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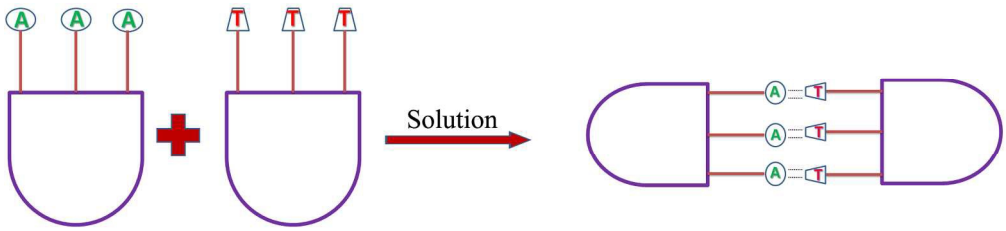

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ARTICLE

Bio-inspired self-assembled molecular capsule

Pardhasaradhi Satha, Giriteja Illa, Arindam Ghosh,† Chandra Shekhar Purohit*

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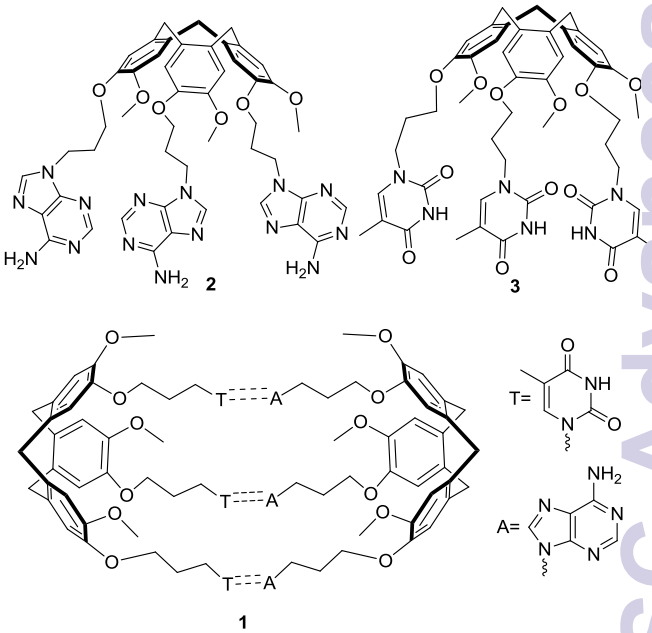
Abstract : Bowl shaped molecules are useful for making molecular capsules with suitable non-covalent bond. Bowl shaped Cyclotriguaiacylene can be suitably modified at its phenolic groups for attaching suitable functionlity to construct molecular capsule. In this work, a molecular capsule has been prepared by appending adenine and thymine in Cyclotriguaiacylene. These blocks when mixed in mixture of solvents give a molecular capsule as ascertained by mass and NMR spectroscopy.

Introduction

Molecular capsules have recently emerged as a subject of great interest due to their possible applications in various fields. For example, their ability to carry guest molecules, and release under mild change in condition, is an important feature in drug delivery.[1] Molecular capsules when used as reaction vessels, can accelerate the reaction speed as compared to the bulk solvent environment,[2] and can trap the unstable molecules or reactive intermediates at room temperature.[3] Self-assembled molecular capsules can also be used for molecular recognition and as sensing materials.[4] Molecular capsule formed by non-covalent interaction(s) such as hydrogen bonding, is highly desirable as these bonds can easily be broken by subtle change in environment.

