A Self-Assembled Ionophore with Remarkable Cs$^+$ Selectivity

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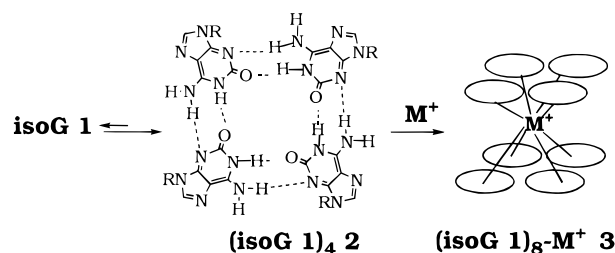University of Maryland at College Park
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Received January 27, 1997

Nuclear waste management requires methods for radionuclide separation, and a major component of the waste is ^{137}Cs.[1,2] Due to its 30 year half-life, most of the ^{137}Cs produced during the nuclear age still exists. Methods for ^{137}Cs$^+$ separation include precipitation as phosphotungstate salts, ion exchange chromatography, and extraction by ionophores.[3] Highly selective ionophores are required to separate ^{137}Cs$^+$, since Na$^+$ and K$^+$ concentrations in nuclear waste are much greater than that of ^{137}Cs$^+$.[3] Selective coordination of Cs$^+$ (r = 1.67 Å) in the presence of Na$^+$ (r = 0.97 Å) and K$^+$ (r = 1.33 Å) is challenging. Because of their flexibility, crown ethers often have only modest Cs$^+$ selectivities.[4] More promising results have been obtained with rigid macrocycles,[5] particularly the calix[4]arenecrowns.[6−8] While the Cs$^+$ selectivities of the calixarenecrowns are impressive, cation and ionophore recovery may prove difficult due to the stability of the ionophore−Cs$^+$ complex.

An alternative ionophore design uses hydrogen bonds to build self-assembled structures that coordinate ions.[9−11] Cation binding affinity and selectivity may be achieved through cooperative assembly of the host. We have focused on 5′-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene isoguanosine (isoG) **1**. IsoG **1** self-associates in organic solvents to form a stable tetramer, (isoG)$_4$ **2** (Scheme 1).[11,12] Tetramer **2**, with four oxygens in its central cavity, has a high affinity for cations.

Isopropylidene **1** coordinates K$^+$ to form (isoG)$_8$−K$^+$ **3**, with a binding constant rivaling that of 18-c-6 derivatives.[11b] We

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Scheme 1

isoG 1 ⇄ **(isoG 1)$_4$ 2**   **M$^+$** →   **(isoG 1)$_8$-M$^+$ 3**

proposed that the conformational rigidity of the isopropylidene facilitates self-association of isoG **1**. Herein, we demonstrate that isoG's sugar influences both the Cs$^+$ affinity and Cs$^+$/K$^+$ selectivity of the self-assembled ionophore. Specifically, isopropylidene **1** forms a self-assembled ionophore with remarkable Cs$^+$ selectivity.

1   **4**   **5**
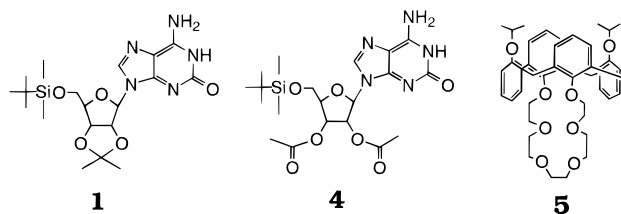
We compared the self-association and Cs$^+$/K$^+$ binding properties of isopropylidene **1** and 2′,3′-*O*-diacetyl isoG **4**. The different propensity for **1** and **4** to self-associate in organic solvents was apparent when comparing ^{1}H NMR spectra. In the absence of metal ion, isopropylidene **1** forms a hydrogen-bonded tetramer **2** in CD$_3$CN,[11] while diacetate **4** is monomeric under identical conditions. These results are consistent with the proposal that nucleobase−sugar hydrogen bonds drive the self-association of isopropylidene **1**.

