Self-organizing Lariat Ether Derivatives ordered by Hydrogen-bonded and Stacked Nucleotide Bases

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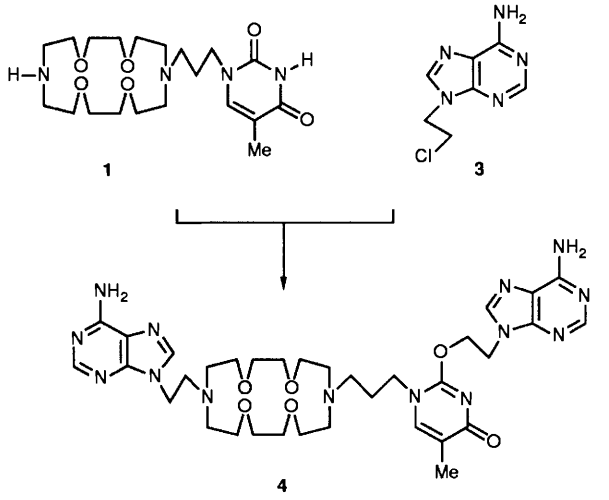
A novel bibracchial lariat ether based upon 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (A2**O**3T*3*A) has been prepared which has CH_2CH_2adenine (2A) and $CH_2CH_2CH_2$thymineOCH_2CH_2adenine (3T*3*A) side-arms; the terminal adenine in the 3T*3*A side-arm folds parallel to and π-stacks with the thymine in the same side-arm while the adenines in opposite side-arms form a single hydrogen bond as judged by two-dimensional NOESY studies.

The nucleotide bases, adenine, cytosine, guanine, thymine and uracil, are remarkable for both their intra- and intermolecular interactions within nucleic acids. Our interest in their extraordinary versatility led us to append adenine and thymine to crown ethers in an attempt to achieve self-assembly in low molecular weight systems.[1] The details of side-arm interactions involving these systems are of obvious importance as models for natural systems. Unnatural products containing these nucleotide bases have been studied in various forms in the groups of Aoyama, Hamilton, Kanematsu, Rebek, Sessler

Table 1 ^{1}H NMR data (δ)

	$CDCl_3$[a]				CD_3CN[a]			
Compound†	C-6-H(T)	CH_2(T)	C-8-H(A)[b]	NH	C-6-H(T)	CH_2(T)	C-8-H(A)[b]	NH
T3O3T	7.178	3.780	—	8.224	7.273	3.694	—	9.050
A3O3A	—	—	7.950	5.610	—	—	7.929	5.876
A2O3T3A	6.941	*ca.* 3.4	7.629	6.462	7.119	*ca.* 3.4	7.806	6.457
				6.795				6.542
A2O3T3A[c]	6.951	*ca.* 3.4	7.641	6.631	—	—	—	—
				6.818				
A2O3T3A·$NaBPh_4$	—[d]	—	—	—	7.053	3.445	7.784	6.044
A3T3O3T3A	7.058	*ca.* 3.4	7.690	6.009	7.163	*ca.* 3.4	7.803	6.135

[a] Concentration is 5 mmol dm^{-3} unless noted otherwise; $CHCl_3$ proton at δ 7.240 was internal reference. [b] AT side-arm. [c] Concentration 150 mmol dm^{-3}. [d] Maximum solubility in $CDCl_3$ <5 mmol dm^{-3}.



Scheme 1

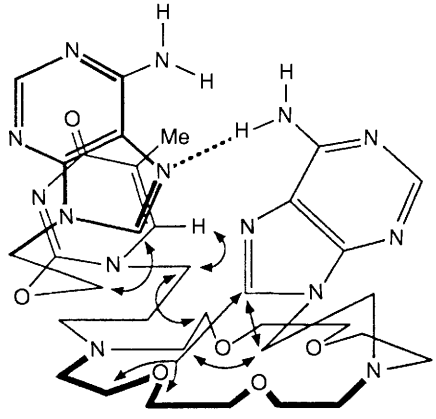


Fig. 1 NOEs for A2O3T3A

and others.[2] These efforts attest to the great interest currently focused on understanding and controlling nucleotide base interactions. During the synthesis of a family of crowns bearing pendant nucleotide bases, we isolated an unsymmetrical derivative having adenine in one side-arm and both adenine and thymine in the other. This unusual structure is, to our knowledge, the first crown ether-based system to show clear evidence for intramolecular stacking[3] and hydrogen bonding of the side-arm bases.

The thyminyl derivative **1** was prepared by treatment of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane with N^1-(3-bromopropyl)thymine[4] **2** (1 equiv.) and Na_2CO_3 (2 equiv.) in MeCN (ambient temp., 7 days). Compound **1** was obtained as a white solid (40%, m.p. 111–112 °C) after crystallization from EtOAc. Reaction of **1** (1 equiv.) with N^9-(2-chloroethyl)adenine[5] **3** (4 equiv.) and Na_2CO_3 (6 equiv.) in Pr^nCN [72 h, reflux, NaI (0.5 equiv.)] gave **4**, here designated A2O3T3A,† in 55% yield as an amorphous, white solid, m.p. 136–138 °C.‡ The ^{1}H NMR spectrum of **4** showed two peaks near δ 6.6 (D_2O exchangeable) and the thymine imido resonance was absent. The apparent molecular weight of **4** (DCI mass spectrometry) was 751 (calc. 750.86). The structure of **4**, shown in Scheme 1, was confirmed by combustion analysis and 2D-correlated spectroscopy (COSY).

