

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 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. The binding of guest substrates in the hosts must show high affinities ($K_A > 10^3 \text{ M}^{-1}$) to ensure that the reactions take place under confinement in the containers.



INTRODUCTION

Deep cavitands such as **1** (Figure 1) are water-soluble container hosts that allow the study of guest molecules

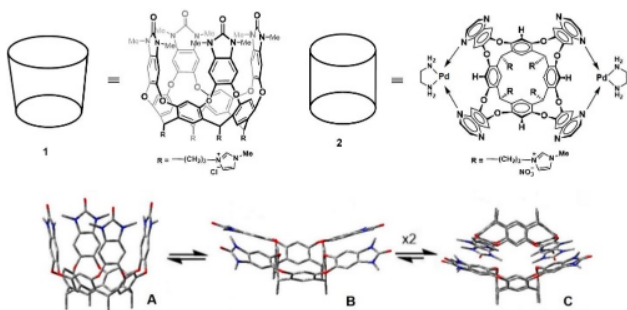


Figure 1. Cartoons and structures of hosts **1** and **2** (Top). Modeled host **1** conformations: vase (A), kite or velcrand (B), and dimeric velcraplex (C). Hydrogen atoms and “feet” are removed for clarity.

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 the binding of suitable guests, and a flattened form, called velcrand or the kite form. In the absence of suitable guests, the kite form, as its more stable dimeric form, called velcraplex, is not detectable by ¹H NMR spectroscopy. Characteristic methine triplets can be observed in the ¹H 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

Reactions such as cyclizations^{3–5} and selective monofunctionalizations^{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 for 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 for the host, and 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

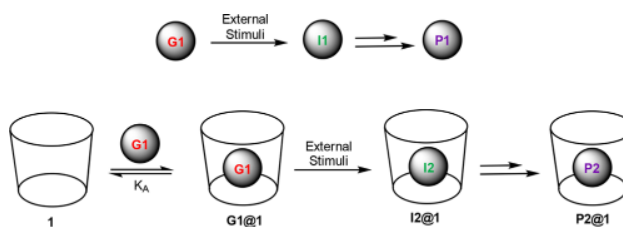


Figure 2. General reactivity in bulk solution (top). General reactivity in host **1** (bottom). G, guest; I, intermediate; and P, product.

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high and low K_A values, respectively. Other factors can affect the K_A value, including solvent, guest solubility, temperature, and intramolecular forces involved in host–guest recognition. For example, highly water-soluble guests as cyclic alkyl amines are relatively happy in solution and have smaller K_A values than less-water-soluble cyclic alkyl halides. Indeed, a free guest is observed in the ^1H NMR spectrum when the cyclohexyl amine and **1** are mixed in water in a 1:1 ratio, while no free guest is observed when cyclohexyl halides are used under the same conditions.¹¹

Where the products are formed is a reasonable question for reactions involving dynamic containers because 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 the presence of **1** may be bound in 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 the 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 time scale.^{12,13} This condition excludes the possibility of generating “side” product **P1** from “free” **G1** in solution.

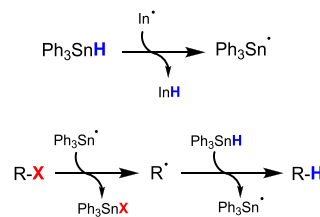
We used cavitands in reactions where radicals are involved. They are generally hard to control and modulate; the fast kinetics (often $k > 10^3 \text{ M}^{-1} \text{ s}^{-1}$) and the possible side reactions make these reactions neither user-friendly nor easy to manage. Even so, radical processes currently 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 the guest and the reaction medium. This aspect strongly limits the use of these systems to mostly photo-activated processes. For example, the 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 is well known.^{19,20} Also, electron transfers through the organic wall after photo-irradiation are reported between encapsulated guests 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. Cavitands **1** and **2** were taken as model hosts: the absence of hydrogen-bond donors in either host prevents the formation of capsules, and both containers maintain an opening to the solution. As model radical reactions in water, we chose the radical reduction of alkyl halides with Ph_3SnH and the aerobic oxidation of alkyl aromatic compounds.

