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Radical Reactions in Cavitands Unveil the Effects of Affinity on Dynamic Supramolecular Systems

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ABSTRACT: Radical reduction of alkyl halides and aerobic oxidation of alkyl aromatics are reported using water-soluble container compounds (**1** and **2**). The reductions involve α,ω-dihalides (**4-8** and **10**) with radical initiators in cavitand hosts with varied binding affinities. Product distributions lead to general guidelines for the use of dynamic supramolecular systems with fast reactions. Binding of guest substrates in the hosts must show high affinities (Ka > 10^3 M^{-1}) to ensure that the reactions take place under confinement in the containers (**11** and **12**).

INTRODUCTION

Deep cavitands such as **1** (Figure 1) are water-soluble container hosts that allow the study of guest molecules under confinement where reactivity may be affected by the limited space [1]. They are conformationally dynamic systems that interconvert between a receptive vase shape, stabilized by binding of suitable guests, and a flattened form, called velcrand or kite form. In the absence of suitable guests, the kite form, as its more stable dimeric form, called velcraplex, is not detectable by ^{1}H NMR spectroscopy. Characteristic methine triplets can be observed in the ^{1}H NMR spectrum at 5.6 ppm and around 4 ppm for "vase" cavitand and velcrand, respectively (Figure 1 - bottom). Host **2** is less flexible and appears as the vase in its resting state [2].

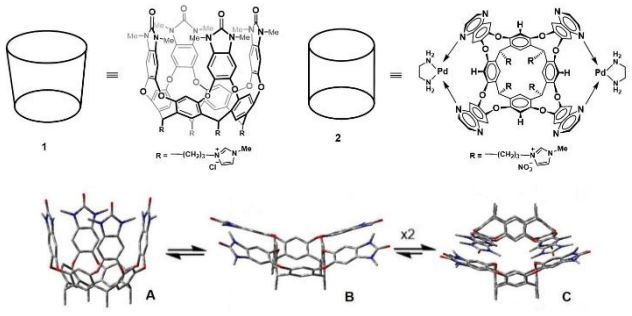


Figure 1. Cartoons and structures of host **1** and **2** (Top). Modeled host **1** conformations: vase (A), kite (B) or velcrand and the dimeric velcraplex (C). Hydrogen atoms and "feet" are removed for clarity.

Reactions such as cyclizations [3-5] or selective mono-functionalizations [6-8] confined in **1** have been reported and show some parallels to the action of enzymes in biological systems [9, 10]. The affinity of a guest to any host is described by the binding constant (K_A) [1] that reflects the kinetics of the in-out equilibrium (guest uptake and release) of the complex (Figure 2). High values of K_A often correspond to slow release with high affinity to the host while lower values can involve fast

release and lower affinity. The binding constant (K_A) reflects the ratio of these rates; the concentration of the free guest is also a factor. Low and high concentrations are observed for high and low K_A values, respectively. Other factors can affect the K_A value, including solvent, the guest's solubility, temperature and the intramolecular forces involved in the host-guest recognition. For example, highly water-soluble guests as cyclic alkyl amines are relatively happy in solution and show lower K_A values than the less water-soluble cyclic alkyl halides. Indeed, free guest is observed in the ^{1}H NMR spectrum when cyclohexyl amine and **1** are mixed in water in 1:1 ratio, while no free guest is observed when cyclohexyl halides are used under the same conditions [11].

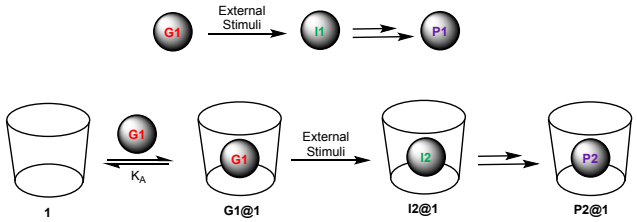


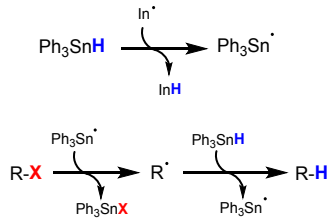
Figure 2. General reactivity in bulk solution (Top) General reactivity in Host **1** (Bottom). G: Guest, I: Intermediate, P: Product.

Where the products are formed is a reasonable question for reactions involving dynamic containers, as it cannot be assumed that the reaction takes place in the host. A general guest **G1** in bulk solution, exposed to external stimuli (i.e. radical initiators or light), leads to the formation of product **P1** through intermediate **I1**. The same guest **G1** in presence of **1** may be bound in a host-guest complex **G1@1**. The confined space in **1** forces **G1** to assume unusual conformations in the cavity, and can promote alternatives after exposure to external stimuli, with consequent formation of "alternative" product **P2** (Figure 2). The necessary and unique conditions needed to observe this behavior are a host-guest complex that is kinetically stable on the NMR chemical shift timescale [12, 13]. This condition excludes the possibility of generating "side" product **P1** from "free" **G1** in solution.

