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Synthesis and characterisation of new ditopic receptors for guanosine

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Abstract—Novel ditopic receptors for guanosine have been prepared and characterised. Their association constants with a lipophilic guanosine derivative are somewhat smaller than the expected values for a guanosine–cytidine base pair, but remain in a useful range for building supramolecular structures.

1. Introduction

The construction of supramolecular complexes[1] based upon the use of hydrogen bonding is a popular and successful strategy.[2] The recognition code embedded in nucleobases[3] makes them attractive sub-units for the preparation of many supramolecular aggregates and there are now a number of examples where nucleobases have been used to make discrete structures[4] and two-dimensional arrays.[5] We have been preparing a modular construction set based around the guanosine–cytidine (G·C) base pair because it forms predictable complexes with a viable association constant in non-polar environments. The G·C base pair has found less application in supramolecular chemistry than the adenine–thymine (A·T) pair, in part due to the notoriously low solubility and self-aggregation of guanosine based systems.[6] Despite these inherent problems the G·C base pair has found some application in supramolecular chemistry including the synthesis of a rigid guanosine derived molecule which self-associates through a novel four-point hydrogen bonding interaction,[7] an 'artificial dinucleotide duplex',[8] a self-assembled electron transfer pair[9] and a tape-like aggregate.[10] We now wish to disclose our own work on a related system. We have designed and synthesised a ditopic molecular receptor based around cytosine linked through an acetylenic axle (Fig. 1). A similar strategy has recently been used to prepare nucleobase 'ferroreceptors'[11] allowing hydrogen bonded complexes to be built up around the rigid acetylenic axle. The synthesis exploits well-precedented Sonogashira coupling reactions[12] allowing ready access to both mono- and bis-alkynyl receptors **1** and **2**, respectively. Through the use of ^{1}H NMR titration we have determined association constants for the interaction of lipophilic guanosine derivatives with the ditopic receptors **1**, **2** and the corresponding half-molecule.

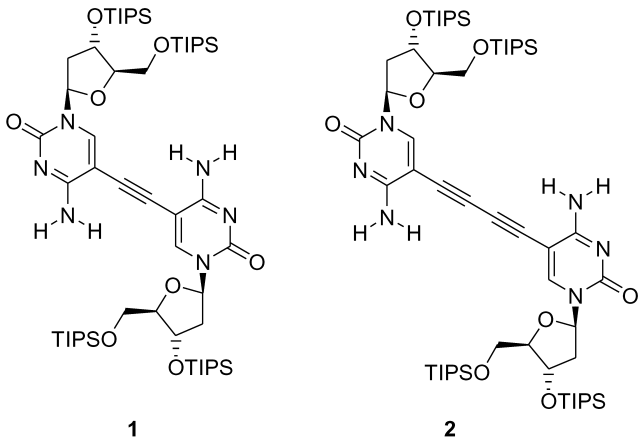

Figure 1.

2. Design

The receptors were designed to have two hydrogen bonding sites linked through a conjugated bridge. This potentially allows electronic communication between hydrogen bonding sites, as well as providing functionality which may find application in the arena of molecular electronics. The ribose hydroxyl functions are ideal sites for attachment of triisopropylsilyl solubilising groups[13] to allow investigations into supramolecular structure to be carried out in non-polar solvent.[14]

3. Synthesis

The route used for the synthesis of receptors **1** and **2** is

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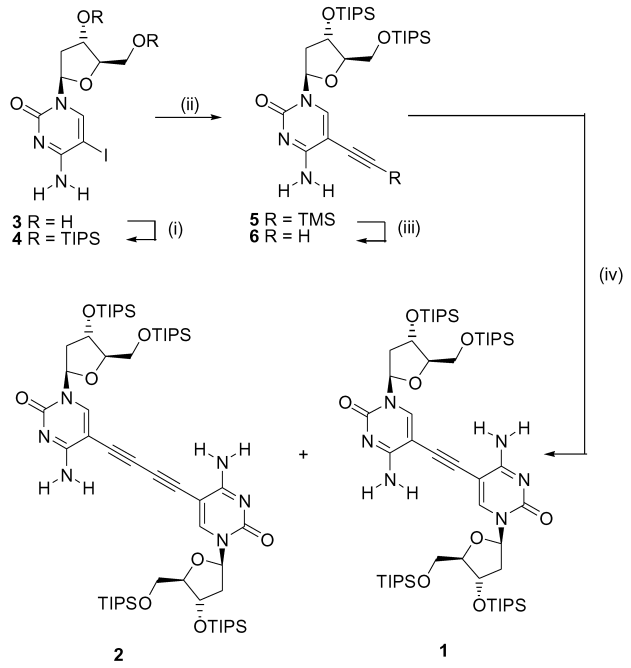


