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Design and synthesis of calix[4]arene–nucleoside hybrids

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Abstract—Synthesis of calixnucleosides (hybrid molecules between calix[4]arenes and nucleosides) has been achieved by amide bond formation between amine functional groups of *para*-1,3-diaminocalix[4]arene and carboxylic acid groups of thymidine nucleosides. Three types of calixnucleosides were efficiently prepared and X-ray crystallography of a homocoupled calixnucleoside revealed an interesting hydrogen-bonding pattern between thymine bases and the amide linkages.

Preorganization and cooperativeness of multifunctional groups play a major role in biological reaction kinetics.[1] Calix[4]arene is proposed as a promising host molecule due to the directional preorganization of functional binding groups and its capacity to cooperate the guest binding site rapidly by low energy conformational change,[2] and has been utilized as a building block for multifunctional enzyme models.[3] Recently, calix[4]arenes have been coupled with sugars,[4] amino acids,[5] peptides,[6] nucleobases (adenine, thymine, uracil),[7] and guanosine[8] to develop biologically active synthetic receptors or enzyme mimics.

We have designed and synthesized calix[4]arene–nucleoside hybrids (calixnucleosides) **1**–**4** as a scaffold for a DNA hairpin structure mimic (Fig. 1). Since calix[4]arene has various structural advantages and meets general criteria for modification of oligonucleotides (ODNs), calixnucleosides can be used as platforms of hairpin type ODNs to recognize complementary DNA or RNA through triplex formation (Fig. 2).[9] To the best of our knowledge, these are the first examples of hybrid compounds between a calix[4]arene and thymidine nucleosides.

The key step of calixnucleoside synthesis is the amide bond formation between amine functional groups of calix[4]arene **7** and carboxylic acid groups of thymidine nucleoside **6** and **8** (Scheme 1). For the activation of the 5′-acid functionality of thymidine derivative **6**,[10] various peptide coupling reagents, such as $(COCl)_2$, EDC, 2,4,6-trichlorobenzoyl chloride, and *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU), were used. But only TBTU provided homocoupled reaction product **3** in 69% yield. In the similar fashion, 3′-acid thymidine derivative **8**[11] was threaded

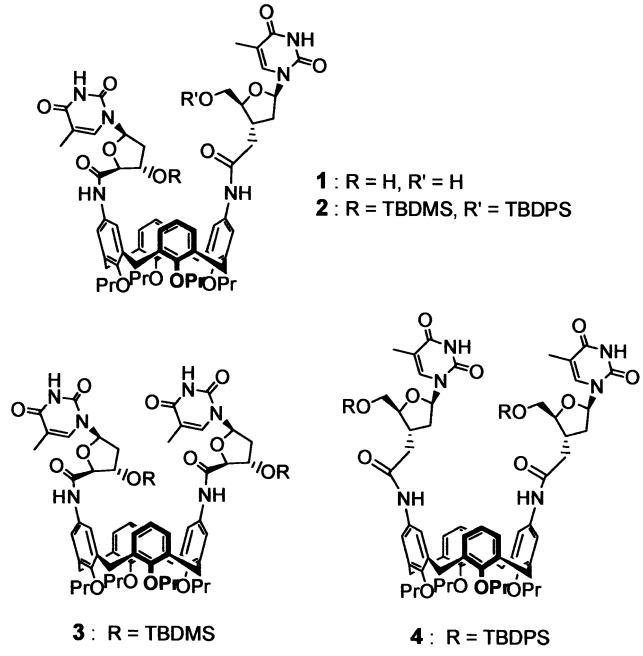

Figure 1. Structures of synthesized calixnucleosides.

