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Assembly of Water-Soluble, Dynamic, Covalent Container Molecules and Their Application in the Room-Temperature Stabilization of Protoadamantene

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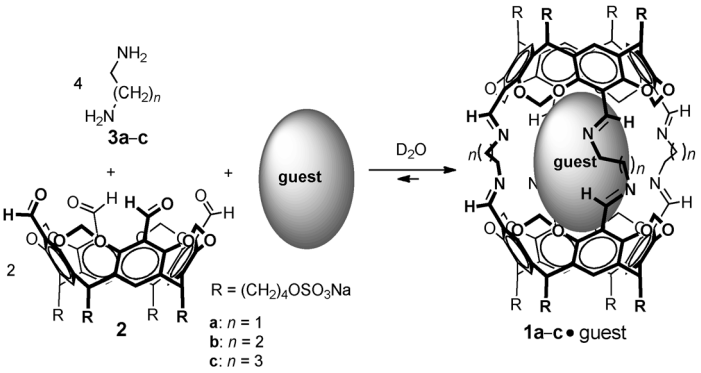
Abstract: The thermodynamically controlled reactions of water-soluble tetraformylcavitand **2** with two equivalents of $H_2N(CH_2)_nNH_2$ ($n=2$–4) in the presence of a suitable templating guest give hemicarceplexes **1a–c**•guest, the yield of which depends on the match between size and shape of the guest and that of the inner phase. These hemicarceplexes are dynamic and dissociate upon addition of acid and reform upon basification. In water, they exchange guests through temporary hydrolysis of imine bonds. To test **1b** as molecular reaction flask, 3-noradamantyldiazirine **6** was encapsulated and photolyzed at 350 nm to produce Bredt olefin protoadamantene **5** and 1-noradamantyldiazomethane **8** in a 4:1 ratio. Encapsulated protoadamantene is stable for days at room temperature in $(CD_3)_2SO/CD_3CN$ ($t_{1/2}=5.5$ days) and has a lifetime of several minutes in D_2O.

Keywords: Bredt olefins · dynamic covalent chemistry · host–guest chemistry · molecular container compound · reactive intermediates

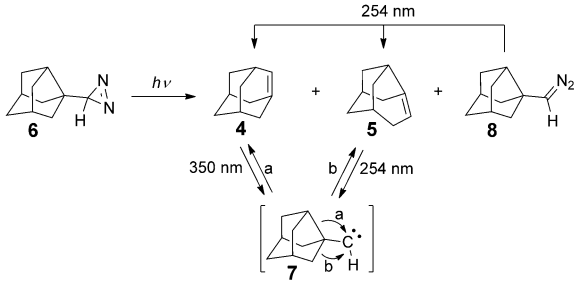
Introduction

In recent years, molecular container compounds have received much attention due to their ability to confine one or more guest molecules inside their cavities.[1] Compartmentalization combined with unique molecular recognition properties form the basis for applications of molecular containers in drug delivery,[2] scavenging of environmental hazards,[3] gas and hydrocarbon storage and separation,[4] and most notably as nanoreactors.[5] As a consequence of guest confinement, reactions carried out inside molecular containers often proceed with a different regiochemistry as compared to the bulk,[6]and in some cases are million-fold accelerated.[7] On the other extreme, encapsulation increases longevity of otherwise fleeting reactive intermediates under ambient conditions.[5c,8] Imprisoning renders the violently pyrophoric P_4 air-stable or transient iminium ions stable towards hydrolysis, prevents thermal homolysis of explosive peroxides, and allows NMR spectroscopic observation of antiaromatic cyclobutadiene or highly strained *o*-benzyne.[8d–f,9]

The development of self-assembly capsules has pushed this field to a new level.[2,5e,10] Firstly, these capsules assemble with remarkable efficiency from multiple components, held together through noncovalent interactions and, secondly, are available in numerous sizes and shapes. Polyimine capsules are covalent analogues that often form with similar efficiency due to the reversibility of imine bond formation.[4a,d,e,11,12] We became interested in testing the suitability of dynamic octaimine hemicarcerands **1a–c** as molecular reaction flasks for the photochemical generation and stabilization of highly strained, reactive species, such as the Bredt olefins adamantene **4** and protoadamantene **5** (Schemes 1 and 2).[13]



Scheme 1. Assembly of hemicarceplexes **1a–c**•guest.



Scheme 2. Photochemistry of 3-noradamantyldiazirine (**6**).

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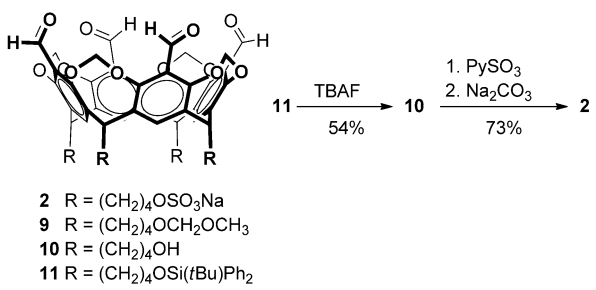
Bredt olefins are of great interest to theoretical and mechanistic organic chemistry due to the forced unusual geometry of their double bonds, which are under substantial strain and highly reactive.[14] For example, **4** and **5** have olefinic strain of 54.8 and 33.5 kcal mol^{-1}, respectively.[15] Both species can be generated photochemically from 3-noradamantyldiazirine (**6**) and are in a photochemical equilibrium with carbene **7** under matrix isolation conditions (Scheme 2).[15b] In solution, they are fleeting and dimerize in benzene or hexane, or react with the solvent in methanol or acetic acid.[15a,c,16] Aside from the prospect to stabilize these species by encapsulation, dynamic octamine hemicarcerands **1a–c** possess another unique property that makes them useful as nanoreactor, namely the ability to alter their dynamics and stability through addition of acid and/or water, which will influence their molecular recognition properties and guest exchange kinetics.[12d,q] For example, we expect that hemicarcerand **1a** will retain aromatic guests indefinitely in dry organic solvents, but that guest release and exchange will be controlled by the imine bond dynamics rather than constrictive binding energy in water. Furthermore, based on extensive encapsulation studies with covalent hemicarcerands that have linkers composed of seven or eight atoms,[17] it is likely that **1b** and/or **1c** will be able to accommodate diazirine **6** and that constrictive binding energy of hemicarceplexes **1b**,**c**·guest (guest = **4**–**6**) will be high enough to prevent dissociation at room temperature without hydrolysis of imine bonds. This is desired in order to generate encapsulated Bredt olefins and to characterize them by NMR spectroscopy. In previous work, we have shown that octamine hemicarcerands **1b** and **1c**, with R = pentyl, form quantitatively in chloroform upon mixing stoichiometric amounts of tetraformyl cavitand **2** (R = pentyl) and diamines **3b** or **3c**, respectively.[12w] Attempts to encapsulate small organic guest molecules inside these octamine hemicarcerands during the assembly process unfortunately failed due to the competition by the solvent and the lack of a strong driving force for guest binding. However, this should be different in water, in which the hydrophobic effect should provide a strong driving force for encapsulation of guests inside the nonpolar cavities of **1b**-**c**, as has been observed for other water-soluble, synthetic hosts.[2,6c,10c,18] Thus, strong guest binding should push the equilibrium shown in Scheme 1 towards hemicarceplex formation despite the instability of the imine bond in water. For example, we showed recently that hexaimine cryptophanes are thermodynamically stable in water in the presence of a suitable guest template, and that templation by the guest is essential for the assembly in water.[12d] Furthermore, we speculated that the strong hydrophobic effect associated with guest encapsulation in water could allow us to assemble the yet elusive hemicarcerand **1a**. Earlier attempts to synthesize **1a** (R = pentyl) in organic solvents by reacting **2** (R = pentyl) with two equivalents of ethylene-1,2-diamine (**3a**) failed and lead instead to larger polycavitand capsules.[12v,w]

