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Supramolecular assemblies based on amphiphilic cyclodextrins

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The capacity of two types of amphiphilic β-cyclodextrin (CD) derivatives, heptakis-C6-alkylamido β-CD (I) and heptakis-C6-ammonium tetradecakis-O2,O3-alkyl β-CD (II), to form organized assemblies with L-α-phosphatidylcholine-dipalmitoyl (dppc) and iota-carrageenan is described. These systems are studied using a Langmuir balance. The formation of stable mixed layers between I and II and dppc is observed. The interaction between II and iota-carrageenan leads to a dimunition in the fluidity of monomolecular layers. The physicochemical properties of I are described via variable temperature ^{1}H-NMR studies.

INTRODUCTION

The cyclodextrins (CDs) are cyclic oligosaccharides produced by the action of CGTase on amylose. They are widely available and have been used in a large range of applications.[1] Their basic form is that of a truncated cone in which a hydrophobic cavity is surrounded by two hydrophilic faces composed of the primary OH-6 and secondary OH-2 and OH-3 groups.

Complete selective modification at one face leads to the formation of amphiphilic molecules capable of forming a wide range of organized assemblies, either alone[2–4] or in the presence of other amphiphiles or guest molecules.[5,6]

We consider that the use of such amphiphilic systems, either for the transport of biologically active molecules or as biosensors, will involve mixed molecular systems. In order to obtain certain fundamental information on the systems, we have investigated the physicochemical properties of heptakis-C6-alkylamido β-CD derivatives where the alkyl group is dodecanoyl (**Ia**) or undecenoyl (**Ib**; Fig 1) in terms of the formation of Langmuir layers, and we have used variable temperature ^{1}H-NMR to investigate phase changes in the alkyl chains and also with regard to head group interactions.

We show (via Langmuir compression isotherms) that **Ia** and the O-2, O-3 dodecyl ether of ammonium C6-β-CD (**IIb**) may be incorporated in mixed L-α-phosphatidylcholine-dipalmitoyl (dppc) layers.

The O-2, O-3 hexyl ether of ammonium C6-β-CD (**IIa**) has seven positively charged ammonium head groups and in order to test the capacity of this molecule to act as a potential biosensor we have observed the interaction of this molecule at the air–water interface with iota-carrageenan, a negatively charged polysaccharide widely used in the food industry.[7]

EXPERIMENTAL

The syntheses of **Ia**, **Ib**[8] and **IIa**, **IIb**[2] are described elsewhere.

Variable temperature NMR experiments were carried out using a Bruker ACP200 spectrometer, locked onto the deuterium solvent resonances and using the solvent signal as an internal reference.

The compression isotherms were measured on a Lauda film balance, with triply distilled water. All experiments were repeated at least three times to ensure reproducibility. In experiments to compare the effects of deposition of a mixed amphiphilic system with a two-stage deposition of the individual components, either zero or 10 minutes were left between the deposition of **Ia** and the deposition of dppc; in both cases the same curve was obtained. For experiments involving the interaction of iota-carrageenan with **IIa**, 1:1, 10:1 and 100:1 charge ratio mixtures were measured. In a separate experiment the effects depositing carageenan at the surface or in the water bath were measured.

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RESULTS AND DISCUSSION

The molecular formulae of **Ia** and **IIb** are given in Figure 1. The molecules represent the two classes of amphiphilic cyclodextrin derivatives: lipophilic modification at the primary face (**Ia**) versus modification at the secondary face (**IIb**). In addition, in **IIb**, positively charged ammonium groups are present at the primary face.

(a) Formation of monomolecular layers

The compression isotherm of **IIa** and **IIb** has already been published elsewhere.[2] For **IIa** the curve is typical of a system in which there is retention of fluid character[9] even at the collapse pressure, with a relatively gentle slope in the compression isotherm. The compression curve of **IIb** is typical for the passage of a compound from a liquid expanded state, through a liquid compressed state, to a solid compact state. The observed A_0 values are 351 Å^2 (**IIa**) and 366 Å^2 (**IIb**), with a collapse area of 260 Å^2 at approximately 50 mN/m.

The curves for **Ia** and **Ib** are given in Figures 2(*a*) and 2(*b*) respectively. The curves both show the expected transitions from liquid expanded to a compact state. The A_0 values are 230 Å^2 (**Ia**) and 220 Å^2 (**Ib**) with a compact state A_0 of 190 Å^2 which is close to the area of β-CD obtained from molecular modelling.[5] The collapse pressures are approximately 55 mN/m.

