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Self-assembled ionophores as phase transfer catalysts

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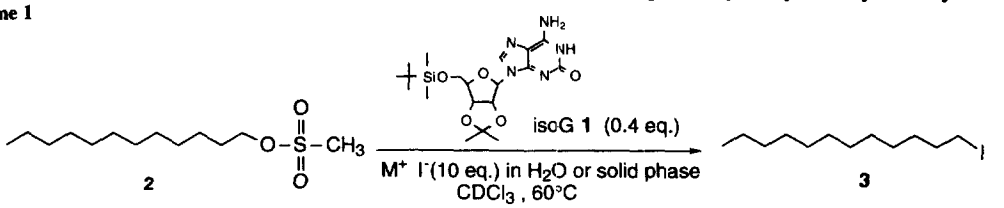
Abstract

The nucleoside, 5'-(*t*-butyl-dimethylsilyl)-2',3'-O-isopropylidene isoG **1**, catalyzes the S_N2 reactions of alkali and ammonium iodides with dodecyl mesylate **2** under both liquid-liquid and solid-liquid phase transfer conditions. IsoG **1** self-associates to give a complex that extracts the salts into $CDCl_3$ solution. Sodium iodide, in the presence of isoG **1**, reacts faster with **2** than the other iodides under solid-liquid conditions. This reactivity difference is attributed to the open-faced structure of the ionophore-M^+ complex under solid-liquid conditions.

Keywords: self-assembly; ionophore; hydrogen bonding; phase transfer

Many compounds form stable structures by self-complementary hydrogen bonding, but examples of self-assembled systems with function are fewer.[1-3] This communication pertains to supramolecular catalysts made from simple monomers. We previously described "self-assembled" ionophores made from 5'-(*t*-butyl-dimethylsilyl)-2',3'-*O*-isopropylidene isoguanosine (isoG) **1** (Figure 1).[4-6] IsoG **1** has the appropriate H-bond donors and acceptors to enable strong self-association. Like the well-known G-quartet,[7] isoG self-association gives an aggregate, $(\text{isoG } \mathbf{1})_n\text{-}M^+$, in the presence of cations.[8-10] While Cs^+-selective,[6] other alkali and ammonium cations also template self-association of isoG **1** in aprotic solvents. After liquid-liquid (L-L) or solid-liquid (S-L) extraction of a salt by this lipophilic nucleoside, there is an anion associated with the ionophore-cation complex. This anion should be available for nucleophilic reaction in the organic solution. We report that self-assembled ionophores formed from isoG **1** can function as phase-transfer (PT) catalysts. Moreover, the cation influences the rate of the S-L PT reaction, substitution of a primary alkyl mesylate by iodide.

Scheme 1



IsoG **1** catalyzed the S_N2 reaction of dodecyl mesylate **2** with NaI, KI, RbI, CsI and NH_4I to give dodecyl iodide **3** (Scheme 1). To monitor the reaction's progress by ^1H NMR,

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$CDCl_3$ was used as solvent for both the L-L and S-L PT reactions. The complexes, (isoG **1**)$_n$-M^+ I^-, generated by L-L or S-L extraction were robust, as ^1H NMR indicated that isoG **1** remained fully aggregated in $CDCl_3$ at 60 °C, the temperature at which reactions were done.

The L-L PT reactions were performed in a $CDCl_3$-H_2O mixture at 60 °C,[11] with a 25-fold excess of substrate **2** relative to the presumed active species, (isoG **1**)$_{10}$-M^+ I^- **6**.[12] As shown in Table 1, addition of isoG **1** (8 mM) to a mixture of mesylate **2** (20 mM) in $CDCl_3$ and the iodide salt (200 mM) in water gave dodecyl iodide **3**.[11] Without isoG **1**, no alkyl iodide **3** was formed under the same reaction conditions.

Table 1. Percentage of dodecyl iodide **3** produced after 24 hours under PT conditions with isoG **1** as catalyst.[a]

metal iodide salt	Liquid-Liquid PT	Solid-Liquid PT
LiI	b	b
NaI	10 % ± 3	44 % ± 1
KI	10 % ± 1	18 % ± 1
RbI	10 % ± 1	15 % ± 1
NH_4I	11 % ± 1	13 % ± 1
CsI	11 % ± 1	9 % ± 1

[a]All reactions, both S-L and L-L, were performed in triplicate with rapid stirring. Percentage conversion to dodecyl iodide **3** was determined by ^1H NMR analysis of the reaction mixtures.

[b]PT reactions with LiI showed no product formation under both L-L and S-L conditions. In both L-L and S-L cases NMR analysis indicated that isoG **1** could not extract LiI into $CDCl_3$.