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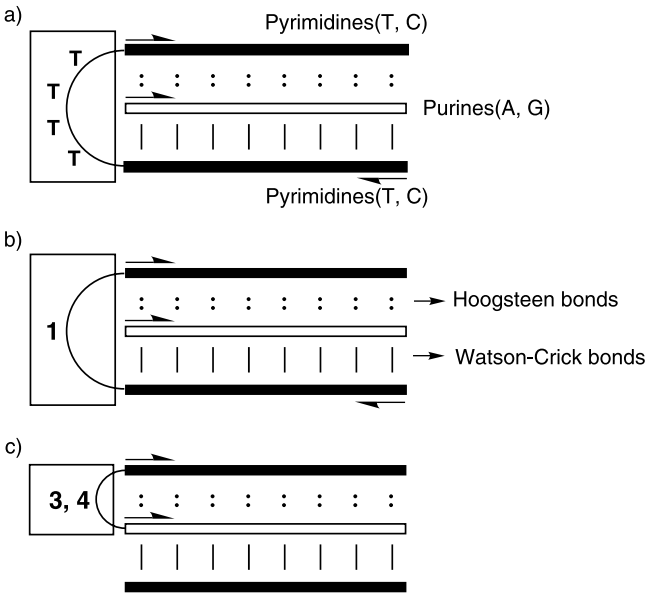
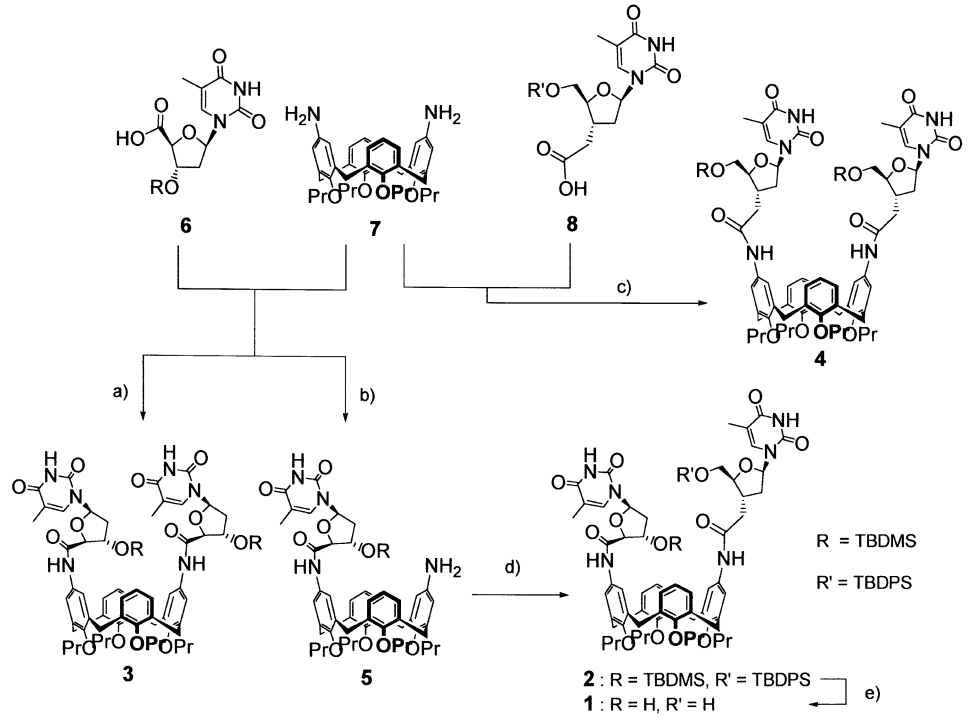


Figure 2. Possible triplex formation patterns with hairpin structures in (a) natural type, (b) hairpin moiety replaced by calixnucleoside **1**, (c) hairpin moiety replaced by calixnucleoside **3** or **4**.

with 1,3-diaminocalix[4]arene **7**[12] to give homocoupled calixnucleoside **4** in 43% yield. For the synthesis of heterocoupled calixnucleosides **1** and **2**, we first prepared monocoupled calixnucleoside **5** through peptide coupling of 5′-acid thymidine derivative **6** (1.2 equiv.) with 1,3-diaminocalix[4]arene **7** in 58% yield. Calixnucleoside **2** was obtained through another peptide coupling of 3′-acid thymidine derivative **8** with monocoupled calixnucleoside **5** in 64% yield. Calixnucleoside **1** was finally prepared by deprotection of **2** in 83% yield. In our synthesis we utilized the amide bond as the hybridizing linkage because it is a well known moiety in nucleotide backbone modification for antisense ONDs.[13]