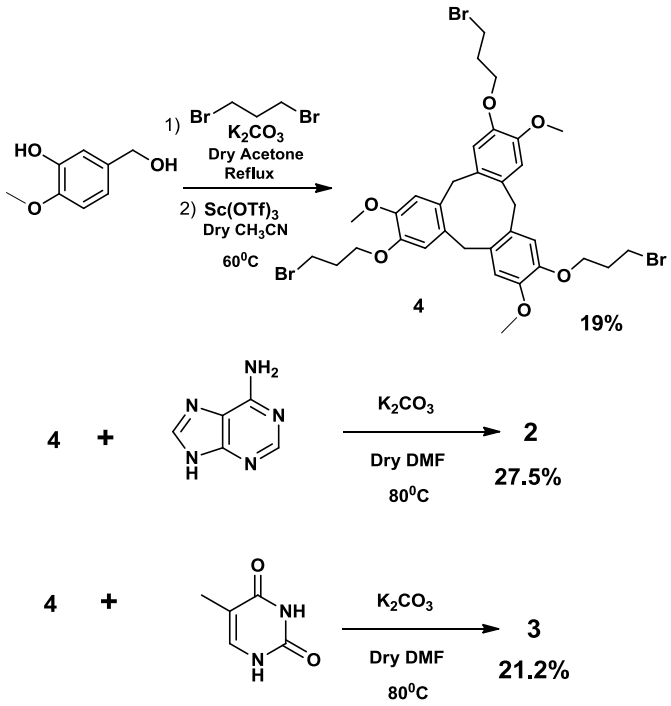
Molecular recognition and self-assembly is strongly governed by the molecular components they contain and the type of interaction(s) that hold them together. Among naturally occurring molecules, nucleobases are well known for their specific Watson-Crick hydrogen bonding. Due to directionality and specificity in Watson-Crick base pairing and π–π stacking capability of nucleobases, they hold DNA single strands to form a double helical structure in cellular milieu that helps DNA to replicate and preserve genetic code. Chemists used this interaction beyond natural realm to assemble molecular building blocks.[5] Many examples such as triblock copolymer,[6] biocompatible materials with embedding nucleobase to poly(e-caprolactone),[7] molecular recognition motif,[8] energy- and electron-transfer systems have been reported in literature.[9] Chemists also use them as metal coordinating ligand for formation of different super structures;[10] constructs MOF and use their coordination polymer as catalyst, absorption materials, and drug delivery vehicles.[11] The major challenge, however, remains with preparation of predefined super-structures that are soluble in suitable solvent.[12]

Macrocyclic-based systems such as cyclodextrins, carcerands, calix[4]arenes, and resorcinol-based systems are extensively used for making capsules.[13] Bowl shape of cyclotriguaiacylene (CTG) (Scheme 1), a calixarine analogue, is considered appropriate for making such molecular capsules due to its bowl shape. Few examples are known; by means of covalent bond, hydrogen bond, and due to complex formation with metal ions.[14] Some of them are also known to capture metal ion, organic molecules in their cavity.[15] In continuation of our work,[16] we modified the CTG, to append nucleobase adenine and thymine, so that they can form molecular capsule upon combination in a solution. Very few studies with calixarine nucleobase conjugates are reported in literature. The conjugates are evaluated for various functions.[17] No attempt has been made so far to make nucleobase CTG or related molecules to best of our knowledge.



Scheme 1: Structure of CTG-nucleobase conjugates and most probable way of capsule formation. Dotted line represents hydrogen bonding.

[a] National institute of science education and research, IOP campus, Sachivalayamarg, Bhubaneswar, Odisha, 751005.
† Query related to NMR may directly be send to AG (aringh@niser.ac.in).
Electronic Supplementary Information (ESI) available: synthesis scheme, details experimental procedure and characterization data. See DOI: 10.1039/x0xx00000x



Scheme 2: Preparation of the target molecules

Results and discussions:

Being bowl shaped, CTG is a good candidate for preparation of molecular capsule. Also, it has phenolic functional groups that can easily be modified to desired functional group. We planned to prepare two molecules by introducing two complimentary nucleobase on CTG by modifying the phenolic group. The central idea behind introducing two complimentary nucleobases is that, these modified CTG would then dimerize by well-known Watson-Crick hydrogen bonding to give a supramolecular capsule when brought together in a solution. (Scheme 1). We choose adenine and thymine for incorporation. This was done by reacting dibromopropane with Vanillyl alcohol to produce alkyl halide suitable for trimerisation using literature procedure. Briefly, trimerisation was carried out using $Sc(OTf)_3$ as a lewis acid in acetonitrile to get the trialkylhalide derivative of CTG with 19% yield. It was then reacted with adenine or thymine under basic condition to get the desire molecules (Scheme 2).

