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Cucurbituril Adamantanediazirine Complexes and Consequential Carbene Chemistry

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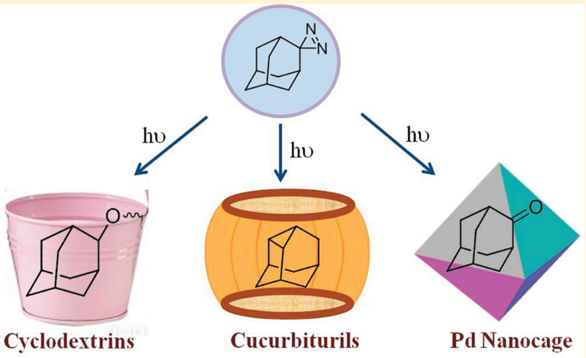
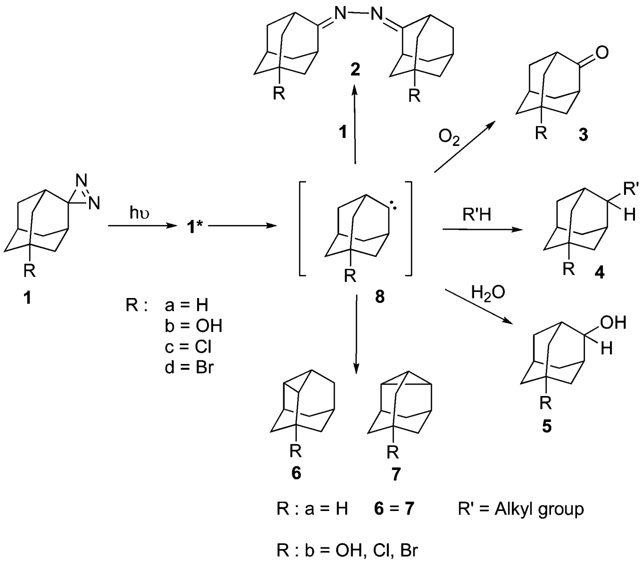
Ⓢ *Supporting Information*

ABSTRACT: Adamantanediazirines, precursors of adamantanylidenes, form 1:1 complexes (guest to host) with cucurbit[7]uril and cucurbit[8]uril and a 3:1 complex with a Pd nanocage in water. ^{1}H NMR spectra suggested that these complexes are stable in water on the NMR time scale. While photolysis of adamantanediazirines in water gave mainly adamantanone and adamantanol via adamantanylidene as intermediate, the 1:1 complexes of adamantanediazirine with cucurbiturils gave intramolecular C−H insertion products of adamantanylidene in >90% yield. The study establishes that significant control of carbene reactivity can be achieved when the precursor is encapsulated within a tight inert cavity. While the general characteristics of molecular containers can be understood on the basis of concepts such as "confinement" and "weak interactions", each one is unique and deserves careful scrutiny.



Numerous investigations on controlling the chemical stability and behavior of photochemically generated reactive intermediates and unstable molecules within molecular containers (e.g., cyclodextrins, cucurbiturils, calixarenes, octa acid, water-soluble Pd nanocage, and zeolites)[1−5] were prompted by Cram and co-workers' report on the stabilization of 1,3-cyclobutadiene within a hemicarcerand.[6] Our recent finding[7] that adamantanylidenes photochemically generated from adamantanediazirines yielded larger amounts of intramolecular C−H insertion products (Scheme 1) when trapped in a closed container (octa acid (OA) capsule) as opposed to an open vessel (cyclodextrins, resorcinarenes, and zeolites)[8−11] led us to question the need for a closed container to obtaining intramolecular insertion products. In this context, we have investigated the photochemical behavior of four adamantanediazirines **1a**−**d**[12] included in open containers such as cucurbit[7]uril (CB[7]),[13−15] cucurbit[8]uril (CB[8]), and Pd nanocage (PdNC)[16,17] (Figure 1) in water. The study included examination of the complexation behavior by ^{1}H NMR, isothermal titration calorimetry (ITC), and computation as well as monitoring of the photochemical product distributions by gas chromatography (GC). The results suggest that the behavior of photochemically generated adamantanylidenes within cucurbiturils and cyclodextrins, comparable containers in terms of size and shape, is distinctly different. In addition, photoreaction within PdNC suggests a possibile involvement of triplet adamantanylidenes as opposed to singlet adamantanylidenes within CBs. Unlike most previous studies that were carried out in the solid state, the current ones are performed in aqueous solution.

