	G	G
Dichloromethane	G	G	G	I	I	Gc	S	I	G	Gc
Chloroform	G	G	G	G	Gc	G	S	I	S	S
Carbon disulfide	G	G	G	SW	G	G	I	I	S	S
Diethyl ether	I	S	SW	I	R	S	I	I	S	S
Tetrahydrofuran	S	S	S	S	I	S	I	I	S	S
1,4-Dioxane	G	S	S	G	S	S	S	S	S	S
Ethyl acetate	S	S	R	R	S	S	R	I	S	S
Acetone	R	S	R	R	R	R	R	R	I	R
Methanol	R	R	R	I	I	I	I	I	I	I
Ethanol	S	S	S	I	R	R	R	I	R	R

[a][Gelator]=0.1-5 wt%; Gel formed when cooled to 23 °C (G) or cooled in a refrigerator to -7 °C (Gc); Gel not formed because of crystallization (R), soluble (S), or insoluble (I), SW=swollen.
[b]Colour induced in composite liquid crystal membrane.

With the monosaccharides lyxose and xylose in certain solvents both isomers form gels, but the relative stability of the gel is not the same. The stability of the gel can be conveniently ascertained by plotting the sol-gel phase transition temperature versus mol% of the complex (Figure 5). From Figure 5 it is clear that L-xylose and D-lyxose have strong intermolecular interactions (blue shift) whereas D-xylose and L-lyxose possess weak intermolecular interactions (red shift). For further evaluation of the gel phase both SEM (Figure 6) and CD spectroscopy were preformed on the gels formed with D- and L-xylose complexes. The CD spectra of the optical pairs are inverted, implying a different chirality for the gels. However, it is unclear if the band observed is a simple single Cotton or an exciton band, the absolute chirality of the gels is therefore not assigned. The SEM pictures (Figure 6) show that open fibrous gels are formed by these complexes; twists are also clearly visible but these strucures are too large for individual fibrils and so must be the result of multiple copies intertwining (super helixes). Both the CD and SEM results confirm that the cholesterol moiety is preforming a similar task in the gel and liquid crystal system; holding together a chiral helix.

In corollary, this work represents a rare example of monosaccharide gelation. Also, the gelation ability of the complexes is controlled in a predictable manner by the chirality of the monosaccharide. This description of saccharide chirality is general since it is confirmed by the predictions made in the liquid crystal system.[5]

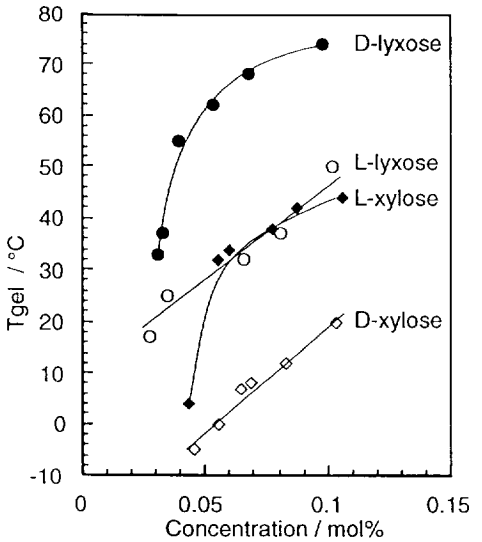

Figure 5. Gel-solution phase transition temperature (*Tgel*) in chloroform *vs*. mol% of complex

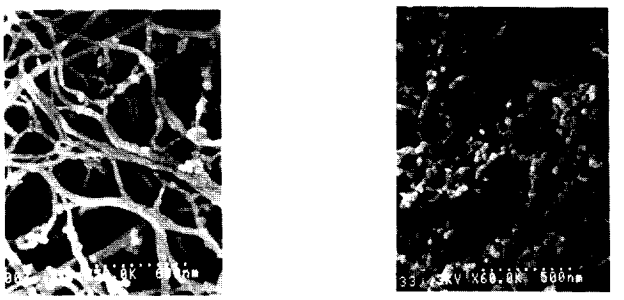

Figure 6. SEM pictures of the gels formed in benzene from D-lyxose (right) and L- lyxose (left).