To verify our assumption that these monomers will indeed give molecular capsule through formation of AT dimer, we recorded HRMS spectra. Well characterized monomer solutions were prepared in CH_3CN:CH_3OH (1:1, v/v) and mixed in 1:1 ratio. The solvent mixture was necessary to solubilise the molecules. They were sonicated for one hour at 50°C, cooled to room temperature, filtered and then injected for recording mass spectra (Fig. 1). The spectrum contains a peak at 1841.80 which corresponds to the desired capsule mass, along with another peak at 1868.83 that matches well with AA dimer. Corresponding complexes with Na ion were also found as shown in the spectra. No peak corresponding to TT dimer was observed.

To prove further, that the self assembly exists in solution, we carried out a NMR experiment, namely, Diffusion-ordered spectroscopy (DOSY). This method is being used as a powerful non-invasive technique to estimate the effective size and molecular weight of a molecular species in a given set of conditions and with the assumption that the molecule is spherical.[18] The poor solubility of the compounds in both low polar and high polar solvents imposed a constraint for NMR studies in any single NMR solvent. To overcome this, we have chosen a mixture of polar and non-polar solvents (CD_3OD and CCl_4) in 1:1 (v/v) ratio, to perform the NMR experiment.

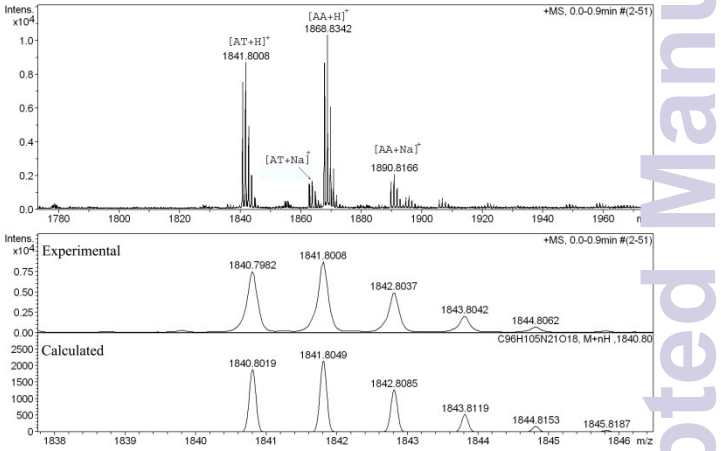


Fig. 1: Expanded ESI-Mass Spectra of the Capsule.

The famous Stokes-Einstein formula for translational diffusion coefficient (D) of spherical solute molecules that are large compared to the solvent molecules relates D with radius of solute molecule (a) as, $D=(kT)/(6\pi\mu a)$, where, k is the Boltzmann constant, T is absolute solvent temperature, μ is the coefficient of viscosity of the diffusion medium.[19] The radius a, in turn relates to the mass, M, of the solute molecule as $M=4\pi a^3\rho/3$, ρ being the density. Two molecules with different masses, M_1 and M_2, would then give two translational diffusion coefficients, D_1 and D_2, related as $D_1/D_2=(M_2/M_1)^{1/3}$, provided all other experimental conditions remain unaltered. In the present system, the monomers are having nearly identical molecular weight. Therefore, if the dimer which would be a self-assembled molecular capsule, exists in solution, can be easily known by this technique, comparing the ratio of diffusion coefficients. The translational diffusion coefficients were measured using the pulsed field gradient stimulated echo (PGSE) experiment with bipolar gradients to minimize Eddy current caused by the gradients. In this experiment attenuation of a NMR resonance signal is measured as a function of gradient strength. The peak intensity (I) for any particular gradient strength (g), normalized with respect to the non-attenuated intensity (I_0) follows a relationship $I/I_0=\exp(-D\zeta g^2)$. ζ is a constant that depends on the gyromagnetic ratio of the spins under investigation and few experimental parameters and can easily be calculated. Log of (I/I_0) plotted against squared gradient strength (g^2) gives a straight line with a negative slope of $D\zeta$ from where D is calculated. During the experiments, we have recorded diffusion coefficients of **2** to be $3.9\times10^{-10}m^2/s$. The