RESULTS AND DISCUSSION

Radical Reduction of Alkyl Halides in **1** The radical reduction of alkyl halides, using a reducing agent 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} it has recently 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.

The radical is rapidly quenched by the remaining tin hydride ($k \approx 10^6 \text{ M}^{-1} \text{ s}^{-1}$ in benzene), producing the relevant alkane and regenerating the tin radical for the next cycle (Scheme 1).

Scheme 1. Generation of a Tin Radical in the Presence of a Radical Initiator (Top) and General Mechanism for the Radical Reduction of Alkyl Halides R-X , Where $\text{X} = \text{Br}$ or I (Using Ph_3SnH as a Reducing Agent Bottom)



Theoretical TS calculations were performed on the bromo cyclohexane and trimethylsilyl radical (taken as a model alkyl halide and reducing agent, respectively) in order to investigate the orientation of the attack.

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

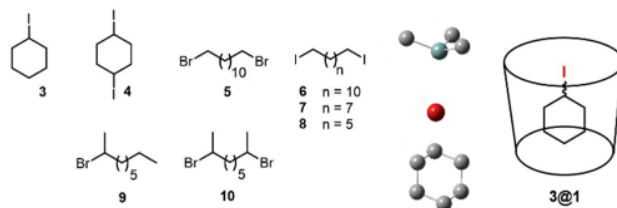


Figure 3. (Left) Alkyl halides used in this investigation (**3–10**). (Middle) Calculated TS for the radical dehalogenation of bromo cyclohexane with the trimethylsilyl radical at the DFT/6-31G(d,p) level of theory. (Right) Cartoon of **3@1**. Hydrogens on the calculated structure are omitted for better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

hydride was chosen as the reducing agent for its faster hydrogen donation compared to that of silanes (10^6 vs $10^{55} \text{ M}^{-1} \text{ s}^{-1}$ in benzene). The radical reduction of **3** using Ph_3SnH (1 equiv) and a catalytic amount of AAPH as the radical initiator was performed in D_2O , but no products were detected after 12 h at 40°C (SI14). The same reaction using tris(trimethylsilyl)silane ($(\text{TMS})_3\text{SiH}$) as the 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 β -hydrogen in bound **3** has a δ 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** (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 δ value for the same hydrogen is now 2.83 ppm (averaged value) (SI35). Unfortunately, guest **4** shows the same inertia as **3**, and no reduction product was observed (SI15). Linear dialkyl halides were therefore selected as substrates to increase the 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 (SI16), yet it easily reacts with Ph_3SnH in bulk solution.²⁹ The δ value for the β -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** toward the tin radical and not by its accessibility: radical dehalogenation using reducing agents such as Ph_3SnH is well known to be affected by the nature of the halogen atom.

