# Photochemical Generation and Reactivity of Carbenes within an Organic Cavitand and Capsule: Photochemistry of Adamantanediazirines
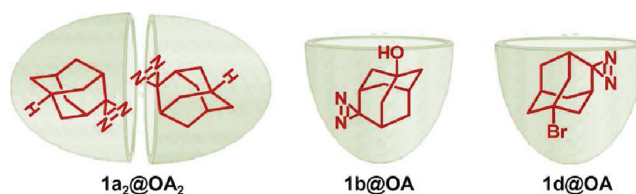
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**ABSTRACT**



1a₂@OA₂   1b@OA   1d@OA

Chemical behavior of carbenes (adamantylidenes) generated by photolysis of adamantanediazirines has been investigated while they were incarcerated within an organic container in water and on silica surfaces. Confined carbenes behave differently from the free ones, and their behavior is dictated by the nature and the structure of the host−guest complexes. The substituent present on the adamantyl skeleton controls the stoichiometry (1:1 or 2:2) and the orientation of guest molecules within the host.

The report by Cram and his co-workers describing that 1,3-cyclobutadiene, which has a fleeting existence in solution, could be stored within a hemicarcerand at room temperature in solution prompted a number of chemists to search for organic containers that would prolong the lifetimes of reactive molecules and intermediates at ambient temperature in solution.[1−6] Our interest in this area has been to explore the confined space offered by organic containers to control chemical and physical properties of caged molecules in their excited states and of the intermediates generated from these excited molecules. We have

shown recently that products obtained from diradicals and radical pairs within a closed container made up of two octa acid (OA) molecules (Figure 1) are distinctly different from those in solution.[7−10]

This prompted us to explore the chemical behavior of incarcerated carbenes generated by photolysis of adamantanediazirines **1a−d** (Figure 1) enclosed within an octa acid cavitand. The photochemical behavior of some of these adamantanediazirines has been well investigated in solution, the crystalline state, and the solid state as inclusion complexes with zeolites, cyclodextrins, and a resorcinarene-based cavitand.[11−20] We present NMR, isothermal titration calorimetry (ITC), and computational results that

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(1) Cram, J. D.; Tanner, E. M.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024.

(2) *Molecular Encapsulation*; Brinker, U. H., Mieusset, J.-L., Eds.; John Wiley & Sons, Ltd: Chichester, 2010.

(3) Kirmse, W. *Angew. Chem., Int. Ed.* **2005**, *44*, 2476.

(4) Rosenberg, M. G.; Brinker, U. H. *Eur. J. Org. Chem.* **2006**, 5423.

(5) (a) Warmuth, R. *Eur. J. Org. Chem.* **2001**, 423. (b) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95–105.

(6) Warmuth, R. In *Molecular Encapsulation*; Brinker, U. H., Mieusset, J.-L., Eds.; John Wiley & Sons, Ltd: Chichester, 2010; p 227.

(7) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. *J. Am. Chem. Soc.* **2004**, *126*, 14366.

(8) Kulasekharan, R.; Choudhury, R.; Prabhakar, R.; Ramamurthy, V. *Chem. Commun.* **2011**, *47*, 2841.

(9) Sundaresan, A. K.; Ramamurthy, V. *Org. Lett.* **2007**, *9*, 3575.

(10) Gibb, C. L. D.; Sundaresan, A. K.; Ramamurthy, V.; Gibb, B. C. *J. Am. Chem. Soc.* **2008**, *130*, 4069.

(11) Moss, R. A.; Chang, M. J. *Tetrahedron Lett.* **1981**, *22*, 3749.

(12) Isaev, S. D.; Sherstyuk, O. F.; Kozlov, O. F.; Skripkin, V. V.; Yanku, I. *Teoretcheskaya i Eksperimental' naya Khimiya* **1991**, *27*, 211.

suggest adamantanediazirines **1b−d** form a strong 1:1 (guest to host) complex with OA in aqueous solution. As per NMR spectral data adamantanediazirine **1a** formed a 2:2 complex. Results presented below highlight that carbenes generated within the OA cavitand in aqueous solution and on a silica surface by photolysis of adamantanediazirines@OA show a distinctly different chemical behavior from that of free molecules in aqueous solution.
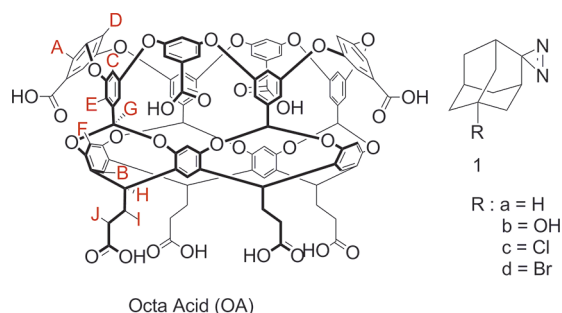