(b) Variable temperature ^{1}H-NMR

The use of variable temperature ^{1}H-NMR may provide information concerning phase changes and head group–solvent interactions in amphiphilic cyclodextrin derivatives.[3]

In Figures 3(*a*) and 3(*b*) we show the variable temperature of **Ib** in dmso-d$_6$. The low temperature spectrum (20 °C) shows broad peaks for the cyclodextrin resonances, which are typical for aggregated species. At 90 °C these peaks have sharpened considerably as have the resonances arising from the olefin protons.

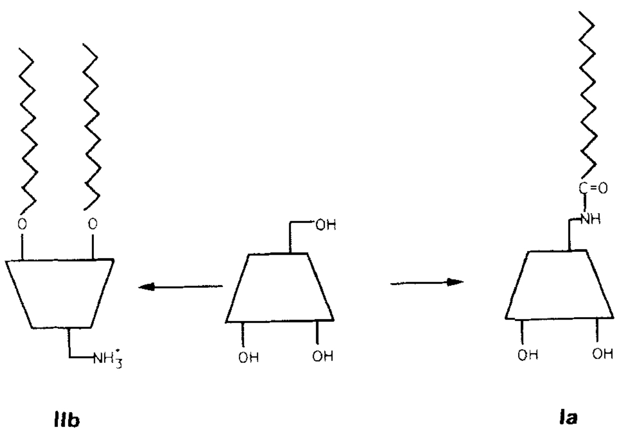


Figure 1 Structures of **Ia** and **IIb** and their relationships to β-CD.

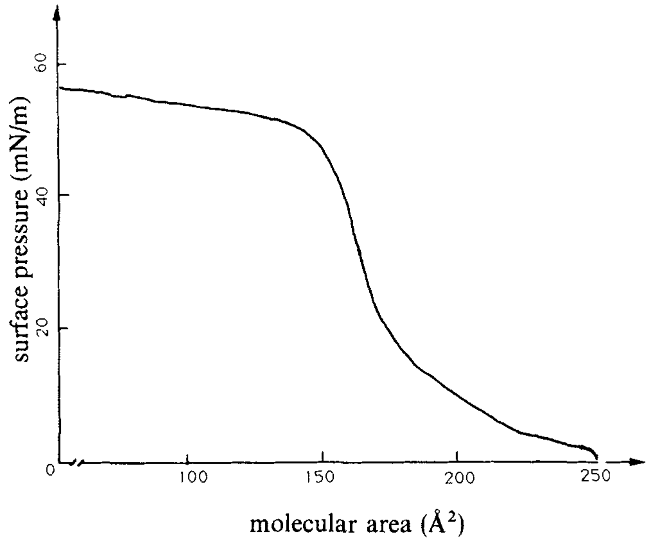


Figure 2(a) Compression isotherm of **Ia** at the air/water interface.

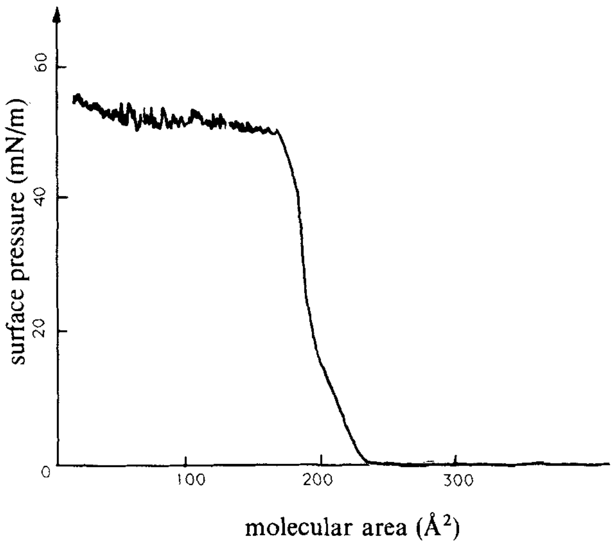


Figure 2(b) Compression isotherm of **Ib** at the air/water interface.

