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Structure−Reactivity Relationships: Reactions of a 5-Substituted Aziadamantane in a Resorcin[4]arene-based Cavitand

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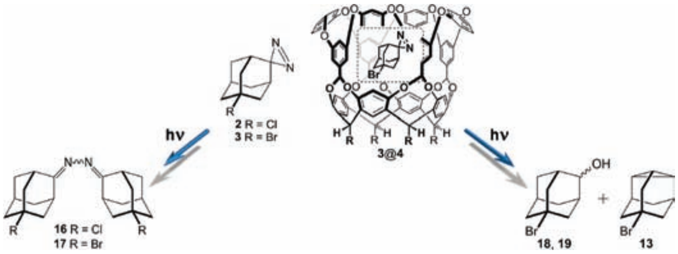
ABSTRACT



The complexation properties of two novel C5-substituted adamantanediazirines within the resorcin[4]arene-based cavitand 4 were investigated in DMSO-d_6, revealing that binding is up to 1.4 kcal/mol stronger for halogenated adamantanediazirines when compared with the unsubstituted species. The thermal behavior of 5-bromo-2-aziadamantane (3) was investigated by DSC analysis as the first representative of the adamantanediazirine family in the neat solid state, as well as encapsulated within the aromatic cavity of cavitand 4. In the solid phase, the reactions of photolytically or thermolytically generated 5-bromo-2-adamantanylidene (11) can be controlled by complexation within cavitand 4.

The encapsulation of reactive intermediates inside the nanoscopic cavity of suitable host molecules can increase their lifetime and hence facilitate their spectroscopic characterization and/or alter their reaction behavior.[1] Classic examples of reactive species like 1,3-cyclobutadiene,[2] benzyne,[3] or phenylnitrene[4] have been spectroscopically analyzed in complexed form. We have investigated the influence of complexation of carbenes and phenylnitrene in the cavity of cyclodextrins[5] and a resorcin[4]arene-based cavitand.[6] Furthermore, the supramolecular chemistry of native adamantanylidene and 5-hydroxy-2-adamantanylidene (**20**) has been studied.

Moreover, the reactions of electron-donating and electron-withdrawing substituents at C5 have been investigated experimentally by Brinker's and theroretically by Tomoda's group to gain a deeper understanding of the observed diastereoselectivities of such adamantanylidenes in intra- and intermolecular reactions.[7]

Herein, we report the reactions of carbenes **10** and **11** generated from two hitherto unknown diazirines, i.e., 5-chloro-2-aziadamantane (**2**) and 5-bromo-2-aziadamantane (**3**). Carbenes **10** and **11** were generated by gas-phase pyrolysis,

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DSC (differential scanning calorimetry), and photolysis in the solid state.

In contrast, the binding properties of the supramolecular complexes between cavitand **4** and adamantanediazirines **2** and **3** were investigated in the liquid phase (Figure 1).

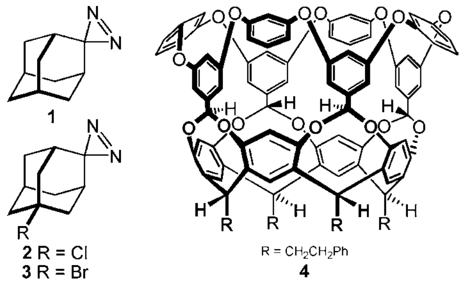
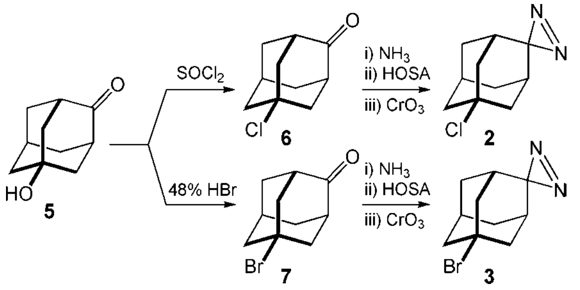


Figure 1. C5-substituted 2-aziadamantanes **2** and **3** investigated and resorcin[4]arene-based cavitand **4**.