LB Film Systems

Recently great interest has developed around the application of monolayers formed at the air-water interface to molecular recognition.[28-30] Of particular interest is the potential application to chiral discrimination: chiral guest molecules in the subphase interact with chiral amphiphilic compounds forming the monolayer and the resultant "diastereomeric complexes" change the π-A isotherm in an asymmetric manner.[31, 32] It was recently demonstrated that certain cholesterol derivatives (natural chiral source) form beautiful monolayers.[33]

Addition of D-PheOMe•HCl to a monolayer of **2** induced a large expansion of the monolayer; when L-PheOMe•HCl (L-phenylalanine methyl ester hydrochloride) was added only a small expansion occured (Figure 7). Chiral discrimination was also achieved for other α–amino acid derivatives (Table 3), but the largest effect was observed with PheOMe•HCl. Why is such chiral discrimination of α-amino acid derivatives that is difficult with conventional chiral amphiphilic compounds readily realized in a cholesterol-based monolayer system?

It is certain that the NH_3^+ moiety is bound to the 18-crown-6 ring. As the α-amino acid residue CH_2R is more hydrophobic than the CO_2Me group, this group should be trapped in the hydrophobic cholesterol stacks. In this binding mode, the cholesterol skeleton with a wide chiral plane can more advantageously constrain the orientation of α-amino acid derivatives than conventional chiral amphiphiles with simple point chirality. Thus,

the α–amino acid derivatives are recognized at two points (NH_3^+ by the crown ring and CH_2R by the cholesterol plane) by a monolayer of **2** (Figure 8).

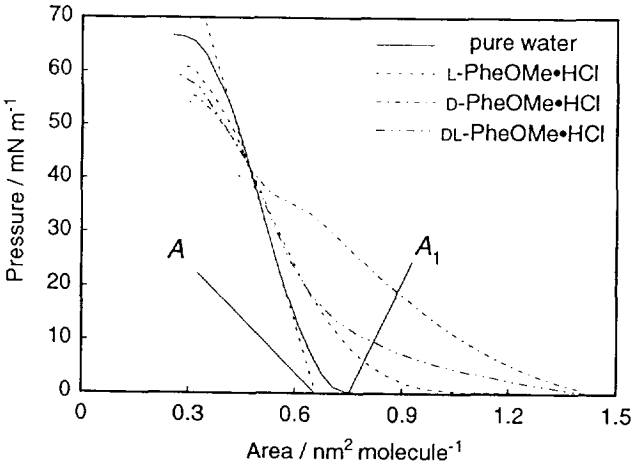

Figure 7. Surface pressure-area isotherms of **2** at 20°C on 100 mM phenylalanine methyl ester hydrochlorides.

Table 3. Limiting area A_0 and lift-off area A_1 of **2** on 100 mM amino acid methyl ester hydrochlorides

	A_0 / nm^2molecule^{-1}		A_1 / nm^2molecule^{-1}	
Amino acid	L-Isomer	D-Isomer	L-Isomer	D-Isomer
Phe	0.72	0.91	1.06	1.44
Ala	0.82	0.79	1.20	1.44
Trp	0.81	0.84	1.34	1.33
Val	0.71	0.77	1.04	1.14

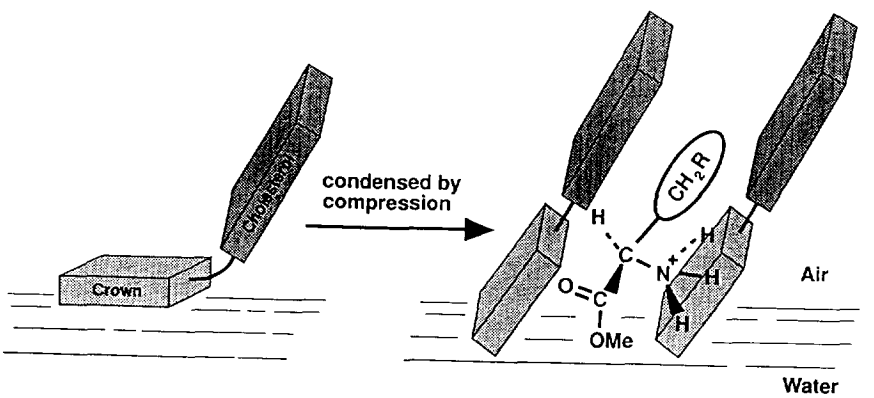

Figure 8. Recognition of an α-amino acid derivative by a monolayer of **2**.

