Binding Cesium Ions with Nucleosides: Templated Self-Assembly of Isoguanosine Pentamers**

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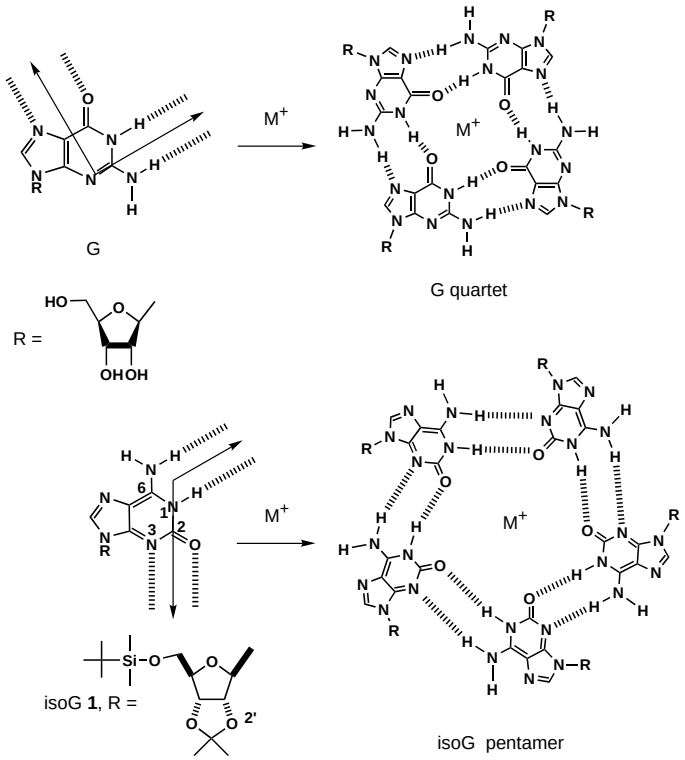
Guanosine (G) derivatives self-associate in the presence of metal ions to give the hydrogen-bonded G quartet (Scheme 1).[1] The G quartet, the cavity of which is surrounded by four oxygen atoms, binds cations with a selectivity of $K^+ > Na^+$, $Rb^+ \gg Cs^+$, Li^+.[1] Isoguanosine (isoG), a guanosine isomer with transposed carbonyl and amino groups, also self-associates in the presence of cations. Poly(isoguanylic acid) aggregates more strongly than four-stranded poly(G),[2] and oligonucleotides containing 2′-deoxy-isoG[3, 4] or 7-deaza-2′-deoxy-isoG[5] form tetraplexes in the presence of Na^+ and K^+.



Scheme 1. Aggregation of guanosine and isoguanosine in the presence of metal ions.

While exploring the self-association of lipophilic nucleosides,[6] we discovered that 5′-*tert*-butyldimethylsilyl-2′,3′-*O*-isopropylidene-substituted isoG **1** forms a hydrogen-bonded complex with Cs^+.[7] This isoG derivative extracts cesium salts from water into $CHCl_3$ with an affinity and selectivity rivaling that of covalent macrocycles.[7] Given the potential for using a Cs^+-selective ionophore to bind the fission product $^{137}Cs^+$,[8] we sought to characterize the complex formed by **1** and Cs^+.[9]

We recently proposed that, in addition to a tetramer, isoG can form a hydrogen-bonded pentamer in a cation-templated process.[10] Subsequent biochemical and computational studies support this proposal, as oligonucleotides containing 2′-deoxy-isoG form stable Cs^+ pentaplexes.[11, 12] Chaput and Switzer proposed that the relative orientation of the hydrogen-bond donor and acceptor groups (see arrows in Scheme 1) favors formation of a planar cyclic pentamer.[11] Here we present evidence from both solid-state and solution studies that **1** coordinates to Cs^+ to give the complex $(\mathbf{1})_{10}\cdot Cs^+$, which contains two hydrogen-bonded isoG pentamers.