**Figure 1.** Structures of host OA and adamantanediazirines used in this study.

Stirring a 1 mM solution of adamantanediazirines **1a−d** and OA in water (D$_2$O; sodium borate buffer) resulted in a transparent solution whose $^1$H NMR spectra confirmed inclusion of adamantanediazirines **1a−d** within host OA (signal assignments were made based on COSY and NOESY spectra, Figures S1−S4 in the Supporting Information (SI)). $^1$H NMR spectra of a 1:1 mixture of host and guest (see Figure 2 for **1a** and **1b** and Figures S5−S8 in SI for full spectra of all four complexes) revealed that the aliphatic hydrogen signals of the adamantyl group were shifted upfield, which is suggestive of organic guests being included within the host OA. $^1$H NMR titration spectra (Figures S9−S12 in SI) performed for all four guests suggested that adamantanediazirines **1a−d** formed 1:1 (host to guest) stoichiometric complexes with OA in water. To infer whether the 1:1 complex is a 1:1 inclusion complex or a 2:2 complex with encapsulated guests, 2D-DOSY experiments were carried out at room temperature. The diffusion constant for free OA in water was measured to be $1.88 \times 10^{-6}$ cm$^2$/s while that for **1a**@OA was $1.23 \times 10^{-6}$ cm$^2$/s and those for **1b**@OA, **1c**@OA, and **1d**@OA were

$1.56 \times 10^{-6}$, $1.55 \times 10^{-6}$, and $1.56 \times 10^{-6}$ cm$^2$/s (see Figure S13 in the SI) suggesting that **1a** formed a 2:2 complex while the other three formed 1:1 complexes (see Table S1 and Scheme S2 in the SI).[21] ITC data provided in Table 1 further confirmed the stoichiometry of the complex between **1b**, **1c**, and **1d** and OA to be 1:1.

Thermodynamic parameters for complexation of **1b−d** with OA were estimated by monitoring the heat changes during titration of the guest into a host OA solution (for ITC data see Figures S14−S16, and for experimental details see pp S26−27 in the SI). Since guests **1b−d** were not sufficiently soluble in 100% buffer solution, all ITC experiments were carried out in 40% DMSO + 60% sodium borate buffer solution. The association constant ($K$), $\Delta G$, $\Delta H$, $\Delta S$, and stoichiometry of the complex 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 $10^4$ to $10^6$ M$^{-1}$ suggested the complex to be stable in the above solvent mixture. We believe the complexes should be even more stable in 100% water in which photochemical studies were conducted. High enthalpies of binding ($\sim -12$ kcal/mol) could be a result of the tight fit of the adamantyl group within the OA cavitand resulting in stronger van der Waals and C−H---$\pi$ interactions, and in addition a C−X---$\pi$ interaction (X = Cl and Br) in the case of **1c** and **1d** (see Figure S17 in the SI). Negative entropies (range −12 to −21 cal/mol) are consistent with the loss of freedom of the guest as it binds to the host OA. Based on ITC data, we believe the binding of **1b−d** to host OA is essentially driven by enthalpic rather than entropic considerations.[22,23] Surprisingly, the entropic loss was much more for the system with the OH substituent (**1b**) than for the Cl and Br substituted ones (**1c** and **1d**).

**Scheme 1.** Excited State Chemistry of the Expected Products
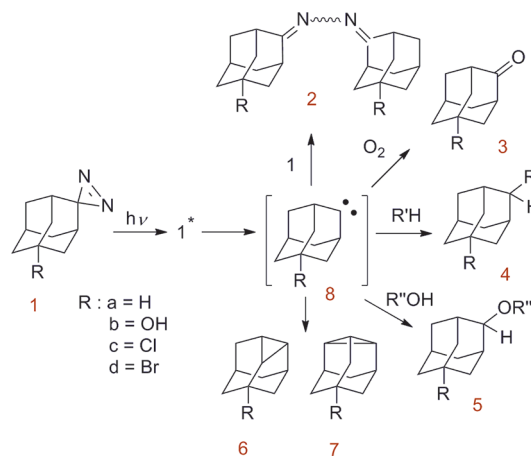
(13) Morgan, S.; Jackson, J. E.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 2782.