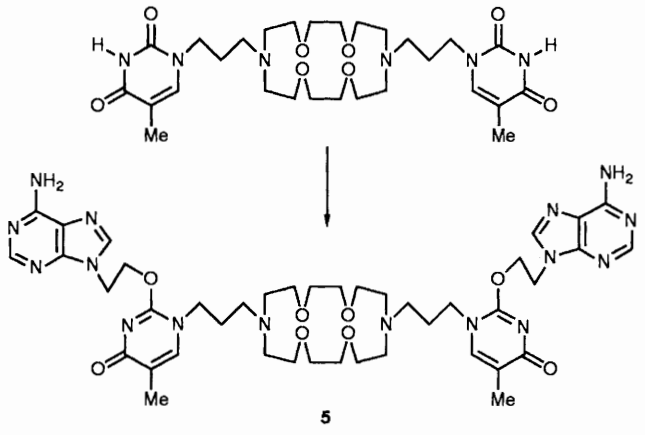
The ^{1}H NMR spectrum (400 MHz) of **4** proved this system to be the first small molecule model for DNA base interactions that showed clear and readily interpretable evidence for simultaneous π-stacking and hydrogen bonding. Detailed solution structural assignments were possible by obtaining the 2D nuclear Overhauser and exchange spectrum (NOESY) and analysing various possible side-arm arrangements using Corey–Pauling–Koltun (CPK) molecular models. The assignments, based upon the information recorded in Table 1, are shown in Fig. 1.

In the structure shown in Fig. 1, NOEs between different hydrogens (H atoms not illustrated) are represented by two-headed arrows. We conclude that the 5-membered ring of adenine (in the AT sidearm) stacks upon the adjacent thymine (upfield shift of adenine C^8-H). A study of CPK molecular models suggested that either amino group may hydrogen bond in a Hoogsteen arrangement[6] although not simultaneously. Either mode of hydrogen bonding brings the second adenine into position (for clarity, not shown to scale) to shield thymine's C^6-H and N^1–CH_2 (upfield shifts observed). According to this model, adenine's C^8-H is proximate to the deshielding region of the combined A–T rings (in AT side-arm), resulting in a downfield shift (δ 8.263 in A2O3T3A; δ 7.950 in A3O3A). It is interesting to note that a chemical shift change is experienced by the N–H protons when the concentration is altered (30-fold) from 5 to 150 mmol dm^{-3}. The protons for which evidence of intramolecular hydrogen bonding is apparent are shifted little. The others undergo an eight-fold greater change in chemical shift suggesting intermolecular association of the folded species at higher concentration.

Although the detailed NOE analysis secures the solution structural assignments, we predicted that significant changes in the NMR spectrum would be observed if the solvent were changed from $CDCl_3$ to CD_3CN or if complexable metal ions were added. In the latter case, we expected reorganization of the macroring to accommodate a metal cation to sunder the weak interactions organizing the side-arms. The change in solvent was expected to modify the side-arm arrangement,

† A2O3T3A: A = adenine, T = thymine, **O** = 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, 2 = $-CH_2CH_2-$, 3 = $-CH_2CH_2CH_2-$, and *3* = $-OCH_2CH_2-$.

‡ Combustion (C, H, N) analyses within ±0.4% were obtained for both A2O3T3A and A2O3T3A·Na_2BPh_4·H_2O.



5

Scheme 2

perhaps by adjusting favoured hydrogen bonding arrangements, but we were unable to predict precise alterations. Indeed, structural changes were apparent from the NMR spectral data (see Table 1). When the solvent was changed from $CDCl_3$ to CD_3CN, small but distinct upfield shifts were observed. When Na^+ was added, a significant upfield shift and coalescence of the > N–H resonances were observed.

The interesting incongruity of biological systems is that very large molecules rely for their overall conformation, stability and function on an accumulation of individually feeble forces. We have been able to define in the above system precise interactions for a small molecule model of DNA. To confirm the generality of this approach, we extended **4** to a related novel analogue, A*3*T3O3T*3*A **5**,[7] (Scheme 2). Preliminary evidence suggests that the stacking pattern in **5** may be slightly modified (compared to **4**) and H bonding is generally weakened (see last line of Table 1). A more detailed study of this family of compounds, expected to reveal details of stacking and H bonding interactions at a previously inaccessible resolution, is currently underway.

We thank the NIH for a grant, GM 36262, that supported this work.

Received, 13th January 1992; Com. 2/00135G

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7 Experimental details for **5** will be published elsewhere.