Scheme 1. Photolysis of Adamantanediazirines and Products Formed



^{1}H NMR spectra of **1a**−**d** in D$_2$O and in the presence of CB[7], CB[8], and PdNC are shown in Figure 2 and Figures S1−S12 in the Supporting Information, respectively. It is clear from the spectra shown in Figure 2 for **1a** and Figures S1−S12

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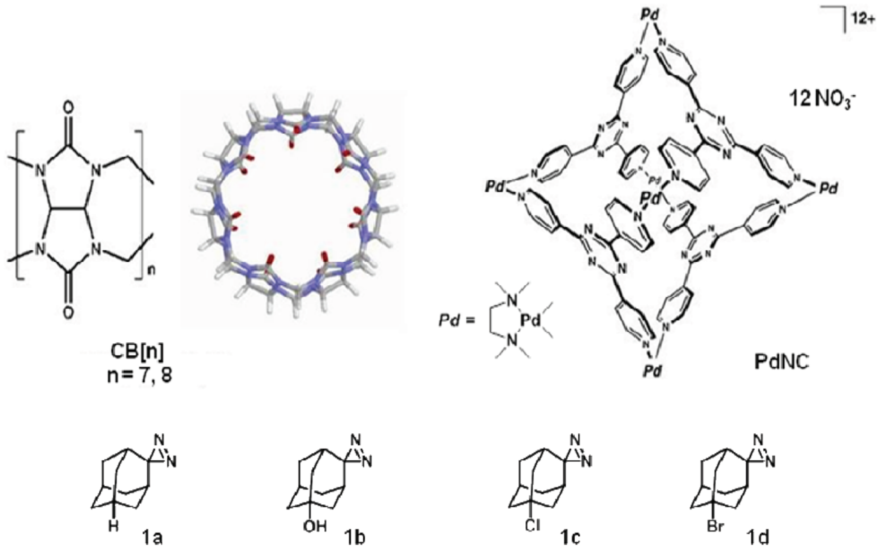

Figure 1. Structures of host cucurbiturils CB[7], CB[8], palladium nanocage (PdNC), and guest molecules adamantanediazirine and its derivatives used in this study.

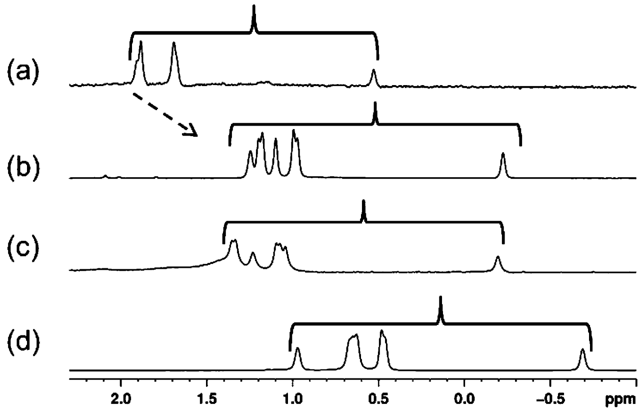

Figure 2. Partial ^{1}H NMR spectra of: (a) **1a** in D_2O, (b) **1a**@CB[7] in D_2O, (c) **1a**@CB[8] in D_2O, and (d) **1a**@PdNC in D_2O.

(Supporting Information) for **1b**, **1c**, and **1d** that upon inclusion within CB[7], CB[8], and PdNC the signals due to the guest molecules were shifted upfield. These changes suggested that the above-mentioned guest molecules were included within the studied hosts in D_2O solutions. Absence of independent signals due to free guest molecules suggested that on the NMR time scale all guest molecules are complexed under our conditions. On the basis of ^{1}H NMR titration experiments (Figures S1−S12, Supporting Information), we concluded that adamantanediazirines **1a**−**d** formed 1:1 complexes (guest to host) with CB[7] and CB[8] and a 3:1 complex with PdNC.