With isoG **1** as the catalyst, the extent of iodide substitution in the L-L PT reactions was independent of the cation's identity. After 24 hours, dodecyl iodide **3** was produced in 10% yield for all the salts examined, with the exception of LiI, which was not extracted into $CDCl_3$ by isoG **1**. There are various explanations for the L-L results. First, anion exchange may be rate limiting. If so, iodide transfer from water to $CDCl_3$ (or mesylate transfer from $CDCl_3$ to water) may be difficult regardless of the cation. Alternatively, anion exchange is facile, and all the ionophore-salt complexes react with mesylate **2** at the same rate. This explanation is reasonable if the structures of the isoG **1**-salt complexes are similar. For NaI and CsI, ion chromatography (IC) was used to determine the amount of cation (M^+) and anion (I^-) extracted by isoG **1** (8 mM) into $CDCl_3$ under L-L and S-L conditions (Table 2).

Table 2. Concentrations of M^+ and I^- extracted by isoG **1** (8.0 mM) as determined by ion chromatography.[a]

metal iodide salt	Liquid-Liquid Extraction[b] M^+ (mM)	I^- (mM)	Solid-Liquid Extraction[b] M^+ (mM)	I^- (mM)
NaI	1.16 ± 0.12	0.76 ± 0.04	2.48 ± 0.16	2.56 ± 0.08
CsI	0.72 ± 0.04	0.60 ± 0.04	0.76 ± 0.04	0.76 ± 0.04

[a] A $CDCl_3$ solution of isoG **1** (2 mL; 8 mM) was added to a water solution of iodide (2 mL; 200 mM) or to the solid salt (0.4 mmol). After stirring for 3 h, 1 mL of $CDCl_3$ was removed. To break up the (isoG **1**)$_n$-M^+I^- complex and back-extract the salt from $CDCl_3$, 1 mL of BuOH and 2 mL of H_2O was added to the $CDCl_3$. This mixture was stirred for 2 h, and then 1 mL of the H_2O layer was removed and diluted with 1 mL of H_2O. This aqueous solution was analyzed for ions with a Dionex-120 IC system, with an IonPac CS12 column for cation separation and an IonPac AS14 column for anion separation.

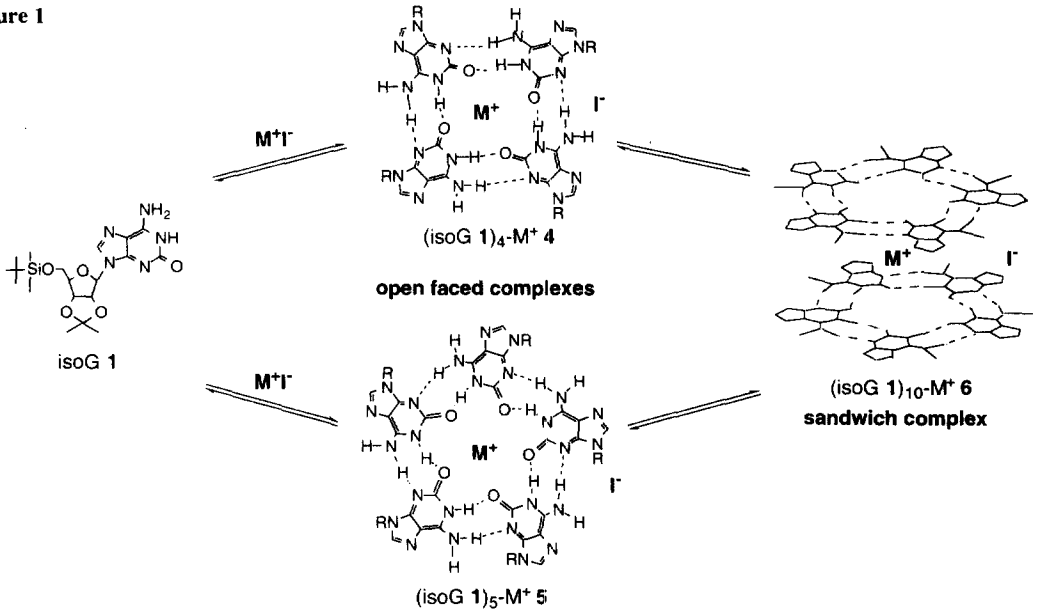
[b] Extractions and IC analyses were performed in triplicate with the appropriate blanks to correct for background M^+ and I^-.

Data in Table 2 suggests that isoG **1**-Na^+ and isoG **1**-Cs^+ complexes generated under L-L conditions have similar stoichiometry since approximately the same amount of NaI and CsI was extracted. Furthermore, NMR spectroscopy indicated that a decamer, (isoG **1**)$_{10}$-M^+ **6**, was formed in $CDCl_3$ upon L-L extraction of CsI or NaI.[12] Decamer **6** is likely a sandwich complex, with a cation coordinated between two H-bonded pentamers (**5**) (Figure 1).