Scheme 1. *Reagents and conditions*: (i) triisopropylsilyl chloride, imidazole, DMAP, DMF (62%); (ii) trimethylsilyl acetylene, $Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, dark, rt (90%); (iii) Na_2CO_3, H_2O–MeOH, 2 h, rt (97%); (iv) **4**, $Pd(PPh_3)_2Cl_2$, CuI, diisopropylamine, dark, rt (**1**: 54%; **2**: 36%).

shown in Scheme 1. Protection of the hydroxyls in 5-iodo-2′-deoxycytidine **3** using triisopropylsilyl chloride gave material **4** which is soluble in non-polar solvent. Sonogashira coupling of this intermediate with trimethylsilyl acetylene under conditions described for related systems[15,16] proceeded in good yield to give intermediate **5** which was deprotected under basic conditions to give terminal acetylene **6**. Purification by flash chromatography required dry loading of the compound onto silica gel prior to loading onto the column, otherwise blockage of the column resulted. The synthesis of the mono-alkynyl receptor **1** was then accomplished through a second Sonogashira coupling of **6** with protected 5-iodo 2′-deoxycytosine **4**.

It was found that on certain occasions an appreciable amount of self-coupling of **6** also occurred to give the di-alkynyl receptor **2**. At first this was believed to be due to ingress of oxygen, although the presence of residual copper(II) in the CuI may itself encourage self-coupling of acetylenes after the fashion of an Eglinton–Hay coupling (vide infra). Acetylene **6** was crystalline and slow growth from isopropanol gave crystals whose molecular structure was solved by X-ray crystallography (Fig. 2). Interestingly this cytosine derivative showed no intermolecular hydrogen bonding contacts other than to solvent. This was somewhat surprising given cytidine's ability to self-associate into a dimer in the solid state[17] and solution[14] and this observation may be due to a preferential packing interaction of the triisopropylsilyl groups with one another.

Although crystals of receptor **1** of a suitable size for analysis by X-ray crystallography were grown from alcoholic

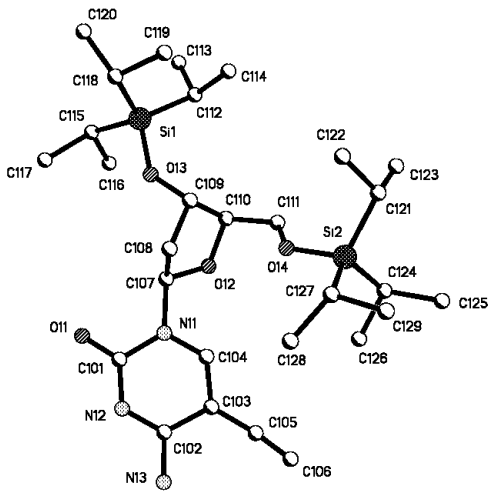


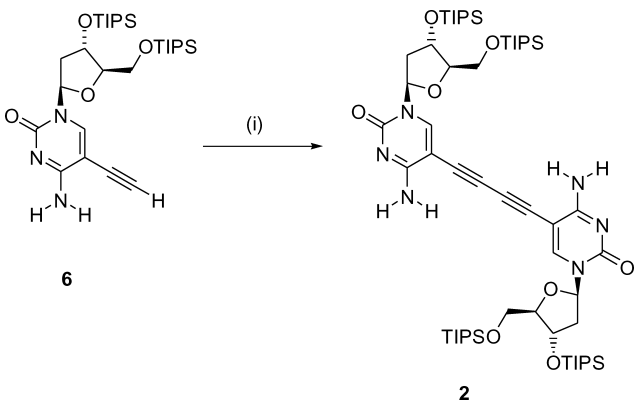
Figure 2. Molecular structure of **6** (X-ray: H's not shown).

solvents, none diffracted well enough to allow high quality data to be collected.

The longer dialkynyl receptor **2** was better prepared by one of two methods. The first method used was a classical Eglinton–Hay[18] coupling under atmospheric oxidation conditions. The second was a more recent method involving the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ and CuI using iodine as the co-oxidant to regenerate the active Pd(II) catalyst.[19] This gave a good yield of receptor **2** without the need to remove large amounts of copper impurities (Scheme 2).

Crystals of **2** grown from isopropanol were of a sufficient quality to allow the molecular structure to be solved by X-ray diffraction (Fig. 3). In contrast to the half-molecule **6**, contacts between the pyrimidine amino groups (N-9 and N-14) were evident in the form of classical cytidine dimers[17] (Fig. 4) leading to a helical supramolecular ribbon with a narrow central channel (Fig. 5).