The complexation behavior was further probed by ITC measurements.[18,19] Thermodynamic parameters for complexation of **1a**−**d** with CB[7] were determined by monitoring the heat changes during titration of the guest into a host CB solution (for representative ITC data, see Figures S13−S16, Supporting Information). Since guests **1a**−**d** were not sufficiently soluble in aqueous solution, all ITC experiments were carried out in 60% DMSO + 40% water solution. ITC measurements could not be carried out with CB[8] owing to its poor solubility in the above solvent mixture and with PdNC due to lack of programs to deal with 3:1 complexes. The association constant (K), ΔG, ΔH, ΔS, and stoichiometry of the complex (guest@CB[7], i.e., guest included in host) were obtained by fitting the experimental titration curve with the computed one based on an independent binding model (Table 1). The binding constants in the range of 10^4−10^5 M^{-1} suggested all complexes to be stable in the above solvent mixture. The complexes should be even more stable in 100% water in which the photochemical studies were conducted. Stoichiometry of the host to guest complex (1:1) inferred from ITC data (Table 1) is consistent with the ^{1}H NMR titration studies. Generally, stronger binding to CBs results from Coulombic interaction between the negatively polarized carbonyl rim and the positively charged or polarized guest molecules.[13] Such interaction is not expected in the case of **1a**−**d**. Accordingly, the observed high enthalpies of binding (ca. −11 to −16 kcal/mol) result from van-der-Waals interactions

Table 1. Binding Constants (K) and Relevant Thermodynamic Parameters for Complexation of Adamantanediazirines with CB[7] at 298 K

guest	K_a^{a} (M^{-1})	ΔG^b(kcal/mol)	ΔH^c(kcal/mol)	$T\Delta S^d$(kcal/mol)	stoichiometry
1a	$6.5(\pm 0.7) \times 10^5$	-7.9 ± 0.06	-12.9 ± 0.1	-5.02 ± 0.2	0.9 ± 0.07
1b	$1.0(\pm 0.2) \times 10^5$	-6.8 ± 0.1	-14.4 ± 0.5	-7.59 ± 0.6	0.8 ± 0.1
1c	$4.4(\pm 0.4) \times 10^4$	-6.3 ± 0.06	-15.6 ± 0.5	-9.26 ± 0.5	0.88 ± 0.03
1d	$4.6(\pm 0.4) \times 10^4$	-6.3 ± 0.05	-10.9 ± 0.1	-4.6 ± 0.1	0.92 ± 0.01

[a] Mean values measured from at least three ITC experiments at 25 °C in DMSO−water (3:2). Standard deviations are given in parentheses. [b] Gibbs free energy values calculated from K_a values. [c] Enthalpy values measured by ITC. [d] Entropic contributions to ΔG calculated from K_a and ΔH values.

between host and guest. Negative entropies are consistent with the loss of freedom of the guest as it binds to the host. As expected, the gain in enthalpy is compensated by loss in entropy (compare **1c** and **1d** in Table 1).

To gain insight into the structure of the guest@host complexes, we optimized several structures of complexes of **1a−d** with CB[7] at the BLYP/6-31G(d) level of theory using the Gaussian 03 revision D.01 program.[20] The final energies of the optimized structures were improved by performing single-point calculations using a 6-311+G(d, p) basis set of the triple-ζ quality. The dielectric effect of the surrounding water molecules was taken into account using the self-consistent reaction field IEF-PCM method. Of the various structures generated, those with lowest energy in each case presented in Figure 3 clearly show that the bulky adamantyl group is accommodated within the CB cavity and possibly stabilized by van-der-Waals interactions. The structures also suggest that the carbenes that would be generated by photochemical extrusion of nitrogen will be protected to some extent by the cavity in all cases.