(14) Bayley, H.; Knowles, J. R. *Biochem. J.* **1978**, *17*, 2420.

(15) Modarelli, D. A.; Morgan, S.; Platz, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7034.

(16) Krois, D.; Brecker, L.; Werner, A.; Brinker, U. H. *Adv. Synth. Catal.* **2004**, *346*, 1367.

(17) Brinker, U. H.; Buchkremer, R.; Kolodziejczyk, M.; Kupfer, R.; Rosenberg, M. G.; Poliks, M. D.; Orlando, M.; Gross, M. L. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1344.

(18) Kupfer, R.; Poliks, M. D.; Brinker, U. H. *J. Am. Chem. Soc.* **1994**, *116*, 7393.

(19) Wagner, G.; Knoll, W.; Bobek, M. M.; Brecker, L.; van Herwijnen, H. W. G.; Brinker, U. H. *Org. Lett.* **2010**, *12*, 332.

(20) Bobek, M. M.; Brinker, U. H. *J. Am. Chem. Soc.* **2000**, *122*, 7430.

(21) Jayaraj, N.; Zhao, Y.; Parthasarathy, A.; Porel, M.; Liu, R. S. H.; Ramamurthy, V. *Langmuir* **2009**, *25*, 10575.

(22) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.

(23) Rekharsky, M. V.; Inoue, Y. *Chem. Rev* **1998**, *98*, 1875.

**Table 1.** Binding Constants (K) and Relevant Thermodynamic Parameters for Complexation of Adamantanediazirines with OA at 298 K

| guests | $K_a{}^a$ (M$^{-1}$) | $\Delta G^b$ (kcal/mol) | $\Delta H^c$ (kcal/mol) | $\Delta S^d$ (cal/mol) | stoichiometry |
|---|---|---|---|---|---|
| **1b** | $5.5 \pm 0.6 \times 10^4$ | $-6.45 \pm 0.06$ | $-12.9 \pm 0.5$ | $-21.5 \pm 1.5$ | $0.80 \pm 0.05$ |
| **1c** | $9.9 \pm 0.8 \times 10^5$ | $-8.20 \pm 0.04$ | $-12.0 \pm 0.1$ | $-12.8 \pm 0.4$ | $0.91 \pm 0.02$ |
| **1d** | $1.8 \pm 0.1 \times 10^6$ | $-8.52 \pm 0.04$ | $-11.87 \pm 0.07$ | $-11.2 \pm 0.1$ | $0.98 \pm 0.04$ |

*[a]* Mean values measured from at least three ITC experiments at 25 °C in 1 mM sodium tetraborate, pH ~9.0. 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 $\Delta G$ calculated from $K_a$ and $\Delta H$ values. A solvent mixture of DMSO and sodium borate buffer in water (2:3) was used for all the titrations.

To gain an insight into the difference in entropic loss between the three molecules, we generated the most likely structure of the three complexes in aqueous solution using the GROMACS program that employs the OPLS-AA force field (see Figures S18 to S21 for initial and final structures).[24−27] Most representative structures obtained through the above simulation are provided in Figure 3 and in the SI (Figure S18 for **1a**@OA). It is readily seen that **1a**@OA, **1c**@OA, and **1d**@OA have structures different from that of **1b**@OA. These structures are also supported by 2D-NOESY spectra provided as Figures S1b−S4b in the SI. We believe the hydrophilic OH group reorients the guest **1b** in such a way that the diazirine group is held tightly at the narrower end of the cavitand with OH facing water. It is quite likely that this tight fit and the hydrogen bonding of the OH group with exterior water molecules lower the mobility of **1b** and the solvating water molecules resulting in a larger loss of entropy as compared to **1c** and **1d**. From the above ¹H NMR and ITC studies it is clear that guests **1b−d** form a stable 1:1 complex with OA. Since the parent system **1a** formed a 2:2 complex we could not estimate the thermodynamic parameters due to the lack of software that would simulate multistep binding phenomena.
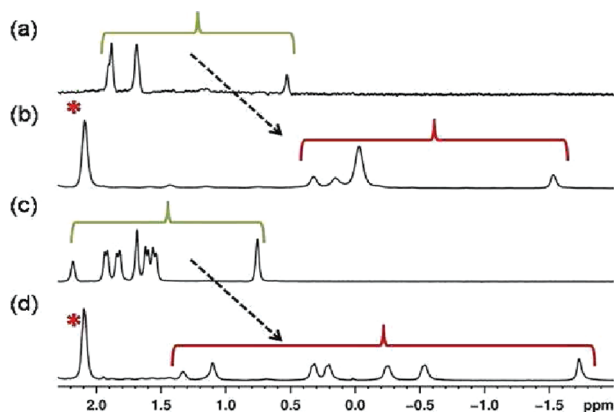


