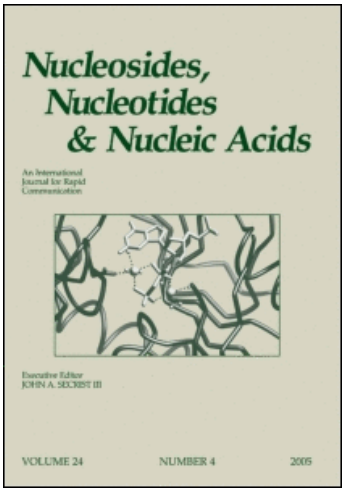

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SELF-ASSEMBLY AND LYOMESOPHASES FORMED BY LONG-CHAIN ALKOXYMETHYL-NUCLEOBASE DERIVATIVES

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ABSTRACT: Amphiphilic complementary nucleobase derivatives, containing n-octadecyl-oxymethyl substituents at the N^1 position of pyrimidine and N^9 of purine, dissolved in chloroform form non-specific lyotropic mesophases, which were analyzed by optical polarizing microscopy. Molecular modeling studies visualize hypothetical horizontal and vertical nucleobase hydrogen-bonding and stacking arrangements, as well as aliphatic long-chain interstrand interaction.

INTRODUCTION

Condensation processes of highly concentrated aqueous nucleic acid solutions have been extensively investigated, because of their essential roles in (pre)biological systems[1,2]. The analysis of the structure-phase behavior of nucleic acid patterns seems to be important for the understanding of basic processes as, for instance, (pre)biotic self-organization, replicational forces in transitions to life, up to complex biomesogenic regulations of present life patterns. For modeling special features of nucleic acid-membrane interactions, we designed nucleobase-membrane hybrids of the type 9-(n-octadecyloxymethyl)purine and 1-(n-octadecyloxymethyl)pyrimidine (Fig. 1). The segregation of the lipophilic and hydrophilic parts of these compounds display basic molecular features for self-assembly processes. Base-pair arrangements according to Watson-Crick and Hoogsteen mode could

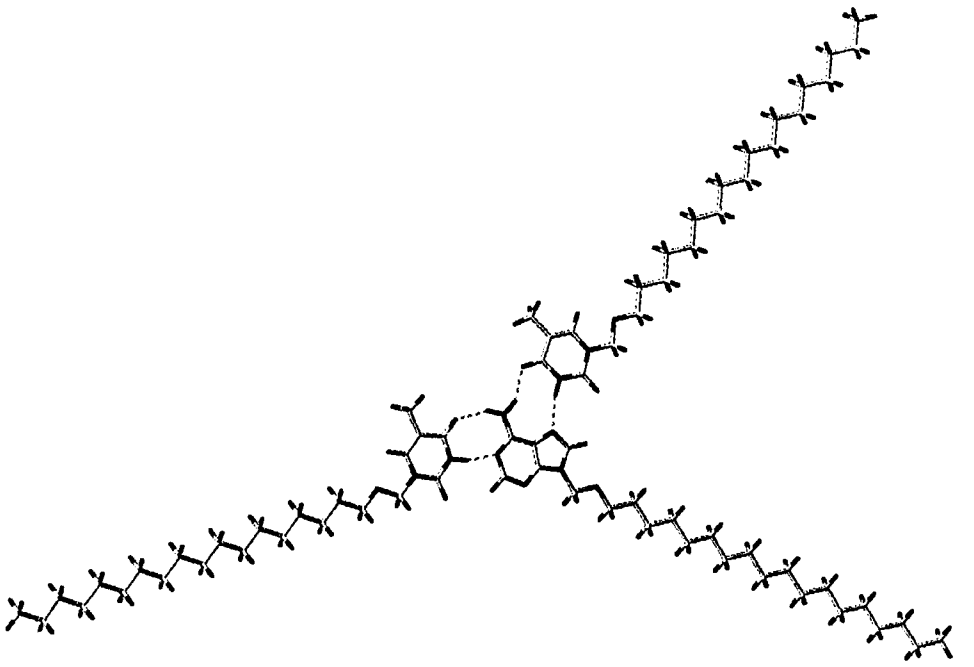

FIG. 1: Possible arrangements of 9-(n-octadecyloxymethyl)adenine (I) and 9-(n-octadecyloxymethyl)thymine (II) between Watson-Crick and Hoogsteen recognition in stick presentation