In addition there is another hydrogen bond contact evident between the pyrimidine carbonyl and the amino groups leading to a secondary supramolecular structure (not shown). The triisopropyl groups were sufficiently disordered to preclude refinement of the alkyl side-chains,



Scheme 2. *Reagents and conditions*: (i) $Pd(PPh_3)_2Cl_2$, CuI, I_2, diisopropylamine, rt (78%).

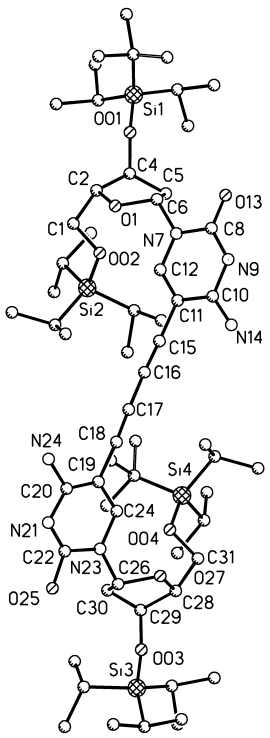


Figure 3. Molecular structure of receptor **2** (X-ray).

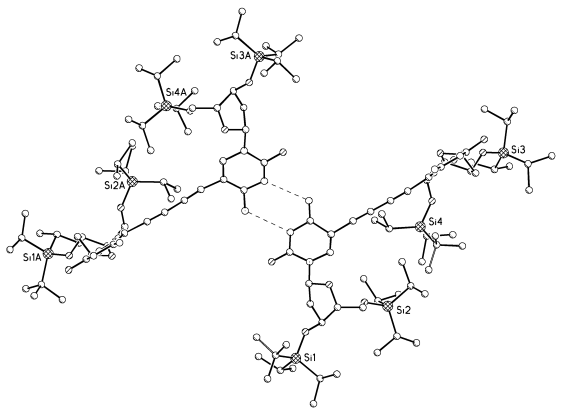


Figure 4. Cytidine dimer contacts in receptor **2**.

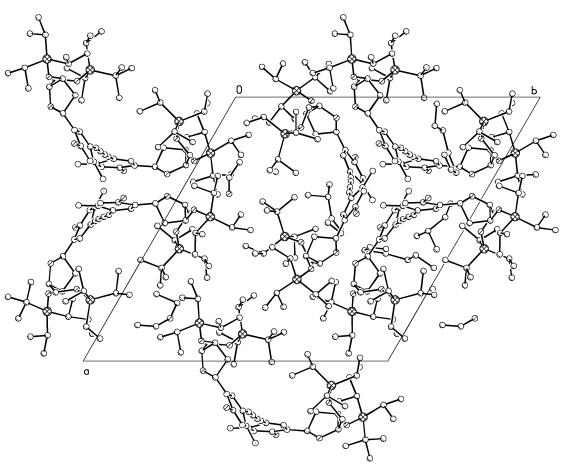
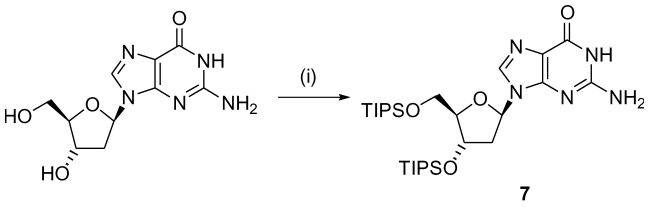


Figure 5. Packing diagram showing helical channel.



Scheme 3. *Reagents and conditions*: (i) triisopropylsilyl chloride, imidazole, DMAP, DMF (61%).

although hydrophobic contacts between individual helical arrays are evident in the unit cell.

The partner lipophilic guanosine molecule **7** was readily prepared following a literature procedure by silylation of the hydroxyls with triisopropylsilyl chloride (Scheme 3).[13,14]

4. Self-assembly

The association of nucleobases, in particular guanosine and cytidine is well documented and has been studied using various physico-chemical techniques including ^{1}H, ^{13}C NMR[14,20,21] and infra-red[22] spectroscopies. We wanted to carry out ^{1}H NMR titrations to determine the association constants of the mono- and ditopic receptors to verify that the association constants remained in the usable ($\geq 10^{3}\ M^{-1}$) range.