We used cavitands in reactions where radicals are involved. They are generally hard to control and modulate; the fast kinetics (often $k > 10^3$ M^{-1} s^{-1}) and the possible side reactions make these reactions neither "user friendly" nor easy to manage. Even so, radical processes currently enjoy popularity and efforts have been made to investigate their chemistry in supramolecular contexts such as capsules [14, 15], cages [16, 17] and organometallic systems [18]. The use of external chemical agents is ineffective in these systems, due to the protective action of the capsule (or cage) that maintains a mechanical barrier between guest and reaction medium. This aspect strongly limits the use of these systems to mostly photo-activated processes. For example, homolytic cleavage of C-C bonds in carbonyl compounds (Norrish reactions) or C-O bonds in esters (Fries reactions) with subsequent radical-radical coupling processes are well known [19, 20]. Also, electron transfers through the organic wall after photo-irradiation are reported between encapsulated guest and external compounds [21]. To our knowledge, no radical reactions involving radical initiators, have been reported in dynamic hosts with open ends. This unexplored area prompted the present research. Cavitand **1** and **2** were taken as model host: The absence of hydrogen-bond donors in either host prevents formation of capsules and both containers maintain an opening to the solution. As model radical reactions in water, we chose radical reduction of alkyl halides with Ph_3SnH and aerobic oxidation of alkyl aromatic compounds.

RESULTS AND DISCUSSION

Radical Reduction of Alkyl Halides in 1. Radical reduction of alkyl halides, using reducing agents such as triphenyltin hydride (Ph_3SnH) or the "greener" trialkylsilanes (R_3SiH), is a classical chain reaction [22]. Historically used for the synthesis of alkanes [23, 24] or as a tool for generating building blocks [25, 26]; recently it has even been applied in DNA-encoded library (DEL) settings [27]. The alkyl halide quickly reacts with the tin radical in solution, leading to tin halide and a carbon-centered radical.



Scheme 1. Generation of tin radical in presence of radical initiator (Top). General mechanism for radical reduction of alkyl halides (RX where X = Br or I) using Ph_3SnH as reducing agent (Bottom).

The radical is rapidly quenched by the remaining tin hydride ($k \approx 10^6$ M^{-1} s^{-1} in benzene) producing the relevant alkane and regenerating the tin radical for the next cycle (Scheme 1). Theoretical TS calculations were performed on bromo cyclohexane and trimethylsilyl radical (taken as model alkyl halide and reducing agent, respectively) in order to investigate the orientation of the attack.

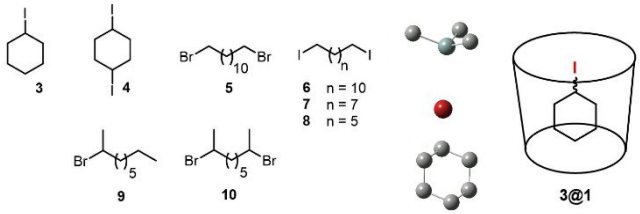


Figure 3. (Left) Alkyl halides used in this investigation (**3**-**10**); (Middle) Calculated TS for radical dehalogenation of bromo cyclohexane with trimethylsilyl radical at DFT/6-31G(d,p) level of theory; and (Right) cartoon of the **3@1**. Hydrogens on calculated structure are omitted for better clarity.

A linear TS structure with attack in the cyclohexyl plane is the most stable structure, which would be compatible with the expected orientation of the guest in **1** (Figure 3). Triphenyltin hydride was chosen as reducing agent for its faster hydrogen donation compared to silanes (10^6 vs $10^{\leq 5}$ M^{-1} s^{-1} in benzene). Radical reduction of **3** using Ph_3SnH (1 eq.) and a catalytic

amount of AAPH as radical initiator was performed in D_2O but no products were detected after 12 h at 40°C (See SI14). The same reaction using tris(trimethylsilyl)silane ($(TMS)_3SiH$) as reducing agent in toluene led to the formation of the reduction product (cyclohexane) in 97% yield [28]. The iodine atom of **3** as a guest in **1** may not be exposed enough to the reaction medium to engage in the radical reduction cycle. Indeed, the NMR signal of the α-hydrogen in bound **3** shows a Δδ value of -3.84 ppm, placing it, on average, deep within the cavity [11]. Moreover, the size of Ph_3SnH with three phenyl groups prevents its binding in **1** (See SI11) and makes its approach to bound **3** even less likely. Guest **4**, having an additional iodo atom in position 4, appears to be more exposed to the reaction medium and the Δδ value for the same hydrogen is now -2.83 ppm (averaged value) (See SI35). Unfortunately, guest **4** shows the same inertia as **3** and no reduction product was observed (See SI15). Linear dialkyl halides were therefore selected as substrates to increase accessibility in their complexes: one of the terminal halogen atoms is always exposed to the reaction medium and their conformations in **1** are dynamic [7]. Commercially available guest **5** was tested but no reactivity was observed in the complex under the usual conditions (See SI16), yet it easily reacts with Ph3SnH in bulk solution [29]. The Δδ value for the α-hydrogens of bound **5** was -1.93 ppm (averaged value), confirming the better exposure of the carbons bearing the halogen atoms [7]. The inertia could be caused by the lower reactivity of bound **5** towards tin radical and not by its accessibility: radical dehalogenation using reducing agents as Ph_3SnH is well-known to be affected by the nature of the halogen atom.

