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Highly Selective Radical Mono Reduction of Dihalides Confined to a Dynamic Supramolecular Host

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Abstract: Reduction of alkyl dihalide guests (**2**-**5** and **7**) with trialkylsilanes (R_3SiH) was performed in water-soluble host **1** to investigate the effects of confinement on fast radical reactions ($k \geq 10^3$ M^{-1} s^{-1}). High selectivity (> 95%) for mono-reduced products was observed for primary and secondary dihalide guests under mild conditions. The results highlight the importance of host-guest complexation rates to modulate the product selectivity in radical reactions.

The specificity of enzyme-substrate interactions often leads to exquisite selectivity for reaction products, [1] and provides a source of inspiration in the development of new catalysts [2-7] and supramolecular systems. [8-11] Applications of open-ended container compounds play an expanding role in biomimetic literature, [12-15] and water-soluble cavitand **1** is one of the actors (see Figure 1). The cavitand exists in solution in the receptive vase shape or unreceptive flattened shape, called the kite or velcrand form. [16] The equilibrium between vase and kite form in solution is dynamic and regulated by experimental conditions. [17] The vase form is identified by characteristic methine proton signals that appear at 5.6 ppm in the ^{1}H NMR spectrum, while a signal around 4 ppm is observed for the kite form. The vase is stabilized by guests that fill the inner space, and the guests' nuclei experience upfield shifts in their NMR spectra, due to the anisotropic effect of the many aromatic panels of the host. Recently, we successfully reported these cavitands as reaction vessels in non-radical processes involving cyclizations [18-20] and mono-functionalizations. [21-23] Free radicals are highly reactive species with fast kinetics (often $k > 10^3$ M^{-1} s^{-1}) and low discrimination. Selectivity in product distribution is often a challenge for such species and only a few selective radical processes have been reported in supramolecular hosts. Ramamurthy and Gibb [24, 25] have investigated radicals generated in capsular hosts, where they determined the effects of confinement on product selectivity. [26] Our recent studies revealed the effects of guest affinity on radical processes in dynamic containers [27] that are open-ended. In order to shed further light on the selectivity due to confinement, detailed studies of the process are reported here.

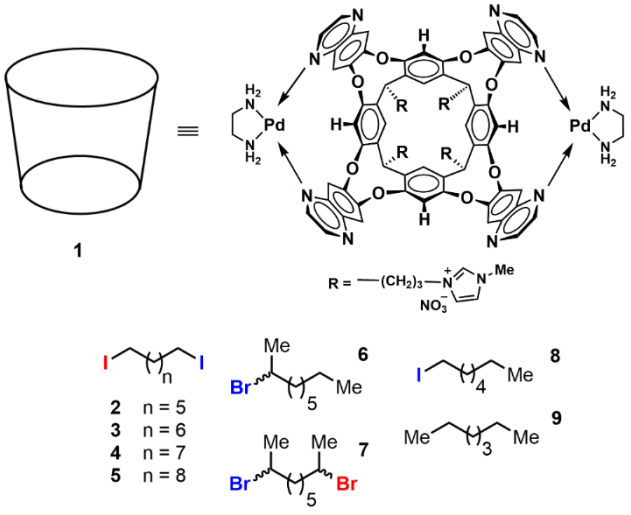

Figure 1. Cartoon and chemical structure of water-soluble host **1** (Top). Chemical structure of alkyl dihalides guests (Bottom).

Dynamic host **1** was chosen for its ability to bind organic molecules tightly in aqueous solution, and radical dehalogenation using reducing agents such as trialkylsilanes (R_3SiH) was selected as the model process. [28] Alkyl diiodides (**2**-**5**) were selected as good, highly reactive primary halides, while secondary monobromide **6** and dibromide **7** were investigated to further explore the scope in confined spaces. Host-guest complexes, kinetically stable (on the NMR timescale), must have a K_A value higher than 1.2×10^3 M^{-1} to guarantee that the reaction, involving the guest molecules takes place in the host cavity. [27] In a previous work, isothermal titration calorimetry (ITC) was used to determine a K_A value of 1.5×10^5 M^{-1} for *n*-BuOH in **1**. [16] Binding competition experiments on **1** with **7** in the presence of *n*-BuOH showed a comparable affinity of **7** to that of *n*-BuOH for **1** (see SI47-48). Since **7** showed the lowest K_A value among alkyl dihalides in binding to a related water-soluble cavitand, [27] we assumed that reactions outside the host **1** are also prevented for other alkyl halides (**2**-**6**).

