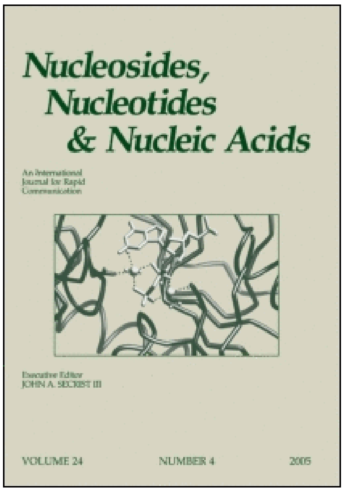

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CHEMICAL SYNTHESIS AND PROPERTIES OF LONG-CHAIN ALKOXYMETHYL-NUCLEOBASE DERIVATIVES

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ABSTRACT: New nucleobase derivatives were synthesized, containing both octyloxymethyl (LCA8) and octadecyloxymethyl (LCA18) substituents at N^1 position of pyrimidine and N^9 of purine. These substances were studied with respect to the formation of supramolecular structures, i.a. molecular associates as the result of noncovalent interactions. Special attention has been paid to complex formation. The properties of these molecules were investigated by DSC and polarizing microscopy.

INTRODUCTION

In biological systems hydrogen bonding plays an essential role. The nucleic acid world is mainly founded on the specifity and selectivity of hydrogen bond patterns by Watson-Crick and Hoogsteen mode supported by stacking interaction of the nucleobases. Modifications of nucleobases with long paraffin chains transform these compounds into amphiphilic molecules, the driving force for their aggregation and supramolecular structure formation. The segregation of lipophilic and hydrophilic parts of these

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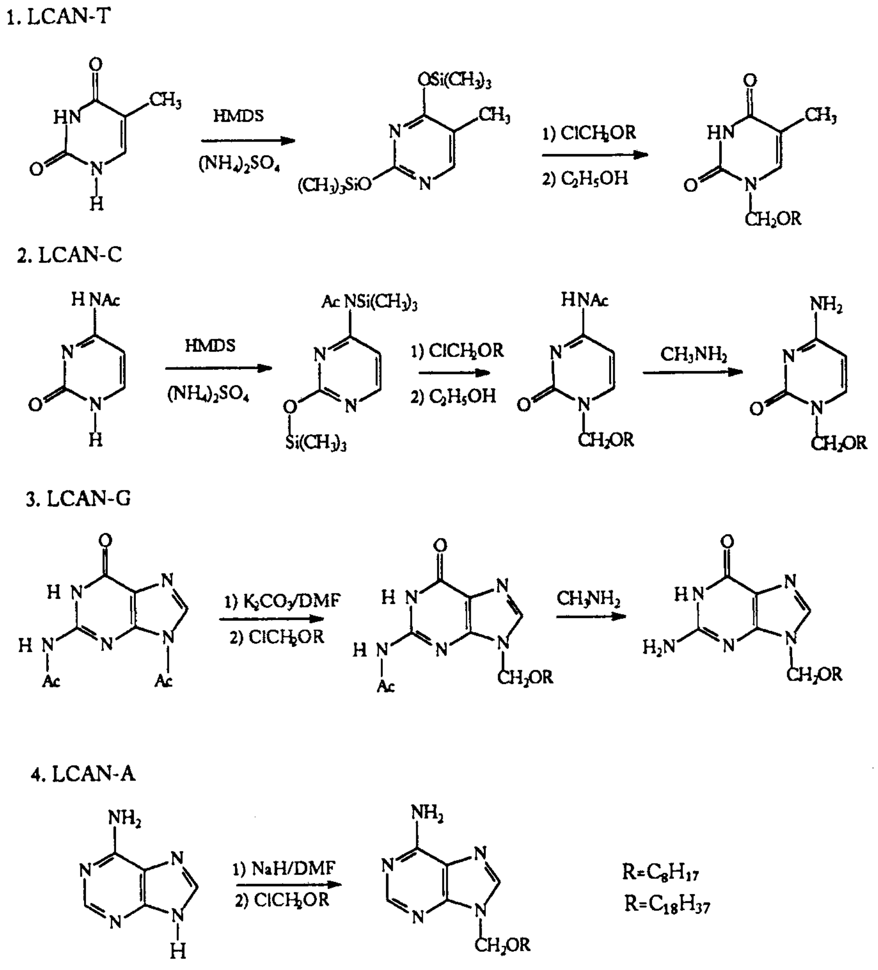