IsoG **1** was also a catalyst under S-L PT conditions. Thus, isoG **1** (8 mM) catalyzed formation of dodecyl iodide **3** when a solution of mesylate **2** (20 mM) in $CDCl_3$ was stirred with a suspension of excess iodide (200 mM) at 60 °C.[13] The isoG **1**-catalyzed displacement of mesylate **2** with iodide under S-L conditions was significantly different from the reactions under L-L PT conditions. Thus, the particular iodide salt influenced the S-L reaction, with product formation increasing in the order: CsI<NH_4I<RbI<KI<NaI (Table 1). Sodium iodide was most effective, with 44% formation of dodecyl iodide **3** after 24 hours. Under identical S-L reaction conditions with NaI, (isoG **1**)$_4$-Na^+ gave a similar amount of product **3** (44%) as did the commercial PT catalyst dicyclohexano-18-crown-6 (0.1 equiv., 55%).

NMR studies indicated that isoG **1** forms complexes of differing ligand-salt stoichiometry depending on the cation and the extraction conditions. For example, extraction of NaI into $CDCl_3$ under S-L conditions produced an open-faced complex, (isoG **1**)$_4$-Na^+ **4**, while L-L extraction generated a sandwich complex (isoG **1**)$_{10}$-Na^+ **6**.[12] In addition, the IC data in Table 2 confirmed that isoG **1** extracted significantly more NaI under S-L conditions than it did under L-L extraction.

Figure 1



Again, there are different possible explanations for the trend in the S-L data, where NaI gave more product than the other salts. Anion exchange may be rate limiting; it may be easier to exchange iodide and mesylate between phases with (isoG **1**)$_4$-Na^+ **4**. Alternatively, the reactive species' structure may influence the nucleophilic displacement step. Under S-L conditions NMR studies indicate that an open-faced complex is favored for all the iodides,

except CsI. An open-faced complex, such as **4** or **5**, should be sterically less demanding than a sandwich complex like **6**. Electronic factors may then attenuate the reactivity of the open-faced complex. For example, cation catalysis in the S-L S_N2 reaction is possible if open-faced structures such as (isoG **1**)$_4$-M^+ **4** or (isoG **1**)$_5$-M^+ **5** predominate. An open-faced structure may be well suited for electrostatic interaction with the substrate's leaving group. If electrophilic activation of the mesylate by the bound cation is a factor, then an increase in the cation's Lewis acidity should accelerate the reaction. Metal ion catalysis of nucleophilic substitutions in non-polar solvents has been observed with crown ethers; cations with greater Lewis acidity gave faster displacement of alkyl mesylates with iodide.[14,15] These results were consistent with a transition state where the complexed cation assists departure of the leaving group. In contrast, the L-L S_N2 reactions catalyzed by isoG **1** may occur at similar rates because a sandwich complex, (isoG **1**)$_{10}$-M^+ **6** predominates for all the cations. A sandwich structure, such as **6**, might inhibit the bound cation from participating in the S_N2 reaction. Indeed, S_N2 rates that are cation-independent have been observed with cryptands as PT catalysts.[15] Cryptands shield the encapsulated cation from participating in the reaction.

More detailed structural analysis, especially X-ray crystal structures, of the (isoG)$_n$-M^+ complexes **4-6** should help explain product formation in these PT reactions. Also, determination of second-order rate constants for reaction of preformed complexes **4-6** with alkyl mesylate **2** should reveal whether electrophilic activation by the cation is important. Such structural and mechanistic studies are ongoing. Regardless of the exact structure and mechanism, the lipophilic nucleoside isoG **1** catalyzes an S_N2 reaction, showing that non-covalent synthesis can be used to form supramolecular catalysts from simple building blocks.

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12. The stoichiometry for each isoG **1**-M^+I^- complex was determined by analogy from ^{1}H NMR experiments with $M^+BPh_4^-$. After $M^+BPh_4^-$ extraction, the relative integration of NMR signals for isoG **1** and the BPh_4^- anion provided the stoichiometry for the (isoG **1**)$_n$-$M^+BPh_4^-$ complexes. The open-faced complex **4** and sandwich complex **6** for each cation had a distinct set of ^{1}H NMR chemical shifts. For each cation, the ^{1}H NMR chemical shifts for the (isoG **1**)$_n$-$M^+BPh_4^-$ complex and the (isoG **1**)$_n$-M^+I^- complex were the same, suggesting that the structures of the iodide and BPh_4^- complexes were identical.
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