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Solvolysis is a possible side reaction when alkyl halides are involved in aqueous medium, due to their relatively high reactivity towards nucleophiles (i.e. water). However, activators such as DMSO are required to promote this reaction, [21, 29] so use of this co-solvent was avoided in these studies.

The binding orientation of alkyl-spaced diiodides (**2-5**) in **1** was first investigated by NMR (see Figure 2). A characteristic signal pattern is observed in the ^{1}H NMR spectra and increasing the length the alkyl spacer does not affect the signals in the upfield region for these guests (see Figure 2 – magenta letters). The limited space affects the orientation of bound guests and their movement: they are positioned in an extended conformation in the cavity as reported for similar linear guests in **1**. [16] The NMR signals for external –CH_2- are observed between 1.5 and 2 ppm (see Figure 2 and SI). In the bulk solution, terminal sites of long chain substrates are truly remote and act independently, leading to low reaction selectivity for mono-functionalization. But the two iodides of bound **2-5** experience very different environments in **1**, and are expected to respond differently when treated with external reducing agents such as $(TMS)_3SiH$.

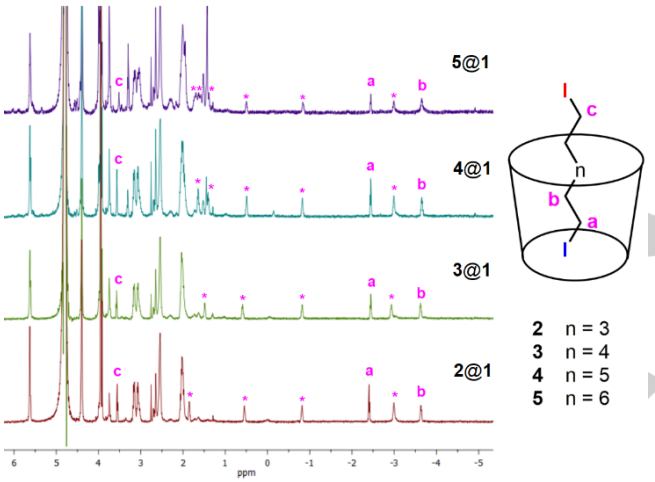

Figure 2. Full ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of host-guest complexes formed between **1** and **2-5**. Characteristic and other signals are marked with magenta letters and stars, respectively (See SI9-16 for details).

This reducing agent $(TMS)_3SiH$ was chosen as it features low affinity and reactivity towards **1**; no differences in the ^{1}H NMR spectrum of **1** (in the vase form) were observed after 12 h at 40 °C in the presence of the agent and catalytic amount of 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH) as radical initiator (see SI8). Also, no differences were observed in the ^{1}H NMR spectra of bound **7** in **1** after 8 h at 45 °C in the absence of reducing agent (see SI6 and SI7). Typically, silanes such as $(TMS)_3SiH$ are efficient reducing agents in water, [30] and excellent yields can be obtained when stoichiometric or excess silanes are used on alkyl halides. [31] When a solution of **2@1** was treated with 1 equivalent of $(TMS)_3SiH$, characteristic peaks for remaining **2** are observed (see Figure 3 – blue squares). The mono-reduced product is seen at 1.29 and -4.56 ppm (see Figure 3B and C), as two different complexes **8a** and **8b**, which interconvert slowly on the NMR timescale. These were identified by the binding of authentic, mono-reduced product in **1** (see Figure 3C). Lower conversion (17%) but higher selectivity for mono-reduced product (>95%) respect to reaction in bulk solution, were observed for bound **2** in **1** (see Table 1 – Entry 1). The detection of a single orientation (Complex 8a) after the radical reduction of **2** (see Figure 3B) confirms that the reaction takes place strictly inside the host's cavity (see SI21). The result was determined by NMR spectroscopy as described in the SI (see SI31), and the accuracy of the NMR method was confirmed for **2** by GC analysis (see SI41).