be supported by nucleobase stacking and long alkyl-chain interstrand interaction as driving forces for supramolecular structure formation. But until now, it is not clear, whether these complementary, amphiphilic long-chain alkyl-nucleobases display liquid crystalline behavior. Our thermotropic experiments manifested some „plastic" states of these compounds[3], which correlates with the parallel findings by Paleos et al., analyzing long-chain alkyl-nucleobases, partially modified by additional amide groups[4]. In an attempt to overcome these limitations of mesophase formation, we made use of chloroform as an organic solvent, that enhances significantly nucleobase hydrogen-bond interactions.

EXPERIMENTAL

Sample preparation

9-(n-octadecyloxymethyl)adenine (I): ^{1}H-NMR (DMSO-d_6), δ=8.23 (1H, s, 8-H); 8.14 (1H, s, 2-H); 7.24 (2H, s, NH_2); 5.50 (2H, s, NCH_2); 3.42, 1.22, 0.84 (37H, m, $C_{18}H_{37}$);

MS(ESI) 418.5 [*M* +H]$^+$; Anal. calcd for $C_{24}H_{43}N_5O$: C, 69.0; H, 10.4; N, 16.8; found C, 68.8; H, 10.4; N, 17.0; and 9-(n-octadecyloxymethyl)thymine (II): ^{1}H-NMR (DMSO-d_6), δ=11.18 (1H, s, NH); 7.50 (1H, s, 6-H); 5.00 (2H, s, NCH_2); 1.76 (3H, s, CH_3); 3.40, 1.24; 0.84 (37H, m, $C_{18}H_{37}$); MS(ESI) 409.5 [*M* +H]$^+$; Anal. calcd for $C_{24}H_{44}N_2O_3$: C, 70.5; H, 10.9; N, 6.9; found C, 70.6; H, 11.0; N, 6.7; were synthesized, hplc-purified and recrystallized [mp(°C) I: 131-132; II: 100-102 - for solid-solid, solid-plastic and plastic-isotropic transitions see ref. 3] according to established procedures[5]. The sample solutions were prepared by mixing the chloroform-diluted compounds according to their molar ratio, evaporating to dryness and rediluting in chloroform at a start concentration of about 50 mg/ml.

Optical polarizing microscopy

Optical polarizing microscopy observations were performed employing a Labor Lux 12S equipped with a Hitachi video color camera. A droplet of each sample was deposited between partially sealed slide and coverslip, observed through crossed polarizers and photographed with a magnification rate of 167.5x. The progressive increase of the sample concentration was obtained by a controlled peripheric evaporation of the solvent at 20°C.

Molecular modeling

Molecular models have been generated by SYBYL 6.2 programs. For optimization Gasteiger-Marsili algorithms were used. Dynamics are based on TRIPOS force field and simulate processes at 300K.

RESULTS AND DISCUSSION

Water-based lyomesophase systems of the here involved compounds appear to be only possible, if extremely hydrophilic substituents of the alkyl-chains allow for a partial solubilization. So we demonstrated, that in the case of L-(S-cysteine)-functionalized alkyl-nucleobases attractive water-based mesogenic matrix systems could be build up[6].