Furthermore, the modified reaction behavior of 5-bromo-2-adamantanylidene (**11**), encapsulated in cavitand **4**, has been investigated in the solid state by DSC analysis and irradiation experiments. Resorcin[4]arene-based cavitand **4** possesses a lipophilic and preorganized cavity, deep-functionalized with a ring of weakly acidic benzalic C−H groups capable of forming multiple hydrogen bonds with a large variety of guest molecules, preferentially halogen-substituted adamantanes.[8]

The novel diazirines **2** and **3** were synthesized following established procedures.[9] Ketones **6** and **7** were treated with hydroxylamine-*O*-sulfonic acid (HOSA) followed by direct oxidation to afford the corresponding diazirines **2** and **3** in 27 and 48% yield, respectively (Scheme 1).

Scheme 1



DSC analysis of 5-bromo-2-aziadamantane (**3**) afforded exclusively 5-bromo-2-adamantanone azine (**17**) in 47% yield, according to NMR and GC/MS analysis. The diagram (Figure 2) shows a sharp endothermic peak at 95 °C (onset: 94 °C) corresponding to melting (m), followed by a broad exothermic transition assigned to thermal decomposition and reaction (onset: 118 °C). DSC analysis of 5-chloro-2-aziadamantane (**2**) provides similar results and gives solely 5-chloro-2-adamantanone azine (**16**) in 37% yield. In that case, the broad decomposition peak (onset: 122 °C) overlaps with a small peak due to melting (onset: 107 °C).

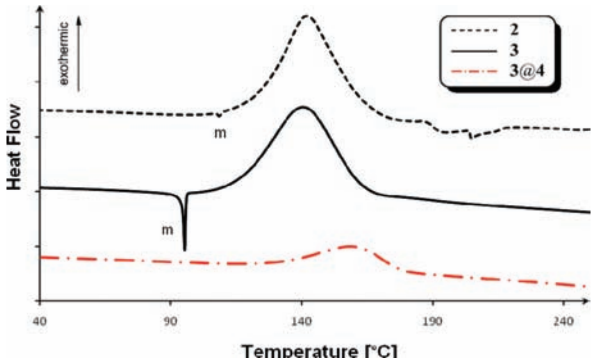
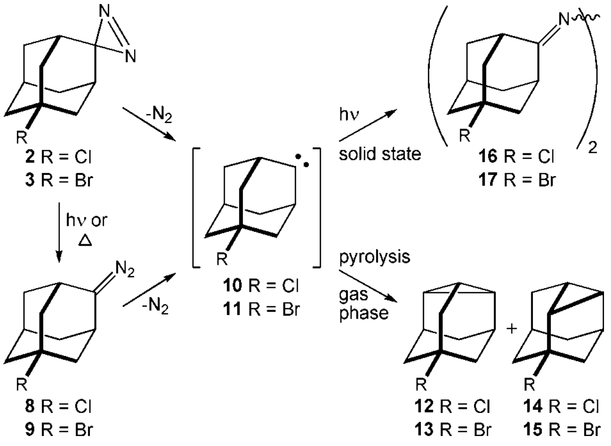


Figure 2. DSC analysis of diazirines **2**, **3**, and complex **3@4**.

Most probably, azine **16** is formed via reaction of the thermolytically generated singlet carbene with its nitrogenated precursor adjacent in the crystal lattice.[10]

In contrast, vacuum pyrolysis at ca. 230−270 °C of **3** affords nearly quantitatively the diastereomeric didehydroadamantanes **13** and **15** (ratio: 89:11), originating from an intramolecular 1,3 C−H insertion of carbene **11**. Pyrolysis of 5-chloro-2-aziadamantane (**2**) under the same conditions gives the anticipated didehydroadamantanes **12** and **14**, again in quantitative yield in a ratio of 90:10 (Scheme 2).