FIG. 1: Synthesis of long-chain alkoxymethyl-nucleobase derivatives

compounds is the basis for lamellar and micellar structures and informations of mesophases. Due to the different properties of the pyrimidine and purine heterocycles and the alkyl chains, special highly ordered structures could be expected. In the present study we describe an efficient synthesis of nucleobases bearing a desired long-chain alkoxymethyl group (LCA) (FIG. 1)[1-4] and examine the influence of the well-known hydrogen bond formations of the nucleobases, stacking-interactions and the alkyl-chain characteristics on the phase-behavior of the resultant LCA nucleobases by the help of DSC and polarizing microscopy. According to Watson-Crick or Hoogsteen base pairing or by a

TABLE 1:

Pure compounds

(1) 9-Octyloxymethyladenine (LCA8-A)
(2) 1-Octyloxymethylthymine (LCA8-T)
(3) 1-Octyloxymethylcytosine (LCA8-C)
(4) 1-Octyloxymethyl-N^4-acetylcytosine (LCA8-C^{ac})
(5) 9-Octyloxymethyl-N^2-acetylguanine (LCA8-G^{ac})
(6) 9-Octadecyloxymethyladenine (LCA18-A)
(7) 1-Octadecyloxymethylthymine (LCA18-T)
(8) 1-Octadecyloxymethylcytosine (LCA18-C)
(9) 9-Octadecyloxymethylguanine (LCA18-G)

Mixtures

(10) 1:1 molar binary mixture of compounds (6) (LCA18-A) and (7) (LCA18-T)
(11) 1:2 molar binary mixture of compounds (6) (LCA18-A) and (7) (LCA18-T)

combination of both molecular recognition modes molecular modelling show possible structures of the individual compounds and their mixtures (FIG. 3).

RESULTS AND DISCUSSION

Chemical synthesis of long-chain alkoxymethyl-nucleobase derivatives and purification

Our new nucleobase derivatives bearing an octyloxymethyl- or octadecyloxymethyl substituent at the N_1 position of pyrimidine and N_9 of purine heterocycle (TABLE 1) were synthesized as Ftorafur analogs[4] by modified alkylation procedures as illustrated in FIG. 1. The N_1-derivatives of LCA-thymine and -cytosine were synthesized from silylated compounds by reaction with α-chlorether $ROCH_2Cl$ [$R=C_8H_{17}$ (LCA8) or $C_{18}H_{37}$ (LCA18)] as alkylating agent in ethanol. N^2-, N^9-Diacylguanine and adenine reacted with the alkylated agent in the presence of K_2CO_3 or NaH in DMF yielding the desired products, the details of the procedures will be published elsewhere.