However, much more information may be obtained from plots of the temperature dependence of the chemical shifts, in that phase changes will be accompanied by breaks in the associated slopes. In Figure 4 are shown the temperature dependence of the chemical shifts at OH-3; the resonances are highly temperature dependent. Such behaviour is typical of protons in contact with the solvent. If the system is then present as aggregates, these will be in a bilayer structure with the polar OH groups directed towards the solvent, as has been observed for the alkylamino β-CD amphiphiles.[10]

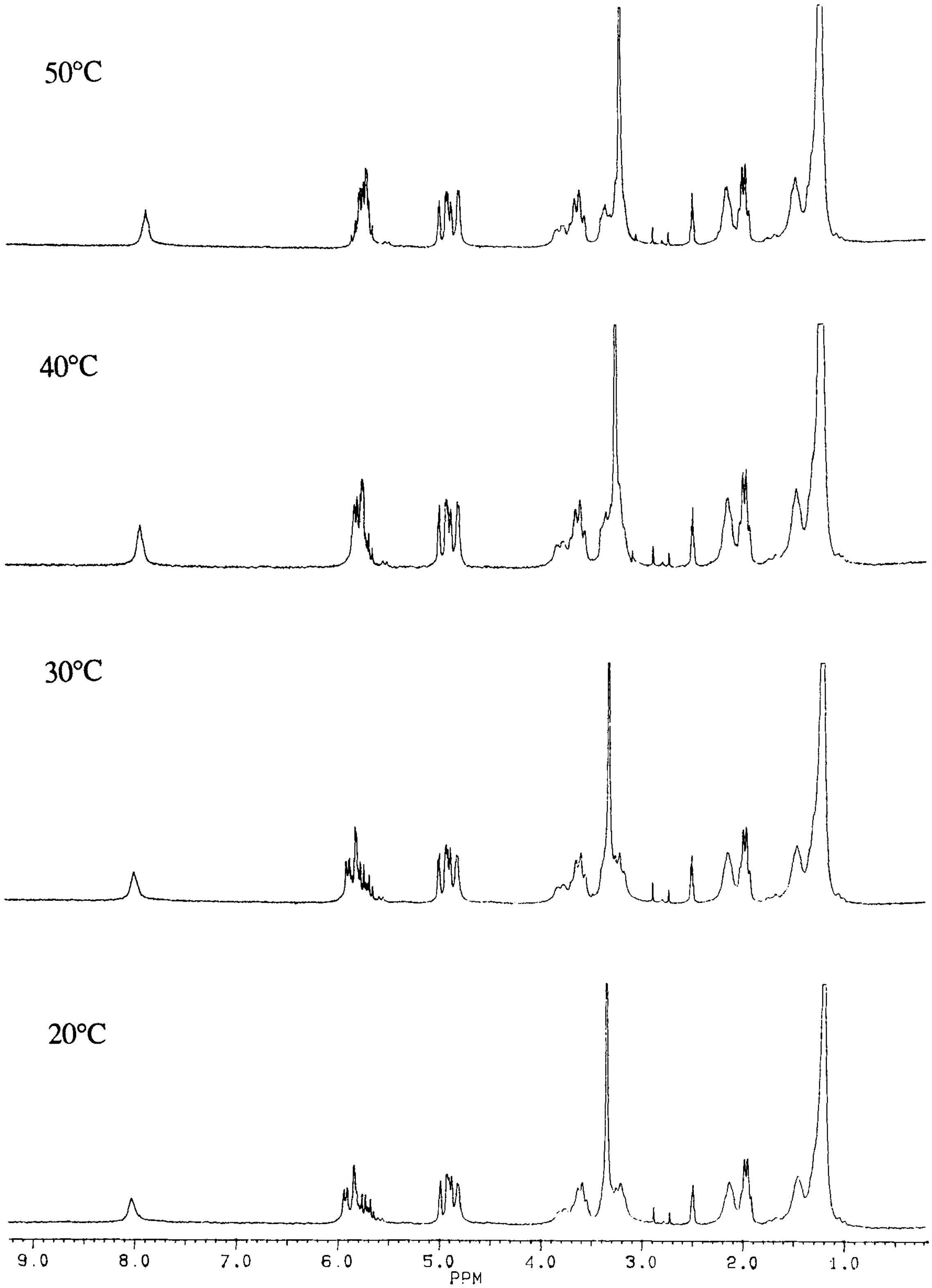


Figure 3(a) More variable temperature spectra of **Ib** in dmso-d_6.