The first association constant we wished to determine was that between monotopic receptor **6** and protected guanosine **7**. The signal chosen to follow was the most mobile, the guanosine amido proton at δ=12.0 ppm which was found to move downfield to 13.1 ppm in the presence of 1 equiv. of the receptor. Under our conditions it was found to remain sufficiently visible without becoming over-broad although it should be noted that a more satisfactory method may be to observe the guanosine H-8 proton.[22] Prior to determining the association constant, a Job's plot analysis[23] was performed to assay the stoichiometry of the interaction and from the maximum of the parabola the expected 1:1 stoichiometry of **7**:**6** (Fig. 6) was obtained. The concentrations chosen for the subsequent analysis were 2×10^{-4} M host stock solution (**7**) and 2×10^{-3} M guest stock solution (**5**) in $CDCl_3$, allowing the association constant to be determined without saturating the receptor at too low a mole fraction of guest.[24]

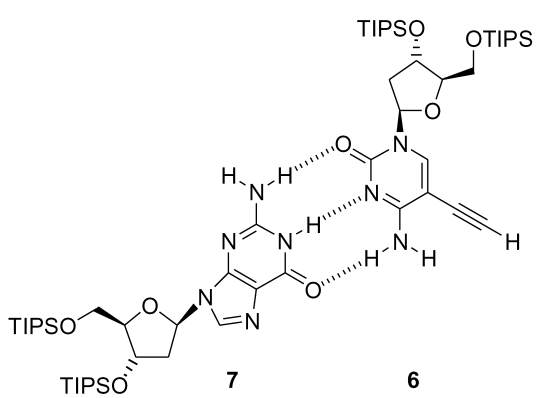


Figure 6. Complex **7**·**6**.

A titration was then carried out using these stock solutions over the range 0–15 equiv. of guest which gave a final δ value of 13.43 ppm for the guanosine amido NH. The 22 data points were then analysed using a non-linear least squares fit implemented through Professor Chris Hunter's 'HG' program.[25] After refinement an R factor of 2.2% was obtained indicating a good fit for the data points and the association constant, K_a=3370 M^{-1} was derived. This is somewhat lower than the value compared to previous measurements made for the G·C pair e.g. K_a=10^4–10^5 M^{-1} (by infrared),[26] K_a=1.6×10^4 M^{-1},[21] and K_a=1.7×10^4 M^{-1} for a related pair.[6a,27] Interestingly the association constant for a similar G·C pair substituted by an anthracene moiety is noted to be significantly higher than either our own, or many of these other values (K_a=38500±1300 M^{-1}).[9] However, it must be noted that no special precautions were taken to dry the solvents used for the titrations. For the ditopic receptor **1** a Job's plot revealed the expected 2:1 stoichiometry for compounds **7**:**1**. A titration of receptor **1** as guest from 0 to 6.25 equiv. was then carried out in $CDCl_3$, once again following the amido NH of the guanosine from 12.49 to 13.33 ppm. The analysis this time was carried out using the 'HHG' program designed for a 2:1 host:guest stoichiometry.[24] An excellent fit for the curve to data points was obtained with an R factor of 1.8%. The microscopic association constant K_a was found to be 2670 M^{-2}, interestingly slightly lower than, but of the same order of magnitude as that obtained for the **7**·**6** pair. Finally, a similar titration was performed for the longer bisalkynyl ditopic receptor **2** complexed with **7** (Fig. 7) giving an R factor of 2.5% and K_a=2200 M^{-2}.

The somewhat lower values found for the association of guanosine to each of the ditopic receptors **1** and **2** is perhaps not unexpected due to the presence of a small amount of competing solvent molecules in the binding experiment. In addition we speculate that it may be that since X-ray crystallography has shown that the ditopic receptor **2** exists as part of a hydrogen bonded polymer, if this persisted in solution, the guanosine molecules have to break up this network before binding to the Watson–Crick site can take place. A second possibility, that the lower association constant may be indicative of an effect exerted by the binding of the first guest molecule to the receptor can probably be discounted due to the similarity of all three binding constants. Although it has been demonstrated that significant effects on the association constant of diaminopyridine binding to a flavin receptor can be brought about by altering the redox state of the host molecule,[28] it seems that in this case any such effect is likely to be quite small.

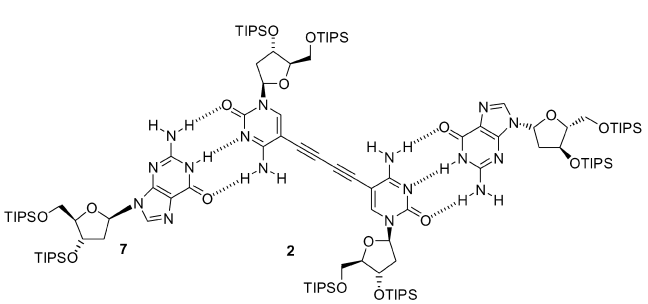


Figure 7. Complex **2**·**7**$_2$.