This concept of guest encapsulation in water, in which the imine bonds are highly dynamic and guest binding thermodynamically very favorable, followed by transfer of the hemicarceplex into a non-aqueous solvent, in which the complex is stable in the absence of acid, could be very useful for the encapsulation of **6** or other thermally unstable interesting molecules and precursors of reactive species under very mild conditions. For example earlier methods developed in our group for the encapsulation of diazirines inside hemicarcerands required the use of the highly toxic and carcinogenic solvent hexamethylphosphoramide (HMPA) in order to prevent competitive solvent encapsulation.[8a,b,19] Here we address the following questions:

1) Will a template effect be strong enough to overcome the unfavorable Schiff base equilibrium in order to assemble octaimine hemicarcerand **1b**,**c** in water?
2) Can we assemble the yet elusive hemicarcerand **1a** under these conditions?
3) How will the medium water affect the guest exchange kinetics and mechanism?
4) What molecular recognition properties will be observed for these hemicarcerands?
5) Can diazirine **6** be encapsulated and photochemically converted into adamantene **4** and/or protoadamantene **5**?
6) Can these Bredt olefins be observed NMR spectroscopically inside octaimine hemicarcerands?
7) How does the dynamics of the imine bond influence the stability of encapsulated reactive intermediate(s)?

Results and Discussion

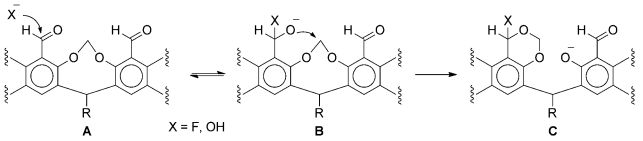
Synthesis of water-soluble cavitand 2: To test the possibility to assemble octaimine hemicarcerands in water, we prepared water-soluble cavitand **2** by reacting hydroxytetramethylene-footed cavitand **10** with pyridine–SO_3 in dry $(CH_3)_2SO$ (Scheme 3). Initial attempts to prepare **10** by acid-catalyzed deprotection of MOM-protected **9** failed (MOM = methoxymethyl ether),[20] since the acetal linkers cleaved faster under these conditions. A higher selectivity for deprotection over acetal linker cleavage could be ach-



2 R = $(CH_2)_4OSO_3Na$
9 R = $(CH_2)_4OCH_2OCH_3$
10 R = $(CH_2)_4OH$
11 R = $(CH_2)_4OSi(tBu)Ph_2$

Scheme 3. Synthesis of water-soluble cavitand **2**.

ieved for TBDPS-protected **11** (TBDPS = *tert*-butyldiphenylsilyl) with tetrabutylammonium fluoride (TBAF) in dry THF.[20] Nevertheless, still about 2–5% of the linkers cleaved under these conditions, presumably by initial nucleophilic addition of fluoride to a formyl group followed by intramolecular *trans*-acetalization (Scheme 4).



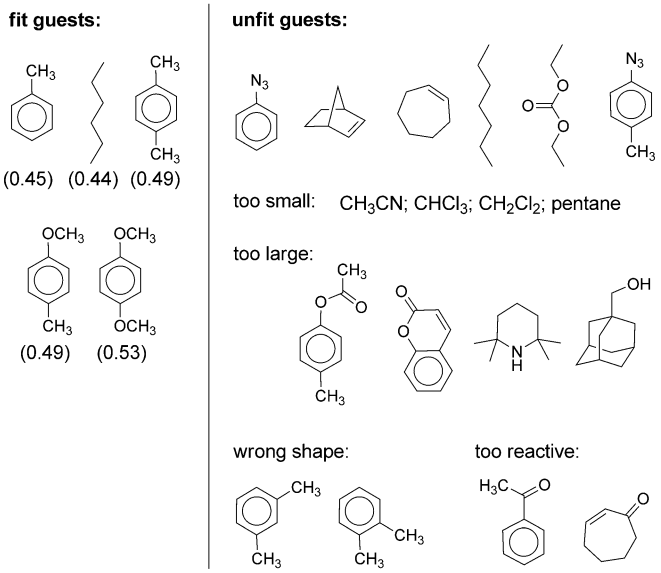
Scheme 4. Proposed mechanism of F^-- and OH^--induced acetal cleavage in tetraformylcavitands (X = F and OH, respectively).

Consistent with this mechanism is the correlation between linker cleavage and decrease of the integration of the formyl protons in the ^{1}H NMR spectra of crude reaction products upon longer exposure to TBAF. Purification of **10** required crystallization, which substantially lowered the yield (54%). The *tert*-butoxydiphenylsilyl group (-Si(O*t*Bu)Ph_2), which is compatible with the conditions needed to prepare the formylated cavitands from related tetrabromocavitands (Br/Li exchange with *t*BuLi and subsequent quench with $(CH_3)_2NCHO$) but cleaves faster with TBAF than the TBDPS group,[21] was also tested, but did not improve the yield of **10**.

Cavitand **2** is soluble in water in the millimolar concentration range and its formyl goups are partially hydrated. It is stable in mildly acidic, neutral, and mildly basic medium. However, under strongly basic conditions, the acetal linkers start cleaving, presumably by the same mechanism that we propose for the TBAF-initiated cleavage (Scheme 4).