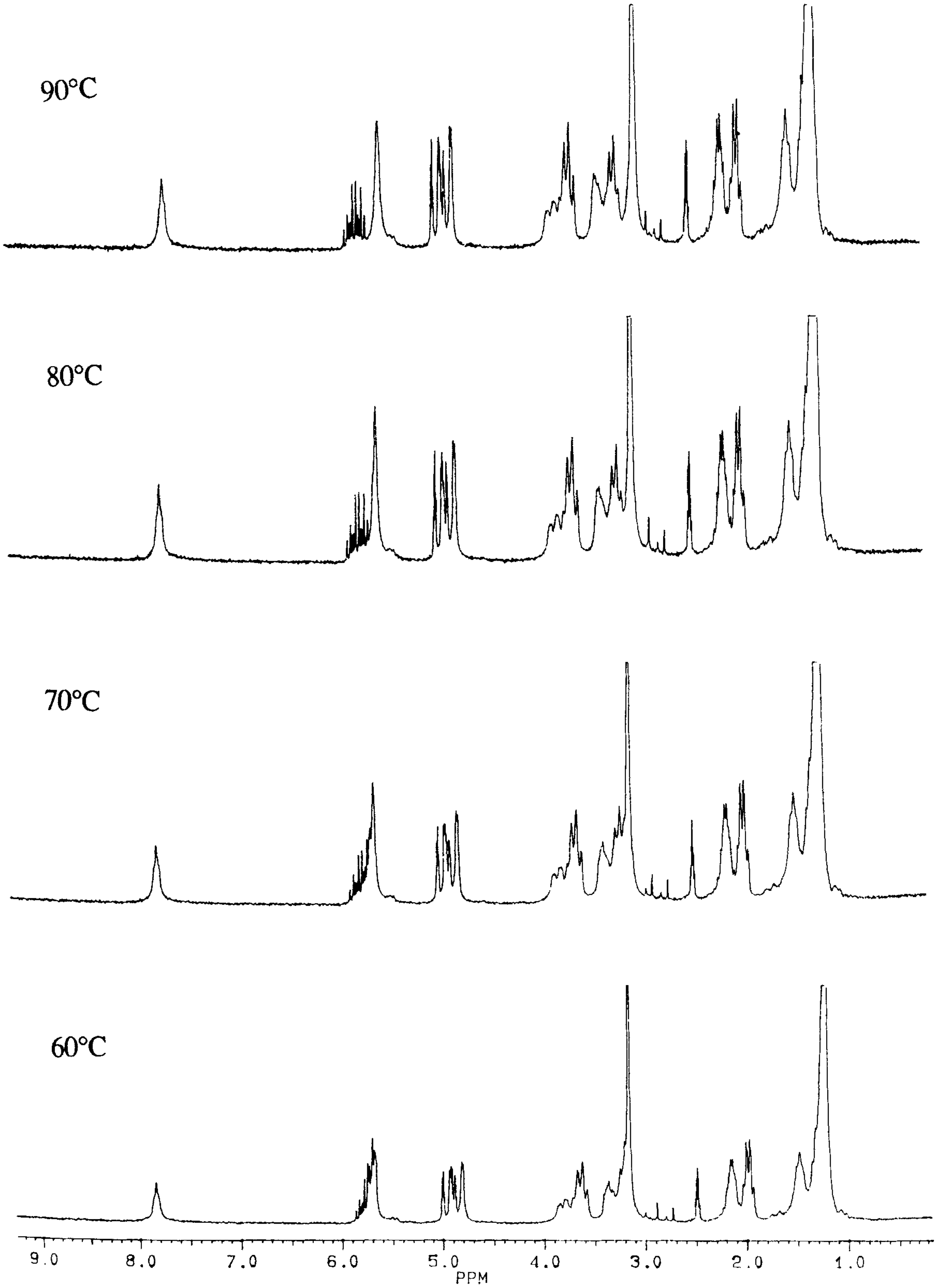


Figure 3(b) Variable temperature spectra of **Ib** in dmso-d_6.