5. Conclusions

Novel ditopic receptors for guanosine have been prepared and their association constants with a lipophilic nucleoside determined. The binding of the first guanosine guest to the ditopic receptor **1** or **2** does not appear to dramatically perturb the binding of the second equivalent compared to the monotopic receptor **4**. The association constants remain in a usable range and indicate the suitability of these components for use as building blocks in making higher order supramolecular and macromolecular structures and this is an area of active investigation.

6. Experimental

6.1. General

Chemicals were purchased from either Aldrich Chemical Co. or Lancaster Synthesis and were used as received unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded using Bruker ACF250, DPX300, DPX400, AV400 instruments with chemical shifts measured in ppm relative to tetramethylsilane. Infrared spectra were recorded on a Bruker Vector 22 spectrometer fitted with an attenuated total reflection (ATR) cell. Routine mass spectra were obtained on a Micromass Autospec instrument in the Warwick Mass Spectrometry Laboratory. Micoanalytical data were obtained on a CE 440 Elemental Analyser operated by Warwick Analytical Services. Melting points were carried out on a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on pre-coated plate (silica gel 60 F 254, Merck Art. No. 5715) and the products visualised using UV light (254 nm), iodine or potassium permanganate solution as appropriate. Flash column chromatography was carried out using silica gel 60H (230–400 mesh) under low pressure. NMR titration data was analysed by a suite of least squares curve-fitting programs kindly supplied by Professor C. A. Hunter.[25] The programs were implemented on an Apple Macintosh 7200/90 and the graphical data was captured as a screen shot. X-Ray crystallographic structural characterisations for all crystals, data were collected with a Siemens SMART three-circle system with CCD area detector, with crystals held at 180 K or 200 K with the Oxford Cryosystem Cryostream Cooler. Refinements used SHELXTL.[29] Systematic absences indicated the appropriate space group. The structure was solved by direct methods with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data and have been assigned the reference codes CCDC 188941 (compound **6**) and 188942 (compound **2**). Copies of the data can be obtained free of charge on application to: The Director, CCDC, 12 Union Road, Cambridge CH2 1EZ UK (fax: +44-1223-336-033; email: deposit@ccdc.cam.ac.uk).

6.2. Preparation of receptors and guest

6.2.1. Preparation of 5-iodo-2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine 4. To a stirred suspension of 5-iodo-2′-deoxycytidine **3** (1.0 g, 2.83 mmol) in DMF (15 ml) under an atmosphere of nitrogen and at room temperature was added imidazole (84.8 mg, 12.4 mmol, 4.4 equiv.), DMAP (34.6 mg, 0.28 mmol, 0.1 equiv.) and triisopropylsilylchloride (1.2 g, 1.34 ml, 6.22 mmol, 2.2 equiv.). The mixture was stirred for 48 h. The reaction mixture was poured into sat NH_4Cl solution (50 ml) and the resulting white suspension was extracted with chloroform (3×50 ml). The combined organic phases were washed with water (3×40 ml), brine (3×40 ml) and dried over $MgSO_4$. Filtration of the resulting solution followed by removal of the solvent under reduced pressure gave a creamy white solid. Purification was then achieved by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol, 5:5:1) to give the title compound **4** as a colourless solid: (1.168 g, 62%); mp 154–156° C; ν_{max} (KBr) 3466, 2941, 1651, 1489, 1463, 1111, 881, 685 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.67 (1H, br s, NH), 8.07 (1H, s, H-6), 6.28 (1H, dd, J=8, 5.5 Hz, H-1′), 5.63 (1H, br s, NH), 4.56 (1H, m, H-3′), 4.06 (1H, dd, J=2.5, 4.5 Hz, H-4′), 3.96 (1H, dd, J=11.3, 2.5 Hz, H-5′), 3.84 (1H, dd, J=11.3, 2.8 Hz, H-5′), 2.55 (1H, ddd, J=13.3, 5.6, 2.0 Hz, H-α2′), 1.96 (1H, ddd, J=13.6, 8.0, 6.0 Hz, H-β2′), 1.10 (6H, m isopropyl methines), 1.05 (36H, s, triisopropylsilyl groups); δ_c (75.43 MHz, $CDCl_3$) 164.0, 155.1, 146.9, 89.2, 87.2, 73.3, 63.9, 43.5, 18.4, 12.4, 12.2; *m/z* (FAB): 666 (M+1). (Found: C, 48.41; H, 7.76; N, 6.20. $C_{27}H_{52}IN_3O_4Si_2$ requires C, 48.71; H, 7.87; N, 6.31%).