Assembly of hemicarceplex 1a·guest: Addition of two equivalents of **3a** to **2** in D_2O gave only oligomeric aggregates containing imine bonds and partially unreacted CHO groups. However, to our delight, in the presence of excess *p*-$CH_3C_6H_4OCH_3$, **1a**·*p*-$CH_3C_6H_4OCH_3$ formed in >90% yield (Scheme 1). Formation of **1a**·*p*-$CH_3C_6H_4OCH_3$ is supported by ^{1}H NMR spectroscopy and ESI-MS. For example, sets of signals for free and encapsulated *p*-$CH_3C_6H_4OCH_3$ are observed with complexation induced shifts (CISs) of 3.79 and 3.95 ppm for the aryl-CH_3 and OCH_3 protons, which is consistent with the guest orientation shown in Scheme 1 (Figure 1 A). Other guests, such as *p*-$CH_3OC_6H_4OCH_3$, *p*-xylene, toluene or hexane also template formation of **1a**·guest. The stability and yield of these hemicarceplexes are very sensitive to the shape and size of the template and follow the order *p*-$CH_3OC_6H_4OCH_3 \approx p$-$CH_3C_6H_4OCH_3 > p$-xylene > hexane > toluene,[18a,b] which correlates with the deviation of their inner phase packing coefficients (PC) from the ideal value of PC = 0.55 (Scheme 5).[22]

Remarkable is the shape selectivity of **1a**, which strongly favors encapsulation of 1,4-disubstituted benzenes over their 1,2- and 1,3-isomers.[18b,23] When *o*- or *m*-xylene were used as template, only trace amounts of **1a**·*p*-xylene formed as



Scheme 5. Molecular recognition properties of **1a**. PCs are given in parenthesis.[22] Guest van der Waals volumes and inner-phase volume of **1a** were computed using the program Swiss Pdb-Viewer.[24]

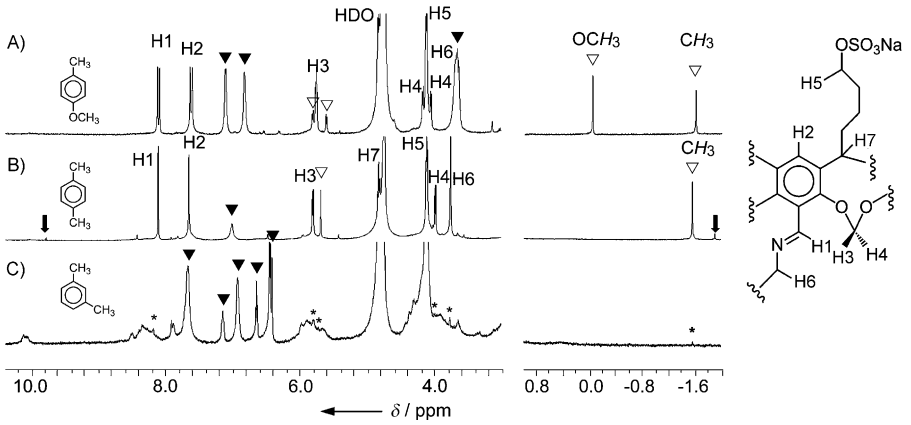


Figure 1. Partial ^{1}H NMR spectra (500 MHz; D_2O; 25 °C) of products formed upon addition of 2 equiv of **3a** to **2** in the presence of A) 4 equiv *p*-$CH_3C_6H_4OCH_3$, B) 1.5 equiv *p*-xylene, or C) 3.5 equiv *m*-xylene. Signals assigned to **1a**·*p*-xylene in C) are labeled with asterisks. Black and white triangles in A)–C) mark signals of free and encapsulated guests, respectively. The formyl proton signal and guest's CH and CH_3 signals of **12a**·*p*-xylene (integration ratio 1:4:6) are marked with black arrows in B).

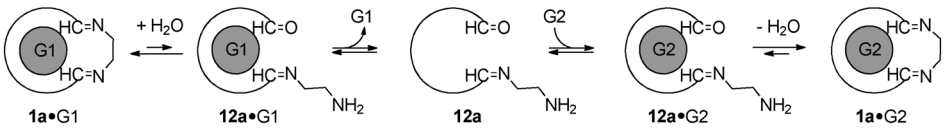
the only identifiable hemicarceplex, the amount of which correlated with the purity of the neat xylene (Figure 1 B, C). Likewise, guests that are too bulky, too small, too long in their most stable conformation and would have to coil inside **1a** (heptane, diethylcarbonate), too short in order to allow C–H–π interactions between guest and both cavitands of **1a** (e.g., norbornene, pentane, or cycloheptene), or that have functional groups capable to react with the linker NH_2 groups are poor templates and lead only to the formation of oligomeric aggregates. Interestingly, $CHCl_3$ and CH_2Cl_2, which, if used as the solvent, produced hexa- and octacavitand nanocapsules, did not template formation of **1a**.[12v,w] This suggests that template effects in addition to conformational effects are likely reasons for the formation of such nanocapsules in these solvents.

As a consequence of the dynamics of the imine bond, the covalent assembly of **1a**•*p*-$CH_3OC_6H_4OCH_3$ is fully reversible. Addition of two equivalents of DCl, disassembles the hemicarceplex. Subsequent addition of two equivalents of NaOD restores **1a**•*p*-$CH_3OC_6H_4OCH_3$ over the course of two days. The dynamic features of the imine bonds also impact guest exchange kinetics and mechanism. Hemicarceplexes **1a**•guest exchange guests within minutes at room temperature in D_2O. For example, addition of excess *p*-$CH_3OC_6H_4OCH_3$ to **1a**•*p*-xylene gave **1a**•*p*-$CH_3OC_6H_4OCH_3$ with a rate constant $k_{ex}=10^{-3}\,s^{-1}$ [Eq. (1)].

$$\mathbf{1a}\cdot G1 + G2 \xrightarrow{k_{ex}} \mathbf{1a}\cdot G2 + G1 \qquad (1)$$

Rate constants for guest exchange between **1a**•*p*-$CH_3C_6H_4OCH_3$ and *p*-$CH_3OC_6H_4OCH_3$ and vice versa are $k_{ex}=1.6\times10^{-3}\,s^{-1}$ and $k_{ex}=0.4\times10^{-3}\,s^{-1}$ ($K_{eq}=4$), respectively.

In contrast to these fast rates, no guest exchange is observed in $(CD_3)_2SO$ in the absence of acid after two days. This suggests that guest exchange in D_2O is not controlled by constrictive and intrinsic barriers,[25] but rather involves a stepwise mechanism with a rate-determining hydrolysis of one imine bond, which leads to an enlarged opening in the host shell allowing for fast guest exchange, followed by shell closing (Scheme 6).[12x] Consistent with this interpretation is the observation of a minor complex that is in equilibrium with **1a**•*p*-xylene and that we tentatively assign to **12a**•*p*-xylene based on the observation of a strongly upfield shifted CH_3 guest signal at $\delta=-1.91$ and a CHO signal at $\delta=$ 9.89 ppm in the expected ratio of approximately 6:1 (Figure 1 B).