Tracer distribution experiments with radioactive $^{137}Cs^+$ showed that a 10 mM solution of **1** in $CHCl_3$ extracts cesium chloride, nitrate, and perchlorate from water. Figure 1 shows

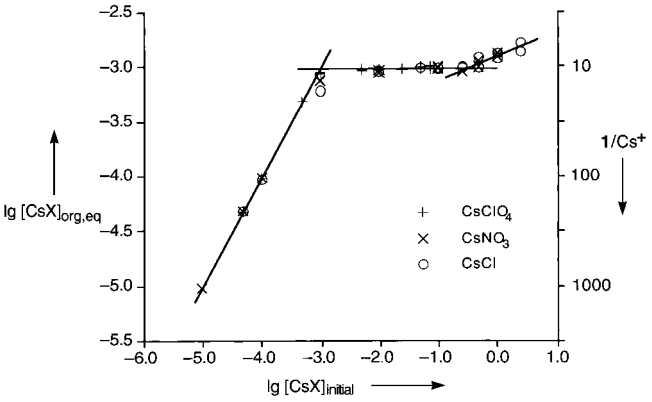


Figure 1. Cesium distribution measurements. A lg/lg plot of the Cs^+ ion concentration [M] extracted into $CHCl_3$ by **1** versus the initial concentration of cesium salt [M] in the aqueous phase. The ligand concentration in $CHCl_3$ was $[\mathbf{1}] = 10$ mM. The aqueous solutions of CsCl, $CsNO_3$, and $CsClO_4$ contained a radioactive ^{137}Cs ion tracer for precise Cs^+ analysis.

an equivalence point and a plateau consistent with the 10:1 composition of $(\mathbf{1})_{10}\cdot Cs^+$. At initial concentrations of less than 1 mM ($lg[CsX]_{initial} < -3$) the cesium salts are almost quantitatively extracted (>96.4% for Cl^-, >99.2% for NO_3^-, and >99.6% for ClO_4^-). The efficiency of cesium salt extraction by **1** is unprecedented for a neutral cation receptor.[13]

The X-ray structure unambigously showed that **1** forms a pentameric macrocycle when templated by Cs^+.[14] Single crystals were obtained from CH_3CN containing **1** (300 mM) and $Cs^+Ph_4B^-$ (30 mM). The asymmetric unit, with over 750

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non-hydrogen atoms, includes twenty molecules of **1** that make up two independent $(\mathbf{1})_{10}\cdot Cs^+Ph_4B^-$ units, as well as 37 acetonitrile and 1.5 water molecules. A top view (Figure 2A) of the structure shows two C_5-symmetric pentamers stacked in a tail-to-tail orientation such that the purine rings directly overlap.[15] The virtual D_5 symmetry of the $(\mathbf{1})_{10}\cdot Cs^+$ moiety renders all ten isoG molecules chemically equivalent. The 12-coordinate Cs^+ ion (there are two apical CH_3CN molecules) is nestled within a cage formed by 10 isoG carbonyl oxygen atoms (Figure 2B). A side view (Figure 2C) shows the two planar isoG pentamers, separated by 3.3 Å, sandwiching the Cs^+ ion.

Each isoG pentamer has 15 hydrogen bonds. The self-association of IsoG **1** is mediated by intermolecular N1–H···O2 and N6–H···N3 hydrogen bonds (av $d_{N1\text{-}O2}=2.73$ Å, $\theta_{N1\text{-}H\cdots O2}=173^\circ$; $d_{N6\text{-}N3}=2.87$ Å, $\theta_{N6\text{-}H\cdots N3}=170^\circ$; for the numbering scheme see Scheme 1). Sugar–base hydrogen bonds between adjacent monomers also promote self-association of **1**.[6] The amino group forms hydrogen bonds with O2′ of the ribose residue of the neighboring molecule (av $d_{N6\text{-}H\cdots O2'}=2.82$ Å, $\theta_{N6\text{-}H\cdots O2'}=139^\circ$). In isoG, the ribose and the hydrogen-bond acceptors (O2 and N3) are located together on the lower edge of the purine residue. In contrast, sugar–base hydrogen bonds are not possible in the G quartet, since the hydrogen-bond acceptors (O6 and N7) and the sugar residue are on opposite sides of the heterocycle.