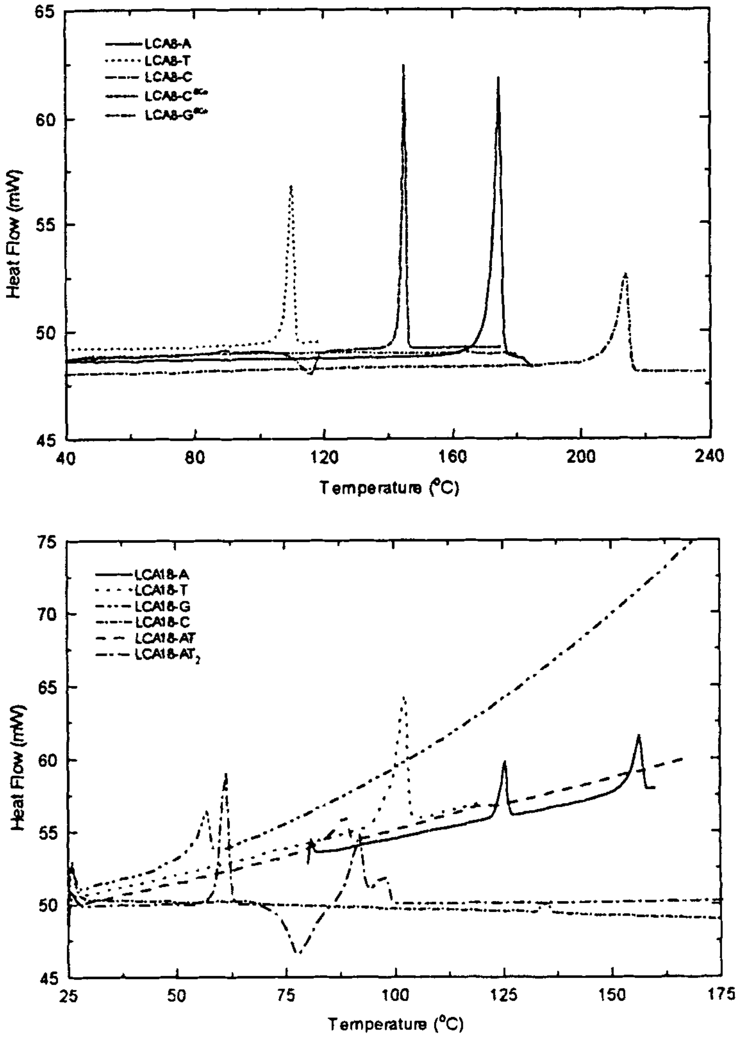

FIG. 2: DSC-thermograms of LCAN-A, LCAN-T, LCAN-C, LCAN-G and their mixtures (top to bottom): octyloxymethyl- and octadecyloxymethyl-nucleobases (heating curves), see TABLE 2a and 2b

TABLE 2: Transition temperatures (T) and enthalpies (ΔH): Pure and partially acetylated octyloxymethyl nucleobases (1-5) (TABLE 2a) and of both pure octadecyloxymethyl-nucleobases (6-9) and of 1:1 (10), 1:2 (11) molar binary mixtures of compounds (6) and (7) (TABLE 2b) as determined by DSC

TABLE 2a:

Compound	Type of curve	T(°C)	ΔH(kJmol^{-1})
LCA8-A	heating	174.3	142.3
	cooling	159.5	-142.9
LCA8-T	heating	109.6	92.2
	cooling	81.6	-89.9
LCA8-C	heating	212.9	163.9
	cooling	204.5	-161.0
LCA8-C^{ac}	heating	89.2	1.6
		115.8	-26.6
		144.9	107.2
	cooling	104.6	-64.8
		57.2	-2.6
LCA8-G^{ac}	heating	169.9*	64.2

TABLE 2b:

Compound	Type of curve	T(°C)	ΔH (kJ·mol^{-1})
LCA18-A	heating	125	16.3
		159	20.7
	cooling	139	-26.6
		113	-5.7
LCA18-T	heating	102	41
	cooling	87	17.2
		79	21.7
LCA18-C	heating	137	28.5
		209	24.6
	cooling	193	-17.3
		130	-1.6
LCA18-G	heating	78	7.0
		141	9.9
	cooling	232	7.5
		32	-9.8
LCA18-A/LCA18-T 1:1	heating	89	15.8
		120	6.5
	cooling	94	-9.1
		74	-16.8
LCA18-A/LCA18-T 1:2	heating	61	31.9
		78	-35.4
		89	19.8 (part.)
		92	50.9 (part.)
	cooling	48	-35

