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PRELIMINARY COMMUNICATIONS

Mesomorphic phases obtained through molecular recognition of complementary adenine and thymine nucleobases functionalized with long aliphatic chains

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Complementary adenine and thymine nucleobases were functionalized with long aliphatic chains. The materials exhibited a mesomorphic character which was attributed to the formation of supramolecular architectures. Molecular recognition through hydrogen bonding of the complementary ends of the molecules was the driving force for their formation. It was also found that these structures are affected by the crystallization medium.

It has been established that amphiphilicity is, in general, the driving force for the organization and aggregation of certain molecules in the bulk and in solution [1]. The behaviour of amphiphilic molecules to aggregate and organize in aqueous media has been studied extensively for the formation of organized molecular assemblies [2]. However, only recently have amphiphilic molecules begun to be investigated for their ability to form thermotropic liquid crystals [3, 4]. The segregation of the lipophilic and hydrophilic moieties of the molecules, in the solid phase, is responsible for the formation of a lamellar structure which, when partially preserved in the melt, leads to the formation of liquid-crystalline phases.

The ability to form lamellar structures is not only induced by typical ionic surfactants, but as it has recently been found, it is also shared by monomeric and polymeric compounds with long aliphatic chains and one carboxylic or two carboxylic groups. Thus, iminodiacetic acid [5] or polymaleamic acid [6] when both functionalized with long aliphatic chains exhibit liquid-crystalline phases. For the polymeric compound, due to the presence of the backbone, one carboxylic group was sufficient to stabilize the polar layer of the lamellar structure while two carboxylic groups were found to be required for the formation of an analogous structure with iminodiacetic derivatives. The polar layer, in both cases, included the system of hydrogen bonds and the lipophilic layer was formed by the long aliphatic chains. With this background, the induction of hydrogen bond formation through the molecular recognition of complementary heterocyclic substrates [7] or the consideration of rules for hydrogen bond preference, recently discussed by Etter [8], may both be fruitfully applied to the formation of liquid crystals with molecules functionalized with lipophilic moieties.

Specifically, according to recent work of Lehn *et al.* [7 (*a*)], three hydrogen bonds are formed by the interaction of the complementary 2,6-diaminopyridine and uracil functionalized with long aliphatic chains. The polar heterocyclic rings with the