X-Ray diffraction-grade single crystals of calixnucleosides **4**[14] were grown by slow solvent evaporation of a MeOH solution of the compound. The resulting X-ray crystallographic data has offered a wealth of structural information and molecular interactions. Calixnucleoside **4** has C_2 symmetry and two thymine bases have anti-parallel orientation. Two amide linkages, which are used for linking nucleosides and calix[4]arene, have anti-parallel orientation too. Dihedral angles of amide linkages and thymine bases are nearly 90° (Fig. 3). Distance between substituted benzene rings is 3.9 Å and unsubstituted ones is 9.9 Å (see supporting information). Calix[4]arene moiety shows a pinched cone conformation. The preference of pinched cone conformation is due to the fact that each amide linkages come into close enough distance for hydrogen bonds with thymine base. Molecules of calixnucleosides **4** are linked in a two dimensional network through eight intermolecular hydrogen bonds (N–H···O) between thymine base and amide linkage (Fig. 4). This



Scheme 1. Synthesis of calixnucleosides. *Reagents and conditions*: (a) (i) **6** (2.4 equiv.), TBTU, HOBT, 4-methylmorpholine, CH_2Cl_2, rt, 30 min, (ii) **7** (1.0 equiv.), 4 h, 69%; (b) (i) **6** (1.2 equiv.), TBTU, HOBT, 4-methylmorpholine, CH_2Cl_2, rt, 30 min, (ii) **7** (1.0 equiv.), 1 h, 58%; (c) (i) **8** (2.4 equiv.), TBTU, HOBT, 4-methylmorpholine, CH_2Cl_2, rt, 30 min, (ii) **7** (1.0 equiv.), 1 h, 43%; (d) (i) **8** (1.2 equiv.), TBTU, HOBT, 4-methylmorpholine, CH_2Cl_2, rt, 30 min, (ii) **5** (1.0 equiv.), 3 h, 64%; (e) TBAF, THF, rt, 10 min, 83%.

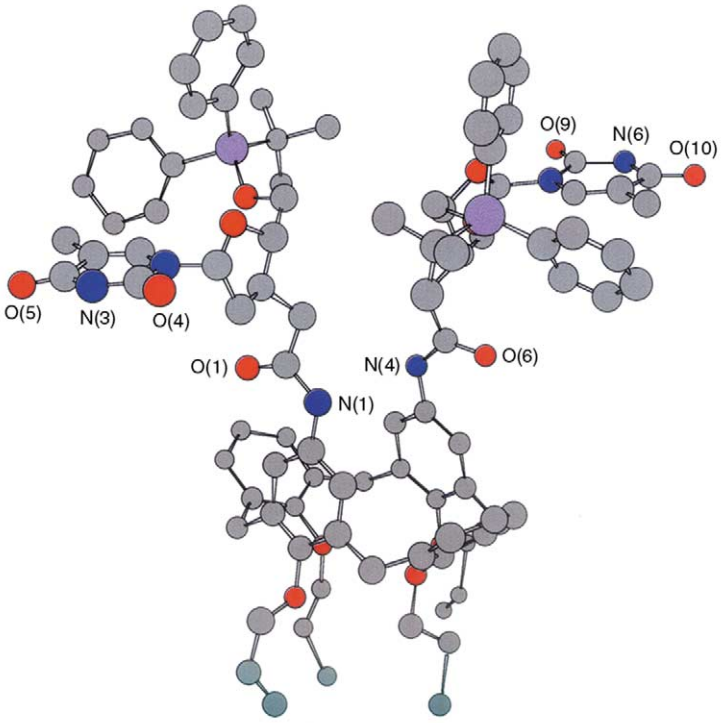


Figure 3. X-Ray crystal structure (Chem 3D rendering) of **4**. Disorder around propyl ether not shown.