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 (Figure 4). This

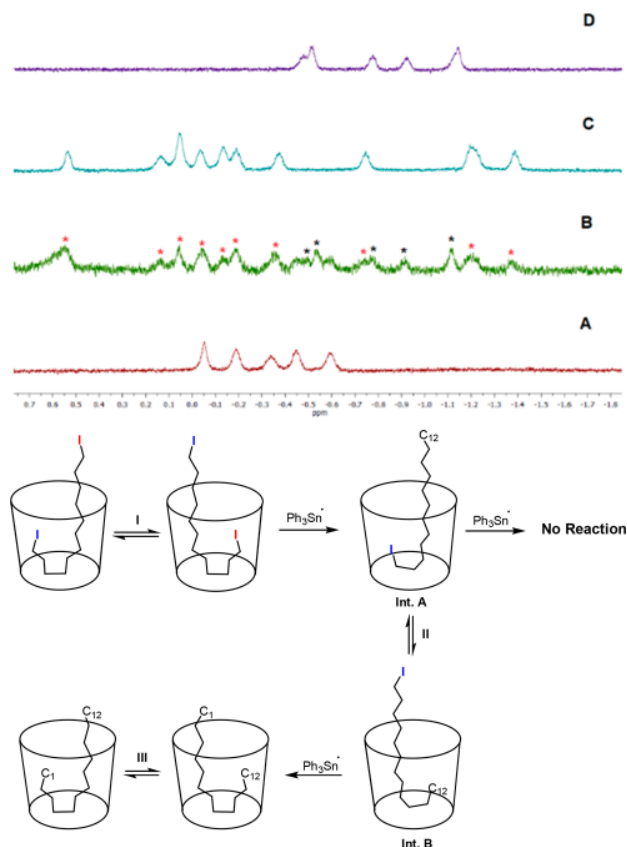


Figure 4. Partial ^1H NMR (600 MHz, D_2O , 298 K) spectra of initial host guest complex **6@1** (A), after the addition of Ph_3SnH (2 equiv), AAPH (cat.) after 12 h at 40 °C (B), authentic 1-iodododecane in **1** (C), and authentic dodecane in **1** (D). Partially reduced and fully reduced products are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

result is not attributed to the intrinsic reactivity of guest **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. The binding of guest **6** features the same behavior reported earlier for guest **5** (SI37) in which iodo atoms quickly exchange their positions in the cavitand (Figure 4, equilibrium I). The high reactivity of the iodo atom toward radical reduction allows the formation of complex A that corresponds to the monoreduced product observed in the ^1H NMR spectrum (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 and is in equilibrium with complex B, where the iodo atom is now exposed to the reaction medium and theoretically accessible to the tin radical (Figure 4, equilibrium II), leading to the formation of dodecane (Figure 4B, black stars). The δ value for β -hydrogens of bound iodododecane is 2.63 ppm (averaged value) (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 an oxygen atmosphere led to the detection of the corresponding monoalcohol as the major product (SI28 and SI29).

The effect of the lipophilic tail on the selectivity for the fully reduced product (alkane) using 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 observed earlier for guests **3** and **4**. Not much difference in conversion (~75–67%) or selectivity in alkane (~30–35%) was observed between guests **6** and **7** (SI30 and SI31), but differences were obtained with the shortest guest, **8** (Figure 5). A selectivity of 13% in the fully

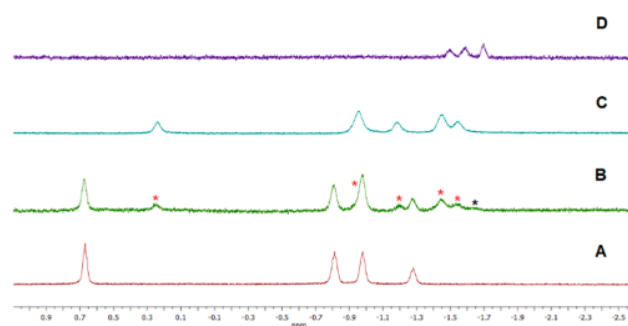


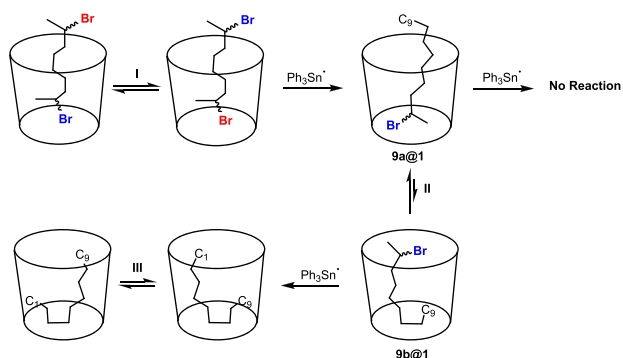
Figure 5. Partial ^1H NMR (600 MHz, D_2O , 298 K) spectra of initial host guest complex **8@1** (A), after the addition of Ph_3SnH (2 equiv), AAPH (cat.) after 12 h at 40 °C (B), authentic 1-iodoheptane in **1** (C), and authentic heptane in **1** (D). Partially reduced and fully reduced products are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

reduced product (heptane) was reached with **8**, confirming the better (but not complete) protection of the iodo atom in the intermediate (SI32). The δ value for β -hydrogens of bound iodoheptane was 3 ppm (averaged value) (SI45), which is higher with respect to the value found for bound **4**, which was completely stable under the same conditions.