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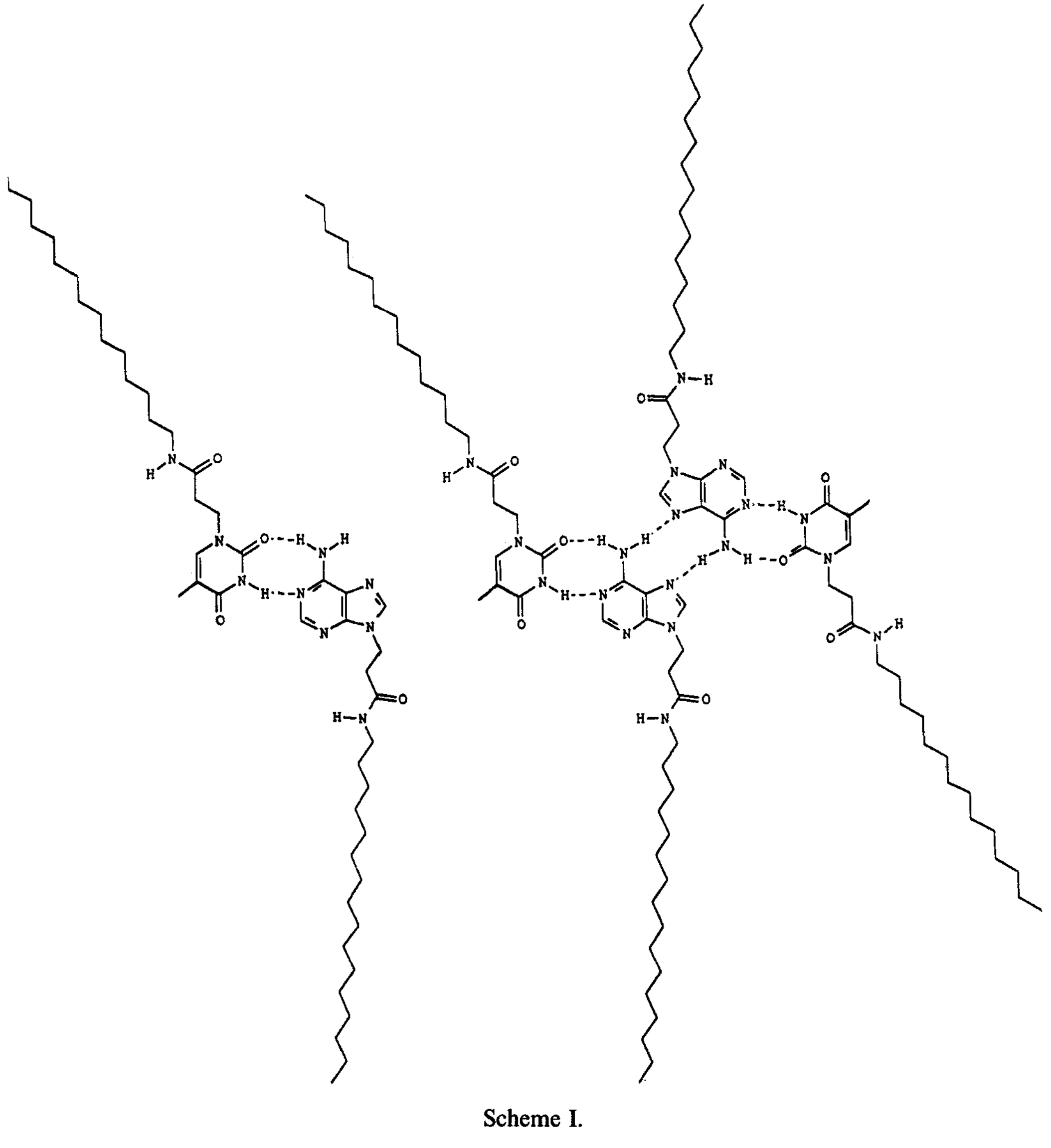
hydrogen bonds are sandwiched between the lipophilic layers leading to the formation of a columnar, hexagonal type structure, expressed macroscopically by the exhibition of liquid-crystalline phases. In the present work, adenine and thymine nucleobases, whose molecular recognition properties are well-known, were functionalized by a long alkyl chain. The mesomorphic phases observed for these compounds were rationalized in view of the formation of the complementary pair(s) or through their self-association.

The synthesis of the adenine + amphiphile (A) was achieved through the intermediate formation of 9-(2-carboxyethyl)adenine [9, 10] and 9-(4-nitrophenyl-2-carboxyethyl) adenine [9, 11] by reacting the 4-nitrophenyl active ester, in dimethylformamide, with hexadecylamine in dichloromethane. The solution was stirred for about 5 h, and subsequently the dichloromethane was distilled off under vacuum. The material was precipitated from dimethylformamide at low temperatures and recrys-



Scheme I.

tallized from ethanol. Analysis, calculated for $C_{24}H_{42}N_6O$: C, 66·94 per cent, H, 9·83 per cent, N, 19·51 per cent. Found: 66·63 per cent; H, 9·67 per cent; N, 19·98 per cent. Thymine amphiphile (T) was prepared in a similar manner as the adenine amphiphile. Analysis, calculated for $C_{24}H_{43}N_3O_3$: C, 68·39 per cent; H, 10·22 per cent; N, 9·96 per cent. Found: C, 68·00 per cent, H, 10·20 per cent; N, 9·83 per cent. Cocrystallization of adenine-C16 and thymine-C16 was performed by mixing equimolar quantities of the nucleobases in chloroform and allowing the solution to evaporate slowly at room temperature. Adenine and thymine were also cocrystallized from ethanol.

It has been established by detailed infrared [12] and NMR studies [13] that nucleobase complementary pairs are associated by at least two hydrogen bonds. It has also been shown that nucleobases self-associate forming dimeric or oligomeric supramolecular structures [14]. The introduction of the long aliphatic chain at the 1 and 9 positions in thymine and adenine respectively, is not expected to affect their pairing since these positions are not in the vicinity of the groups involved in the molecular recognition process. In fact the association of the complementary A and T

Table 1. Transition temperatures and enthalpies of the adenine–thymine pair and of self-associated adenine and thymine derivatives cocrystallized in ethanol.