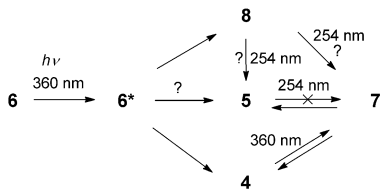
Scheme 6. Proposed guest exchange mechanism in **1a**•guest.

Assembly of hemicarceplexes 1b,c•guest: Water-soluble, dynamic hemicarceplexes **1b**•guest (Guest: *p*-$CH_3C_6H_4OCH_3$ (83% yield), *p*-xylene (81%), *p*-$CH_3OC_6H_4OCH_3$ (81%), *p*-$CH_3C_6H_4N_3$ (75%), 1-adamantylmethanol (41%), $((CH_3)_3C)_2CO$ (40%)) and **1c**•guest (Guest: *p*-xylene (60%), *p*-$CH_3C_6H_4OCH_3$ (47%), 1-adamantylmethanol (55%)) also formed upon addition of two equivalents of **3b** or **3c**, respectively to **2** in D_2O containing excess guest. In each case, sets of signals for free and encapsulated guests were observed in the ^1H NMR spectra. In the reaction between **2** and **3b**, cyclic aminal formation competed with the assembly of **1b**•guest, especially for the lower yielding non-aromatic guests. Cyclic aminals were not observed in the reactions of **3a** and **3c**, but are favorable for **3b** due to ring strain effects and hydrogen bonds between the aminal NH and the proximal acetal O. For this reason, 10% of the CHO groups of **2** are hydrated in D_2O.

Inner phase photolysis of encapsulated 3-noradamantyl-diazirine—encapsulation of 6: In order to test the suitability of water-soluble dynamic hemicarcerands **1a–c** as molecular reaction flasks for the generation of Bredt olefins, we studied the encapsulation of diazirine **6**. These experiments showed, that **6** is too large to template formation of **1a**. However, addition of **3b** or **3c** to **2** in D_2O saturated with **6** gave **1b**•**6** and **1c**•**6** in 55 and 65% yield, respectively, together with oligomeric species and cyclic aminal formation as described earlier. Attempts to improve the yields, in particular of **1b**•**6**, for which cyclic aminal formation competes with hemicarceplex formation, by changing the order of addition (**2** to **3b**) or extending the equilibration time were not successful. Based on the guest exchange dynamics observed for **1a**•guest, D_2O is not a good solvent for the photolysis of encapsulated **6**, since partial release of the expected strained photoproducts may lead to their decomposition during the photolysis. This, however, is not to be expected in a non-aqueous aprotic medium, such as $(CD_3)_2SO$. For this reason, **1c**•**6** is unsuitable for our photolysis studies, since **1c** does not retain the guest when **1c**•**6** is transferred to $(CD_3)_2SO$, in contrast to **1b**•**6**, which remained unchanged for days.

Photolysis of hemicarceplex 1b•6: Irradiation (350 nm, 38 min; −15 °C) of **1b**•**6** in degassed $(CD_3)_2SO/CD_3CN$ (1:1) completely consumed encapsulated **6** and produced two new hemicarceplexes A and B in a 4:1 ratio (solution I). We assign A and B to **1b**•**5** and **1b**•**8**, respectively (Scheme 7 and Figure 2 A and B).

Further irradiation of solution I at 254 nm consumed **1b**•**8** and lead to an increase in the amount of **1b**•**5** (solution II).[26] The room-temperature ^1H NMR spectrum of solution II showed **1b**•**5** together with solvent-filled **1b** and small amounts of oligomers (Figure 2 C).[27] Whether rear-



Scheme 7. Photochemistry of encapsulated **6**.

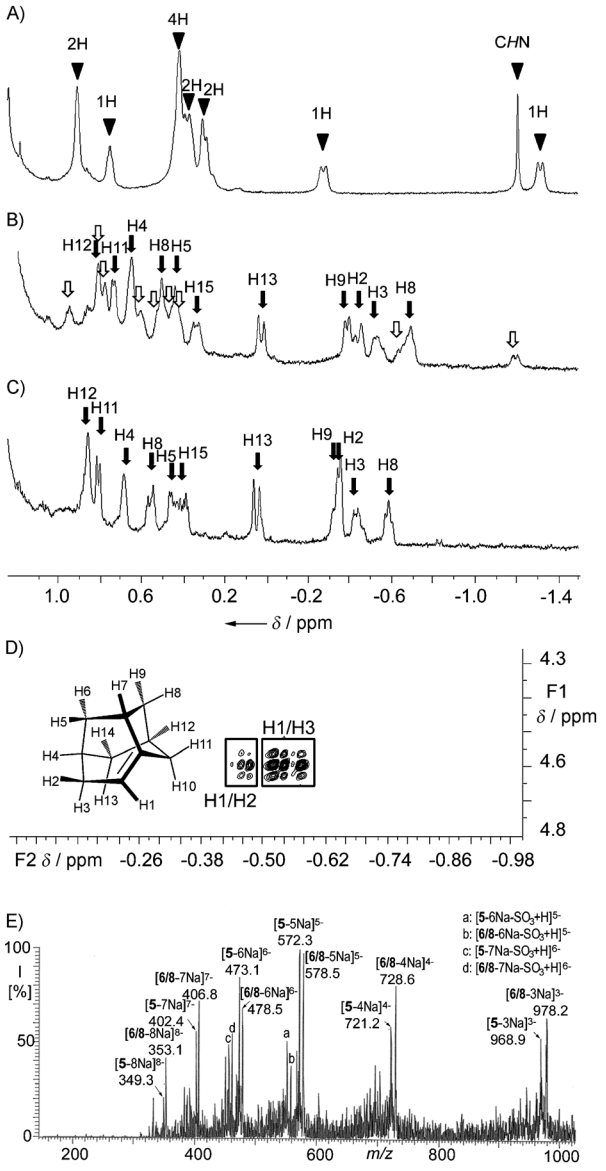


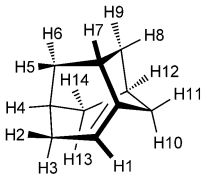
Figure 2. Partial ^{1}H NMR spectra of **1b·6** showing ^{1}H signals of the encapsulated guests (**6** (black arrow); **5** (black triangle); **8** (white arrow)). A) at −10 °C before and B) after irradiation at 350 nm; C) sample B) at 25 °C after further irradiation at 254 nm. D) Partial DQCOSY (500 MHz, $(CD_3)_2SO/CD_3CN$ (1:1), −10 °C) of mixture B). E) ESI-MS of a partially photolyzed solution of **1b·6** in $(CD_3)_2SO$.