The $(\mathbf{1})_{10}\cdot Cs^+$ complex is stable in solution. Electrospray mass spectra of $(\mathbf{1})_{10}\cdot Cs^+Ph_4B^-$ in $CHCl_3$ showed a predominant peak at m/z 4509.4, consistent with the molecular ion (calcd 4508.6 Da). Formation of $(\mathbf{1})_{10}\cdot Cs^+Ph_4B^-$ in CD_3CN was also monitored by ^{133}Cs NMR spectroscopy. At 25 °C, isoG-complexed Cs^+ ($\delta=-54.4$) and solvated Cs^+ ($\delta=8.1$) were in fast exchange ($k_{ex}(Cs^+)>10^5\ s^{-1}$) and gave a single, population-averaged NMR signal. Titration gave a sharp end point when ten equivalents of **1** were added for each equivalent of $Cs^+Ph_4B^-$ (Figure 3), and this indicates that $(\mathbf{1})_{10}\cdot Cs^+$ is thermodynamically stable ($K_a>10^5\ M^{-1}$) but kinetically labile.

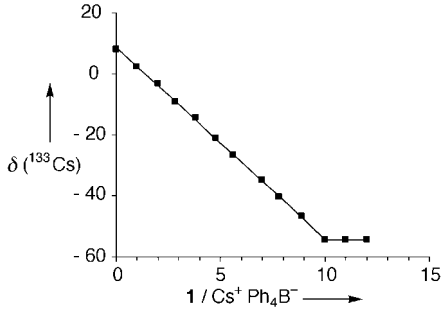

Figure 3. ^{133}Cs NMR (65.6 MHz) chemical shift as a function of the molar ratio of **1**/$Cs^+Ph_4B^-$ in CD_3CN at 25 °C. The salt concentration was held constant at $[Cs^+Ph_4B^-]=10$ mM, while the ligand concentration was varied between $[\mathbf{1}]=0$ and 120 mM.

The unique structure of $(\mathbf{1})_{10}\cdot Cs^+$ illustrates the power of noncovalent synthesis;[16] combining isoG and Cs^+ results in 30 hydrogen bonds and 10 ion–dipole bonds. Furthermore, self-assembly gives a potentially useful supramolecule from a simple monomer. The structure also provides a basis for the next challenge: tuning the dynamics of this Cs^+ ionophore. The relatively rapid Cs^+ exchange by $(\mathbf{1})_{10}\cdot Cs^+$ in CD_3CN bodes well for using self-assembled ionophores as reversible cation receptors. In particular, **1** may find use in demanding separations of radioactive $^{137}Cs^+$ in a variety of nuclear applications.

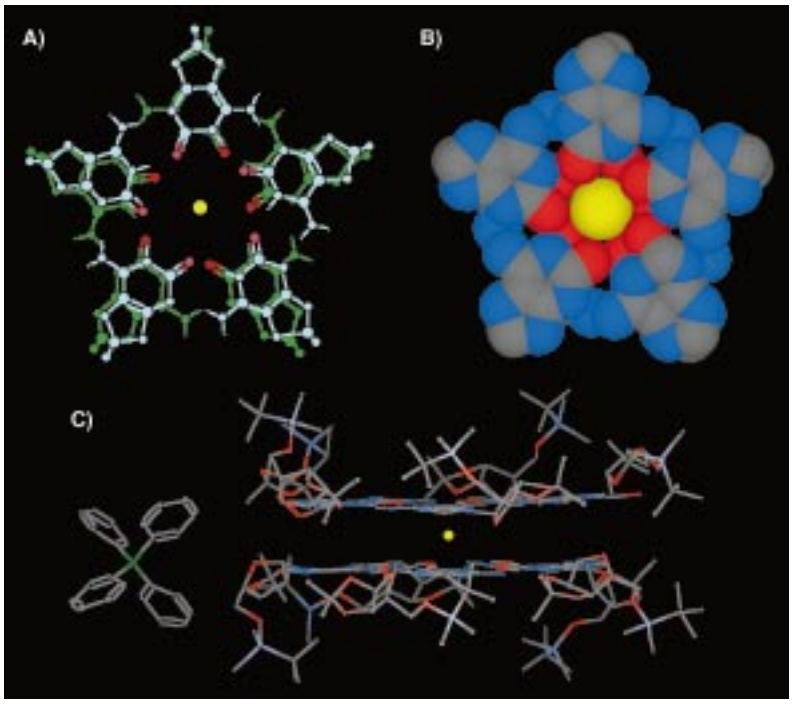

Figure 2. A) A top view of the X-ray crystal structure of $(\mathbf{1})_{10}\cdot Cs^+Ph_4B^-$. The sugar residues are omitted for clarity. One isoG pentamer is blue, and the other is green. B) Space-filling top view. The Cs^+ ion is yellow, O atoms are red, N atoms are blue, and C atoms are gray. The Cs^+ ion is bound to 10 carbonyl O atoms (av $d_{Cs\text{-}O}=3.40$ Å). C) Side view of $(\mathbf{1})_{10}\cdot Cs^+Ph_4B^-$. Some of the atoms on the 5′ side chain of the ribose residue are omitted for clarity. This view shows the stacking of the two planar isoG pentamers. The Ph_4B^- anion is remote from the encapsulated Cs^+ ion.