The product alkane (heptane) should not be attributed to the reactivity of complex B in the host but 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.

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 monofunctionalization. Guest **10** in **1** assumes the same motion observed previously for guests **5–8** (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

Scheme 2. Cartoons of Host–Guest Complexes Involved in the Radical Reduction of 10



guest complexes (on the NMR time scale) in **1**, but the signals are broadened due to the faster in/out exchange rates (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. δ 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 (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 (Figure 6).

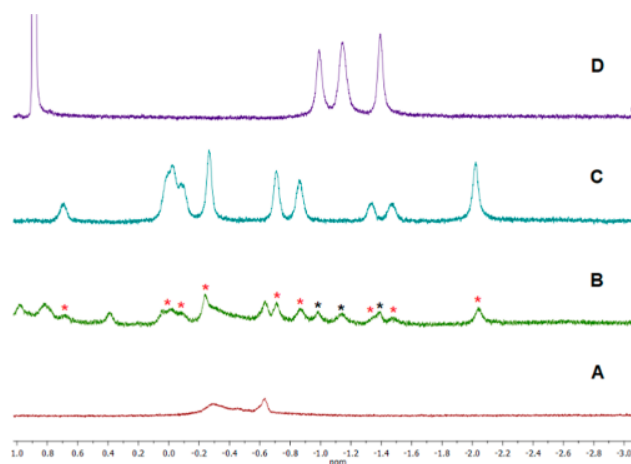


Figure 6. Partial ^1H NMR (600 MHz, D_2O , 298 K) spectra of initial host–guest complex **10@1** (A), after the addition of Ph_3SnH (2 equiv), $\text{AAPH}_{(\text{cat.})}$ after 12 h at 40 $^\circ\text{C}$ (B), authentic 2-bromononane in **1** (C), and authentic nonane in **1** (D). Partially reduced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

The partially reduced product was observed as expected (Figure 6B, red stars), but the fully reduced product (nonane) was also present in the ^1H NMR spectra (Figure 6B, black stars).

As mentioned above, intermediate **9a@1** should not be reactive due to the protected orientation of the bromo atom inside the cavity, as indicated by ^1H COSY NMR and δ values (SI46 and SI47). A radical reduction of guest **9** with Ph_3SnH was performed in order to confirm this (Figure 7). The host–guest complex between **9** and **1** is kinetically stable

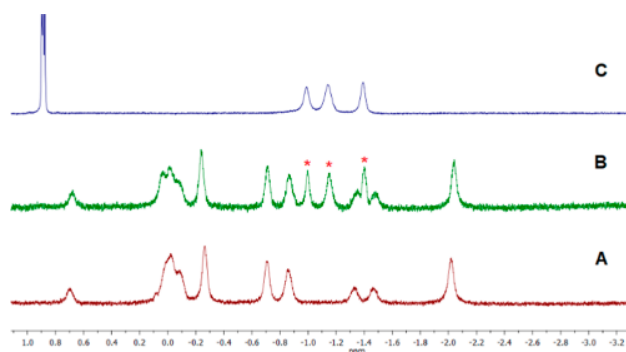


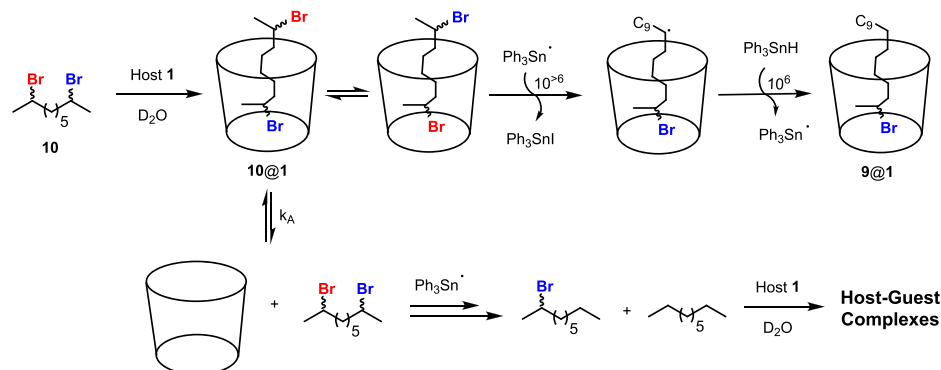
Figure 7. Partial ^1H NMR (600 MHz, D_2O , 298 K) spectra of initial host–guest complex **9@1** (A), after the addition of Ph_3SnH (2 equiv), AAPH (cat.) after 12 h at 40 $^\circ\text{C}$ (B), and authentic nonane in **1** (C). Reduced product (nonane) is marked in the reaction mixture with red stars.