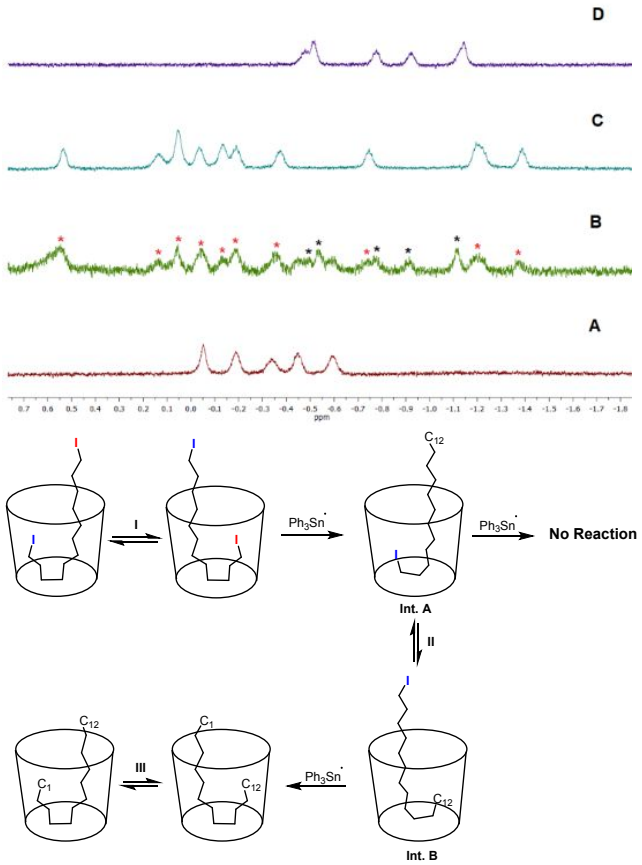


Figure 4. Partial ^1H NMR (600 MHz, D_2O, 298 K) spectra of: Initial host-guest complex **6@1** (A), after addition of Ph_3SnH (2 eq.), AAPH (cat.) after 12 h at 40 °C (B), authentic 1-iodododecane in **1** (C) and authentic dodecane in **1** (D). Partially-reduced and fully-reduced product are marked in the reaction mixture with red and black stars, respectively (top). Cartoon of **6@1** involved in the radical reduction (bottom).

Alkyl iodides are more reactive and **6**, in which bromo atoms were replaced with iodo atoms, was tested. Reduced products were finally detected by ^1H NMR (See Figure 4). This result is not attributed to the intrinsic reactivity of guests **3** or **4** but to the enhanced reactivity of **6** in **1**. In bulk solution **3** and **4** are more reactive than **6**, due to the formation of a secondary carbon centered radical rather than a primary one. Binding of guest **6** features the same behavior reported earlier for guest **5** (See SI37) in which iodo atoms quickly exchange their positions in the cavitand (See Figure 4 - Equilibrium I). The high reactivity of iodo atom towards radical reduction allows the formation of "Complex A" that corresponds to the mono-reduced product observed in the ^1H NMR spectrum (See Figure 4B – red stars). The remaining iodo atom is at the bottom of the cavity, where it is protected and inaccessible to radical initiators.

But "Complex A" is dynamic, in equilibrium with "Complex B" where the iodo atom is now exposed to the reaction medium and theoretically accessible to the tin radical (See Figure 4 – Equilibrium II), leading to the formation of dodecane (See Figure 4B – black stars). The Δδ value for α-hydrogens of bound iodododecane is -2.63 ppm (averaged value) (See SI39) relatively close to the value of 2.83 ppm, observed for bound **4** which was buried and unreactive. Thus the iodo atom of "Complex B" (Figure 4) would not be accessible to the radical initiator. Accordingly, the alkane detected (dodecane) *could not be generated inside the host*. The intermediate involved was confirmed to be a radical since the reduction of **6** in **1** under oxygen atmosphere led to the detection of the corresponding mono-alcohol as the major product (See SI28 and SI29).

The effect of the lipophilic tail on the selectivity for the fully-reduced product (alkane) using the shorter guests **7** and **8** was also explored. These guests should be "less exposed": placing the iodo atom much closer to the bottom of the cavity in "Complex B" decreases the reactivity as earlier observed for guests **3** and **4**. Not much difference in conversion (≈ 75-67%) and selectivity in alkane (≈ 30-35%) were observed between guest **6** and guest **7** (See SI30 and SI31) but differences were obtained with the shortest guest **8** (See Fig. 5). Selectivity of 13% in fully-reduced product (heptane) was reached with **8**, confirming the better (but not complete) protection of the iodo atom in the intermediate (See SI32). The Δδ value for α-hydrogens of bound iodoheptane was -3 ppm (averaged value) (See SI45) that is higher respect to the value found for bound **4** which was completely stable under the same conditions.