Both isopropylidene **1** and diacetate **4** coordinate K$^+$ and Cs$^+$ strongly in CDCl$_3$ and CD$_3$CN. Integration of ^{1}H NMR and UV−vis spectra after metal picrate extraction from water into CDCl$_3$ indicate that **1** and **4** bind K$^+$ and Cs$^+$ to form (isoG)$_8$−M$^+$ **3**.[13] Spectroscopic measurement of the picrate anion is indirect evidence for cation binding by **1** and **4**. Cesium-133 NMR directly showed that these isoG analogs bind Cs$^+$.[14] Distinct ^{133}Cs NMR spectra were obtained after cesium picrate extraction by isopropylidene **1** (σ −55.2 ppm) and by diacetate **4** (σ −28.4 ppm).[15] The unique ^{133}Cs chemical shifts indicate that the electronic environment around Cs$^+$ is different in the two (isoG)$_8$−Cs$^+$ species.

Cation binding was also indicated by a decrease in the ^{133}Cs T_1 value in the presence of isopropylidene **1**. Typically, ^{133}Cs T_1 values decrease upon complexation by ionophores, since ^{133}Cs relaxation is dominated by its nuclear quadrupole and by its reorientational correlation time, t_c.[16,17] First, coordination and desolvation can change the electric field gradient near Cs$^+$. Second, t_c for an ionophore−metal complex should be larger than that for a solvated Cs$^+$. The ^{133}Cs T_1 values in CD$_3$CN were 3.25 s for cesium picrate and 0.0023 s for (isoG **1**)$_8$−Cs$^+$. This 1400-fold decrease in ^{133}Cs T_1 is consistent with Cs$^+$ coordination by (isoG **1**)$_8$.

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Table 1. Cs^+ Binding Constants and Cs^+/K^+ Extraction Selectivities

ionophore	$\log K_a (Cs^+)$	extraction selectivity f_{Cs^+/K^+}	ref
calix[4]crown **5**	8.8[a]	250	7a
(IsoG **4**)$_8$	8.8[b]	0.86($\pm$0.09)[c]	this work
(IsoG **1**)$_8$	>9.8[b]	333($\pm$33)[c]	this work

[a] Determined by Cram's picrate extraction method in $CHCl_3$ saturated with H_2O at 22 °C. The precision of this method, between 14 and 50%, is as described by Cram.[18] [b] Determined by ^{133}Cs NMR competition experiments with calix[4]crown **5** in $CDCl_3$ saturated with H_2O at 20 °C. The K_a values are $\pm$10% relative to the K_a value for calix[4]crown **5**. [c] Determined by ^1H NMR competition experiments in $CDCl_3$ saturated with H_2O at 20 °C. The accuracy of the f_{Cs^+/K^+} values is $\pm$10%.

Cesium binding constants (K_a) for **1** and **4** in $CDCl_3$ were estimated from NMR competition experiments with 1,3-diisopropylcalix[4]arenecrown-6 (**5**). Calixarene **5** is a Cs^+ selective ionophore, with $\log K_a (Cs^+) = 8.8$ in $CDCl_3$ (Table 1).[7a] Coordination of Cs^+ by calixarene **5**, or isoG analogs **1** and **4**, can be monitored by both ^{133}Cs and ^1H NMR, since the free and Cs^+ bound calixarene **5** and the isoG tetramer **2** and Cs^+-bound octamer **3** are in slow exchange. Addition of 1 equiv of calixarene **5** to a $CDCl_3$ solution of (isoG **4**)$_8$−Cs^+ gave two separate ^{133}Cs NMR signals in a 1.0:1.0 ratio, with one resonance for (isoG **4**)$_8$−Cs^+ at −28.6 ppm and one for Cs^+-bound calixarene **5** at −61.4 ppm. Analysis of the ^1H NMR spectrum also indicated a 2.0:1.0 ratio of (isoG **4**)$_4$ and (isoG **4**)$_8$−Cs^+. Given that the precision of NMR integration is within 10%, this experiment indicates that the diacetate octamer, (isoG **4**)$_8$, has a Cs^+ binding constant that is the same order of magnitude as that for calixarene **5** (Table 1). The diacetate **4** forms a potent ionophore. Similar competition experiments showed that isopropylidene **1** binds Cs^+ even more strongly than does calixarene **5**. Upon addition of 10 equiv of calixarene **5** to a $CDCl_3$ solution containing (isoG **1**)$_8$−Cs^+, there were no changes in the ^1H and ^{133}Cs NMR spectra that would indicate Cs^+ binding by calixarene **5**. This experiment establishes a lower limit of $\log K_a (Cs^+) = 9.8$ for isopropylidene **1**. Calixarene **5** did not remove Cs^+ from the isopropylidene octamer (isoG **1**)$_8$−Cs^+, as it did in competition experiments with diacetate (isoG **4**)$_8$−Cs^+. These competition experiments show that the Cs^+ binding constant for isopropylidene **1** is greater than that for diacetate **4**. The sugar group of isoG influences the strength of the ionophore−cation interaction.