The effect of the lipophilic tail on the conversion and selectivity using the longer guests **3-5** was also explored. Conversion of 27% was reached for bound **3** in **1** (see Table 1 – Entry 2) while values of 31% and 41.5% (see Table 1 – Entry 3 and 4) were detected for bound **4** and **5**, respectively.

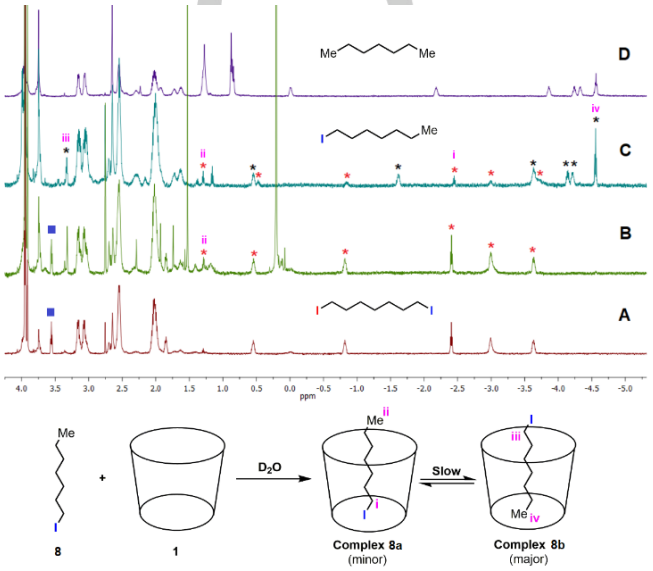

Figure 3. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of (A) host-guest complex between **1** and **2**, (B) after 12 h at 40 °C in presence of **1** eq. of $(TMS)_3SiH$, (C) authentic mono-reduced product (**8**) in **1**, (D) authentic alkane (**9**) in **1** (Top). Cartoon and relative equilibrium for bound **8** in **1** (Bottom). Peaks from Complex **8a** and **8b** are marked with red and black stars, respectively. Characteristic peaks from **2** (external I-CH_2-) are marked with blue squares.

In all cases, the fully-reduced (alkane) product was not detected, supporting the excellent selectivity (> 95%) for mono-reduced products (1-iodoalkanes). Longer alkyl diiodides (C_{11} and C_{12}) showed low affinity for the cavitand and reveal the limitations of this supramolecular approach (see SI19-20). No correlation between conversion % and length of the lipophilic spacer is observed in bulk solution under same experimental conditions. [32] However, a length correlation with conversion holds for bound **2-5** in **1** (see SI39). Longer guests as **4** and **5** are more accessible to the reducing agent, leading to higher conversions while shorter guests, being deeper in the cavity, are less exposed and consequently less reactive. Similar results were obtained for the radical reduction of bound **2** when 2 or 3 equivalents of $(TMS)_3SiH$ were used (see SI43-46), indicating that higher concentrations of reducing agent have little or no effect on the conversions. Selectivity higher than 95% for the mono-reduced products was observed in all cases, confirming the effects of confinement in **1**.

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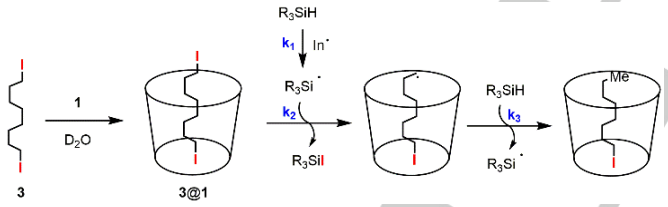
Table 1. Effect of the lipophilic spacer on the conversion and selectivity for mono-reduced product in **1** after treatment with 1 eq. of reducing agent for 12h at 40 °C (see SI32-35 for details).