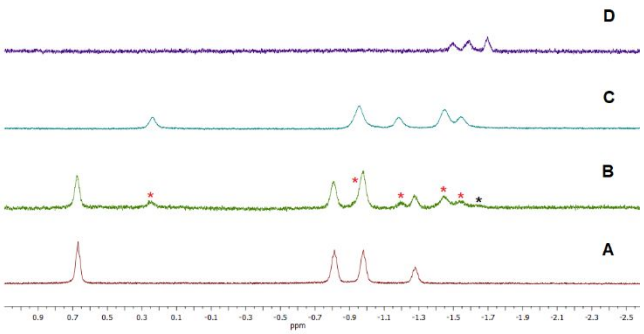
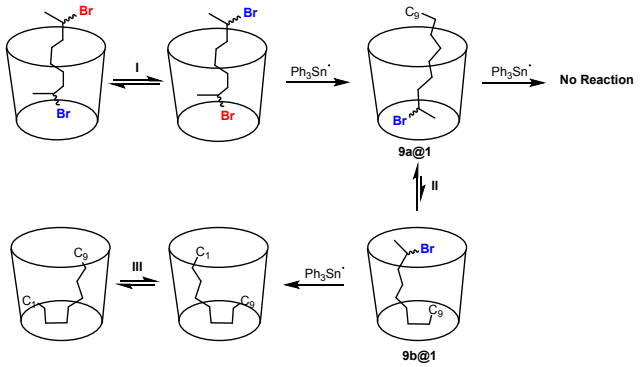


Figure 5. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of: Initial host-guest complex **8@1** (A), after addition of Ph_3SnH (2 eq.), AAPH $_{(cat.)}$ after 12 h at 40 °C (B), authentic 1-iodoheptane in **1** (C) and authentic heptane in **1** (D). Partially-reduced and fully-reduced products are marked in the reaction mixture with red and black stars, respectively.

The product alkane (heptane) should not be attributed to the reactivity of "Complex B" in the host but it should come from another process. The dynamic equilibrium of **8** in **1** makes an unambiguous interpretation of the result difficult. Therefore, guests with less dynamic intermediates in **1** were tested in order to further confirm this hypothesis.



Scheme 2. Cartoons of host-guest complexes involved in the radical reduction of **10**.

Secondary alkyl halides such as guest **10**, where the partially reduced product (**9**) is "fixed" and protected in **1** (Scheme 2), should show higher selectivity for mono-functionalization. Guest **10** in **1** assumes the same motion observed previously for guests **5**-**8** (See SI49). Better reactivity than guest **5** was guaranteed by the formation of a secondary carbon center radical. The branched ends still give kinetically stable host-guest complexes (on the NMR timescale) in **1** but the signals are broadened due to the faster in-out exchange rates (See SI48). In what follows, the different ends in **9** are called "bromo end" and "methyl end" in order to describe the relative stability of the conformations. The Δδ values of -3.72 and -3.44 ppm were calculated for the methyl group and hydrogen of the Br-CH group of the bromo-end, respectively, confirming their position at the bottom of the cavity (See SI47). Guest **9a@1** should therefore be protected by the host's walls and no reduction should be observed as previously reported for guests **3** and **4**.

Surprisingly, radical reduction of **10** using Ph_3SnH showed a different result (See Fig. 6).

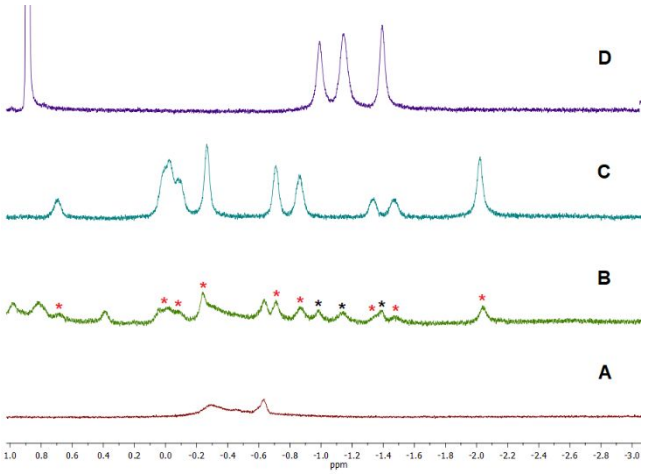


Figure 6. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of: Initial host-guest complex **10@1** (A), after addition of Ph_3SnH (2 eq.), AAPH $_{(cat.)}$ after 12 h at 40 °C (B), authentic 2-bromononane in **1** (C) and authentic nonane in **1** (D). Partially-reduced and fully-reduced products are marked in the reaction mixture with red and black stars, respectively.

Partially-reduced product was observed as expected (See Figure 6B – red stars) but the fully-reduced product (nonane) was also present in the ^{1}H NMR spectra (Figure 6B – black stars).