corresponding value for a mixture of **2** and **3**, prepared the previous night, was found to be 3.25×10^{-10} m^2/s (Fig. 2). The ratio of these values is 1.2 which agrees reasonably well with the theoretical value of $2^{1/3}$=1.25, expected for a capsule of double molecular weight of that of the corresponding monomers.

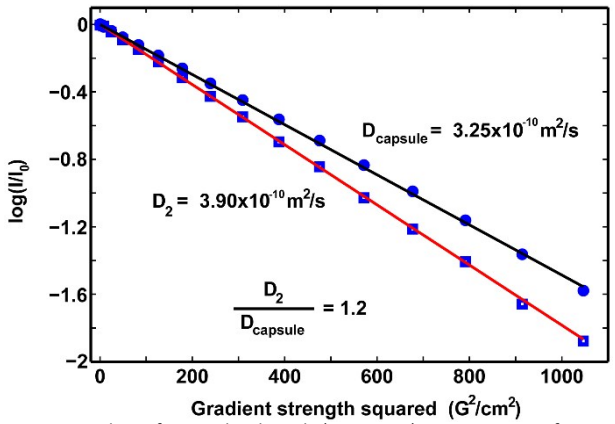


Fig. 2:. Logarithm of normalized peak (at 8 ppm) intensity as a function of squared gradient strength. The slopes determine diffusion coefficients for the capsule of **2**. The ratio of coefficients is 1.2 against theoretically expected value of 1.25.

We also measured the diffusion coefficient of a freshly mixed monomer solutions to capture the formation of the capsule through gradual change of diffusion coefficient from the monomeric value to the value of the capsule. The experiment gave an interesting result (Fig. 3). While the final data points fit to a slope matching with the D for a fully formed capsule, the initial data points give a D that is one order of magnitude larger than that of the monomer. Possible explanation could be the pockets of high temperature generated within the solvent due to the formation of hydrogen bonds (exothermic reaction) in the process of the capsule formation. It is expected that the Stokes-Einstein formula would be violated if solvent temperature does not remain constant during the entire experiment.

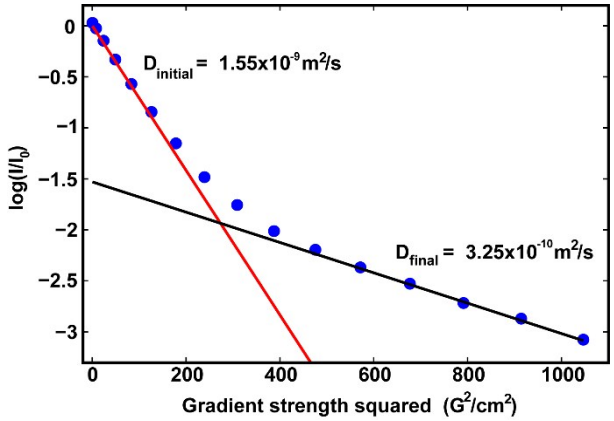


Fig. 3: Diffusion coefficient measured for a fresh mixture of **2** and **3**. The existence of two slopes indicates formation of the capsule