Compound	Run	Transition temperatures/°C	ΔH/kJ mol^{-1}†
A–T	A, heating	115–138–155	32·22–19·67–64·03
	B, heating	112–112–139–154	18·41–13·81–75·33
	C, heating	112–122–139–154	
	A, cooling	130–122–114–108	
A–A	A, heating	125–151	3·76–25·95
	B, heating	122–151	7·53–21·34
	C, heating	122–150	
	A, cooling	129	
T–T	A, heating	140–190	35·57–37·24
	B, heating	140–190	34·32–38·08
	A, cooling	157–124	

† Enthalpies of the first and second transitions were combined since it was not possible to calculate these separately.

Table 2. Transition temperatures and enthalpies of the adenine–thymine pair and of self-associated adenine and thymine derivatives cocrystallized in chloroform.

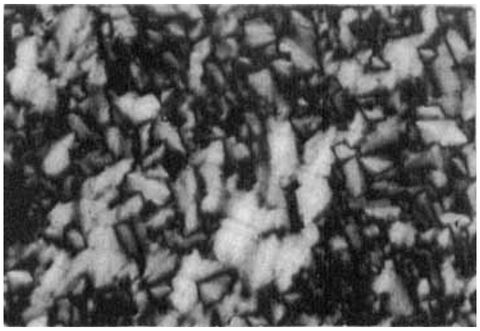
Compound	Run	Transition temperatures/°C	ΔH/kJ mol^{-1}
A–T	A, heating	110–142	24·69–56·08
	B, heating	100–141	10·04–32·64
	A, cooling	110–90	
A–A	A, heating	160	23·44
	B, heating	160	23·02
	A, cooling	145	
T–T	A, heating	138–186	35·57–37·24

amphiphilic nucleobases was shown by the significant downfield shifts of NH and NH_2 proton NMR signals, in dueteriochloroform, of the thymine and adenine derivatives, i.e. from 7·98 to 10·47 and from 5·65 to 6·1 ppm, respectively in accord with analogous literature data [7(*a*), 13(*a*)].

The materials obtained by slow evaporation from chloroform or from ethanol showed multiple melting behaviour as evidenced by DSC and microscopy studies. The transition temperatures obtained from DSC and verified by optical microscopy are shown in tables 1 and 2. The enthalpies of the complementary pair obtained from chloroform and ethanol cocrystallization respectively, in repeated heating–cooling runs are also shown in the same tables. It is apparent that the solvent of cocrystallization affects the transition temperatures and enthalpies, reflecting differentiations in the structure of the adenine–thymine complementary pair. Ethanol, a strong hydrogen bond donor, is hydrogen-bonded with the cocrystallizing substrates apparently affecting the structure of the complex in a different manner as compared with chloroform which is a relatively non-competing solvent [15] with respect to the hydrogen bonding of nucleobases. Four dimeric and three tetrameric structures may be envisaged by Watson and Crick [16] or Hoogsteen [17] base pairing or by a combination of these modes of molecular recognition. In scheme I we show one of each of these supramolecular structures to which the mesomorphic behaviour of the complex may be attributed. However, before X-ray studies are performed we cannot decide definitely which is the predominant structure of the complex in the solid or mesomorphic phase at various temperatures. The transitions before the clearing point transition, were attributed to the conformational melting of the long aliphatic chains. It is interesting to note that melting during microscopic observation was induced by exercising pressure on the cover slides which is a characteristic property of amphiphilic-type liquid crystals. On the other hand, the clearing point of the complex remained constant in repeated heating–cooling runs which indicates thermal stability.

