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

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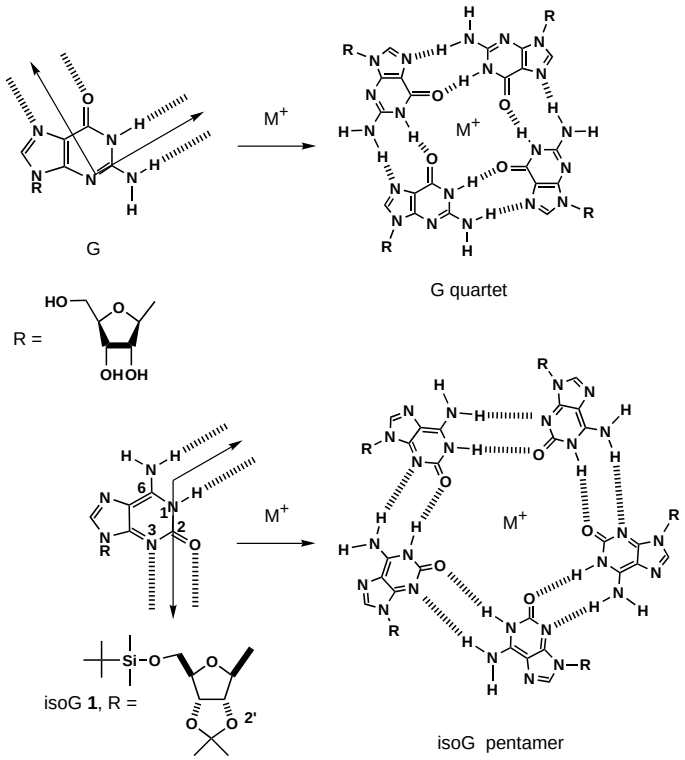
Guanosine (G) derivatives self-associate in the presence of metal ions to give the hydrogen-bonded G quartet (Scheme 1).[1] The G quartet, the cavity of which is surrounded by four oxygen atoms, binds cations with a selectivity of $K^+ > Na^+$, $Rb^+ \gg Cs^+$, Li^+.[1] Isoguanosine (isoG), a guanosine 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

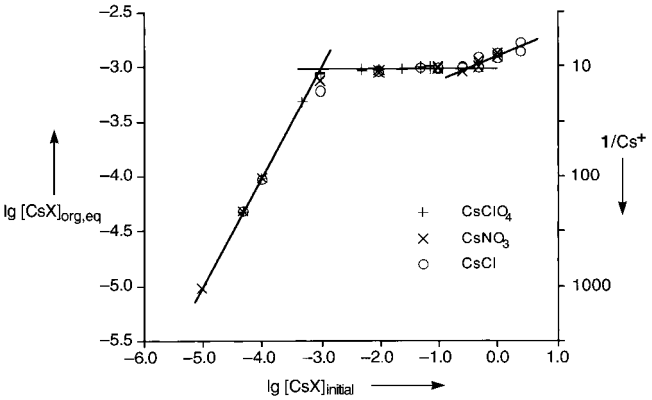


Figure 1. Cesium distribution measurements. A lg/lg plot of the Cs^+ ion concentration [M] extracted into $CHCl_3$ by **1** versus the initial concentration of cesium salt [M] in the aqueous phase. The ligand concentration in $CHCl_3$ was $[\mathbf{1}] = 10$ mM. The aqueous solutions of CsCl, $CsNO_3$,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

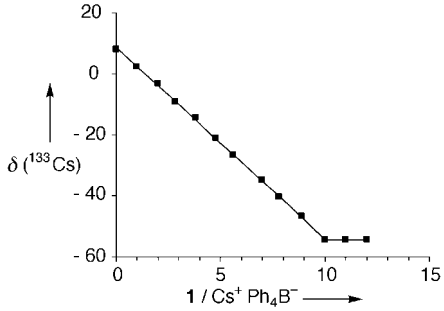

Figure 3. ^{133}Cs NMR (65.6 MHz) chemical shift as a function of the molar ratio of **1**/$Cs^+Ph_4B^-$ in CD_3CN at 25 °C. The salt concentration was held constant at $[Cs^+Ph_4B^-]=10$ mM, while the ligand concentration was varied between $[\mathbf{1}]=0$ and 120 mM.

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.