Scheme 2



According to calculations, the carbene bridge in several adamantanylidenes swings back and forth between the *syn*

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and *anti* side (Figure 3a).[7c] Ab initio calculations of 5-hydroxy-2-adamantanylidene (**20**) and 5-amino-2-adamantanylidene (**21**) show that the bridge carrying the divalent carbon in its lowest-energy state is bent *away* from the substituent by an average of $\theta = 17.1°$ and 16.5°, respectively (Figure 3a).[11,7a,c,d] The unoccupied p-orbital of the carbene (LUMO) interacts with both the C_1-C_8 and the C_3-C_{10} bonds, which due to the electronegatively charged heteroatoms at C-5 are more electron-rich than the opposite C_1-C_9 and C_3-C_4 bonds. The electronegative substituents Cl and Br induce a similar distortion of the "carbene bridge" toward the *anti* side with $\theta = 17.1°$ and 16.9°, respectively.[12] The observed diastereoselectivities from the 1,3 C−H insertions of **10** and **11** can be explained best by the principle of least motion.[13] This would make the insertions more likely toward the *anti* side of the carbenes affording preferentially symmetric products **12** and **13**, respectively. The similarity in the selectivity for adamantanylidenes **10** and **11** may be attributed to similar electronegativities and field effects of chlorine and bromine.[14]

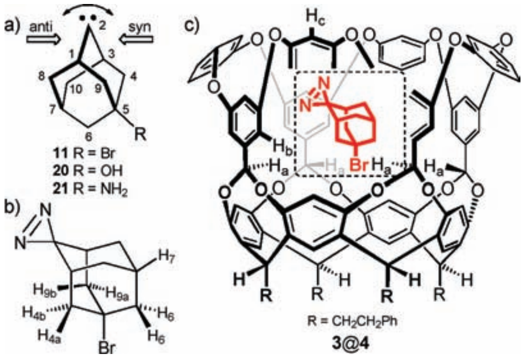

Figure 3. (a) Swinging motion of carbene bridge in adamantanylidenes. (b) Signal assignment in 5-bromo-2-aziadamantane (**3**). (c) Structure of **3@4** in DMSO-d_6 determined by ROESY NMR spectroscopy.

When irradiating diazirines, three competing pathways can take place. The corresponding carbenes may be generated directly by extrusion of nitrogen or indirectly after rearrangement to the diazo compounds. Third, a rearrangement in the excited state (RIES) may occur.[15]

Broadband irradiation ($\lambda > 300$ nm, 4−5 h) of diazirine **3** in the solid state at 10 °C afforded the anticipated azine **17** in almost quantitative yield with traces of 5-bromo-2-adamantanone (**7**) and insertion products **13** and **15**. Similar results were obtained after photolysis of 5-chloro-2-aziadamantane (**2**) under the same conditions as above: azine **16** is formed almost exclusively, again with traces of ketone **6** and didehydroadamantanes **12** and **14**. While for the azine formation various mechanisms have been discussed,[16] the involvement of an intermediate carbene−diazirine ylide was proven.[17]

Table 1. Yields[a] in % and Product Ratios in Parentheses

	reaction conditions	**12** + **14** or **13** + **15**	**18** + **19**	**16** or **17**	**6** or **7**
	DSC				
2				37	
3				47	
3@4		82			
	pyrolysis				
2		excl.[b] (90:10)[c]			
3		excl.[b] (89:11)[c]			
	photolysis				
2		tr.[d]		>95	tr.[d]
3		tr.[d]		>95	tr.[d]
3@4[e]		25	74 (65:35)[f]		1

[a] Unless otherwise noted, the yields were determined by NMR analysis of the crude product mixtures. [b] Exclusively. [c] Error: ±2%. Ratios were ascertained by direct injection of **2** and **3** into the injector of a GC at 270 °C. [d] "Traces". [e] Conversion: 100%, determined by HPLC analysis. [f] Error: ±5%, determined by NMR and GC/MS analysis.

With diazirines **1**, **2**, and **3**, cavitand **4** forms 1:1 complexes in which exchange is slow on the NMR time scale (400 MHz) in DMSO-d_6 (Table 2). The Gibbs free energy of binding increases from unsubstituted adamantanediazirine (**1**) to 5-chloro-2-aziadamantane (**2**), to 5-bromo-2-aziadamantane (**3**), where complexation is 1.4 kcal/mol stronger than for **1**.

Table 2. ^{1}H NMR Association Constants K_a[a] and Gibbs Free Energies of Complexation in DMSO-d_6 at 298 K

complex	K_a [M^{-1}]	ΔG^0 [kcal/mol]
1@4	630	−3.8
2@4	2130	−4.5
3@4	6480	−5.2

[a] Error: ±15%. Values were determined by H_a integration (Figure 3c).