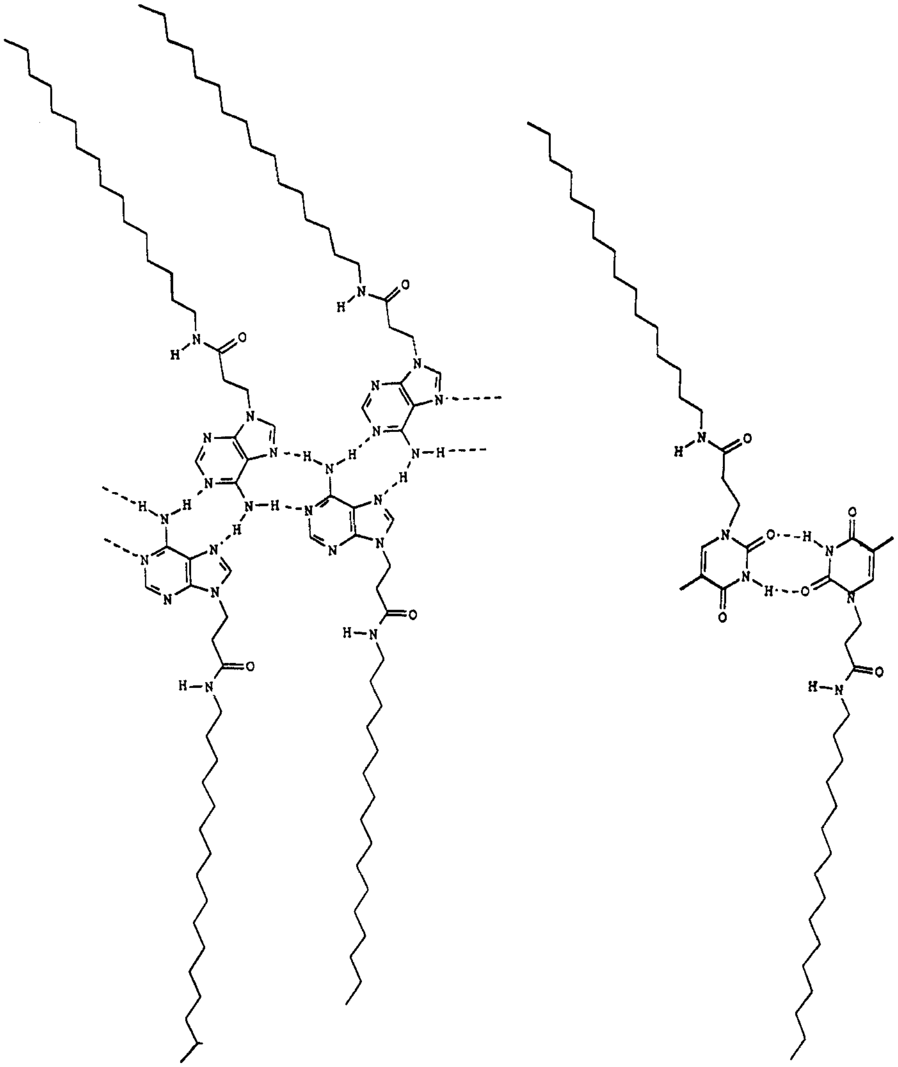
The textures observed on heating or cooling runs change following the various transition temperatures. A liquid-crystalline texture of the adenine–thymine pair is shown in the figure, from a sample derived from ethanol cocrystallization and obtained during its cooling from the isotropic melt.

The multiple melting behaviour of long chain functionalized adenine and thymine derivatives (see tables 1 and 2) coupled with the exhibition of anisotropic textures, also establish the mesomorphic character of these compounds. The phase transitions of the adenine derivative are dependent on the solvent of crystallization whereas this is not



Mesomorphic texture of the adenine–thymine pair obtained during cooling from the isotropic melt of a sample derived from cocrystallization in ethanol.

the case with the thymine derivative. For adenine, however, in the fourth heating run, the DSC trace of the sample obtained from ethanol resembles that obtained from chloroform on its first heating run. This indicates that only after repeated heating–cooling runs is the structure obtained from ethanol converted to a structure similar to that obtained from chloroform. The differentiation in the behaviour of the adenine amphiphile as compared to that of thymine is due to the presence in adenine of the NH_2 group with two binding sites. This donor group is capable of forming two hydrogen bonds, and together with the other three hydrogen accepting groups, it may form polymeric structures. Such structures are shown in scheme II. Again X-ray diffraction studies will hopefully be able to discriminate between these two polymeric structures. Thymine, on the contrary, self-associated forming two dimeric structures one of which is shown in scheme II. For both derivatives two dissimilar, non-miscible layers form, to which are attributed the appearance of thermally stable mesomorphic phases.



Scheme II.

In conclusion, molecular recognition of amphiphilic nucleobases, achieved by a system of hydrogen bonds, and shown macroscopically by the exhibition of mesomorphic behaviour, was found to be affected by the medium of crystallisation. With this model system in mind we should be alerted as to the possibilities offered and also of the complexities that may be encountered in biological systems where more than a mere change of a solvent occurs.

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