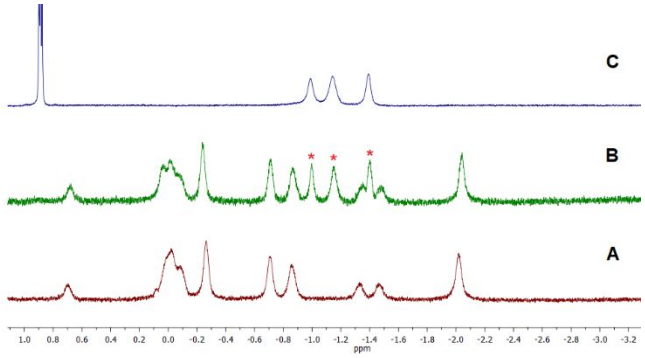
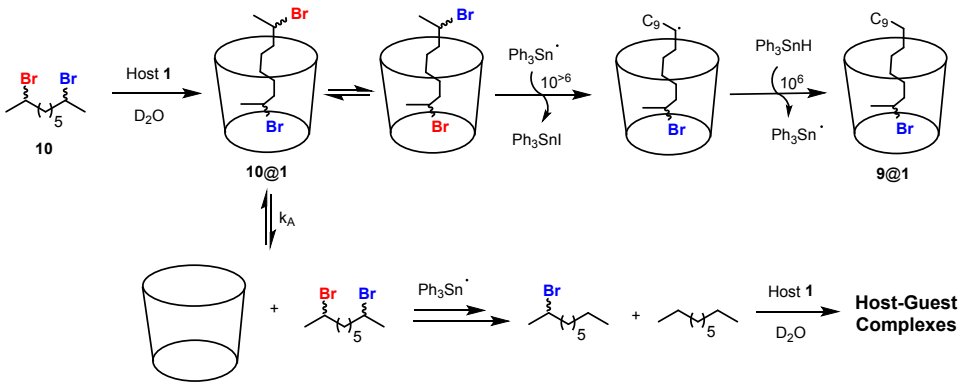


Figure 7. Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of: Initial host-guest complex **9@1** (A), after addition of Ph_3SnH (2 eq.), AAPH (cat.) after 12 h at 40 °C (B) and authentic nonane in **1** (C). Reduced product (nonane) is marked in the reaction mixture with red stars.

As mentioned above, intermediate **9a@1** should not be reactive due to the protected orientation of the bromo atom inside the cavity – indicated by ^{1}H COSY NMR and Δδ values (See SI46 and SI47). Radical reduction on guest **9** with Ph_3SnH was performed in order to confirm this surmise (Fig. 7). The host-guest complex between **9** and **1** is kinetically stable (on the NMR timescale) *but not protected*. A conversion of 29% (See SI33) to the alkane (nonane) was observed (Figure 7B). The kinetic stability of the host-guest complex on the NMR timescale was a fundamental and only requirement with dynamic supramolecular systems such as host **1**. Instead, the formation of kinetically stable host-guest complex on the NMR

time scale seems to be a necessary but not sufficient condition when fast processes such as radical reactions are involved in dynamic supramolecular systems. To repeat, kinetically stable host-guest complexes at NMR time scale are detected when guest **9** and guest **10** are encapsulated in **1**, but fully-reduced product (nonane) is still formed.



Scheme 3. Cartoons of the host-guest complexes and the mechanism of the radical reduction of **10**.

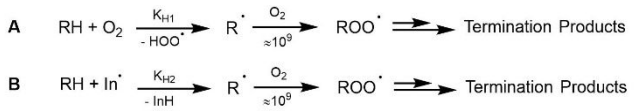
If the radical reduction of **10** takes place inside **1**, only compound **9** should be detected as final product. If the reaction takes place outside the host **1**, the relevant alkane (nonane) must also be detected (See Scheme 3). No free guest was observed in the ^{1}H NMR spectrum after the encapsulation of **10** (or any other guest reported here) in **1**, leading us to propose that the "free-guest" should come from the in-out exchange, regulated by the binding constant (K_A). If this hypothesis was correct, a relation between binding constants of each involved guest and the observed reactivity towards tin radical should be found. For a relatively low K_A value (usually fast in-out exchange), the tin radical can capture the guest during the short time it will be in solution, whereas higher K_A values (slower in-out exchange) result in lower concentrations of the guest in solution, making the free radical trapping less favored. A binding constant of 5×10^3 M^{-1} was calculated for guest **4** after NMR titration (See Table 1, Entry 1) while a value of 1.2×10^3 M^{-1} was obtained for guest **5** (See Table 1, Entry 2).

Table 1. Binding constants (K_A) for representative guests in host 1.

Entry	Guest	K_A (M^{-1})
1	4	5.0×10^3
2	5	1.2×10^3
3	6	0.7×10^3
4	9	0.9×10^3

Both **4** and **5** are unreactive in the presence of tin radical and no reduction products are detected after the reaction. A K_A value of 1.2×10^3 M^{-1} appears high enough to prevent the reaction outside the host. Reactive guests as **6** or **9** should have a K_A value lower than 1.2×10^3 M^{-1} in order to explain the observed reactivity. Guest **6** was taken as a model alkyl iodide due to its similarities with **7** and **8** while guest **10** shows broad peaks, making the NMR titration hard to follow. This problem, compounded by the low solubility of the guests in water prevents the accurate measure of in-out rate constants by, say, EXSY experiments. The broad peaks in **10@1** point to a faster in-out exchange or a lower K_A value than guests **6** or **9**. Guest **6** shows a K_A value of 0.7×10^3 M^{-1} (Table 1, Entry 3) while guest **9** is 0.9×10^3 M^{-1} (Table 1, Entry 4), confirming the hypothesis. These host-guest complexes must show a K_A of at least 1.2×10^3 M^{-1} to guarantee that the reaction takes place in the host.