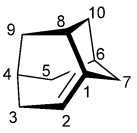
rangement in the excited state of **8** or rearrangement of transient carbene **7** produced **5** during the photolysis of solution I is unclear. High-level computations by Tae et al. predict barriers of 7.84 and 0.35 kcal mol^{-1} for the rearrangement of **7** to **5** and of **7** to **4**, respectively.[15b] The latter barrier is small enough to compete with possible competitive innermolecular reactions between **7** and the surrounding host.[19] However, rearrangement of **7** to **5** is not likely, which would favor rearrangement in the excited state of **8**.[28]

This assignment of photoproducts A and B to hemicarceplexes **1b·5** and **1b·8**, respectively, is based on ^{1}H NMR, 2D NMR, and ESI-MS spectra of solutions containing both products and the reactivity of A and B towards oxygen and towards further irradiation, which will be briefly detailed.

Due to the fact that it was not possible to generate both complexes in pure form and due to partial overlap of host and guest signals, assignment of all hemicarcerand and guest proton resonances of **1b·5** and **1b·8** was only possible with the help of a TOCSY spectrum of a partially photolyzed solution of **1b·6** containing **1b·5**, **1b·8**, unreacted **1b·6**, and solvent-filled **1b** (solution II), and NOESY, DQCOSY and HMQC spectra of solution I, (Tables 1–3 and Supporting Information). ^{1}H–^{1}H correlations and NOEs in the TOCSY, DQCOSY, and NOESY spectra support the fact that the guest in A has 14 chemically different protons, which is consistent with either **4** or **5**. The chemical shifts are listed in Table 1. The multiplet at $\delta_H = 4.6$ ppm is of particular note; it is the most downfield-shifted signal and we assign it to the vinylic proton H1 of **5**. This chemical shift is very close to the chemical shift of the vinylic proton in Bredt bridgehead olefins bicyclo[2.2.2]oct-1-ene ($\delta_H = 4.55$ ppm) and (*Z*)-bicyclo[3.2.1]oct-1-ene ($\delta_H = 4.41$ ppm) encapsulated in a related hemicarcerand.[8a] However more importantly, the

Table 1. Experimental and computed ^{1}H and ^{13}C chemical shifts of encapsulated protoadamantene.

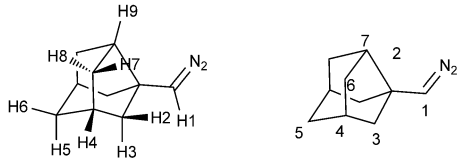




H	δ_{exptl}[a] [ppm]	δ_{calcd}[b] [ppm]	$\Delta\delta$[c] [ppm]	C	δ_{exptl}[a] [ppm]	δ_{calcd}[b] [ppm]	$\Delta\delta$[c] [ppm]
1	4.60	6.75	2.15	1	–	165.8	–
2	−0.45	2.13	2.58	2	136.0	146.0	10.0
3	−0.53	2.3	2.83	3	35.9	42.1	7.8
4	0.64	1.99	1.35	4	33.0	39.8	5.8
5	0.42	1.85	1.43	5	33.2	38.4	5.2
6	0.51	1.81	1.3	6	39.1	46.1	7.0
7	1.35	2.57	1.22	7	51.6	56.3	4.7
8	−0.7	1.24	1.94	8	37.6	44.9	7.3
9	−0.4	1.95	2.35	9	40.5	45.1	4.6
10	1.22	2.75	1.53	10	42.1	47.1	5.0
11	0.73	2.85	2.12	–	–	–	–
12	0.8	2.31	1.51	–	–	–	–
13	0.02	1.58	1.56	–	–	–	–
14	0.33	1.3	0.97	–	–	–	–

[a] In $(CD_3)_2SO/CD_3CN$ (1:1) at 263 K. [b] PBE1PBE1/6-311G++(2d,2p).[29b–e] [c] CIS = $\delta_{calcd} - \delta_{exptl}$.

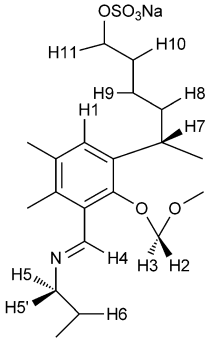
Table 2. Experimental and computed ^{1}H chemical shifts of encapsulated **8**.



H	δ_{exptl}[a] [ppm]	δ_{calcd}[b] [ppm]	$\Delta\delta$[c] [ppm]	C	δ_{exptl}[a] [ppm]	δ_{calcd}[b] [ppm]	$\Delta\delta$[c] [ppm]
1	0.79	3.48	2.69	1	–	46.3	–
2	0.45	1.70	1.25	2	–	49.7	–
3	0.64	1.78	1.14	3	47.0	51.1	4.1
4	0.77	2.26	1.49	4	36.2	42.6	6.4
5	−0.64	1.73	2.37	5	–	38.9	–
6	−1.20	1.77	2.97	6	42.4	47.0	4.6
7	0.60	1.94	1.34	7	–	53.6	–
8	0.49	1.68	1.19				
9	0.95	2.26	1.31				

[a] In $(CD_3)_2SO/CD_3CN$ (1:1) at 263 K. [b] PBE1PBE1/6-311G++(2d,2p).[29b–e] [c] CIS = $\delta_{calcd} - \delta_{exptl}$.

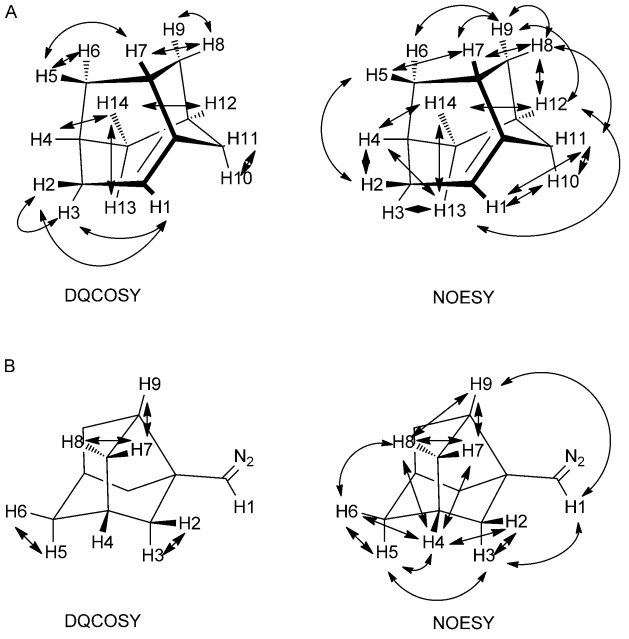
Table 3. Hemicarcerand ^{1}H chemical shifts for **1b·5** and **1b·8**.