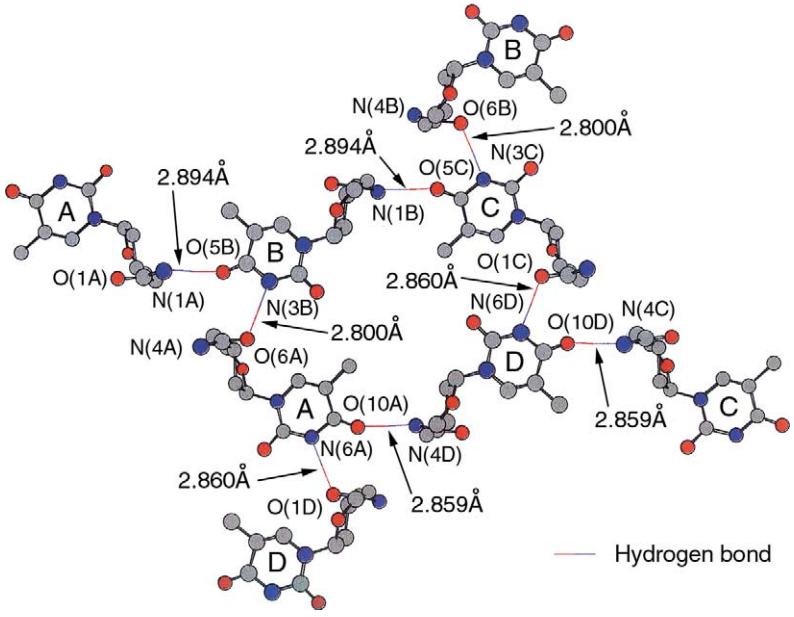


Figure 4. (Top view) Hydrogen-bonding patterns in the packing diagram (Chem 3D rendering) of **4**. Four calixnucleoside molecules **A**–**D** are shown and the calix[4]arene moieties and protection groups are omitted for clarity.

network could be separated into four layers (Fig. 5). Layers 1 and 4 contained hydrophobic residues (calix[4]arene moieties) and layers 2 and 3 contained hydrophilic residues (thymidine derivatives and amide linkages). This packing diagram of crystal structure looks like a bilayer. The signal obtained in the ^{1}H NMR spectra of this sample recorded at 300 MHz in $CDCl_3$ was too broad to assign. However, addition of a small amount of CD_3OD made the signal quite sharp to assign. This dramatic change notified us that compound **4** was not remained monomeric species but aggregated each other through hydrogen bonding in $CDCl_3$ as like crystal structure (see supporting information, Figure S4).

A Job plot was carried out using ^{1}H NMR for the determination of complex pattern between calix-thymidine compound **2** and 3′,5′-di-*O*-acetyl-2′-

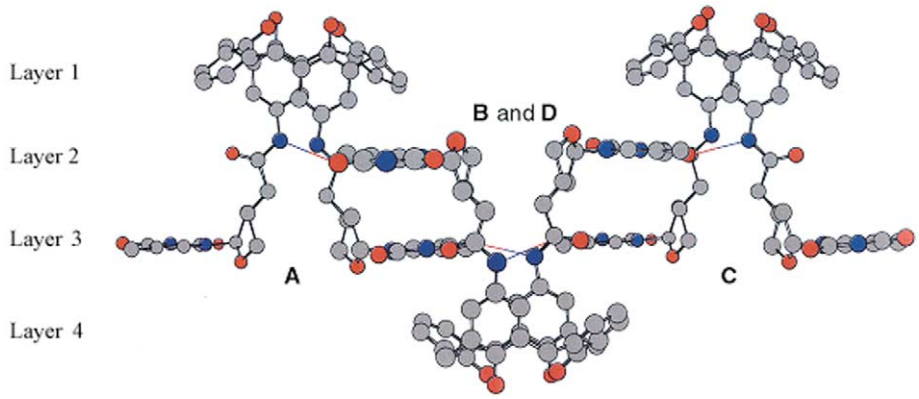


Figure 5. (Side view) The packing diagram of **4**. Four calixnucleoside molecules **A**–**D** are shown and the propyl and protection groups are omitted for clarity. Calixnucleoside molecules **B** and **D** are exactly overlapped.