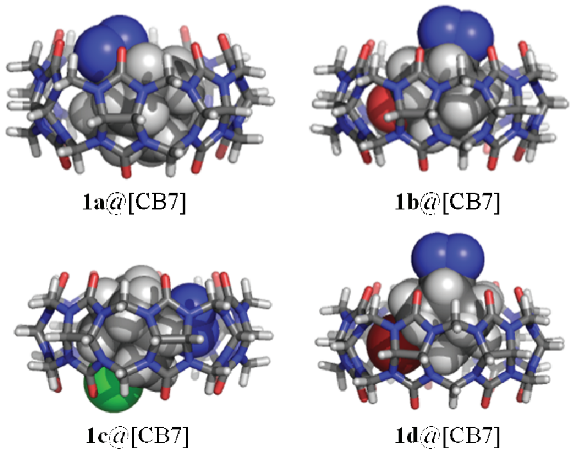
1a@[CB7] **1b**@[CB7] **1c**@[CB7] **1d**@[CB7]

Figure 3. BLYP/6-311G(d,p) energy-minimized structures of adamantanediazirine and its derivatives within CB[7]. Color code for atoms: C, gray; N, blue; O, red; Cl, green; Br, dark red; H, white.

Photolysis of **1a−d** in hydrocarbon and alcohol solutions and during thermolysis in the gas phase have been established to generate products shown in Scheme 1 via the corresponding adamantanylidenes (**8**) as reactive intermediates.[12,21−23] In water, the major products were adamantanones **3** and alcohols **5** resulting from reaction of carbene **8** with oxygen and water, respectively. The most important point to note is that the intramolecular C−H insertion products **6** and **7** were obtained only in trace amounts (<10%) in water, alcohol, and hydrocarbon as solvents. Irradiation of **1a** included in cyclodextrins[8,10] and **1d** in a resorcinarene-based cavitand in the solid state gave the corresponding insertion products **6** and **7** (note with **1a**, compounds **6a** and **7a** are identical and we denote them by **6a**; Scheme 1) in about 25% yield.[9] Similar irradiation of **1a** included in the NaX zeolite gave **6a** in ~40% yield.[11] Photolysis of adamantanediazirine@α-CD in water afforded two insertion products into the OH groups of the host in addition to parent adamantane,[24] but there was almost no intramolecular C−H insertion product **6a** formed. Most importantly, complexes of **1b−d** within an octa acid capsule afforded **6** and **7** in 37−92% yields.[7] Photolysis of $1a_2$@OA_2 gave azine **2a** as the major product.

In this study, all irradiations were carried out with a medium-pressure mercury lamp fitted with a Corning glass O-52 filter (>320 nm). CB[7] and CB[8] have no absorption above 250 nm and would not sensitize the photoreactions of guests **1a−d**. However, PdNC showing a weak absorption tailing up to 350 nm is likely to absorb a small part of the light that is used to excite the guests. Absorption spectra of the three hosts are provided in the Supporting Information (Figure S17), and that of **1a** is available in the literature.[25,26] Although sensitization by PdNC cannot be completely ignored,[27] that by CB[7] and CB[8] can certainly be ruled out. In all cases, irradiations were conducted to total conversion (1−3 h) as determined by ^1H NMR (see Figures S18−S29 in the Supporting Information). At that stage, products were extracted three times with $CDCl_3$, and the combined concentrated extract was analyzed by GC−MS, GC, and ^1H NMR. ^1H NMR and ESI-MS or MALDI-MS spectra of photolyzed samples did not show any products of reaction between the hosts CB[7], CB[8], and PdNC and the guest carbene. No changes in the ^1H NMR spectra of extracted hosts before and after photolysis were noted. However, ^1H NMR spectra of extracted hosts upon photolysis of 1- and 2-azidoadamantanes included in CB[7] and CB[8] showed the presence of insertion products from reactions of nitrenes with the hosts. No such changes were observed in this study, suggesting that there is no reaction between the carbenes and hosts. Product distributions obtained upon photolysis of **1a−d** in water alone and from complexes with CB[7], CB[8], and PdNC in water are provided in Table 2 (see Scheme 1 for structures of products and the Supporting Information for experimental details).