Entry	Guest	Reducing Agent	Conversion (%)	Selectivity (%)
1	2	$(TMS)_3SiH$	17.0	> 95%
2	3	$(TMS)_3SiH$	27.0	> 95%
3	4	$(TMS)_3SiH$	31.0	> 95%
4	5	$(TMS)_3SiH$	41.5	> 95%
5	2	Ph_3SiH	15.0	> 95%
6	3	Ph_3SiH	27.0	> 95%
7	4	Ph_3SiH	33.0	> 95%
8	5	Ph_3SiH	43.5	> 95%

Activation and termination reactions (k_1 and k_3 in Scheme 1, respectively) are faster when $(TMS)_3SiH$ is involved, due to its lower Si-H BDE with respect to Ph_3SiH that allows a faster hydrogen abstraction in presence of radical initiators. For example, k_3 is reported to be ≈ $10^{4\text{-}5}$ M^{-1} s^{-1} in benzene for $(TMS)_3SiH$ while a value of ≈ 10^3 M^{-1} s^{-1} is reported for Ph_3SiH. [31] Radical reduction of bound **2-5** in **1** was performed in the presence of 1 equivalent of Ph_3SiH, in order to explore the effect of a slower termination processes on conversion and selectivity. Slower kinetics (relatively low k_3) result in longer lifetimes and often lead to undesired side reactions. However, no differences were detected in the conversions (see Table 1 and SI39-40). For instance, bound **3** in **1** shows the same conversion in presence of Ph_3SiH or $(TMS)_3SiH$ under same conditions (see Table 1 – Entry 2 and 6). Nor is the selectivity affected, as values higher than 95% were detected for mono-reduced product (iodo-alkanes) in all cases (see SI26-29).



Scheme 1. General scheme for the radical reduction of bound **3** in **1** using a general reducing agent (R_3SiH).

A more reactive guest **7**, involving a secondary carbon centered radical instead of a primary one was investigated with both trialkylsilanes (Ph_3SiH and $(TMS)_3SiH$) (see SI17-18). Bound **6** and **7** show linear orientation and relative slow movements with respect to NMR time scale, due to the limited space in **1** (see Figure 4 - Bottom). Diastereotopic signals are observed for bound **7** in **1** as the presence of the stereogenic center (Br-CH*-) close to the open-end of **1** is able to transmit chiral information to the rest of the complex (see Figure 4A and see SI17). Bound **7** was stable under experimental conditions in absence of reducing agents (see SI6 and SI7). Addition of 2 eq. of Ph_3SiH causes the loss of diastereotopic signals due to the disappearance of the asymmetric center close the open-end of **1** (see Figure 4B and see SI30). Again, the detection of a single orientation (**6a@1**) after the reduction indicates that the reaction took place in the complex as expected by the K_A value for **7@1**.