Going on in experiments for the liquid crystalline behavior of the here discussed amphiphilic and thermotropically more „plastic" nucleobase-membrane hybrids, however, we analyzed by the help of optical polarizing microscopy, that highly condensed chloroform solutions of complementary nucleobase derivatives bearing 9-(n-octadecyloxy-

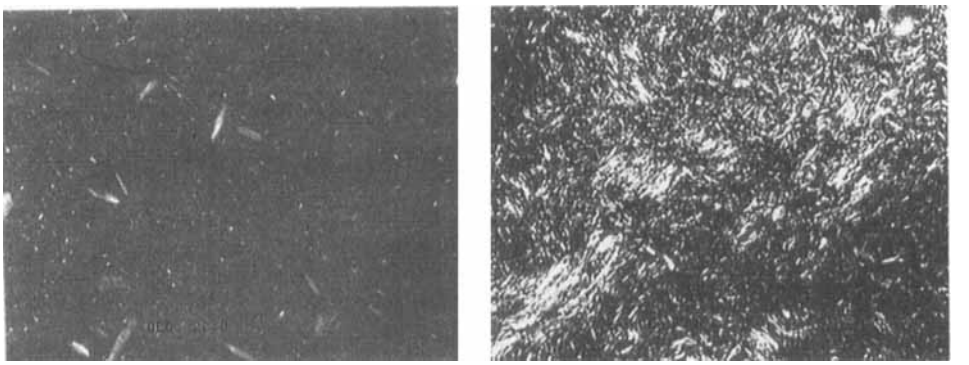

FIG. 2: Non-specific optical textures of condensed sample-chloroform-solutions (left to right): I/II-(1:1 and 1:2)-complexes; 167.5x

methyl)-substituents at the N^1 position of the pyrimidine base thymine and at the N^9 of the purine heterocycle adenine, would undergo self-assembly and display non-specific lyomesophases at start concentrations > 50mg/ml. In Fig. 2 the anisotropic „moveable" textures of the (1:1) and (1:2) molar mixtures of the chloroform solutions of the adenine and thymine derivatives during the evaporation process are illustrated.

In order to further elucidate the driving forces of (lyo)mesophase formation within broad ranges of imaginable representatives, two highly artificial molecular modeling approaches have been performed (Fig. 3). The first is represented by a hypothetical lamellar bilayer arrangement, made up by suitable segregations of horizontal hydrogen-bonding and vertical stacking interactions of Watson-Crick AT base-pairs and long alkyl-chain interstrand interactions. In addition to these two-dimensional hypothetical bilayer arrangements, a second model is based on triplex-derived Watson-Crick/Hoogsteen TAT triple arrangements, that build up some sort of reversed micelle, where the extended base triple core is embedded into a cylindric long alkyl-chain envelope in the direction of a base-stack and alkyl-chain continuous reversed hexagonal phase. The vacuum-picosecond-evolution of the two- and three-dimensional models - unfortunately, by the procedure devoid of solvophilic and solvophobic stabilizations - visualize increasing labilizations of the hydrogen-bonds - up to the disruption of the hydrogen-bond networks in case of the bilayer model, while the triplex-derived micelle appears to be less impaired. Nucleobase stacks and long alkyl-chain packages - though progressively characterized by larger