Before initiating the discussion on the photochemistry of adamantanediazirines and the resulting carbenes within the cavities of CB[7], CB[8], and PdNC, it is important to take note of what is known about the spin characteristics of adamantanylidene in solution. It has been reported by several

Table 2. Relative Percentages of Products upon Photolysis of Guests 1a−d in Various Media

guests[a]	media[c,d]	**2**[b]	**3**[b]	**5**[b]	**6** + **7**[b,e,f]
1a[e]	D_2O	5.5	31.0	62.0	1.5
	1a@CB[7]		6.0		94.0
	1a@CB[8]		9.0		91.0
	1a@PdNC	11.0	85.0		4.0
1b	D_2O		3.0	95.0	2.0
	1b@CB[7]		44.0		56.0 (1:8)
	1b@CB[8]		51.0		49.0 (1:3)
	1b@PdNC	6.0	90.0		4.0
1c	D_2O	8.0	2.5	88.0	1.5
	1c@CB[7]		41.0		59.0 (1:1.5)
	1c@CB[8]		21.0		79.0 (1:1.4)
	1c@PdNC	13.0	80.0		7.0 (1:4)
1d	D_2O	5.0	27.0	62.0	6.0
	1d@CB[7]		34.0		66.0 (1:4.5)
	1d@CB[8]		40.0		60.0 (1:2.6)
	1d@PdNC	4.0	83.0		13.0 (1:2)

[a] The samples were irradiated using a medium pressure mercury lamp and an O-52 (320 nm) filter. [b] Product yields were determined by GC after total conversion with adamantane as internal standard. [c] Concentration of **1a−d**: CB[7], CB[8] = 1 mM/1 mM, **1a−1d**: PdNC = 3 mM/1 mM, concentration of **1a−d** in D_2O = 1 mM. [d] Host/guest complex ratios not included. [e] Compounds **6a** and **7a** obtained from **1a** are identical. [f] Ratio of **6**:**7** provided in parentheses.

groups that the ground state of adamantanylidene has singlet spin configuration with the triplet state within 5 kcal/mol.[25,28,29] Thus, the interconversion between singlet and triplet adamantanylidenes is prohibited only by spin and not by a thermal barrier. On this basis, it is tempting to speculate that in a medium that facilitates spin interconversion between singlet and triplet states one could expect the triplet state of adamantanylidene to be substantially populated at room temperature and, therefore, larger yields of products derived from the carbene's triplet state. Adamantanone is reported to be formed from a reaction between triplet adamantanylidene and oxygen with a rate constant of $2.3 \times 10^9\ M^{-1}\ s^{-1}$.[25] Singlet adamantanylidene reacts with most solvents and adamantanediazirine at a diffusion-limited rate constant.[25] Intramolecular rearrangement that is believed to occur via a singlet carbene has a very low rate constant ($<1 \times 10^6\ s^{-1}$), and it is expected to be formed only when the adamantanylidene is protected from solvents.[25]

We initiate the discussion of the role of a confined environment on products' distribution with the observations on **1a**. To our surprise and delight, we noted that the intramolecular C—H insertion product (**6a**) was obtained in >90% yield upon irradiation of **1a** included in CB[7] and CB[8]. To our knowledge for **1a**, no such dominance of formation of intramolecular insertion product in any other medium has been observed. Even in an octa acid capsule with the formation of a 2:2 complex, **6a** was obtained only in 6% yield.[7] In contrast, irradiation of **1a** included in PdNC resulted in adamantanone **3a** (oxygen addition product) as the major product (85%) and **6a** in 4% yield. Complete removal of oxygen from water was impossible, and we suspect the presence of some residual dissolved oxygen under our experimental conditions. We speculate the dramatic shift in product distribution in favor of adamantanone **3a** within PdNC to be due to the heavy atom Pd favoring the spin interconversion of the singlet adamantanylidene to its triplet state.[30−32] To make sure that azine **2a** is not the precursor of adamantanone, **2a** included within PdNC was irradiated at λ >320 nm. Under this condition no adamantanone was detected. Also, when the photoreaction of **1a**@PdNC was followed by ^{1}H NMR, no accumulation and disapperance of **2a** was noticed. These observations suggested that formation of adamantanone was not preceded by **2a**. In hydrocarbon solution the major product of photolysis is azine **2a**, which according to one possible mechanism is the product of a reaction between adamantanylidene and adamantanediazirine. However, this was not formed within CB and was only a minor product within PdNC. Its absence in CB is understandable on the basis that each adamantanediazirine and the resulting adamantanylidene species are individually wrapped by the host CB. Lack of formation of **2a** in spite of presence of three molecules of **1a** within PdNC could be due to either the triplet adamantanylidene's inertness toward **1a** or improper alignment of adamantanediazirine molecules present within PdNC for a bimolecular reaction.

