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Intramolecular interactions in acyclic and macrocyclic compounds containing nucleotide bases

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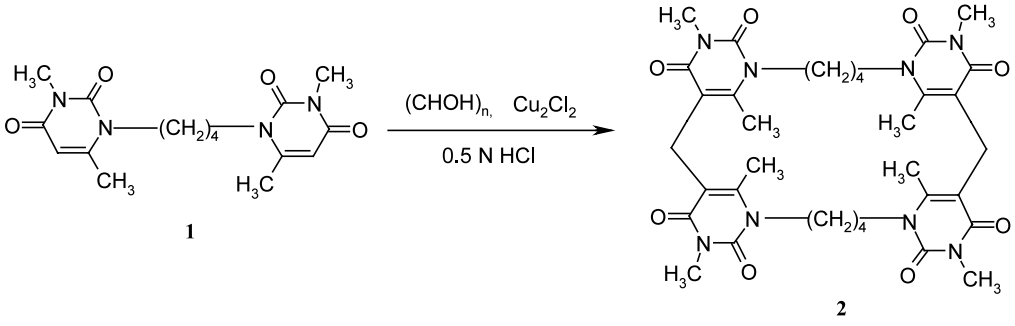
Abstract—Acyclic and cyclic counterparts containing thymine and two 3,6-dimethyluracil fragments bridged by methylene chains have been prepared and studied by UV and NMR spectroscopy; in water the uracil units of the acyclic counterpart form an intramolecular stack but arrange in a linear array in chloroform while the fragments of the uracilophane form an intramolecular stack both in chloroform and water; uracil units of bis(3,6-dimethyluracil-1-yl)butane and the macrocyclic counterpart form a stack in chloroform.

In recent years the stacking interactions of nucleic acid bases have received much attention not only for studying the rules and restrictions of the recognition and binding processes in nature but also for the construction of artificial receptors.[1] The design and synthesis of artificial receptors, based on the same principles as their natural prototypes, is an important and rapidly growing field of chemistry.[2] A variety of models consisting of the nucleotide bases has been synthesized and their assembling properties have been studied by the methods of UV[3] and NMR[4] spectroscopy. Most compounds synthesized so far contain two nucleotide rings fixed with different modes of stacking by polymethylene chains[3,4d,e] or crown ethers[4a–c] and have acyclic structures except for purinophanes.[3d] Investigations of stacking of unnatural products containing more than two nucleotide bases or their derivatives were not performed.

Recently we developed the synthesis of a new type of uracilophane **2** containing four uracil units[5] bridged with aliphatic chains. Uracilophane **2** was obtained by the reaction of bis(3,6-dimethyluracil-1-yl)butane **1** with paraformaldehyde in aqueous 0.5 N HCl in the presence of 0.5 equiv. of Cu_2Cl_2 (Scheme 1).

In this paper we report the synthesis of new acyclic and cyclic counterparts **5** and **6** consisting of uracil derivatives—thymine and 3,6-dimethyluracil (Scheme 2).

Reaction of thymine disodium salt **3** (1 equiv.) with N_1-(4-bromobutyl)-3,6-dimethyluracil[6] **4** (2 equiv.) in



1 2

Scheme 1.

Keywords: uracilophanes; hyperchromism; hypochromism; stacking.