It is well known that AT dimer is preferred over AA or TT dimer and easily emerge under suitable condition.[20] From the DOSY data, it is very clear that dimer exists in solution. Most possibly, a capsule is forming due to hydrogen bonding between adenine and thymine residue in the molecules. To confirm this, we carried out a variable temperature NMR experiment. In Watson-Crick hydrogen bonding, the exocyclic N^6 hydrogen atoms of adenine get involved. As the strength of hydrogen bonding depends on temperature, a temperature dependent NMR would reveal the participation of adenine-N^6 in dimer formation, which in-turns will prove the formation of Watson-Crick type of bonding between the monomers. We deliberately did not change the solvent system used in DOSY experiment, although there is a possibility of deuterium exchange, which might reduce the signal intensity.

For this experiment, initially, ^{1}H NMR was recorded for compound **2**. A broad singlet peak at 7.7ppm can be attributed to the NH_2 of adenine (ESI, Fig. S13). A mixture of 1:1 molar ratio of **2** and **3** are used to record a 1H NMR at 298K and the peak at 7.7ppm was shifted to 0.1ppm downfield to 7.8ppm. By varying temperature from 253K to 328K the amine peak was varied from 7.9ppm to 7.72ppm where as the other peaks remains in the same position (Fig. 4). This indicates the involvement of adenine exocyclic amine group in hydrogen bonding. As expected, the signal intensity decrease with increase in temperature but the shift could be well established.

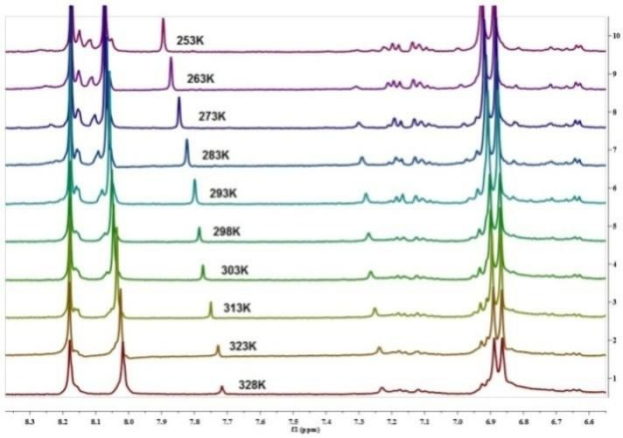


Fig. 4: The temperature dependent NMR of the (1:1 of 1:2) complex from 328 k to 253K from bottom to top.

Through DOSY it is proved beyond doubt that there is a dimer formation. However, it is important to ascertain that the dimer is formed by a three point interaction (capsule) and not by one or two point hydrogen bonding between molecules (open dimer). The capsule formation is confirmed by analysing 1D NMR spectra of **2** and **1**. **2** has three sets of equivalent amino protons. In the case of capsule formation, as all of them form hydrogen bond, they become equivalent and therefore would give a single peak. But if the interaction is either one or two point in case of **1**, there would be two signals of these protons and one of them would come at the identical ppm value that of **2.** In case of **2**, peak at 7.7 ppm is assigned to the amino protons. This is shifted to 7.79 in **1** and no other peak could be found at 7.7ppm (Fig-S16). This clearly indicates that the dimer is a symmetrical molecule and thus is a capsule formed by three point interaction.

Several attempts to grow suitable single crystals of the compounds for X-ray analysis were not successful. Therefore,

we examine the morphology in solid state of the compounds, by using scanning electron microscopy (SEM). Images of the individual half moieties and the capsule **1** were recorded (Fig. S17)**.** Same concentration of samples were prepared in CCl_4:CH_3OH (1:1, v/v) and capsule was prepared by mixing 1ml of **2** with 1ml of **3** and kept for overnight. From these solutions, 30μL was taken and deposited on a 100 silicon wafer, dried for 12 hours in a vacuum desecrator, then imaged. **2** show extensive microfibers all over the surface (Fig. 4a and 4b), while **3** shows aggregated spherical structures. The combined solution supposedly capsule, were not found rather look like a combination of **2** and **3,** with spheres are linked with fibre. This might be due to the evaporation of solvent molecules causing the spheres to collapse. However, it is difficult to find the possible cause for this morphological change.