**Figure 2.** Partial ¹H NMR spectra of (a) **1a** in buffered D₂O, (b) **1a₂**@OA₂ in buffered D₂O, (c) **1b** in buffered D₂O, and (d) **1b**@OA in buffered D₂O. Buffer: 10 mM sodium tetraborate solution in D₂O (* denotes signal due to OA hydrogens).

Photolysis of adamantanediazirines **1a−d** in hydrocarbon and alcohol solution is reported to give a number of products shown in Scheme 1.[11−15,20] Of these, azine **2**, adamantanone **3**, and solvent insertion products **4** and **5** were the major ones. Importantly, intramolecular C−H insertion products **6** and **7** were formed only in trace amounts. In general, the formation of all products listed in Scheme 1 was presumed to involve adamantylidene **8** as the intermediate.

We have carried out photolyses of **1a₂**@OA₂, **1b**@OA, **1c**@OA, and **1d**@OA under two different conditions. Due to high binding constants ($K_a$) the adamantanediazirines are present practically quantitatively as complexes, even in solution. In one condition, the complex was irradiated in water (sodium borate buffer), and in the other the complex was transferred to a silica surface and irradiated as powder. For comparison irradiations of **1a−d** alone in water were also carried out. The progress of the photolysis was followed by ¹H NMR (Figures S22−S29 in the SI), and products were extracted upon completion of the reaction and analyzed by GC. Results are summarized in Table 2. In water in the absence of OA **1a-d** gave adamantanone (**3**) and adamantanol (**5**) as major products (~90%). On the other hand, irradiation of **1a₂**@OA₂ in aqueous solution gave azine **2a** in 89% yield (Table 2). Obviously, the formation of azine is an outcome of caging two molecules of **1a** within a single capsule. Most likely as soon as the adamantylidene is generated it reacts with the adjacent adamantanediazirine **1a** molecule present in the same capsule to yield azine **2a**. This model is consistent with the absence of azines upon photolysis of **1b**@OA, **1c**@OA, and **1d**@OA where only one molecule is present within the OA cavitand.

Irradiation of **1b**@OA in water gave 92% of intramolecular insertion products **6b** and **7b**. In this case adamantanone was formed in 8% yield, most likely a result of a reaction between carbene and oxygen. The formation of unprecedented amounts of **6b** and **7b** from **1b**@OA is consistent with its structure (Figure 3) wherein the photolytically generated adamantylidene **8b** intermediate would have its reactive end facing the narrower end of the cavitand; such a geometry would offer very little option. Based on the proposed structures for **1c**@OA and **1d**@OA

(24) Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657.

(25) Kaminski, G. A.; Friesner, R. A.; Tirado-Rives, J.; Jorgensen, W. L. *J. Phys. Chem. B* **2001**, *105*, 6474.

(26) Spoel, D. v. d.; Lindahl, E.; Hess, B.; Groenhof, G.; Mark, A. E.; Berendsen, H. J. C. *J. Comput. Chem.* **2005**, *26*, 1701.

(27) Lindahl, E.; Hess, B.; Spoel, D. v. d. *J. Mol. Model.* **2001**, *7*, 306.

(28) De Mayo, P. *Pure Appl. Chem.* **1982**, *54*, 1623.

(Figure 3), we expect adamantylidenes **8c** and **8d** generated upon photolysis would have the reactive end facing water allowing them to explore options such as reacting with oxygen and water. As seen in Table 2, **6c** and **7c** are formed in 45% yield from **1c**@OA and **6d** and **7d** in 37% yield from **1d**@OA. Corresponding adamantanones accompanied the above products in larger amounts. The results noted within the OA host are distinctly different from what has been recorded within zeolites, cyclodextrins, and a resorcinarene-based cavitand.[16−19] Irradiation of adamantanediazirine **1a** adsorbed within faujasite zeolites gave the intra-molecular C−H insertion products **6a** and **7a** in less than 10% yield. However, photolysis of solid complexes ada-mantanediazirine **1a** with cyclodextrin and **1d** with a resorcinarene-based cavitand gave the above insertion products in slightly higher yield (~25%). Formation of intramolecular insertion products in nearly quantitative yield from **1b**@OA brings out the potential of manipulat-ing the behavior of reactive intermediates such as carbenes by constraining them in a narrow space.