(on the NMR time scale) *but not protected*. A conversion of **29** (SI33) to the alkane (nonane) was observed (Figure 7B). The kinetic stability of the host–guest complex on the NMR time scale was fundamental and the only requirement with dynamic supramolecular systems such as host **1**. Instead, the formation of a 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 on the NMR time scale are detected when guests **9** and **10** are encapsulated in **1**, but fully reduced product (nonane) is still formed.

If the radical reduction of **10** takes place inside **1**, only compound **9** should be detected as the final product. If the reaction takes place outside host **1**, then the relevant alkane (nonane) must also be detected (Scheme 3). No free guest was observed in the ^1H 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 is correct, then a relation between the binding constants of each involved guest and the observed reactivity toward the 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 $5 \times 10^3 \text{ M}^{-1}$ was calculated for guest **4** after NMR titration (Table 1, entry 1), while a value of $1.2 \times 10^3 \text{ M}^{-1}$ was obtained for guest **5** (Table 1, entry 2).

Both **4** and **5** are unreactive in the presence of the tin radical, and no reduction products are detected after the reaction. A K_A value of $1.2 \times 10^3 \text{ M}^{-1}$ appears to be high enough to prevent the reaction outside the host. Reactive guests such as **6** and **9** should have K_A values lower than $1.2 \times 10^3 \text{ M}^{-1}$ in order to explain the observed reactivity. Guest **6** was taken as a model alkyl iodide due to its similarities to **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 EXSY experiments. The broad peaks in **10@1** point to a faster in/out exchange or a lower K_A value than for guests **6** and **9**. Guest **6** has a K_A value of $0.7 \times 10^3 \text{ M}^{-1}$ (Table

Scheme 3. Cartoons of the Host–Guest Complexes and the Mechanism of the Radical Reduction of 10

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

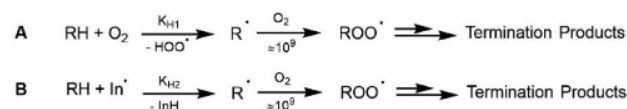
1, entry 3), while guest 9 is $0.9 \times 10^3 M^{-1}$ (Table 1, entry 4), confirming the hypothesis. These host–guest complexes must show a K_A of at least $1.2 \times 10^3 M^{-1}$ to guarantee that the reaction takes place in the host.

Aerobic Oxidation of Alkyl Aromatic Compounds in 1

The role of K_A in radical processes was further tested in the aerobic oxidation of alkyl aromatic compounds (11 and 12) in 1 and shows that this behavior is independent of the nature of the radical process. The relatively low C–H BDE for substituted alkyl aromatic compounds (from 82 to 87 kcal/mol) makes these compounds easily oxidized through a radical mechanism under aerobic conditions. The auto-oxidation of cumene, for example, is reported under an air or oxygen atmosphere at high temperature ($>80^\circ C$). Milder conditions can be effective using radical initiators such as AIBN ((2,2-azobis(2-methylpropanitrile))³⁰ and with specific catalysts as *N*-hydroxy compounds^{31–33} or metal complexes.³⁴

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 peroxy radical. The peroxy radical may undergo termination processes and the consequent formation of neutral products such as alcohols, ketones, aldehydes, or carboxylic acids, depending on the substrate³⁵ (Scheme 4A). The addition of radical initiators does not alter the mechanism of the oxidation but acts on the activation steps kinetics. Kinetic constant K_{H2} is very often higher than kinetic constant K_{H1} (Scheme 4B). The oxidation mechanism of 11 and 12 as guests used radical initiator 2,2-azobis(2-amidinopropane)