*Decomposition above 200°C

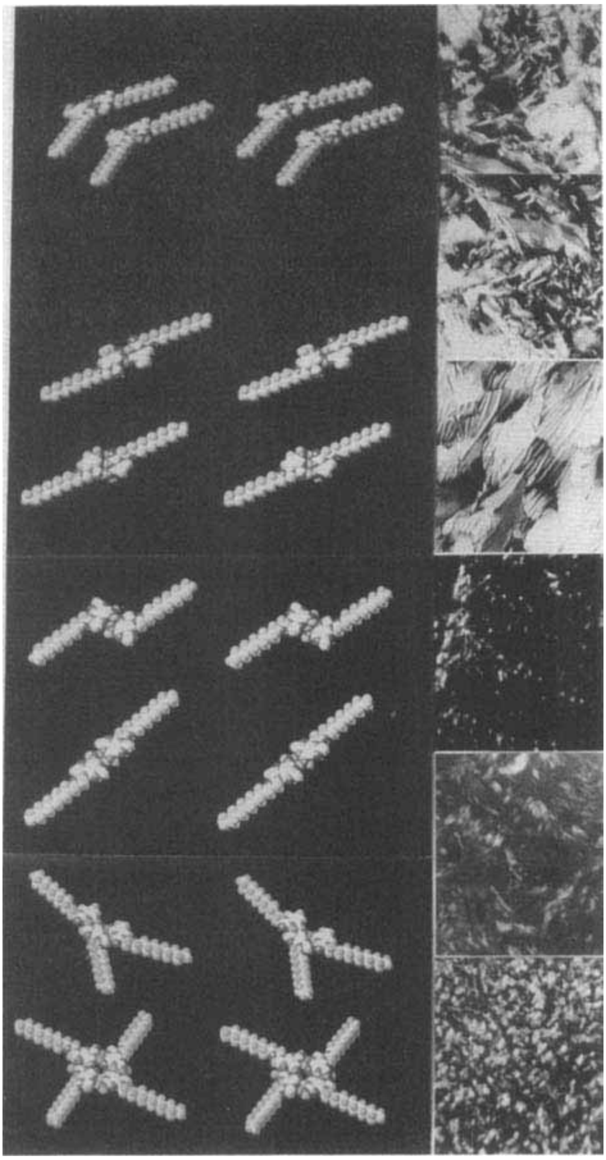

FIG. 3: Hypothetical hydrogen bond patterns of LCA nucleobase derivatives between Watson-Crick and Hoogsteen recognition (top to bottom). A·T - C·G-Watson-Crick-arrangements; T·T-versions; A·A-schemes with Watson-Crick- and Hoogsteen-site recognition: T·A·T-triplex- and G·G·G·G-quadruplex-combinations; optical textures upon cooling from the melt (top to bottom): compound (6) (153°C), (7) (90°C), (8) (200°C), (9) (210°C), (10) (93°C), (11) (71°C); magnification 100x.

Differential scanning calorimetry (DSC) studies

DSC studies were carried out using a Perkin-Elmer DSC-7. For the preparation of 1:1 (10) and 1:2 (11) molar binary mixtures (TABLE 1), the compounds (6) and (7) were dissolved in ethanol at room temperature, mixed in the used molar ratios and slowly evaporated to dryness. The thermal stability of each sample was analyzed with a heating and cooling rate of 10K/min. The transition temperatures and enthalpies obtained are shown in FIG. 2 and TABLE 2a and 2b.

The octyloxymethyl-nucleobase (LCA8) derivatives (1-5) show only solid-liquid transitions. In contrast to this behavior two transition peaks were found in the case of the octadecyloxymethyl-nucleobase (LCA18) derivatives (6-9) and their mixtures (10-11). The LCA18-G (8) and LCA18-C (9) 1:1 molar binary guanine-cytosine mixture was decomposed above 200°C.

The high transition enthalpies of this untypical LCA18 mesophase behavior can only be discussed as a new kind of phase.

Texture observations

A small amount of the sample (1-11) was placed between slide and coverslip.

The optical polarizing microscopy observations were performed employing a Labor Lux 12S, equipped with a Hitachi video color camera upon cooling from the melt. The samples were observed through crossed polarizers and photographed with a magnification rate of 100x. In FIG. 3 the anisotropic „moveable" textures of the pure (6-9) and mixed LCA18 derivatives (10-11) between the two transition states upon cooling from the isotropic melt and their hypothetical patterns are illustrated. These experimental findings of the LCA18 derivatives are indicative of a phase behavior[5-8] „between the common crystalline state and so far unknown mesophase characteristics".

Our results correlate with the parallel findings by Paleos et al.[9-12] in case of long-chain nucleobases, partially modified by additional amide groups. The special characteristics of the here found so-called „plastic" states seem to deserve further attention and are the starting point for a variety of new LCA nucleobase derivatives which will be studied by biophysical methods to lead to a deeper insight into this special kind of molecular state and function.

Beside the here offered elucidations of putative mesophase characteristics of the discussed nucleic-acid/membrane-hybrids, the components seem interesting as biosensor components and might turn out useful as assisting patterns for mediating membrane passage of nucleic acid and implanting nucleic acids into membrane micelle arrangements in order to establish selfreplication systems.[13,14]

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