Irradiation of CB complexes of **1b**, **1c**, and **1d** in water gave the intramolecular insertion products **6** and **7** in ca. 50−80% yield (Table 2). Although the ratios of the two isomers were not the same, the trend in favor of symmetrical compound **7** is similar to the one observed in the gas phase.[12] Consistent with the results on **1a**, PdNC did not favor intramolecular insertion products **6** and **7** with **1b**, **1c**, and **1d** (<13% yield) but favored formation of the corresponding adamantanones **3** (>80%). This could once again be attributed to the role played by Pd as a heavy atom. Thinking along this line, we are tempted to attribute the lower yield of the corresponding insertion products **6** and **7** and the higher yields of the corresponding adamantanones **3** upon irradiation of CB complexes of **1c** and **1d** (as compared to that obtained from the **1a**@CB complex) to a heavy atom effect of the Cl and Br substituents.[30−32] However, we are unable to offer a rationale for the lower yield (significant as it may be) of the corresponding **6b** and **7b** and the higher yield of corresponding adamantanone **3b** resulting upon irradiation of CB complexes of **1b** as compared to that obtained from the **1a**@CB complex.

One of the important observations relates to the difference between the closely analogous cyclodextrins and cucurbiturils in modulating the behavior of the photochemical reactions of **1a**—**d**. The molecular geometries of these hosts, though closely similar in dimensions and internal shape, are different. In cyclodextrins with several reactive OH groups, intermolecular reactions directly compete with intramolecular C—H insertions of carbenes **8**. In contrast, the inertness of the CB interior helps to promote intramolecular C—H insertions of **8** and prevents bimolecular reactions with the host, which have been shown for cyclodextrins. Compared to cyclodextrins, cucurbituril complexes have better solubility in water, making CBs better hosts for conducting reactions in water. Finally, the contrasting behavior of CB and PdNC highlights the importance of choosing the right container to achieve the desired goal. While the general characteristics of molecular containers could be understood on the basis of concepts such as "confinement" and "weak interactions", each one is unique and deserves careful scrutiny.[33]

In this study, we have shown that adamantanediazirines form stable complexes with hosts such as cucurbiturils and Pd nanocage in water. Photolysis of these complexes yields products in ratios distinctly different from those in conventional solvents and gas phase. During irradiation, products are believed to arise via adamantanylidenes as intermediates. Since adamantanylidenes can exist in both singlet and triplet states we tentatively propose that the confined medium may have an effect on the equilibrium between the two states. Thus the spin state control by the confined environment could be used as yet another tool to control product selectivity. CBs favoring intramolecular C—H insertion products may be due to suppression of bimolecular reactions with water and oxygen. Most likely the reactive center is protected by the inert cavity of CB from these reactants. The lifetime of adamantanylidene is reported to be dependent on the water and oxygen content and in dry benzene it is found to be fairly long (700 ns).[25] In this context, it would be interesting to conduct time-resolved photophysical studies of adamantanediazirines included in various hosts with different internal characteristics. Such studies form a part of our future investigation

■ EXPERIMENTAL SECTION

Encapsulation of Guests in CB[7], CB[8], and PdNC. For each experiment, a 60 mM stock solution of the guest was prepared in DMSO-d_6. A 10 μL portion of this solution was added to 0.6 mL of D_2O, making the concentration of the guest ~1 mM, and a ^{1}H NMR spectrum was recorded. To a solution of 0.6 mL of 1 mM of CB[7], CB[8], or PdNC D_2O was added 10 μL of a 60 mM guest solution. The solution was shaken vigorously for 5 min, and the NMR spectra were recorded.