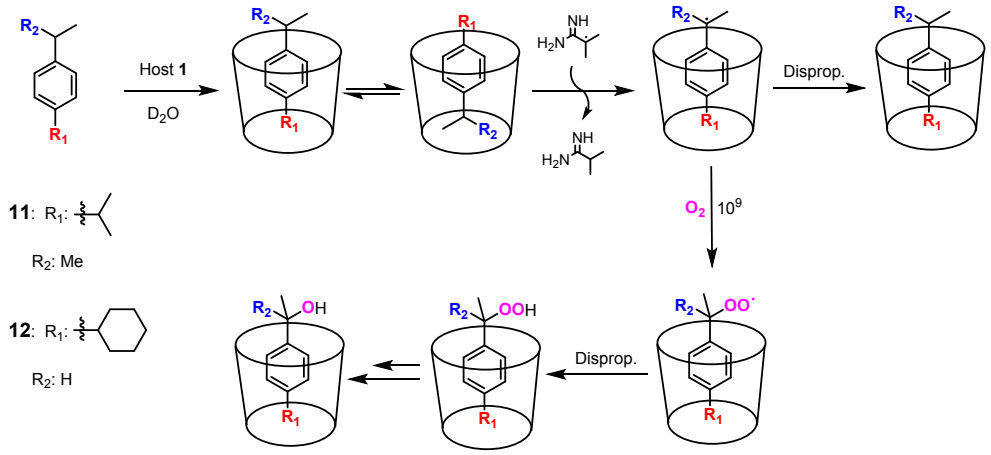
Aerobic Oxidation of Alkyl Aromatic Compounds in 1. The role of the K_A for radical processes was further tested on aerobic oxidation of alkyl aromatic compounds (**11** and **12**) in **1**, and show this behavior is independent of the nature of the radical process. The relative low C-H BDE for substituted alkyl aromatic compounds (from 82 to 87 kcal/mol) makes these compounds easily oxidized though a radical mechanism under aerobic conditions. Auto-oxidation of cumene, for example, is reported under air or oxygen atmosphere at high temperature (> 80°C). Milder conditions can be effective using radical initiators such as AIBN ((2,2'-azobis(2-methylpropionitrile)) [30] and with specific catalysts as N-hydroxy compounds [31-33] or metal-complexes [34].



Scheme 4. General pathway for A) auto-oxidation of alkyl aromatic compound (R-H) ; B) and oxidation with a radical initiator (In·) under aerobic conditions.

Oxygen abstracts hydrogen from an alkyl aromatic compound, giving a carbon centered radical that, under an aerobic atmosphere, is quenched at diffusion-controlled rates to form a peroxyl radical. The peroxyl radical may undergo termination

processes and consequent formation of neutral products as alcohols, ketones, aldehydes or carboxylic acids, depending on the substrate [35] (Scheme 4A). The addition of radical initiators does not alter the mechanism of the oxidation but acts on the activation step's kinetics. The kinetic constant K_{H2} is very often higher than the kinetic constant K_{H1} (Scheme 4B). Oxidation mechanism of **11** and **12** as guests used the radical initiator 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH) is shown (Scheme 5). AAPH was selected for its high water-solubility, its thermal activation at relatively low temperatures (≈36°C) and very low affinity and reactivity towards host **1**: no oxidative products were observed after treatment of **1** with 2 eq. of AAPH after 5h at 55°C (See SI9 and SI10).



Scheme 5. Mechanism of aerobic oxidation of alkyl aromatic compounds (**11** and **12**) in **1**.

In the absence of **1**, quantitative conversion to the corresponding diol was reached with **11** and AAPH (1.1 eq) in D_2O at 40°C after 12h. This result reflects the high reactivity of **11** and alkyl aromatic compounds in general towards AAPH in bulk solution (See SI12). A K_A value for **11** in **1** of 12.1×10^3 M^{-1} was determined (See SI), predicting no reaction outside the host. Calculations indicated the most stable trajectory of the attack is perpendicular to the phenyl plane (Figures 8A and 8B) but the orientation of **11** (or **12**) in host **1** makes the approach inaccessible to the radical initiator (Figure 8C).

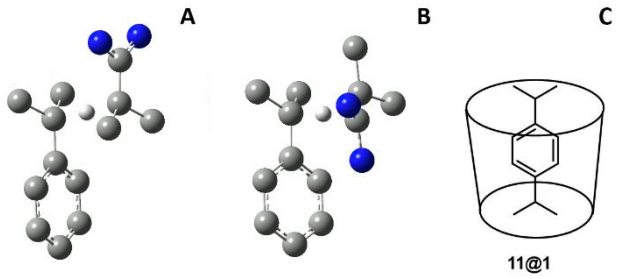


Figure 8. (Right) Theoretical TS-anti (A) and TS-syn (B) conformers for HAT reaction between "AAPH radical" and cumene at B3LYP/6-31G(d,p) level of theory. (Left) Cartoon of **11@1** (C). Hydrogens not involved in the HAT are missed for better clarity.