Most probably, binding of halogenated aziadamantanes is enhanced as a result of hydrogen bond formation to the

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centrally positioned benzalic hydrogens (H_a), in a halogen group down orientation. This effect continues to grow as the halogen atom increases in size and polarizability.[8] ROESY NMR spectroscopy (Figure 3c) corroborates the supposed orientation for **3@4**. NOE signals derive from H_7 (Figure 3b) to H_c and from H_6 and H_{9a}/H_{4a} to H_a and H_b.

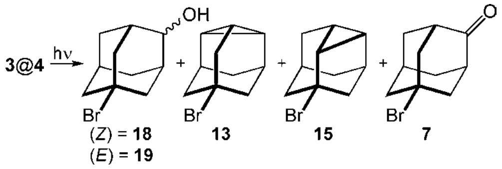
Bromine-substituted diazirine **3** was selected for encapsulation within cavitand **4** in the solid state, due to the expected strong influence of complexation on the innermolecular reaction behavior of thermolytically or photolytically generated carbene **11**.

Complex **3@4** is formed in a 1:1 stoichiometry in up to 74% yield by crystallization from a saturated solution of cavitand **4** in CH_2Cl_2 with a 3-fold excess of 5-bromo-2-aziadamantane (**3**). Single-crystal X-ray diffraction showed that the bromine atom of **3** is centrally located between the benzalic H_a protons of cavitand **4**.[18]

DSC analysis of **3@4** (Figure 2) reveals one broad exothermic peak (onset: 131 °C) corresponding to thermal denitrogenation and reaction. Since the onset for denitrogenation of neat 5-bromo-2-aziadamantane (**3**) already starts at 118 °C, complexation seems to lead to an enhancement of the thermal stability of the diazirine. NMR and GC/MS analysis after DSC provides definite proof for the exclusive formation of intramolecular insertion products **13** and **15** in a combined yield of 82% (ratio: 90−95:10−5 by GC/MS analysis).[19]

Broadband irradiation ($\lambda > 300$ nm, 5 h) of **3@4** in the solid state at 10 °C (Scheme 3) afforded as major products the diastereomeric alcohols **18** and **19** in a combined yield of 74% as well as 25% of the two didehydroadamantanes **13** and **15** (ratio: 90−95:10−5). While 5-bromo-2-adamantanone (**7**) was found only in traces, the large amount of alcohols formed probably has to be attributed to the presence of fortuitous water molecules tightly attached to the complex, which could not be removed completely. The predominant formation of (*Z*)-alcohol **18** over (*E*)-isomer **19** (Table 1) probably results from the distortion of the geometry of **11**. This makes the approach of the reagent more favorable from the more accessible *syn* site (see Figure 3a). However, **18** and **19** can result either from a direct insertion of carbene **11** into the O−H bonds of a water molecule or from a protonation of diazo compound **9** and subsequent loss of nitrogen, following a carbocation mechanism.[20]

Scheme 3



The unique large amount of didehydroadamantanes **13** and **15** formed during photolysis or thermolysis of **3@4** can be attributed most probably to an ideal spatial separation of the generated carbene from other reaction partners inside the cavity of **4**. Thus, the reaction inside cavitand **4** is largely controlled by packing motives of the complex. It might be anticipated that incarceration of **11** does influence the ratios found for **13** and **15**. This effect, however, is hard to pinpoint since **15**, the minor isomer isolated, is difficult to distinguish anyway. Our results suggest only a very weak influence on the ratios found.

In summary, the association properties of novel 5-bromo-2-aziadamantane (**3**) encapsulated in cavitand **4** were investigated in solution and in the solid phase. The formation of substantial amounts of didehydroadamantanes (**13**, **15**) after photolysis or thermolysis of complex **3@4** can obviously be attributed to an optimal arrangement of carbene **11** within the confined space of cavitand **4**.

Acknowledgment. We are indebted to the FWF in Österreich (Project P12533-CHE) for financial support and to Professor V. B. Arion (Institute of Inorganic Chemistry, University of Vienna, Austria) for his efforts to determine the structure of **3@4** by single-crystal X-ray diffraction. We are grateful to Ing. H. Fartely (Department of Physical Chemistry, University of Vienna, Austria) for granting access to DSC devices.

Supporting Information Available: Experimental procedures and details of NMR studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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