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The Localization of Guests in Water-Soluble Oligoethyleneoxy-Modified Poly(propylene imine) Dendrimers**

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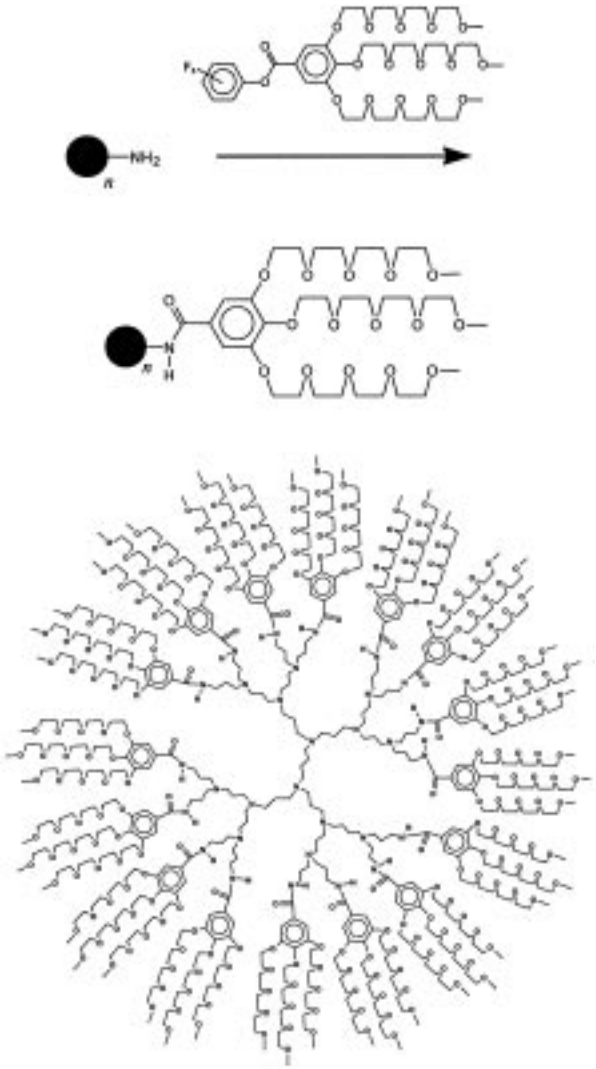
The highly branched, three-dimensional geometry of dendritic macromolecules[1] makes these new molecular architectures ideal container molecules.[2] It has been suggested that these molecules could be used in a number of applications including those related to the controlled release of pharmaceuticals.[3, 4] Several host – guest systems have already been developed, for example, dendritic hosts with unimolecular (inverted) micellar structures,[5] the "dendritic box",[6] crown ether dendrimers,[7] and cyclophane dendrimers.[8] A restricted number of guests, such as rose bengal, can be encapsulated in the "dendritic box", (a fifth generation poly(propylene imine) dendrimer modified with a dense shell of amino acids)[6] and released by simple chemical modification of the shell.[6c] Dynamic hosts in organic media[9a] or supercritical CO_2[9b] are based on hydrophobically modified poly(propylene imine) dendrimers and have proved to be efficient extractants of aqueous solutes. Recently, more attention has been focussed on water-soluble dendritic systems,[10] but their host – guest properties have not been addressed so far. Herein we present poly(propylene imine) dendrimers modified with 3,4,5-tris(tetraethyleneoxy)benzoyl units, which have a basic interior of tertiary amines and a hydrophilic periphery (Scheme 1). Titrations and small angle X-ray scattering



Scheme 1. Top: Synthesis of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers; $n = 4$: **1**; $n = 16$: **2**; $n = 32$: **3**, and $n = 64$: **4**. Bottom: Schematic structure of host **2**.

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