6.2.2. Preparation of 5-(trimethylsilylethynyl)-2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine 5. A mixture of 5-iodo-2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine **4** (500 mg, 0.75 mmol), trimethylsilylacetylene (140 mg, 0.21 ml, 1.42 mmol, 2 equiv.), bis(triphenylphosphine) palladium (II) dichloride (52 mg, 0.07 mmol, 0.1 equiv.) and copper (I) iodide (7 mg, 3.75 μmol, 0.05 equiv.) in degassed dry diisopropylamine (50 ml) was stirred in the dark under nitrogen at room temperature overnight. The solvent was then removed under reduced pressure and the resulting solid was dissolved in diethyl ether (60 ml) and the insoluble portion removed by filtration. The solvent was then removed under reduced pressure to yield the product as a creamy yellow solid. Purification was then achieved by flash column chromatography (silica gel, dichloromethane/ethyl acetate/petroleum ether (40–60)/methanol, 1:1:3:1) to give the title compound **5** as a colourless solid: (428 mg, 90%); mp 175–178°C; ν_{max} (KBr) 3464, 2940, 1673, 1505, 1464, 1440 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.58 (1H, s, NH), 8.04 (1H, s, H-6), 6.28 (1H, t, J=6.5 Hz, H-1′), 5.83 (1H, s, NH), 4.54 (1H, dd, J=3.0, 2.5 Hz, H-3′), 4.03 (1H, d, J=1.9 Hz, H-4′), 3.97 (1H, dd, J=11.5, 2.1 Hz, H-5′), 3.84 (1H, dd, J=11.5, 2.1 Hz, H-5′); 2.50 (1H, dd, J=13.4, 4.4 Hz, H-α2′), 1.96 (1H, m, H-β2′), 1.15 (6H, m, triisopropylsilyl methines), 1.00 (36H, m, triisopropylsilyl), 0.13 (9H, s, trimethylsilyl); δ_c (75.43 MHz, $CDCl_3$) 164.6, 154.3, 144.1, 101.1, 96.0, 90.9, 88.8, 86.9, 72.8, 63.4, 43.2, 38.1, 18.1, 12.1, 11.7; *m/z* (FAB): 637 $(M+1)^+$. (Found: C, 60.16; H, 9.49; N, 6.54. $C_{32}H_{61}N_3O_4Si_3$ requires C, 60.42; H, 9.67; N, 6.61%).

6.2.3. Preparation of 5-ethynyl-2′-deoxy-3′,5′-di (triisopropylsilyl)cytidine 6. Sodium carbonate (90 mg, 0.84 mmol, 2 equiv.) was dissolved in water (2.5 ml) and the resulting solution was then added to a stirred solution of 5-(trimethylsilylethynyl)-2′-deoxy-3′,5′di(triisopropylsilyl) cytidine **5** (328 mg, 0.51 mmol) in methanol (5 ml). This reaction mixture was then stirred for a further 2 h. The solution was then poured into water (10 ml) and the product extracted with chloroform (3×50 ml). The purification of the product was then achieved by flash column chromatography (silica gel, chloroform/dichloromethane/methanol, 5:5:1) to give the title compound **6** as a colourless solid: (279 mg, 97%); mp 144–146°C; ν_{max} (KBr) 2936, 2866, 2300, 1642, 1500, 1458, 1288, 1242, 1109, 1071, 1030, 875 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.97 (1H, br s, N–H), 8.09 (1H, s, H-6), 6.27 (1H, dd, J=7.4, 6.0 Hz, H-1′), 5.83 (1H, br s, N–H), 4.53 (1H, dt, J=5.5, 2.7 Hz, H-3′), 4.01 (1H, dd, J=2.6, 1.7 Hz, H-4′), 3.96 (1H, dd, J=11.3, 2.4 Hz, H-5′), 3.84 (1H, dd, J=10.7, 2.3 Hz, H-5′), 3.25 (1H, s, ethynyl), 2.50 (1H, ddd, J=13.2, 5.8, 2.7 Hz, H-α2′), 1.97 (1H, m, H-β2), 1.02 (42H, m, triisopropylsilyl); δ_c (75.43 MHz, $CDCl_3$) 164.3, 155.8, 144.6, 88.5, 86.6, 75.0, 72.2, 63.0, 42.9, 17.7, 11.8, 11.5; *m/z* (FAB): 564 $(M+H)^+$. (Found: C, 61.49; H, 9.43; N, 7.20. $C_{29}H_{53}N_3O_4Si_2$ requires C, 61.77; H, 9.47; N, 7.45%). Crystals suitable for X-ray diffraction were grown from isopropanol by slow evaporation. Crystal data C32 H61 N3 O5 Si2, M=624.02; triclinic; space group $P1$; a=8.5125(8), b=13.2827(13), c=18.1934(17) Å; α=72.817(2)°, β=86.490(2)°, γ=76.500(2)°; U=1910.9(3) $Å^3$; T=170(2) K; λ=0.71073 Å; Z=2; D(cal)=1.085 mg/m^3; F(000)=684; μ(Mo Kα)=0.131 mm^{-1}. $R1$[for 3130 reflections with $I>2\sigma(I)$]=0.0789, $wR2$=0.2182.