Experimental Section

Materials: All the reagents are purchased from Aldrich and used as received. All the solvents received from Merck limited and dried according to the standard conditions.

Physical measurements: ESI-Mass was recorded on a Bruker micrOTOF-QII.NMR was recorded with a Bruker 400MHz instrument.

Synthesis of the compounds:

(3-(3-bromopropoxy)-4-methoxyphenyl)methanol(5):[21]

Vanillyl alcohol (5g, 32.45m.mol) was dissolved in 30 ml of dry acetone and anhydrous K_2CO_3 (5.4g, 38.94mmol) was added under N_2 atmosphere, to this solution 1, 3 dibromo propane (30.485g, 162.25m.mol) was added and refluxed overnight. The reaction mixture was filtered and solvent was evaporated under reduced pressure, to this diethyl ether was added most of the di-allkylated product was precipitated and filtered. The diethyl ether layer was washed with water and ether layer evaporated and crude product was purified by column chromatography using (20%Hexane+80%EtOAc) as elutent. The product obtained as a white solid (6.7g, 74%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.27-2.38, m, 2H), (3.61, t, 2H), (3.86, s, 3H), (4.13, m, 2H), (4.61, s, 1H), (6.85-6.94, m, 3H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (30.27, 32.49, 56.05, 65.35, 67.00, 111.16, 113.80, 119.56, 134.33, 147.84, 149.87). m/z calculated for $C_{11}H_{14}BrO_2$ (corresponding tropylium cation) is 257.0206, found 257.0172.

2,7,12-tris(3-bromopropoxy)-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g]cyclononene(CTG-Br(4)):

CTG-Br was prepared according to a reported procedure.[22] The allkylated vanilly alcohol (5) (6.6g, 23.98m.mol) was dissolved in dry acetonitrile 15 ml under N_2 atmosphere, to this solution Sc(OTf)3(118mg, 0.239m.mol) was added and kept at 700c for overnight. The solution was evaporated under reduced pressure to this DCM was added and washed with water the DCM layer was dried under anhydrous Na_2SO_4 and the DCM was evaporated under reduced pressure. The crude product purified by column chromatography (silica 100-200) DCM as elutent yielded a white coloured solid (3.5g, 19%).^{1}HNMR (400MHz, $CDCl_3$) δ: (2.29-2.37, m, 2H), (3.54, d, J=16Hz, 1H), (3.59-3.64, m, 2H), (3.83, s, 3H), (4.09-4.17, m, 2H), (4.74-4.78, m, 2H), (6.85, s, 1H), (6.91, s, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δ: (30.45, 32.28, 36.46, 56.24, 67.08, 113.70, 115.88, 131.81, 132.66, 146.85, 148.47). ESI-Solid state mass m/z calculated for $C_{33}H_{39}Br_3O_6$ (M+2) is 770.0021 found 770.0273

9,9',9''-(((3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,7,12-triyl)tris(oxy))tris(propane-3,1-diyl))tris(9H-purin-6-amine) (2)):

Adenine (522mg, 3.862mmol) was suspended in 10ml Dry-DMF, to this suspension anhydrous K_2CO_3 (533 mg, 3.862m.mol) was added and kept under N2 for 30 min. To this suspension CTG-Br (0.9g, 1.17 mmol) dissolved in 15ml Dry-DMF was added and kept at 80^{0}C for 48 hours and filtered, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica 100-200) DCM:MeOH (92:8) the product obtained as a white coloured solid(300mg, 27.5%).^{1}HNMR (400MHz, DMSO-d6) δ: (2.21-2.28, m, 2H), (3.43, d, J=12Hz, 1H), (3.62, s, 3H), (3.82-3.96, m, 2H), (4.27-4.30, t, 2H), (4.64, d=12Hz, 1H), (7.00, s, 1H), (7.03, s, 1H), (7.21, s, 2H), (8.10, s, 1H) (8.15, s, 1H); ^{13}CNMR (100MHz, DMSO-d_6) δ: (28.88, 34.98, 48.57, 55.82, 65.89, 113.83, 115.60, 118.82, 131.92, 132.62, 140.91, 146.13, 147.73, 149.51, 152.32, 155.92); ESI-HRMS: m/z calculated for $C_{48}H_{51}N_{15}O_6$ ($M+H^+$) is 934.4220, found 934.4244.