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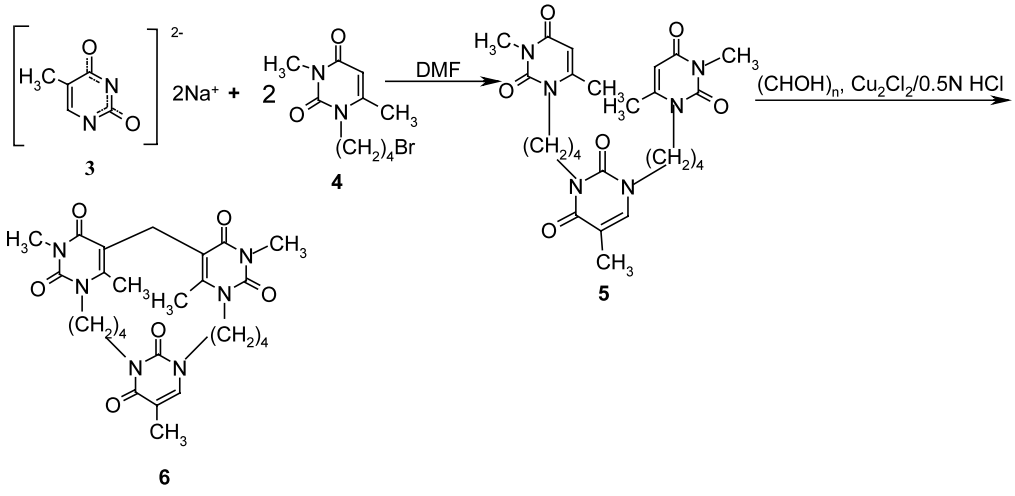
DMF (60–70°C, 8 h) gave **5** in 40% yield as an amorphous white solid, m.p. 175–176°C. The cyclic counterpart **6** was prepared from **5** by **a** ring-closure reaction with paraformaldehyde under the same conditions as for uracilophane **2** (29%, white solid, m.p. 272–274°C, found for M^+ 526.2526, calculated 526.2540 [EI]).

The synthesized compounds were studied optically at concentrations low enough to preclude formation of intermolecular complexes so that the interactions of the bases could be characterized by ultraviolet spectroscopy in chloroform and aqueous solutions at room temperature. Ultraviolet spectra of the compounds have been interpreted in terms of hyperchromic and hypochromic effects (increase or decrease of light absorbance, respectively, compared with monomeric compounds). The latter phenomenon, i.e. hypochromism has been widely used as the evidence of stacked structures of various π-systems, including nucleic acid bases in solution. According to the theories of Tinoco[7a] and Rhodes,[7b] depending on the relative orientation of the transition moments, hypochromism (parallel stacking of the chromophores) or hyperchromism (linear array of the chromophores) is observed. Values of hypochromism were calculated from oscillator strength, $f=4.32\times10^{-9}\int(\varepsilon(\lambda)/\lambda^2)d\lambda$, of the compounds **1**, **2**, **5, 6** and monomeric reference compounds **4** and 1,3-dibutylthymine **7**.[8] For example, in calculating the hypochromism, $\%H=\{1-[f_t/(2f_4+f_7)]\}100$, of trimeric compounds **5** and **6**, f_t is the oscillator strength of **5** or **6**, and $2f_4+f_7$ is the sum of the oscillator strengths of reference compounds **4** and **7**.

It is known that the nucleic acid bases form Watson–Crick and Hoogsteen base-pairing and triplets in organic solvents but stack in water.[9] The versatile solubility of the compounds **5** and **6** allows the study of them in different solvents. Moreover, it should be noted that the classical hydrogen bonding is excluded due to the absence of imido groups and the observed effects are determined only by π–π interactions of the uracil units.

As seen from Table 1 compounds **1** and **2** do not exhibit large hypochromic effects in $CHCl_3$. A decrease in the hypochromism value for **2** with respect to **1** can be explained by a relative arrangement of the 3,6-dimethyluracil units in **2** different from that in **1** due to steric requirements of macrocycle closure. Uracilophane **6** shows large hypochromism both in $CHCl_3$ and water. To our knowledge, this is the largest value (41.9% in water), caused by pyrimidine derivatives, so far reported. Only purinophane exhibited a greater hypochromism value (47.6% in water).[3d] It is obvious that the bis(3,6-dimethyluracil-5-yl)methane fragment stacks with the thymine unit and the interplanar distance is quite short. Such a difference between hypochromism values of uracilophanes **2** and **6** is a



Scheme 2.