Experimentally, the Δδ observed for the isopropyl group at the open end of **1** (Figure 9 – Red Isopropyl group) is 0.2 ppm (See SI52), placing it close to the open end of the host but not outside the cavity. Oxidation product(s) are therefore predicted only if the reaction takes place outside the host, but this is prevented by the K_A value of 12.1×10^3 M^{-1}. In the experiment, guest **11** was completely stable in **1** after 5 h at 50°C in the presence of AAPH (1 eq.). All the characteristic signals of bound **11** remain after the reaction and no new signals are observed (Figures 9B and SI50), confirming the hypothesis concerning the role of the binding constant (K_A). Similar behavior was observed for guest **12** under the same conditions (See SI51 and SI53). In order to demonstrate the importance of K_A (rather than on the host) radical reduction of **10** using a new metallo cavitand **2** [2] are described below.

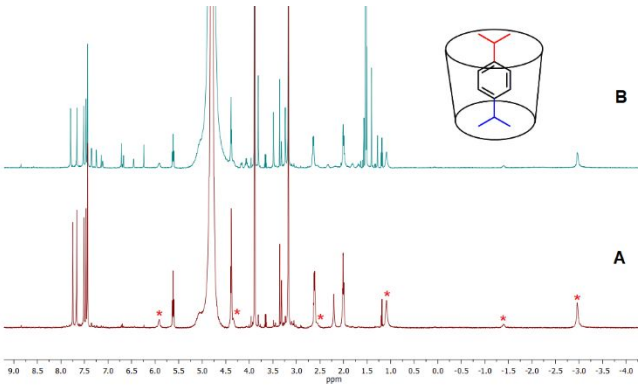
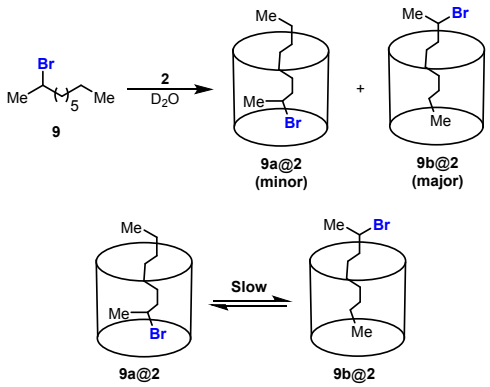


Figure 9. ^1H NMR (600 MHz, D_2O, 298 K) spectra of **11** in **1** in 1:1 ratio in D_2O (A) and after addition of AAPH (1 eq.) after 5 h at 55 °C (B). Characteristic signals of guest **11** are marked with red stars (See SI50 for detail).

Radical Reduction of 10 in 2. Guests bound in **2** experience a narrower space and movements compared to **1** are limited [2]. For example, a K_A value of 1.5×10^5 M^{-1} was obtained by isothermal titration calorimetry (ITC) using *n*-BuOH as a guest in **2** [2]. This value is two orders of magnitude higher than K_A values of any guest in **1**, and a similar K_A value was determined for bound **10** in **2** by direct competition experiments with *n*-BuOH (See SI61). Two complexes are detected by ^{1}H NMR spectrum when **9** is bound in **2** (Figure 10C). The complexes correspond to the two possible orientations of **9** in **2**, but the limited space of the cavity makes their interconversion extremely slow (Scheme 6). If the reduction of **10** takes place in the cavity, only complex **9a@2** should be detected, while both complexes must be observed if the reduction takes place outside the host. Reduction of **10** in **2** gave bound **9** in *a single orientation* and no nonane, (the product detected when the reaction involved **1**) was observed (Figure 10).



Scheme 6. Cartoons and orientations of **9@2** (Top) and the equilibrium between host-guest complexes (Bottom).

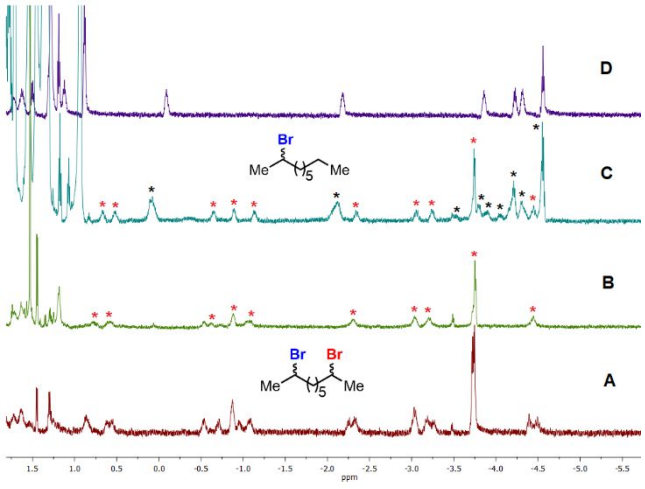


Figure 10. A) Upfield regions of the ^{1}H NMR spectra (600 MHz, 305 K) of **10** (10 µL, 50 mM acetone-d_6 then removed) in a solution of **2** (1 mM) in 0.5 ml of D_2O. B) After 12 h at 40 °C in presence of Ph_3SiH/AAPH under nitrogen atmosphere. C) Authentic 2-bromononane (**9**) in **2**. D) Authentic alkane (nonane) in **2**. Signals of **9a@2** and **9b@2** are marked in red and black stars, respectively.