Stoichiometry of the Complexes As Determined by ^{1}H NMR Titration. For each experiment, a 60 mM stock solution of the guest was prepared in DMSO-d_6. A 1 μL portion of this solution was added to 0.6 mL of 1 mM of CB[7], CB[8], or PdNC in D_2O, making the concentration of the guest ~0.1 mM. The NMR tube containing the above solution was shaken for ~5 min, and a ^{1}H NMR spectrum was recorded. This process was repeated by stepwise addition of 1 μL of the guest stock solution. The addition of guest was stopped when signals due to excess of peaks deriving from unbound guest molecules were detected or broadening of the signals was observed.

Nature of the Complexes Probed by ITC. All titrations were performed at 25 °C while stirring at 350 rpm. Electrical calibrations were performed periodically before experiments. Each microcalorimetric titration experiment consisted of 30−50 successive injections. In each titration, a constant volume (6 μL/injection) of guest solution was injected into the reaction cell (969 μL) charged with host solution. Solutions of guests and hosts were prepared by weighing a required amount of compound and dissolving it in a mixture of DMSO and deionized water. The concentration of the host solution was 0.1−0.15 mM, whereas the guest concentration was 1−2 mM. All titrations were performed in a DMSO−water (3:2) solution. The heat of dilution was corrected by injecting the guest solution into a DMSO−water (3:2) solution and subtracting these data from those of the host−guest titration. The data was analyzed and fitted by the Nanoanalyze software adapted for ITC data analysis. The accuracy of the calculated thermodynamic quantities for all 1:1 complexations was checked by performing several independent titration runs.

Photolysis of Adamantanediazirines Encapsulated Inside Hosts CB[7], CB[8], and PdNC. A D_2O solution containing a 1:1 ratio of 1 mM of the guest@host for CB[7] and CB[8] and a 3:1 ratio of guest@host for PdNC solution was prepared for irradiation experiments. A ^{1}H NMR spectrum of the solution prior to irradiation was recorded. The solution was evacuated and purged with argon for 30 min. This solution was irradiated with a medium-pressure mercury lamp (450 W) fitted with a 340 nm cutoff glass filter (Corning O-52). ^{1}H NMR spectra of the solutions were recorded at regular intervals to follow the completion of the reaction. **1a**@CB[7]:CB[8] and PdNC solutions were irradiated for 45 min, whereas **1b**−**1d**@CB[7]:CB[8] and PdNC solutions were irradiated for 3 h.

Characterization of Photoproducts. After irradiation was complete the products were extracted three times with $CDCl_3$. The $CDCl_3$ solution was dried over anhydrous sodium sulfate and concentrated to approximately 0.6 mL, and a ^{1}H NMR spectrum was recorded. The solution was further concentrated to approximately 0.1 mL, and was injected into the GC (HP-5). The program used for GC: starting at 70 °C, held for 5 min, applying ramp of 10 °C per min, up to 270 °C, held for 10 min. All reactions were repeated (at least three times) for consistency. The product solution was injected into a GC−MS. The molecular weight obtained from the molecular ion peak and the fragmentation pattern further confirmed the identity of the products. In addition, the 1,3-insertion products from the adamanantanylidenes **8** and the corresponding azines were synthesized and coinjected with the products obtained. For all other derivatives, it is known from the literature that these adamantanediazirine derivatives form mostly 1,3-insertion products upon thermolysis. Hence, they were injected as such into the GC and GC−MS, respectively, whereupon they would decompose in the injection port to afford the corresponding 1,3-insertion products. In all cases, adamantanone and adamantanol and their derivatives were synthesized and coinjected with other products. The commercially available corresponding adamantanes and their derivatives were injected as such into GC and GC−MS.

Energy Minimization Study. The optimization study of the adamantanediazirines@CB7 complexes was performed at the BLYP/6-31G(d) level[34,35] using the Gaussian 03, revision D.01[20] program based on the X-ray crystal structure of the host. The final energies of the optimized structures were improved by performing single-point calculations using the 6-311+G(d, p) basis set of triple-ζ quality. The dielectric effect of the surrounding water molecules was taken into account using the self-consistent reaction field IEF-PCM method.[36] Of the various structures generated, the ones with the lowest energy in each case are reported.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR titration spectra, NMR spectra of irradiated samples, ITC data, experimental procedures for modeling, ITC, and irradiations. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

The University of Vienna group considers this publication as Carbene Rearrangements. 86.

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