Table 1. Ultraviolet absorption spectra and percentage hypochromism[a]

Compound	$CHCl_3$[b]				H_2O[b]			
	λ_{max}	ε	f	H	λ_{max}	e	f	H
1	267	17179	0.3510	12.7				
2	275	33778	0.75332	6.3				
4	266	9735.25	0.20104		267	11064	0.21879	
5	267.5	28746	0.61541	−5.4	268.5	22647	0.47764	21.5
6	273	19608	0.43750	25.1	274	16318	0.35351	41.9
7	272	8507.5	0.18190		273	8418	0.17051	

[a] λ, wavelength in nm; ε, molar extinction coefficient in M^{-1} cm^{-1}; f, oscillator strength; H, hypochromism value.
[b] Concentration is 0.1 mM.

Table 2. ^{1}H NMR data[a]

Compound	$CDCl_3$				D_2O			
	H^5_{ur}	H^6_{th}	NCH_3	$C^6_{ur}CH_3$	H^5_{ur}	H^6_{th}	NCH_3	$C^6_{ur}CH_3$
1	5.66		3.33	2.28				
2			3.31	2.19				
4	5.64		3.32	2.31	5.74		3.22	2.30
5	5.62, 5.59	7.08	3.32, 3.31	2.26	5.71	7.44	3.20	2.27
6		6.91	3.39	2.11, *2.05*		7.42	3.28	2.69, 2.06
7		6.97				7.43		

[a] Concentration is 1 mM; ur, 3,6-dimethyluracil unit, th, thymine unit; all signals presented are singlets.

consequence of different modes of stacking of their units. We suppose that the 3,6-dimethyluracil units of the uracilophane **2** are in parallel planes but they are quite offset while 3,6-dimethyluracil and thymine units of the uracilophane **6** are at least close to a face-to-face arrangement. The diverse arrangement of the uracil units in uracilophanes **2** and **6** can be the result of the diverse macrocycles' flexibility.

Compound **5** shows opposite effects in $CHCl_3$ (negative value of H i.e. hyperchromism) and water (positive value of H, i.e. hypochromism). The hyperchromic effect is assigned to a linear array of nucleotide base units.[7a] Such a dramatic decrease in integrated absorption intensity of both **5** and **6** in water compared with monomeric references seems to be explained in terms of an attraction (attractive interaction) between uracil units mediated by water rather than a hydrophobic effect.[10] Naturally, it is hard to determine the unambiguous geometry of stacking of the compounds **2**, **5** and **6** but the trend is obvious.

^{1}H NMR data are presented in Table 2. It is worth drawing attention to the structures and positions of NCH_3 and C^6CH_3 proton resonances of the 3,6-dimethyluracil units of acyclic and macrocyclic counterparts in comparison with reference compounds and their alterations from $CDCl_3$ to aqueous solution. In $CDCl_3$, the C^6CH_3 of the bis(3,6-dimethyluracil-5-yl)methane fragment of the uracilophane **6** gave two singlets highly shielded in comparison with the one singlet of the reference compound **4** and the one singlet of the uracilophane **2**, in its turn shielded compared with that of **4**. Both macrocycles **2** and **6** have the same mode of binding of the 3,6-dimethyluracil units via the $C^5CH_2C^5$ bridge and the altered structure and upfield shifts of the C^6CH_3 indicate an additional contribution in shielding of methyl groups and, on the one hand, can be the result of CH…π-contacts, not only with the 3,6-dimethyluracil unit as in **2**, but also with the thymine ring due to a quite short distance between the 3,6-dimethyluracil and the thymine units. On the other hand, the additional shielding can also be the result of the different dihedral angles between the uracil units in the bis(3,6-dimethyluracil-5-yl)methane fragment of the uracilophanes **2** and **6**.

A strong deshielding of one of the C^6CH_3 groups of uracilophane **6** in D_2O allows the suggestion that it is the group directed outwards into bulk solvent. Protons of the group are in a deshielding region of one of the 3,6-dimethyluracil units due to the increased dihedral angle between these units. Such an increase of the dihedral angle can be caused by water molecules, and as a consequence, hypochromism in water increases.

In conclusion, we have demonstrated the approach of creating new models of nucleotide bases and their derivatives' aggregates with either acyclic or macrocyclic structures. We have shown that depending on the solvent and the structure of the compounds the units of the compounds have interacted with each other with or without stacking.

Acknowledgements

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