**Table 2.** Relative % of Products upon Photolysis[a]

| guests | media | 2 | 3 | 5 | 6+7 |
|--------|-------|---|---|---|-----|
| **1a** | $D_2O$ | 5.5 | 31.0 | 62.0 | 1.5 |
| | **1a**$_2$@OA$_2$ | 89.0 | 5.0 | – | 6.0 |
| | **1a**$_2$@OA$_2$-SiO$_2$ | – | 16.0 | – | 84.0 |
| **1b** | $D_2O$ | – | 3.0 | 95.0 | 2.0 |
| | **1b**@OA | – | 8.0 | – | 92.0 |
| | **1b**@OA-SiO$_2$ | – | 5.5 | – | 94.5 |
| **1c** | $D_2O$ | 8.0 | 2.5 | 88.0 | 1.5 |
| | **1c**@OA | – | 55.0 | – | 45.0 |
| | **1c**@OA-SiO$_2$ | – | 24.0 | – | 76.0 |
| **1d** | $D_2O$ | 5.0 | 27.0 | 62.0 | 6.0 |
| | **1d**@OA | – | 63.0 | – | 37.0 |
| | **1d**@OA-SiO$_2$ | – | 20.2 | – | 79.8 |

[a] Irradiation done using medium pressure mercury lamp and 320 nm filter. Reaction was followed by NMR, and following 100% conversion products were analyzed by GC-MS and GC.

Having established that the chemistry of carbenes could be altered within a cavitand in aqueous solution, we were interested in exploring the possibility of transferring the host−guest complexes onto a silica surface and photolyzing them as powders.[28,29] We envisioned that this methodology would also allow us to exclude side reactions such as those with solvents and oxygen. As noted in Table 2, in all cases the major products were intramolecular insertion products **6**

(29) Turro, N. J. *Tetrahedron* **1987**, *43*, 1589.

(30) Turro, N. J.; Ramamurthy, V.; Scaiano, J. C. *Modern Molecular Photochemistry of Organic Molecules*; University Science Books: Sausalito, CA, 2010; Chapter 13.
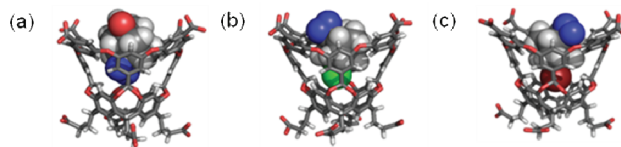
**Figure 3.** Orientation of the adamantanediazirines in (a) **1b**@OA, (b) **1c**@OA, and (c) **1d**@OA based on molecular dynamics simulations (GROMACS, OPLS-AA force-field). Color code for atoms: C, gray; N, blue; O, red; Cl, green; Br, dark red; H, white.

and **7** ( >75%). Even **1a** gave intramolecular insertion products and no azine. As expected, based on the slower diffusion of oxygen on the silica surface, yields of adaman-tanones **3a−d** were lower than in aqueous solution.

In this report we have shown that adamantanediazirines form strong host−guest complexes with the organic cavi-tand octa acid. The nature of the complex (1:1 or 2:2) and orientation of the guest within the host depend on the substituent on the adamantyl framework. Although the primary photochemical step is the same in both the pre-sence and absence of octa acid, *i.e.*, formation of a carbene, the resulting final products are distinctly different within a confined space. The formation of large amounts of intra-molecular insertion products **6** and **7** within the OA cavitand testifies that there is still room for manipulating reactivity patterns of highly reactive intermediates such as carbenes through supramolecular approaches. Predictabil-ity is still far-off, and we hope to make progress in this direction in the coming years.[30,31]

**Supporting Information Available.** 2D NMR spectra of complexes, NMR titration spectra, 2D DOSY spectra, ITC data, experimental procedures for modeling, ITC, and iradiations. This material is available free of charge via the Internet at http://pubs.acs.org.

(31) *Supramolecular Photochemistry*; Ramamurthy, V.; Inoue, Y., Eds.; John Wiley: Hoboken, NJ, 2011.