Binding affinity is only one measure of an ionophore's utility. An effective ionophore should also be ion selective. Since (isoG)$_8$−K^+ and (isoG)$_8$−Cs^+ are in slow exchange on the NMR time scale for both isopropylidene **1** and diacetate **4** in $CDCl_3$, Cs^+/K^+ extraction selectivities could be determined by integrating NMR signals for the separate (isoG)$_8$−M^+ species after extraction. Diacetate **4** had little Cs^+/K^+ selectivity. Extraction of water containing equimolar concentrations (4.5 mM) of potassium picrate and cesium picrate with a $CDCl_3$ solution of diacetate **4** (16 mM) gave 53% (isoG **4**)$_8$−K^+ and 47% (isoG **4**)$_8$−Cs^+, for a Cs^+/K^+ selectivity of 0.89. The free energy difference for coordination of Cs^+ vs K^+ in $CDCl_3$ by **4** is small ($\Delta\Delta G < 0.05$ kcal/mol).[19]

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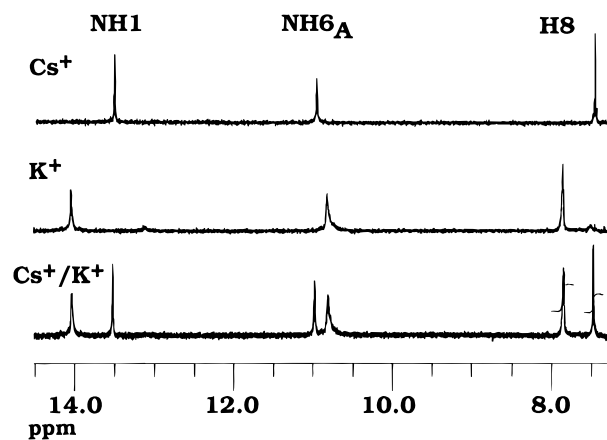

Figure 1. A region of the 500 MHz ^1H NMR spectra of a $CDCl_3$ solution of (isoG **1**)$_8$−M^+ (2.0 mM) at 25 °C. The top spectrum is of a sample formed by extraction of CsI (0.005 M) from water. The middle spectrum is of a sample formed by extraction of KI (2.5 M) from water. The bottom spectrum shows a sample after extraction from water containing KI (2.5 M) and CsI (0.005 M).

In contrast to the indiscriminate diacetate **4**, isopropylidene **1** is a Cs^+ selective ionophore. When a $CDCl_3$ solution of isopropylidene **1** was stirred with water containing equimolar potassium picrate and cesium picrate, only Cs^+ was extracted into the organic phase. To observe any (isoG **1**)$_8$−K^+ complex, the K^+/Cs^+ ratio had to be increased. Thus, extraction of water containing 2.50 M KI and 0.005 M CsI with a $CDCl_3$ solution of **1** gave (isoG **1**)$_8$−K^+ (σ 14.03 for NH1) and (isoG **1**)$_8$−Cs^+ (σ 13.53 for NH1) in a 1.5:1 ratio (Figure 1). This experiment indicates that isopropylidene **1** has a Cs^+/K^+ extraction selectivity of approximately 333:1 for the iodide salts, corresponding to a relative free energy that is 3.5 kcal/mol more favorable for Cs^+ extraction.

The sugar substituents of isoG influence the self-assembled ionophore's selectivity. Compared with diacetate **4**, both the Cs^+ binding constant and the Cs^+/K^+ selectivity are significantly greater for isopropylidene **1**. This change in the 2',3'-substitution of the ribose alters the Cs^+/K^+ selectivity ratio 400-fold. Isopropylidene **1** likely forms such an effective self-assembled ionophore due to "preorganization" on two different levels.[20] First, the 2',3'-isopropylidene constrains the sugar conformation to optimize hydrogen bonds that stabilize the tetramer, (isoG **1**)$_4$. Once self-assembled, the tetramer is then well-oriented to coordinate cations.[11b] One current goal is to identify enthalpic and entropic factors that control this unusual Cs^+ selectivity.[21] From a practical viewpoint, this research may provide a basis for using self-assembled ionophores to separate $^{137}Cs^+$ from nuclear waste.

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