The decrease of diastereotopic signals, due to the loss of the stereogenic center (Br-*CHMe-) further confirms the reaction takes place inside the cavity of the host (See SI62). Quantitative conversion and selectivity higher than 95% for mono-reduced product were detected. This was confirmed by the ^{1}H NMR spectrum of authentic mono-reduced product **9** bound in **2** (Figure 10). Accordingly, the high K_A makes the protection of intermediate **9** complete. The in-out exchange is now so slow as to be irrelevant.

CONCLUSION

Earlier reports [3-7] suggest that host-guest complexes need only to be kinetically stable on the NMR chemical shift timescale to guarantee the reaction takes place in the host. Radical reductions of alkyl halides investigated in host **1** indicate this condition is necessary but not sufficient when reactions with fast kinetics such as radical reactions (often $k > 10^3$ M^{-1} s^{-1}) are involved. Instead, a K_A value larger than 1.2×10^3 M^{-1} for the complex guarantees the reaction occurs inside the container. Lower K_A values, calculated for alkyl α,ω-diiodides, gave reduced products (alkanes), arising from the reaction outside the host **1**. These guests are weakly bound, despite showing kinetically stable complexes on the NMR time scale. The role of the binding constant appears independent of the radical processes. Alkyl aromatic compounds (**11** and **12**) with high K_A values ($K_A \approx 1.2 \times 10^4$ M^{-1}), are stable in **1** in presence of AAPH. No oxidation products are observed, despite showing high reactivity under same conditions in bulk solution. Radical reduction of secondary alkyl dibromide **10** in rigidified host **2** was also investigated. It showed high reactivity yet partially reduced product **9** was completely protected in the host cavity, due to its high K_A value ($\approx 1.5 \times 10^5$ M^{-1}). We hope these results act as guidelines for the use of dynamic hosts in the field of radical chemistry.

ASSOCIATED CONTENT

Supporting Information. Synthesis and experimental procedures, ^{1}H and ^{13}C NMR spectra for synthetized guests, stability and control experiments, Δδ calculation for all host-guest complex and binding constant determination are reported in the supporting information.

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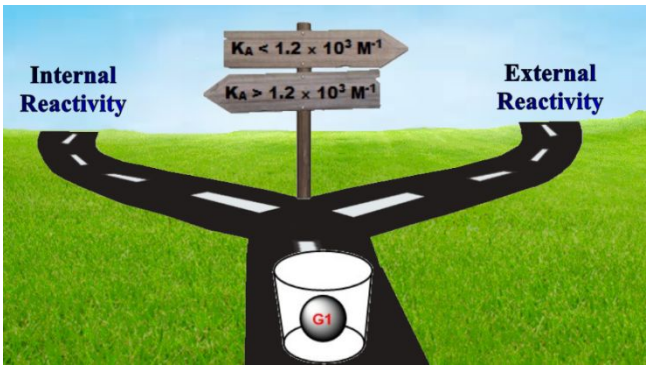
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$K_A > 1.2 \times 10^3\ M^{-1}$
External Reactivity
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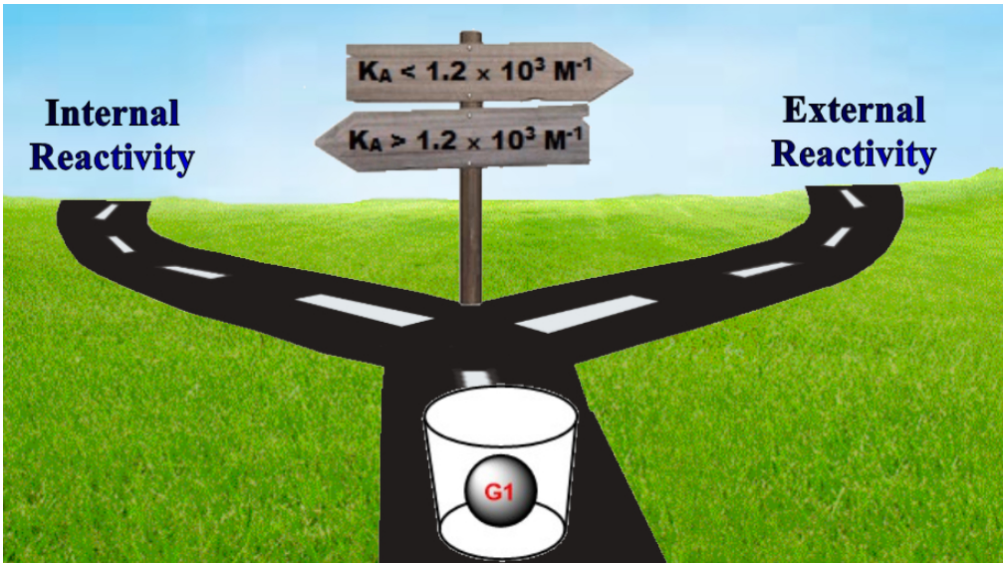

Encapsulation in host-guest complexes reveals effect of affinity on radical reactivity in synthetic receptors.

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