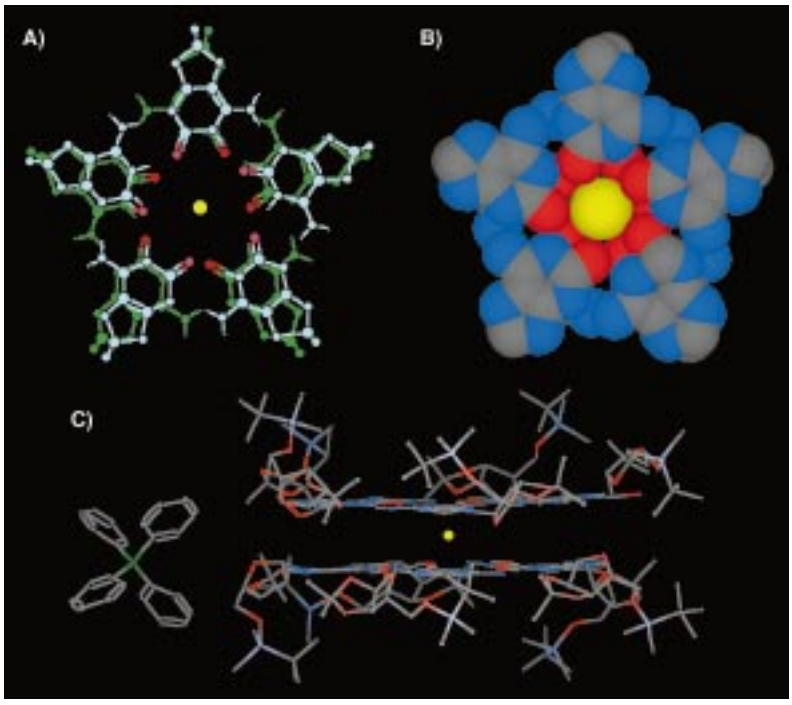

Figure 2. A) A top view of the X-ray crystal structure of $(\mathbf{1})_{10}\cdot Cs^+Ph_4B^-$. The sugar residues are omitted for clarity. One isoG pentamer is blue, and the other is green. B) Space-filling top view. The Cs^+ ion is yellow, O atoms are red, N atoms are blue, and C atoms are gray. The 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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[1] W. Guschlbauer, J. F. Chantot, D. Thiele, *J. Biomol. Struct. Dyn.* **1990**, *8*, 491–511.

[2] T. Golas, M. Fikus, Z. Kazimierczuk, D. Shugar, *Eur. J. Biochem.* **1976**, *65*, 183–192.

[3] a) F. Seela, C. Wei, A. Melenewski, *Nucl. Acids Res.* **1996**, *24*, 4940–4945; b) F. Seela, C. Wei, A. Melenewski, *Origins Life Evol. Biosphere* **1997**, *27*, 597–608.

[4] C. Roberts, J. C. Chaput, C. Switzer, *Chem. Biol.* **1997**, *4*, 899–908.

[5] F. Seela, C. Wei, *Chem. Commun.* **1997**, 1869–1871.

[6] J. T. Davis, S. Tirumala, J. R. Jenssen, E. Radler, D. Fabris, *J. Org. Chem.* **1995**, *60*, 4167–4176.

[7] J. T. Davis, S. Tirumala, A. L. Marlow, *J. Am. Chem. Soc.* **1997**, *119*, 5271–5272.

[8] J.-F. Dozol in *New Separation Chemistry Techniques for Radioactive Waste and Other Applications* (Eds.: L. Cecille, M. Casati, L. Pietrelli), Elsevier, Amsterdam, **1991**, pp. 163–172.

[9] Other Cs^+ ionophores: a) A. Casnati, A. Pochini, R. Ungaro, F. Ugozzoli, F. Arnaud, S. Fanni, M. Shwing, R. J. M. Egberink, F. De Jong, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1995**, *117*, 2767–2777; b) K. K. Klausmeyer, S. R. Wilson, T. B. Rauchfuss, *J. Am. Chem. Soc.* **1999**, *121*, 2705–2711.