H	δ_{exptl}[a] [ppm] **1b·5**	δ_{exptl}[a] [ppm] **1b·8**
1	7.63	7.63
2	4.11	4.16
3	5.56	5.54
4	8.32	8.34
5	3.71; 3.56	3.64
6	1.72	1.72
7	4.69	4.69
8	2.42	2.42
9	1.35	1.35
10	1.68	1.68
11	3.78	3.78

[a] In $(CD_3)_2SO/CD_3CN$ (1:1) at 263 K.

HMQC spectrum of solution I gives rise to a ^{1}H–^{13}C correlation between H1 and a carbon with chemical shift δ_C = 136 ppm (see Figure S27 in the Supporting Information), which we assign to C2 of encapsulated **5** and which is too high for a saturated carbon. The possibility that the guest inside product hemicarceplex A is adamantene **4**, which also has a vinylic proton, was ruled out after observation of two correlations between H1 and guest protons H2 and H3 at $\delta_H = -0.45$ and -0.53 in the DQCOSY of solution I (Figure 2D), which is consistent with **5** but not with **4**.



Scheme 8. ^{1}H-^{1}H correlations and NOEs observed in DQCOSY and NOESY experiments of a solution containing encapsulated **5** (A) and encapsulated **8** (B).

From guest ^{1}H–^{13}C correlations in HMQC experiments and ^{1}H–^{1}H correlations in the DQCOSY and NOEs in the NOESY (Scheme 8), all protons and carbon atoms of **5** were assigned with the exception of the bridgehead alkene carbon C1 (Table 1). The ^{13}C chemical shifts of **5** agree very well with those computed using the GIAO method at the PBE1PBE1/6-311G(++)(2d,2p) level considering a 2–3 ppm CIS for encapsulated **5** and a small overestimation of ^{13}C chemical shifts by this method (Table 1).[8b,29]

The hemicarcerand proton chemical shifts of **1b·5** are listed in Table 3. Their assignment is supported by the observation of NOEs between guest protons and host protons in the NOESY spectrum of solution I. Note the splitting of the N–CH_2 methylene protons H5 into two multiplets at δ_H = 3.56 and 3.71 ppm as a consequence of the chirality of guest **5**.

Photoproduct B is assigned to 1-noradamantyldiazomethane hemicarceplex **1b·8**. 1-Noradamantyldiazomethane is a photoproduct of the irradiation of free diazirine **6**.[15a,b] Other possibilities are the adamantene hemicarceplex **1b·4**, water-trapping products of transiently formed encapsulated carbene **7** or adamantene,[30] or innermolecular reaction products resulting from insertion or addition reactions of transient **7** with the surrounding host.[31] The photosensitivity of B rules out any water-trapping products or innermolecular reaction products, which we expect to be stable towards irradiation. The ^{1}H NMR properties of the guest inside hemi-carceplex B (vide infra) and the lack of reactivity of A and B towards oxygen rules out adamantene as the guest. Free adamantene **4**[15a] and encapsulated bicyclo[2.2.2]oct-1-ene, which has a similar olefinic strain to **4**,[14c,32] react with

atmospheric oxygen within seconds at room temperature,[8a] whereas (*Z*)-bicyclo[3.2.1]oct-1-ene, which has a *trans*-cycloheptene ring like **5**, adds oxygen only at elevated temperature.[8a]

The two most upfield-shifted multiplets assigned to encapsulated **8** at $\delta_H = -1.20$ and -0.65 ppm, which each integrate for one proton, are assigned to H6 and H5 (Figure 2B; Scheme 8). Both couple to each other with $^2J = 11$ Hz, which rules out assignment of one or both of these multiplets to H1 and/or H9. Based on the assignment of H5 and H6, assignment of the remaining protons of encapsulated **8** was possible from the observed ^{1}H–^{1}H correlations and NOEs in the DQCOSY and NOESY spectrum of solution I (Scheme 8B and Table 2). A comparison between the experimental chemical shifts of encapsulated **8** and those computed for free **8** using the GIAO method at the PBE1PBE1/6-311G(++)(2d,2p) level allowed us to estimate the CISs. The estimated CISs are largest for H5, H6 and H1, which suggests a preferred guest orientation in which H5 and H6 are located inside one cavitand of **1b** and H1 inside or close to the cavity of the other cavitand consistent with the shape of the guest and of the hemicarcerand cavity.

The hemicarcerand proton chemical shifts of **1b·8** are listed in Table 3. Their assignment is again supported by the observation of NOEs between protons of **8** and host protons in the NOESY spectrum of solution I. Consistent with the C_2 symmetry of the guest is the absence of a splitting of the N–CH_2 methylene protons, which resonate at $\delta_H = 3.64$ ppm.

Hemicarceplex **1b·5** was also identified in the ESI-MS spectrum of a photolyzed solutions of **1b·6** (solution II, Figure 2E), which shows signals for $[M-8Na]^{8-}$, $[M-7Na]^{7-}$, $[M-6Na]^{6-}$, $[M-5Na]^{5-}$, $[M-8Na]^{3-}$ and $[M-8Na]^{3-}$ at the correct mass-to-charge ratio in addition to the same ions assigned to **1b·8** and/or **1b·6**.[33]

The lifetime of **1b·5** in $(CD_3)_2SO/CD_3CN$ (1:1) containing about 300 mM H_2O is $t_{1/2} = 5.5$ days at room temperature, which, if extrapolated to pure water suggests that encapsulated **5** could be observable even in neat water. Indeed, **1b·5** could be detected by ^{1}H NMR spectroscopy in D_2O at 5 °C (see SI). Under these conditions, the lifetime of **1b·5** is approximately 5 min, which is similar to $1/k_{ex}$ for guest exchange in water. This suggests that the rate of imine hydrolysis limits the lifetime of **1b·5**.

The exclusive formation of **5** and **8** in the inner-phase photolysis contrasts observations in laser flash photolysis of free **6**, which showed that excited **6** rearranges directly to **4**, **5**, and **8** (Schemes 2 and 7).[15a] However, we believe that the photochemistry of encapsulated **6** does not differ much from that of free **6** and that the inability to observe encapsulated **4** by ^{1}H NMR spectroscopy is a result of its much higher molar extinction coefficient at 350 nm compared to that of **6**. Thus, **4** rearranges much more efficiently to **5**, which is a photochemical sink at this wavelength, than it is produced from **6**.[34] Unfortunately, reversal of the photochemical equilibrium between **5** and **4** by selective irradiation of **5** at 254 nm failed,[15a] possibly due to efficient energy transfer from excited **5** to the imine groups of the surrounding host.