We previously found that cholesteric liquid crystals containing **2** can asymmetrically recognize α-amino acid derivatives: L-isomers stabilize the liquid crystal phase to shorten the pitch length whereas D-isomers

destabilize the liquid crystal phase to elongate the pitch length.[4] Although the monolayer phase is different from the liquid crystal phase, the microscopic environment where one amino acid residue is flanked by two cholesterol planes should be similar to each other. Important is the fact that in both systems D-isomers disorder the cholesterol-based organized phases more efficiently than L-isomers. Presumably, the space formed between two cholesterols fits the asymmetrical shape of L-isomers.

The relationship between molecular structure and physical properties of monolayers of complexes between an amphiphilic, steroidal cholesterol-substituted phenylboronic acid (**1**) and monosaccharides were studied at the air-water interface. Phase transition, compressibility and limiting molecular area of monolayers of **1** in the presence of monosaccharides are correlated with the calculated structures of the phenylboronic acid-monosaccharide complexes. The monolayer of **1** exhibits chiral discrimination towards optical isomers of monosaccharides.

From the ^{1}H-NMR spectra[14] of extracted complexes involving phenylboronic acid **1** and D-fructose or D-glucose as well as from semiempirical molecular orbital calculations (AM1)[5] a stoichiometry of 1:2 (monosaccharide:phenylboronic acid) of the complexes with the monosaccharides in the pyranose form was concluded. The calculation also revealed the ph-ph dihedral angle of several complexes which ranges from 0 to 90^o. For the present study, the complement to 180^o of the ph-ph angle is employed in the discussion, because this 'waterfacing' angle of the phenyl rings illustrates the structure at the air-water interface. Figure 9 depicts the relationship between ph-ph angle and waterfacing angle.[34]

Different from the non-aqueous system, monosaccharides preferably exist as furanoses in boric acid complexes in aqueous alkaline bulk solution, where the boron atom is sp^3-hybridized.[35] Conversely, the pyranose form exists in monosaccharide complexes of **1** in non-aqueous media. For the present study, two series of calculations were taken into account for model compounds of all experimentally studied monosaccharide complexes of **1** in order to determine their waterfacing angle: (i) sp^2-hybridized boron and pyranoses, because these complexes are most stable in non-aqueous solvents and the air-water interface provides an environment distinct from the aqueous bulk solution and (ii) sp^3-hybridized boron atom and furanoses, because these complexes are more stable in aqueous alkaline solution, and the pH of the subphase was higher than pK_a (pK_a *ca.* 9). The calculations are shown in Table 4.

Table 4. Waterfacing angles of the complexes between **1** and monosaccharides in the pyranose or furanose form for the MO-optimized structures.

Saccharide	Binding site	Calculated angle of pyranose complexes	Binding site	Calculated angle of furanose complexes
Xylose	1,2-3,4	153.5	1,2-3,5	93.2
Fructose	2,3-4,5	143.3	1,2-4,6	115.3
Galactose	1,2-4,6	134.6	1,2-5,6	132.3
Mannose	2,3-4,6	131.6	2,3-5,6	166.7
Arabinose	1,2-3,4	126.9	1,2-3,5	103.5
Fucose	1,2-3,4	123.3	1,2-3,5	100.9
Glucose	1,2-4,6	95.8	1,2-5,6	145.5
Allose	2,3-4,6	95.6	2,3-5,6	119.1