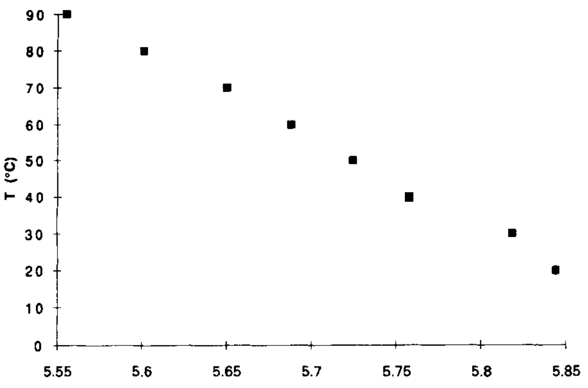


Figure 4 Temperature dependence of the chemical shifts of OH-3 in **Ib** in dmso-d_6.

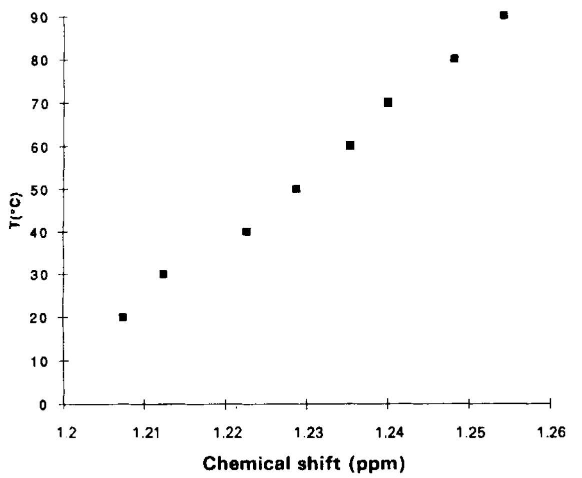


Figure 5 Temperature dependence of the chemical shifts of CH2 groups in **Ib** in dmso-d_6.

In Figure 5 is shown the temperature dependence of one of the CH2 chain groups. As can be seen there exists a discontinuity between 35 and 45°C, as is seen for the hydroxy protons, which is due to a phase change in the chain, probably a passage from gel to liquid. Similar effects have been observed for the alkylamino CDs. That this phase change occurs above room temperature is in agreement with the compression isotherm which shows the presence of a compact (solid) state.

(c) Mixed monolayers

In Figure 6 is shown the compression isotherms of a 50% **Ia**, 50% dppc system along with the isotherm of pure **Ia**. In Figure 7 is shown the variation of the observed molecular area as a function of percentage **Ia** in the mixed syste. Figure 7 shows that there is a clear linear relation for surface area versus % **Ia**. This suggests that **Ia** and dppc form an ideal mixture in which there is no decrease in the stability of the monolayer. That the mixture remains apparently ideal at low concentrations of dppc suggests that no inclusion of dppc occurs within the amphiphilic cyclodextrin cavity.

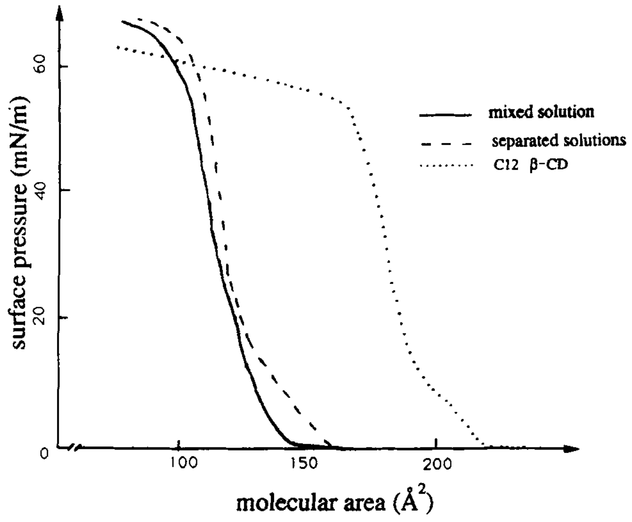


Figure 6 Compression isotherms for 50% dppc: 50% **Ia** systems at the air/water interfaces, showing the effect of two-stage deposition versus deposition of a mixed solution.

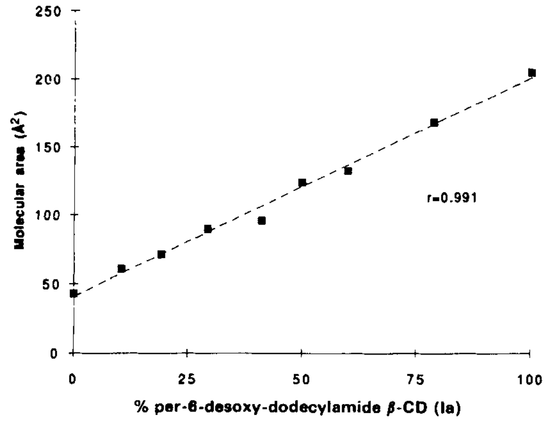


Figure 7 Relationship between observed molecular area and percentage composition of **Ia**.