Conclusion

In summary, we have developed water-soluble, dynamic hemicarcerands **1a–c**, which self-assemble in water from two cavitands and four diamines upon addition of a suitable, templating, guest molecule. These hosts show interesting molecular recognition properties that depend on size and shape of the guest.

Furthermore, dynamic octaimine hemicarcerand **1b** is able to serve as molecular reaction flask for the photochemical generation of highly strained Bredt bridgehead olefin protoadamantene **5**, which becomes observable for days inside **1b** in non-aqueous solution, in which the imine bonds are stable and constrictive binding is too high to be surpassed by the guest at ambient temperature. This situation is different in water, in which the lifetime of the encapsulated reactive species is primarily controlled by the dynamics of the host's imine bonds, which limits it to a few minutes. However, these dynamic properties will be advantageous for applications of dynamic covalent capsules in catalysis, for which rapid product/reactant exchange is desired. We expect, that the concept of precursor encapsulation in water, in which the hemicarcerands are highly dynamic and encapsulation is driven by the hydrophobic effect, followed by transfer of the hemicarceplex into a polar, non-aqueous medium, in which the host loses its dynamic features and guest exchange is very slow or not possible at all, will be useful for the generation of other reactive intermediates and the encapsulation of interesting thermally fragile molecules.

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[1] D. J. Cram, J. M. Cram, *Container Molecules and Their Guests*, The Royal Society of Chemistry, Cambridge (UK), **1994**.
[2] C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2004**, *126*, 11408–11409.
[3] I. A. Riddell, M. M. J. Smulders, J. K. Clegg, J. R. Nitschke, *Chem. Commun.* **2011**, *47*, 457–459.
[4] a) T. Tozawa, J. T. A. Jones, S. I. Swamy, S. Jiang, D. J. Adams, S. Shakespeare, R. Clowes, D. Bradshaw, T. Hasell, S. Y. Chong, C. Tang, S. Thompson, J. Parker, A. Trewin, J. Bacsa, A. M. Z. Slawin, A. Steiner, A. I. Cooper, *Nat. Mater.* **2009**, *8*, 973–978; b) J. R. Holst, A. Trewin, A. I. Cooper, *Nat. Chem.* **2010**, *2*, 915; c) A. I. Cooper, *Angew. Chem.* **2011**, *123*, 1028–1030; *Angew. Chem. Int. Ed.* **2011**, *50*, 996–998; d) Y. Jin, B. A. Voss, A. Jin, H. Long, R. D. Noble, W. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6650–6658; e) M. Mastalerz, M. W. Schneider, I. M. Oppel, O. Presly, *Angew. Chem.* **2011**, *123*, 1078–1083; *Angew. Chem. Int. Ed.* **2011**, *50*, 1046–1051.
[5] a) T. S. Koblenz, J. Wassenaar, J. N. H. Reek, *Chem. Soc. Rev.* **2008**, *37*, 247–262; b) J. I. van der Vlugt, T. S. Koblenz, W. Jeroen, J. N. H. Reek, in *Molecular Encapsulation* (Eds.: U. H. Brinker, J.-L. Mieusset), Wiley, Chichester (UK), **2010**, pp. 145–174; c) R. Warmuth, in *Molecular Encapsulation* (Eds.: U. H. Brinker, J.-L. Mieusset), Wiley, Chichester (UK), **2010**, pp. 227–268; d) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2009**, *42*, 1650–1659; e) M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem.* **2009**, *121*, 3470–3490; *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438.

[6] a) M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251–254; b) M. Yoshizawa, Y. Takeyama, T. Kusukawa, M. Fujita, *Angew. Chem.* **2002**, *114*, 1403–1405; *Angew. Chem. Int. Ed.* **2002**, *41*, 1347–1349; c) L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb, V. Ramamurthy, *J. Am. Chem. Soc.* **2005**, *127*, 3674–3675.

[7] a) C. J. Hastings, M. D. Pluth, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2010**, *132*, 6938–6940; b) C. J. Brown, G. M. Miller, M. W. Johnson, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2011**, *133*, 11964–11966; c) C. J. Hastings, M. P. Backlund, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2011**, *123*, 10758–10761; *Angew. Chem. Int. Ed.* **2011**, *50*, 10570–10573; d) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85–88; e) D. Fiedler, H. van Halbeek, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 10240–10252; f) J. M. Kang, G. Hilmersson, J. Santamaria, J. Rebek, *J. Am. Chem. Soc.* **1998**, *120*, 3650–3656.

[8] a) P. Roach, R. Warmuth, *Angew. Chem.* **2003**, *115*, 3147–3150; *Angew. Chem. Int. Ed.* **2003**, *42*, 3039–3042; b) X. Liu, G. Chu, R. A. Moss, R. R. Sauers, R. Warmuth, *Angew. Chem.* **2005**, *117*, 2030–2033; *Angew. Chem. Int. Ed.* **2005**, *44*, 1994–1997; c) R. Warmuth, S. Makowiec, *J. Am. Chem. Soc.* **2005**, *127*, 1084–1085; d) V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 14464–14465; e) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem.* **1991**, *103*, 1048–1051; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024–1027; f) R. Warmuth, *Angew. Chem.* **1997**, *109*, 1406–1409; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1347–1350; g) M. Ziegler, J. L. Brumaghim, K. N. Raymond, *Angew. Chem.* **2000**, *112*, 4285–4287; *Angew. Chem. Int. Ed.* **2000**, *39*, 4119–4121.

[9] a) P. Mal, B. Breiner, K. Rissanen, J. R. Nitschke, *Science* **2009**, *324*, 1697–1699; b) S. K. Körner, F. C. Tucci, D. M. Rudkevich, T. Heinz, J. J. Rebek, *Chem. Eur. J.* **2000**, *6*, 187–195.

[10] a) J. de Mendoza, *Chem. Eur. J.* **1998**, *4*, 1373–1377; b) J. Rebek, Jr., *Acc. Chem. Res.* **2009**, *42*, 1660–1668; c) B. C. Gibb, *Org. Nanostruct.* **2008**, 291–304; d) S. R. Seidel, P. J. Stang, *Acc. Chem. Res.* **2002**, *35*, 972–983; e) F. Hof, S. L. Craig, C. Nuckolls, J. J. Rebek, *Angew. Chem.* **2002**, *114*, 1556–1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508.