It is seen from Figure 10 that the complexes are clearly divided into two groups according to their structure. Those causing a red shift in the cholesteric liquid crystal system and destabilizing it (D-xylose, L-mannose, L-arabinose, D-fucose, D-glucose and D-allose) fit a linear plot in Figure 10A, while those causing a blue shift in the same system and stabilizing it (L-xylose, D-fructose, D-galactose, D-mannose, D-arabinose, L-fucose and L-glucose) fit a linear plot in Figure 10B. A remarkable correlation between monolayer property and molecular structure is observed: the smaller the angle α between two intramolecular cholesterol moieties, the lower is the transition pressure. The monolayers of complexes with a small waterfacing angle α such as the

glucose complex require a lower surface pressure to achieve phase transition and to rearrange both the structure of the complex and packing in the monolayer compared with complexes with a larger angle α, *e.g.* with fructose. Alternatively, we also tried to correlate the transition pressure with the angle for the complexes with furanose-type monosaccharides with the boron atom sp^3-hybridized,[8] because in aqueous bulk solution monosaccharides adopt this form in boric acid complexes.[35] However, there is no correlation between transition pressure and waterfacing angle for the furanose complexes. The difference in correlation suggests that the pyranose form is predominant under the experimental conditions. The monolayer must be providing an environment unlike the bulk aqueous solution. This finding is in agreement with the previously proposed reduced solvating capability of water molecules near the air-water interface.[36]

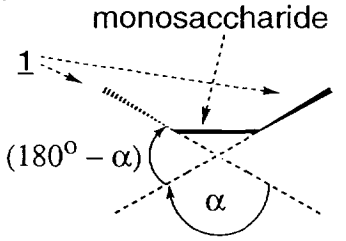

Figure 9. Relationship between ph-ph angle and waterfacing angle α

When the temperature is increased from 293 to 303 K, the phase transition occurs at lower surface pressure. This is contrary to the monolayer behaviour of simple fatty acids and other amphiphiles like cholesterol, where the transition in compressibility occurs at higher surface pressure in case of higher temperature.[37, 38] However, there is a significant difference between the two systems: only physical quantities of the monolayer forming pure amphiphiles depend on the temperature, while temperature-dependent chemical equilibria overlap with the change of the physical properties in case of the boronic acid complexes. From the thermodynamic point of view it is clear that the rearrangement of the chemical structure of the complexes requires a smaller energy contribution from the compression if the energy contribution from the reaction temperature is higher.

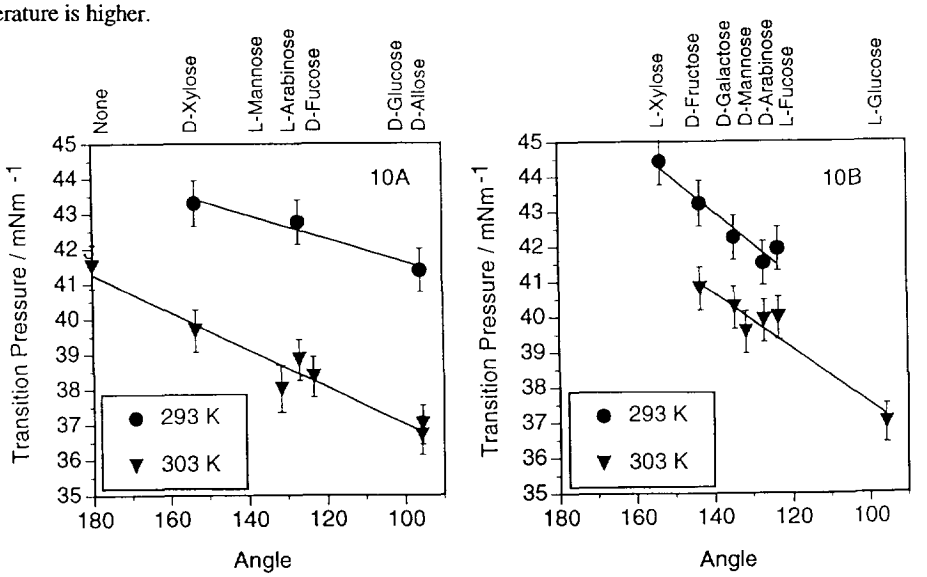

Figure 10. Plots of surface pressure of monolayers of **1** at phase transition vs. waterfacing angle α of the complexes which destabilize or stabilize the cholesteric liquid crystal.

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