  0570-0833/00/3907-1284 $ 17.50+.50/0

[10] A. L. Marlow, J. T. Davis, *Tetrahedron Lett.* **1999**, *40*, 3539 – 3542.
[11] J. C. Chaput, C. Switzer, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 10614 – 10621.
[12] Seela first noted that isoG oligonucleotides aggregate in the presence of Cs^+: F. Seela, C. Wei, A. Melenowski, E. Feiling, *Nucleosides, Nucleotides* **1998**, *17*, 2045 – 2052.
[13] B. A. Moyer in *Comprehensive Supramolecular Chemistry, Vol. 1* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-M. Lehn), Pergamon, Oxford, **1996**, pp. 377 – 416.
[14] Crystal data for $(\mathbf{1})_{10}\cdot CsPh_4B$: $[(C_{19}H_{31}N_5O_5Si)_{10}\cdot Cs][B(C_6H_5)_4]\text{-}[NCCH_3]_{18.5}[H_2O]_{0.75}$, $M_r = 5585.79$, crystal dimensions $0.40 \times 0.40 \times 0.40$ mm, monoclinic, space group $P2_1$, $a = 23.948(5)$, $b = 24.594(5)$, $c = 52.090(10)$ Å, $\beta = 90.015(3)^\circ$, $V = 30680(10)$ Å^3, $Z = 4$, $\rho_{exp} = 1.209$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 0.237$ mm^{-1}. Data were collected on a Bruker SMART 1000 CCD diffractometer at 173(2) K. The structure was determined by direct methods.[17] Refinement on F^2 with the program SHELXL[18] converged at $R(F) = 0.104$ and $wR(F^2) = 0.227$ for all 92533 independent reflections. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-135687. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[15] The "tail" of the isoG pentamer exhibits a counterclockwise rotation of the N–H ··· O=C hydrogen bonds.
[16] D. S. Lawrence, T. Jiang, M. Levitt, *Chem. Rev.* **1995**, *95*, 2229 – 2260.
[17] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467 – 473.
[18] G. M. Sheldrick, SHELXL-93 Program for the Refinement of Crystal Structures, **1993**, University of Göttingen, Germany.

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

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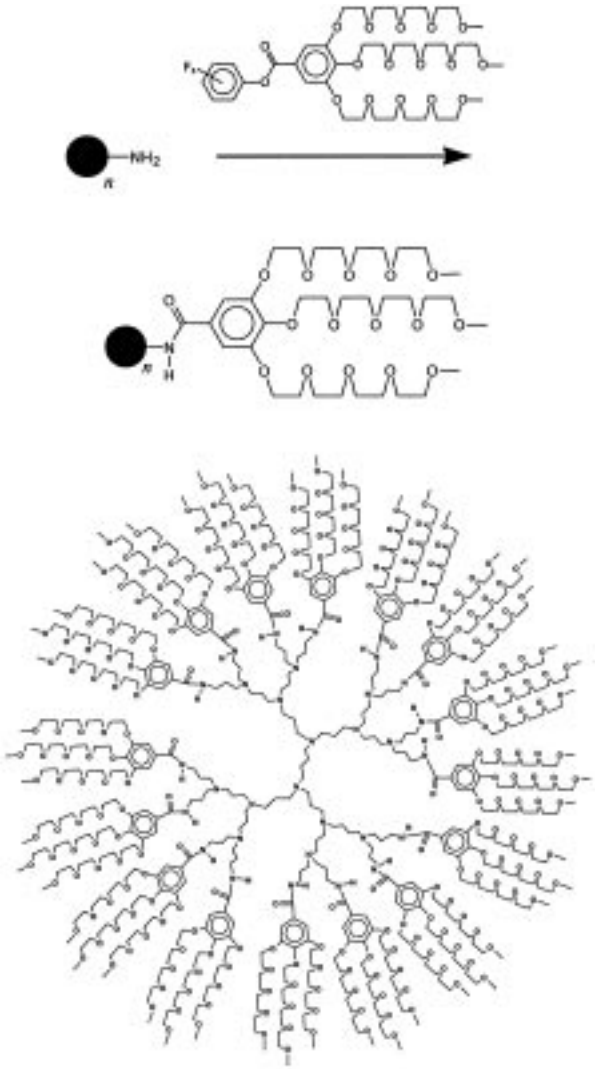
The highly branched, three-dimensional geometry of dendritic macromolecules[1] makes these new molecular architectures ideal container molecules.[2] It has been suggested that these molecules could be used in a number of applications including those related to the controlled release of pharmaceuticals.[3, 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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