In Figure 6 it is interesting to note that the form of the compression isotherms for the deposition of a mixed solution and that of a two-stage deposition (**Ia** followed by dppc) are not equivalent. The compression isotherm of the two-stage deposition resembles more closely that of **Ia** and this may arise from formation of aggregates of **Ia** at the air-water interface prior to compression.

In Figure 8 is shown the compression isotherm of 90% dppc and 10% **IIb**. The curve is intermediate between **IIb** and dppc,[9] with only the expected increase in the observed molecular areas with respect to dppc

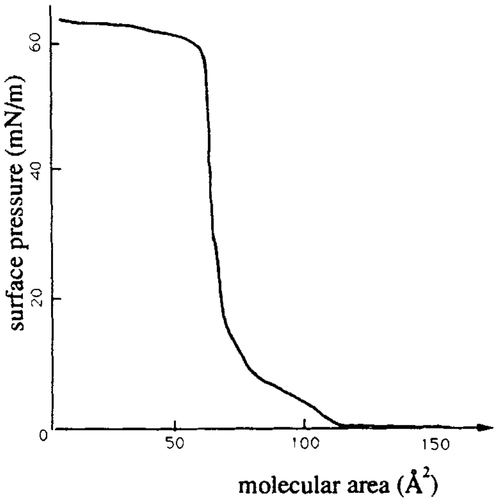


Figure 8 Compression isotherm of a 90% dppc: 10% **IIb** mixture at the air/water interface.

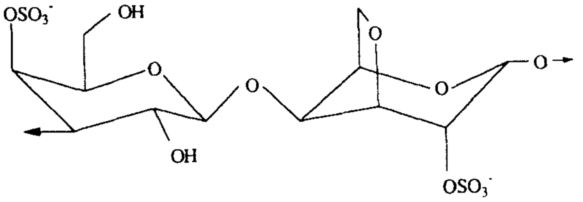


Figure 9 Structure of iota-carrageenan.

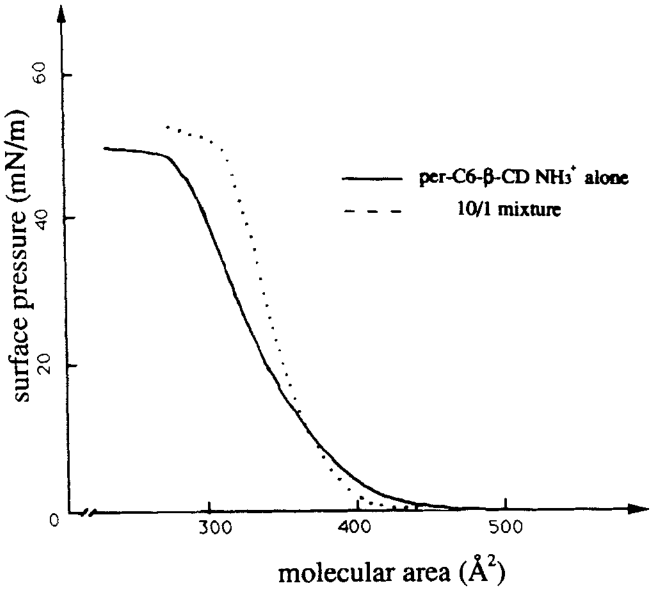


Figure 10 Compression isotherms of **IIa**, and **IIa** in the presence of 10 equivalents of iota-carrageenan.

alone. In view of the possible utilization of such a mixed system as a biosensor, it is noteworthy that no decrease in stability of the dppc layers occurs in the presence of a highly charged amphiphile.

From the above results it is shown that **Ia** and **IIb** may be inserted into monomolecular layers of dppc without decreasing the stability of such layers. The use of deposition of mixed solutions allows precalculation of the obtained apparent molecular area and constant variations in the slopes of the isotherms.

(d) Towards biosensors

If amphiphilic CDs are to be used as biosensors, an interaction between the CD and the biomolecule must occur and also this interaction must lead to a change in the physicochemical properties of the amphiphile.