1,1',1''-(((3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,7,12-triyl)tris(oxy))tris(propane-3,1-diyl))tris(5-methylpyrimidine-2,4(1H,3H)-dione)(3)):

Thymine (541mg, 4.29m.mol) was suspended in 10ml Dry-DMF, to this suspension anhydrous K_2CO_3 (593.8 mg, 4.29m.mol) was added and kept under N_2 for 30 min. To this suspension CTG-Br (1g, 1.30m.mol) dissolved in 15ml Dry-DMF was added and kept at 80^{0}C for 48 hours and filtered, the solvent was evaporated under reduced pressure. The product was partitioned between DCM and water, DCM layer was washed with conc. HCl and organic layer was dried under anhydrous Na_2SO_4 the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica 100-200) DCM:MeOH (94:6) the product obtained as a white coloured solid (250mg, 21.2%).^{1}HNMR (400MHz, DMSO-d_6) δ: (1.68, s, 3H), (1.97, m, 2H), (3.46, d, J=16Hz, 1H), (3.67, s, 3H), (3.74, t, 2H), (3.91-3.95, m, 2H), (4.66, d, J=12Hz, 1H), (7.04, s, 1H), (7.07, s, 1H), (7.45, s, 1H), (11.18, s, 1H). ^{13}CNMR (100MHz, DMSO-d_6) δ: (11.83, 28.10, 35.01, 44.97, 55.86, 66.14, 108.36, 113.83, 131.92, 132.57, 141.44, 146.15, 146.41, 147.71, 150.90, 164.27)

ESI-HRMS: m/z calculated for $C_{48}H_{54}N_6O_{12}$ ($M+H^+$) is 907.3871, found 907.3846.

NMR experiments: All NMR experiments were carried out on a 9.39Tesla 400MHz AVANCE-III Bruker liquid state spectrometer equipped with BBFO-Plus broadband probe. The maximum gradient strength allowed by the probe is 50 G/cm. Experiments were performed at ambient temperature (27°C). During experiments it was found that the machine could not

automatically lock the sample as the sample was prepared in a mixture of two different deuterated solvents (CCl_4 and CD_3OD). A manual lock was therefore performed by suitably adjusting the Z0 field value. The diffusion experiments were performed with 8 scans for each gradient strength and with 16 different gradient strengths varied linearly from 2% to 95% of the maximum gradient strength. Duration of gradient pulses was 1500 μs and diffusion delay of 70 ms was used for all experiments. As identical diffusion delay was used for all experiments, relaxation effect did not interfere with the calculation of D.

SEM experimental details: The sample was prepared by dissolving 1mg of the corresponding compound in 1ml of methanol and carbontetrachloride (1:1, v/v) filtered through a 0.22micron syringe driven filter. 20 μL of this solution was deposited on a clean 100 silicon wafer, dried by air and kept in vacuum desiccators for 8h. This was then imaged through a FESEM (carl Zeiss, germany).

Conclusions

In summary, we have synthesized CTG analogues decorated with adenine and thymine. They were characterized well. Upon mixing them in suitable solvent they form a capsule due to AT dimer formation. This is proven through HRMS and NMR studies. The major problem still remain is their solubility in water like solvent. We are in a process of adding suitable functionality for making them water soluble.

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