6.2.4. Preparation of 5-(ethynyl-2″-deoxy-3″,5″-di(triisopropylsilyl)-5′-cytidinyl)-(2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine), 1 and 5-(2′,4′-butadiynyl 2″-deoxy-3″,5″-di(triisopropylsilyl)cytidinyl) (2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine 2. 5-Ethynyl-2′-deoxy-3′,5′-di(triisopropylsilyl) cytidine **6** (164 mg, 0.29 mmol, 1 equiv.), 5-iodo-2′deoxy-3′,5′-di(triisopropylsilyl) cytidine **4** (194 mg, 0.29 mmol, 1 equiv.), bis(triphenylphosphine) palladium (II) dichloride (20 mg, 0.028 mmol, 0.1 equiv.), and copper (I) iodide (2.8 mg, 0.014 mmol, 0.05 equiv.) were all dissolved in dry degassed diisopropylamine (60 ml) and stirred in the dark under nitrogen for 24 h. The solvent was then removed under reduced pressure and a solid obtained. Purification of the product was carried out by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol, 10:10:1) to give the title compound **1** as a colourless solid: (172 mg, 54%); mp 169–171°C; ν_{max} (KBr) 3458, 2941, 1665, 1490, 1383 cm^{-1}; δ_H (300 MHz) 8.19 (2H, s, H-6), 6.40 (ca. 2H, br s, NH), 6.31 (2H, t, J=6.5 Hz, H-1′), 5.52 (*ca.* 2H, br s, NH), 4.55 (2H, m, H-3′), 4.04 (2H, dd, J=3.0, 2.6 Hz, H-4′), 3.97 (2H, dd, J=10.9, 2.5 Hz, H-5′), 3.86 (1H, dd, J=11.3, 3.0 Hz, H-5′), 2.56 (1H, ddd, J=12.6, 5.7, 2.7 Hz, H-α2′), 1.99 (2H, app. quin., J=6.6 Hz, H-β2′), 1.04 (s, 84H, triisopropylsilyl groups); δ_c (75.43 MHz, $CDCl_3$) 164.2, 154.1, 145.2, 88.7, 86.9, 85.8, 72.3, 63.2, 43.1, 18.0, 12.0, 11.8; *m/z* (FAB): 1101 $(M+1)^+$ HRMS. (Found $(M+1)^+$ 1101.7068. $C_{56}H_{104}N_6O_8Si_4$ requires: $(M+1)^+$ 1101.7071) and title compound **2** (116 mg, 36%); mp 178–182°C; ν_{max} (KBr) 3470, 2949,

1660, 1475, 1375 cm^{-1}; δ_H (300 MHz) 8.26 (2H, s, H-6), 6.70 (2H, br s, NH), 6.25 (2H, t, J=6.4 Hz, H-1′), 5.70 (2H, br s, NH), 4.55 (2H, dt, J=5.5, 2.7 Hz, H-3′), 4.05 (2H, d, J=2.8 Hz, H-4′), 3.99 (2H, dd, J=11.5, 2.3 Hz, H-5′), 3.87 (2H, dd, J=11.5, 2.3 Hz, H-5′), 2.57 (2H, ddd, J=13.5, 5.9, 3.0 Hz, H-α2′), 2.02 (2H, app. quin., J=6.4 Hz, H-β2′), 1.10 (12H, m, isopropyl methines), 1.04 (84H, s, triisopropylsilyl groups); δ_c (75.43 MHz, $CDCl_3$) 164.2, 154.0, 145.2, 89.3, 88.7, 86.9, 85.8, 72.3, 63.2, 43.1, 18.0, 12.0, 11.8; m/z (FAB): 1147 $(M+Na)^+$ HRMS. (Found: $(M+Na)^+$ 1147.6876. $C_{58}H_{104}N_6O_8Si_4$ requires $(M+Na)^+$ 1147.6890).