In order to test this possibility the compression isotherms of **IIa** in the presence of iota-carrageenan were studied. Iota-carrageenan is an anionic polysaccharide whose structure is given in Fig 9 and we may thus hope that strong electrostatic interactions will occur between the positively charged head groups of **IIa** and the polysaccharide.

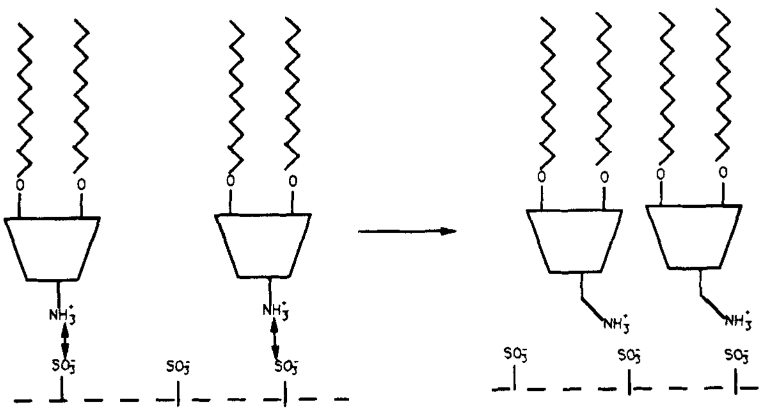
In Figure 10 is given the isotherm of a 10:1 mixture in which the iota-carrageenan had been spread onto the water surface. Although the polysaccharide is water soluble it is probable that concentration gradients exist with higher values observed close to the surface. It is evident that the interaction occurs and modifies the physical properties of **IIa**. The slope of the compression isotherm is consistent with an increase in the rigidity of the organized assembly during the change from an expanded to a compact state – this may be explained by the electrostatic interactions between **IIa** and iota-carrageenan creating 'friction' during the process of forming a close packed structure.

A similar but smaller effect is observed for a 1:1 ratio of **IIa** to iota-carrageenan.

If the carrageenan is injected into the solution and not placed on the surface, the interactions are reduced and the effects on the curve are diminished. The large effects arising from iota-carrageenan spread on the surface undoubtedly arise from a slow diffusion of this molecule into the solution, thereby creating concentration gradients.

With much higher concentrations of iota-carrageenan a second effect is observed (Fig 11): the apparent molecular area A_0 is increased. Thus, even in the gas state region for **IIa** alone, work is required to compress the molecules. The increased electrostatic interactions lead to an 'ordering' close to the surface and it is possible to propose the formation of a thin layer gel zone. Such gels are typical for carrageenan in bulk cationic solutions.

In terms of potential utilization of these systems as biosensors, this increase in the work function causes an induced signal which may be 'read' as a result of the interactions.



Scheme I

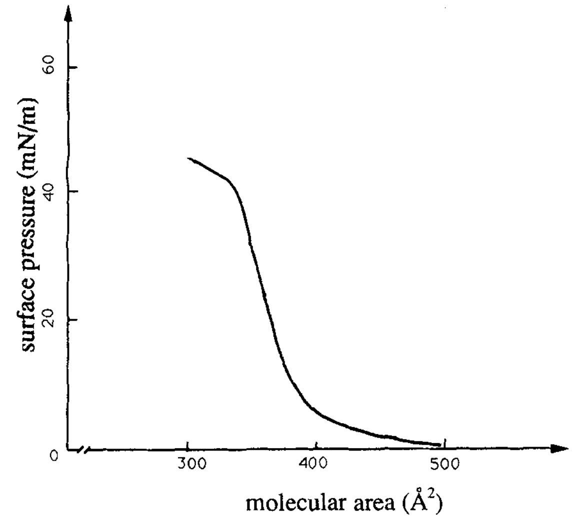


Figure 11 Compression isotherm of **IIa** in the presence of 100 equivalents of iota-carrageenan.

CONCLUSIONS

We have shown that two classes of β-CD derived emphiphiles, the C-6 alkylamides and C-6 ammonium O-2, O-3 ethers, may be incorporated into mixed phospholipid bilayers. The charged ammonium β-CD ethers may be used as biosensors to detect the presence of ionic polysaccharides.

We are currently investigating the interactions of these systems with other polysaccharides and the use of the mixed layers as biosensors.

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