Scheme 4. General Pathway for A) Autooxidation of Alkyl Aromatic Compounds (R–H) and B) Oxidation with a Radical Initiator (In•) under Aerobic Conditions



dihydrochloride (AAPH), as shown (Scheme 5). AAPH was selected for its high water solubility, its thermal activation at relatively low temperatures ($\sim 36^\circ C$), and its very low reactivity toward host 1: no oxidative products were observed after treating 1 with 2 equiv of AAPH after 5 h at $55^\circ C$ (SI9 and SI10).

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

Experimentally, the δ observed for the isopropyl group at the open end of 1 (Figure 9, red isopropyl group) is 0.2 ppm (SI52), placing it close to the open end of the host but not outside the cavity. Oxidation products are therefore predicted only if the reaction takes place outside the host, but this is prevented by the K_A value of $12.1 \times 10^3 M^{-1}$. In the experiment, guest 11 was completely stable in 1 after 5 h at $50^\circ C$ in the presence of AAPH (1 equiv). All of 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 (SI51 and SI53). In order to demonstrate the importance of K_A (rather than on the host), the radical reduction of 10 using new metallo cavitand 2² is described below.

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 $1.5 \times 10^5 M^{-1}$ was obtained by isothermal titration calorimetry (ITC) using *n*-BuOH as a guest in 2.² This value is 2 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 (SI61). Two complexes are detected by the 1H 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, then only complex 9a@2 should be detected, while both complexes must be

Scheme 5. Mechanism of Aerobic Oxidation of Alkyl Aromatic Compounds 11 and 12) in 1

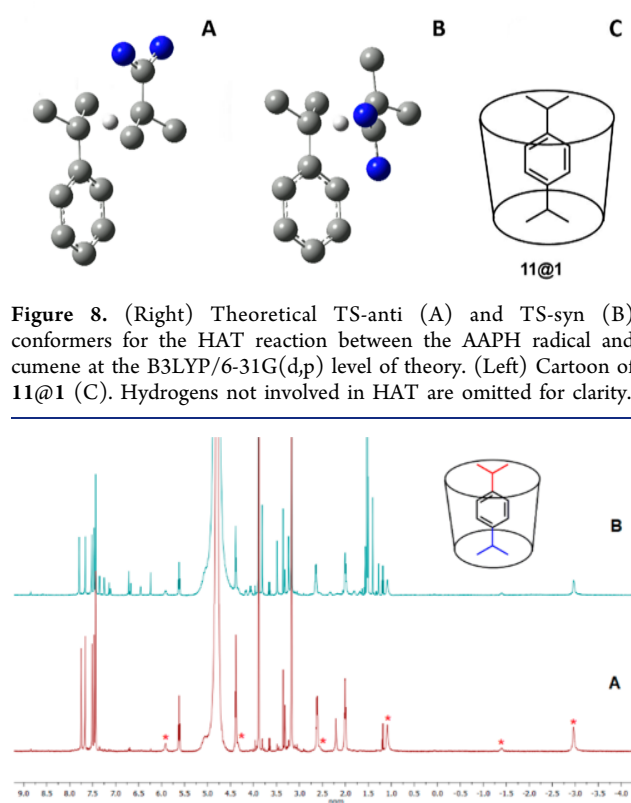
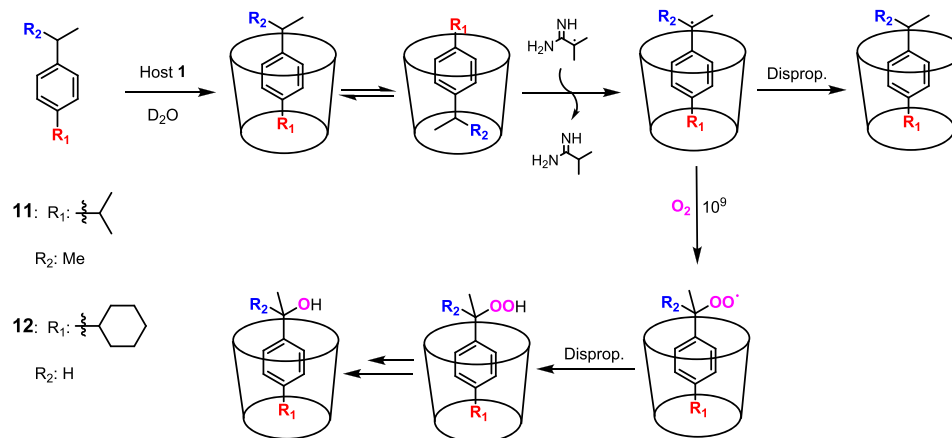