6.2.5. Preparation of 5-(2′,4′-butadiynyl 2″-deoxy-3″,5″-di(triisopropylsilyl)cytidinyl)(2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine 2. 5-Ethynyl-2′-deoxy-3′,5′-di(triisopropylsilyl)cytidine **4** (400 mg, 0.71 mmol), bis(triphenylphosphine)palladium (II) dichloride (6.5 mg, 1.3 mol%), copper (I) iodide (6.8 mg, 0.04 mmol, 5 mol%), iodine (90 mg, 0.35 mmol, 0.5 equiv.) were all dissolved in dry degassed diisopropylamine and stirred in the dark under nitrogen overnight. The solvent was then removed under reduced pressure. Purification of the product was achieved by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol, 10:10:1) to give a yellow solid. Ethyl acetate was added to this solid forming a precipitate which was collected by vacuum filtration to give the title compound **2** as a colourless solid (78%) identical to material prepared previously. Samples for X-ray crystallography were grown by slow crystallisation from isopropanol. Crystal Data C65.33 H105 N6 O8.50 Si4, M=1222.91; trigonal; space group $P3(1)$ a=20.7216(4), b=20.7216(4), c=16.7740(6) Å; α=90°, β=90°, γ=120°; U=6237.5(3) $Å^3$ (by least squares refinement on 3219 reflection positions); T=180(2) K; λ=0.71073 Å; Z=3; D(cal)=0.977 mg/m^3; F(000)=1989; μ(Mo Kα)=0.118 mm^{-1}. Crystal character: colourless laths. Crystal dimensions 0.4×0.15×0.1 mm. The crystal was held at 180(2) K with the Oxford Cryosystem Cryostream Cooler (Cosier & Glazer, 1986). Maximum theta was 21.00°. The *hkl* ranges were −20/20, −20/20, −15/16. 21344 reflections measured, 7872 unique [R(int)=0.1568]. Absorption correction by semi-empirical from equivalents; minimum and maximum transmission factors: 0.42; 0.96.

6.2.6. Preparation of 2′-deoxy-3′,5′-di(triisopropylsilyl) guanosine 7.[13,14] Prepared according to the method reported previously. Purification was then achieved by flash column chromatography (silica gel, chloroform/ethyl acetate/methanol, 5:5:1) to give the title compound **7** as a colourless solid: (0.248 g, 61%); δ_H (300 MHz) 12.11 (1H, s, N–H), 7.71 (1H, s, H-8), 6.27 (1H, dd, J=7.9, 6.0 Hz, H-1′), 5.86 (2H, br s, NH_2), 4.75 (1H, m, H-3′), 4.08 (1H, dd, J=6, 3.5 Hz, H-4′), 3.87 (2H, d, J=3.8 Hz, H-5′), 2.59 (1H, ddd, J=5.4, 8.2, 13 Hz, H-α2′), 2.40 (1H, ddd, J=2.6, 5.6, 12.8 Hz, H-β2′), 1.09 (42H, triisopropylsilyl); m/z (FAB): 603 $(M+Na)^+$ (data not previously reported).[14]

6.3. NMR titrations

NMR titrations were carried out in $CDCl_3$ (Apollo Scientific) used as received and residual $CHCl_3$ was used as the internal reference δ=7.26 ppm. The host stock solution (protected guanosine **7**) was prepared in $CDCl_3$ (2×10^{-4} M) and the guest stock solution (receptor 1, 2 or 5 as appropriate) was similarly prepared in $CDCl_3$ (2×10^{-3} M). The host solution (800 μl) was transferred via Hamilton microlitre syringe to a clean, dry NMR tube and the NMR spectrum acquired on a Bruker DPX400 instrument. The guanosine amino group protons were then monitored as successive aliquots of guest stock solution were added (compound **5**: 22 additions up to 1200 μl, 15 equiv.; compound **1**: 20 additions up to 1000 μl, 6.25 equiv.; compound **2**: 1000 μl, 6.25 equiv.) The chemical shift data were then entered into the appropriate least squares regression analysis program ('HG' for the 1:1 complex, 'HHG' for the 2:1 complexes)[25] and the line of best fit to the data was refined thus giving the association constants for the complexes.

7. Note added in proof

Further examination of the binding equilibria reveals significant self-association of both host and guest not fully accounted for in the analysis presented herein. A more complete investigation is in progress and the association constants should be regarded as underestimates.

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