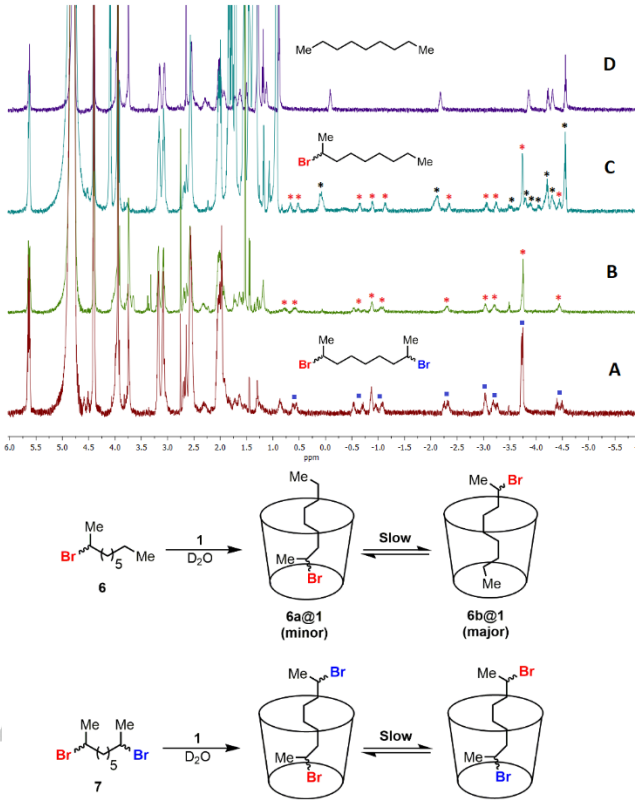


Figure 4. A) Upfield regions of the ^1H NMR spectra (600 MHz, 298 K) of 7 (10 µL, 50 mM acetone-d_6 then removed) in a solution of 1 (1 mM) in 0.5 ml of D_2O. B) After 12 h at 40 °C in presence of 2 equivalents of Ph_3SiH/AAPH$_{(cat)}$ under nitrogen atmosphere. C) Authentic 2-bromononane (6) in 1. D) Authentic alkane (nonane) in 1. Signals of 6a@1 and 6b@1 are marked in red and black stars, respectively. Diastereotopic NMR signals from bound 7 are marked with blue squares (Top). Cartoon of 6@1 and 7@1 and relative amounts of the isomeric complexes (Bottom). "Adopted with permission from Ref. 27. Copyright (2020) American Chemical Society."

Excellent conversion (> 94%), and selectivity (> 95%) for mono-reduced product (**6**) was determined by NMR spectroscopy (see SI30) and GC analyses (see SI42), even when 2 equivalents of the more reactive $(TMS)_3SiH$ were used (see SI25).

In conclusion, selective radical reductions of primary and secondary alkyl dihalides (**2-5** and **7**) using trialkylsilanes (R_3SiH) under mild conditions is reported in water-soluble host **1**. No correlation is seen in bulk solution between conversion and length of the lipophilic spacer in alkyldihalides, while a linear correlation is observed on bound **2-5** in **1**. Longer guests as **4** and **5** are more exposed to the reaction medium in comparison to short ones (**2** and **3**), making the radical reduction more sterically accessible. However, low affinity for the cavity is observed for longer alkyl diiodides (C_{11} and C_{12}), revealing the limits of the system. Moderate yields (15-45%) for primary and excellent yields (> 90%) for a secondary alkyl dihalide were obtained as determined by NMR spectroscopy and confirmed by GC analyses. Selectivity higher than 95% in mono-reduced product was observed in all cases, even when 2 or 3 equivalents of reducing agent (R_3SiH) were used. Low selectivity was observed under same conditions (excess of reducing agent) in bulk solution, highlighting the importance of confinement for product selectivity in radical processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Keywords: Dynamic Host • Water-Soluble Cavitand • Free Radicals • Radical Reduction • Supramolecular Chemistry

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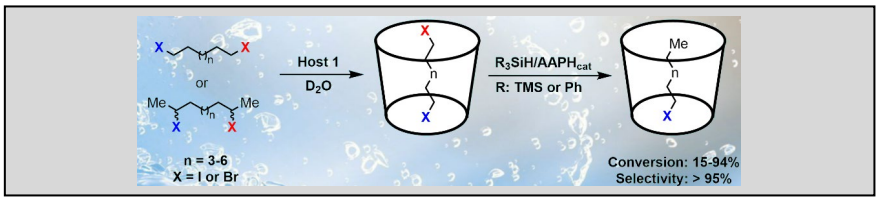

Fast reactions as radical processes (k often 10^3 M^{-1} s^{-1}) have not been study in open-ended, dynamic hosts so far. Moreover, high selectivity is a true challenge due to their fast kinetic. We report the radical reduction of alkyl dihalides in new water-soluble host **1** using green reducing agents as trialkylsilanes. Modest (15-45%) to excellent conversion (> 94%) and excellent selectivity (> 95%) in mono-reduced product was observed, imitating the action of biological enzymes.