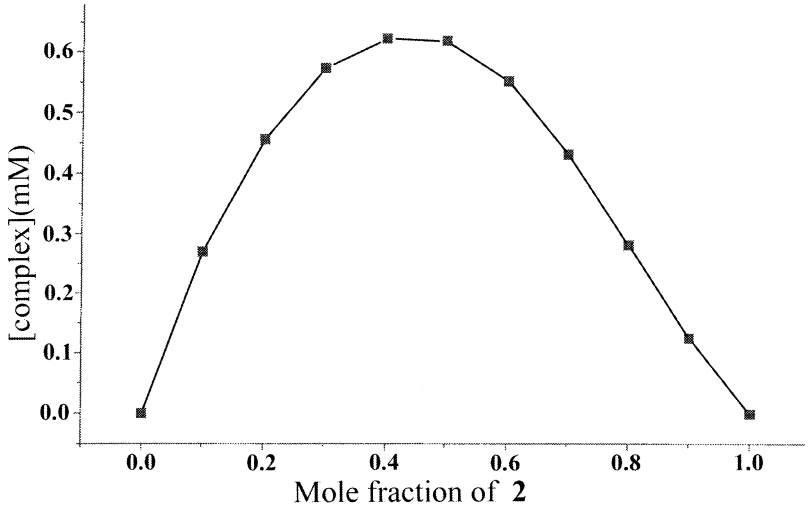


Figure 6. Job plot between **2** and 3′,5′-di-*O*-acetyl-2′-deoxyadenosine ([**2**]+[3′,5′-di-*O*-acetyl-2′-deoxyadenosine]=4.2 mM).

deoxyadenosine (Fig. 6). The signal of thymidine base protons in calixthymidine compound **2** shifted downfield when the 3′,5′-di-*O*-acetyl-2′-deoxyadenosine was added to the solution of compound **2** (see supporting information). This result shows that calixthymidine compound **2** makes 1:1 complex with 3′,5′-di-*O*-acetyl-2′-deoxyadenosine and it may be served as a useful scaffold for the DNA hairpin structure mimic.

In summary, homo- and heterocoupled calixnucleosides have been synthesized through peptide coupling and X-ray crystallographic study of calixnucleoside **4** shows that calix[4]arene moiety has a pinched cone conformation through four independent intermolecular hydrogen-bonding sets between thymine bases and amide linkages. Currently we are preparing calixoligonucleotides (hybrid molecules between calix[4]arenes and oligonucleotides) and investigating whether they can restrict important biochemical process (translation and transcription) by triplex formation. The results of calixoligonucleotides will be reported in due course.

Supplementary material

Synthetic details, characterization data of calixnucleosides **1**–**4**, details of crystal structure and Job plots are available from the author upon request.

Acknowledgements

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14. Crystal data for **4** ($C_{96}H_{114}N_6O_{14}Si_2{\cdot}4H_2O$): $M_r=1704.18$, monoclinic, space group $P2(1)$, $a=14.36670(10)$, $b=19.87010(10)$, $c=18.0957(2)$ Å, $\alpha=90.0000$, $\beta=103.9570(10)$, $\gamma=90.0000°$, $V=5013.23(7)$ Å^3, $Z=2$, $D_{calcd}=1.129$ Mg m^{-3}, Mo Kα radition ($\lambda=0.71073$ Å), crystal dimensions $0.40\times0.30\times0.10$ mm^3. Of 20498 reflections collected on a Siemens SMART diffractometer with CCD detector, 12375 were observed ($R_{int}=0.0327$) and used for all calculations (SHELXL-97 program). After absorption correction (ψ scans) the structure was solved by direct methods and refined anisotropically on F^2. Final residuals $R_1=0.1033$, $wR_2=0.2738$ ($I>2\sigma(I)$); $R_1=0.1334$, $wR_2=0.3134$ (all data), 1103 parameters.