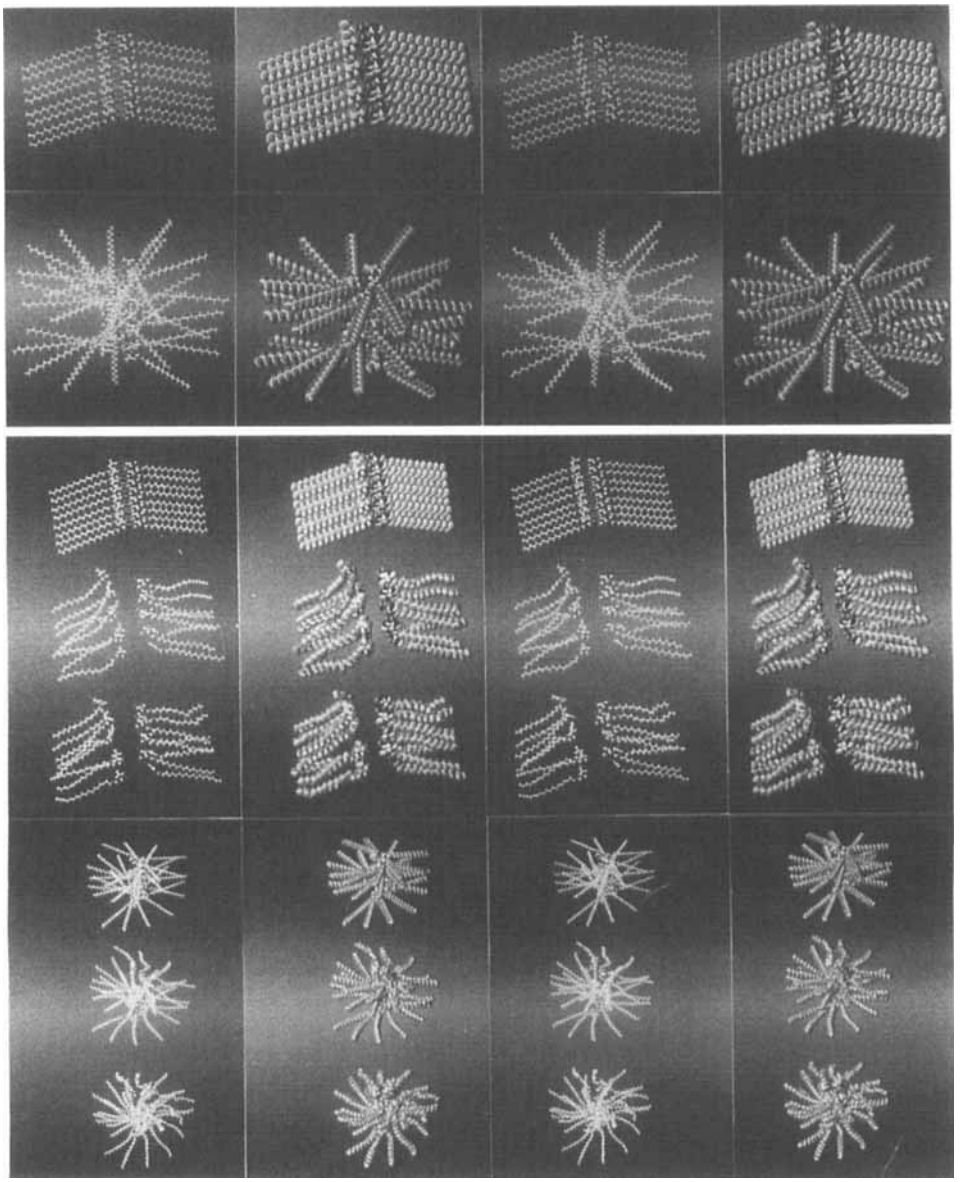

FIG. 3: Hypothetical vacuum mesophase statics and dynamics of I/II-combinations in stick and CPK-stereopresentation (top to bottom): AT-Watson/Crick-based I/II-(1:1)-bilayer and TAT-Watson/Crick-Hoogsteen-derived I/II-(1:2) reversed micelle; picosecond evolution of I and II complexes as derived from top: I/II-(1:1-complex): start, 0.95 ps, 1.55 ps; I/II-(1:2-complex): start, 1.0 ps, 2.0 ps

conformational movements - preserve their overall-shapes, in case of the lamellar bilayer model, however, only after monolayer individualizations.

Further insights might be expected from more general experimental approaches of phase and phase-diagram investigations of the here involved compounds, which are underway in our laboratory.

OUTLOOK

The here reported experiments will shed some light on the structure-phase facilities of hybrids linking together nucleic acids- and membrane components-recognition groups within a special molecular design, which might be of interest for modeling general and forwarding applicational aspects of nucleic acid-membrane interactions.

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