Figure 8. (Right) Theoretical TS-anti (A) and TS-syn (B) conformers for the HAT reaction between the AAPH radical and cumene at the B3LYP/6-31G(d,p) level of theory. (Left) Cartoon of 11@1 (C). Hydrogens not involved in HAT are omitted for clarity.

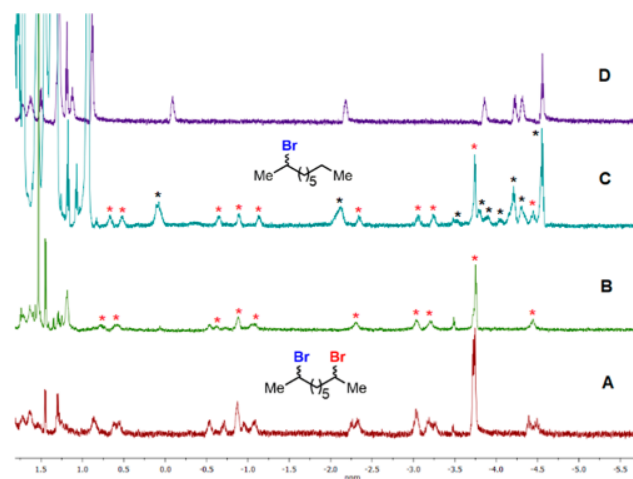
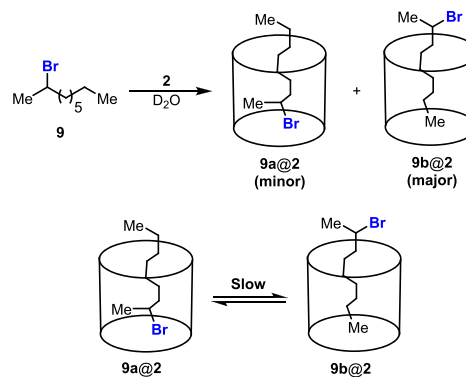


Figure 10. Upfield regions of the ^1H NMR spectra (600 MHz, 305 K) of 10 ($10\ \mu\text{L}$, 50 mM acetone- d_6 then removed) in a solution of 2 (1 mM) in 0.5 mL of D_2O (A). After 12 h at 40°C in the presence of $\text{Ph}_3\text{SiH/AAPH}$ under a nitrogen atmosphere (B). Authentic 2-bromononane (9) in 2 (C). Authentic alkane (nonane) in 2 (D). Signals of 9a@2 and 9b@2 are marked in red and black stars, respectively.

Scheme 6. Cartoons and Orientations of 9@2 (Top) and the Equilibrium between Host Guest Complexes (Bottom)



observed if the reduction takes place outside the host. The 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).

The decrease in the diastereotopic signals due to the loss of the stereogenic center (Br-CHMe) further confirms that the reaction takes place inside the cavity of the host (S162). Quantitative conversion and selectivity higher than 95% for the monoreduced product were detected. This was confirmed by the ^1H NMR spectrum of authentic monoreduced 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.

CONCLUSIONS

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

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.9b11595>.

Synthesis and experimental procedures, ^1H and ^{13}C NMR spectra for synthesized guests, stability and control experiments, δ calculation for all host-guest complexes, and binding constant determination (PDF)

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