[11] a) N. M. Rue, J. Sun, R. Warmuth, *Isr. J. Chem.* **2011**, *51*, 743–768; b) M. Mastalerz, *Angew. Chem.* **2010**, *122*, 5164–5175; *Angew. Chem. Int. Ed.* **2010**, *49*, 5042–5053.

[12] a) M. W. Schneider, I. M. Oppel, M. Mastalerz, *Chem. Eur. J.* **2012**, *18*, 4156–4160; b) N. C. Duncan, B. P. Hay, E. W. Hagaman, R. Custelcean, *Tetrahedron* **2012**, *68*, 53–64; c) J. Sun, R. Warmuth, *Chem. Commun.* **2011**, *47*, 9351–9353; d) C. Givelet, J. Sun, D. Xu, T. J. Emge, A. Dhokte, R. Warmuth, *Chem. Commun.* **2011**, *47*, 4511–4513; e) W. J. Meng, B. Breiner, K. Rissanen, J. D. Thoburn, J. K. Clegg, J. R. Nitschke, *Angew. Chem.* **2011**, *123*, 3384–3384; *Angew. Chem. Int. Ed.* **2011**, *50*, 3326–3326; f) Z. Lin, T. J. Emge, R. Warmuth, *Chem. Eur. J.* **2011**, *17*, 9395–9405; g) S. Jiang, J. Bacsa, X. Wu, J. T. A. Jones, R. Dawson, A. Trewin, D. J. Adams, A. I. Cooper, *Chem. Commun.* **2011**, *47*, 8919–8921; h) K. E. Jelfs, X. F. Wu, M. Schmidtmann, J. T. A. Jones, J. E. Warren, D. J. Adams, A. I. Cooper, *Angew. Chem.* **2011**, *123*, 10841–10844; *Angew. Chem. Int. Ed.* **2011**, *50*, 10653–10656; i) A. Granzhan, T. Riis-Johannessen, R. Scopelliti, K. Severin, *Angew. Chem.* **2010**, *122*, 5647–5650; *Angew. Chem. Int. Ed.* **2010**, *49*, 5515–5518; j) Y. Jin, B. A. Voss, R. D. Noble, W. Zhang, *Angew. Chem.* **2010**, *122*, 6492–6495; *Angew. Chem. Int. Ed.* **2010**, *49*, 6348–6351; k) T. Hasell, X. F. Wu, J. T. A. Jones, J. Bacsa, A. Steiner, T. Mitra, A. Trewin, D. J. Adams, A. I. Cooper, *Nat. Chem.* **2010**, *2*, 750–755; l) S. Hiraoka, Y. Yamauchi, R. Arakane, M. Shionoya, *J. Am. Chem. Soc.* **2009**, *131*, 11646–11647; m) B. Içli, N. Christinat, J. Tönnemann, C. Schüttler, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2009**, *131*, 3154–3155; n) V. Steinmetz, F. Couty, O. R. P. David, *Chem. Commun.* **2009**, 343–345; o) P. Skowronek, J. Gawronski, *Org. Lett.* **2008**, *10*, 4755–4758; p) M. Mastalerz, *Chem. Commun.* **2008**, 4756–4758; q) P. Mal, D. Schultz, K. Beyeh, K. Rissanen, J. R. Nitschke, *Angew. Chem.* **2008**, *120*, 8421–8425; *Angew. Chem. Int. Ed.* **2008**, *47*, 8297–8301; r) D. Xu, R. Warmuth, *J. Am. Chem. Soc.* **2008**, *130*, 7520–7521; s) X. Liu, Y. Liu, R. Warmuth, *Supramol. Chem.* **2008**, *20*, 41–50; t) Y. Liu, X. Liu, R. Warmuth, *Chem. Eur. J.* **2007**, *13*, 8953–8959; u) O. Francesconi, A. Ienco, G. Moneti, C. Nativi, S. Roelens, *Angew. Chem.* **2006**, *118*, 6845–6848; *Angew. Chem. Int. Ed.* **2006**, *45*, 6693–6696; v) X. Liu, R. Warmuth, *J. Am. Chem. Soc.* **2006**, *128*, 14120–14127; w) X. Liu, Y. Liu, G. Li, R. Warmuth, *Angew. Chem.* **2006**, *118*, 915–918; *Angew. Chem. Int. Ed.* **2006**, *45*, 901–904; x) S. Ro, S. J. Rowan, A. R. Pease, D. J. Cram, J. F. Stoddart, *Org. Lett.* **2000**, *2*, 2411–2414.

[13] J. Bredt, *Justus Liebigs Ann. Chem.* **1924**, *437*, 1–13.

[14] a) P. M. Warner, *Chem. Rev.* **1989**, *89*, 1067–1093; b) J. Michl, J. G. Radziszewski, J. W. Downing, J. Kopecky, P. Kaszynski, R. D. Miller, *Pure Appl. Chem.* **1987**, *59*, 1613–1626; c) W. F. Maier, P. von R. Schleyer, *J. Am. Chem. Soc.* **1981**, *103*, 1891–1900.

[15] a) E. L. Tae, Z. Zhu, M. S. Platz, *J. Phys. Chem. A* **2001**, *105*, 3803–3807; b) E. L. Tae, C. Ventre, Z. Zhu, I. Likhotvorik, F. Ford, E. Tippmann, M. S. Platz, *J. Phys. Chem. A* **2001**, *105*, 10146–10154; c) N. Bian, M. Jones, *J. Am. Chem. Soc.* **1995**, *117*, 8957–8961.

[16] D. J. Martella, M. Jones, P. V. R. Schleyer, *J. Am. Chem. Soc.* **1978**, *100*, 2896–2897.

[17] a) Y.-S. Byun, T. A. Robbins, C. B. Knobler, D. J. Cram, *J. Chem. Soc. Chem. Commun.* **1995**, 1947–1948; b) Y.-S. Byun, O. Vadhat, M. T. Blanda, C. B. Knobler, D. J. Cram, *J. Chem. Soc. Chem. Commun.* **1995**, 1825–1827; c) C. Sheu, K. N. Houk, *J. Am. Chem. Soc.* **1996**, *118*, 8056–8070; d) J. Yoon, C. Sheu, K. N. Houk, C. B. Knobler, D. J. Cram, *J. Org. Chem.* **1996**, *61*, 9323–9339; e) M. L. C. Quan, D. J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 2754–2755.

[18] a) J. Yoon, D. J. Cram, *Chem. Commun.* **1997**, 497–498; b) E. L. Piatnitski, R. A. Flowers II, K. Deshayes, *Chem. Eur. J.* **2000**, *6*, 999–1006; c) C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2006**, *128*, 16498–16499; d) H. Sun, C. L. D. Gibb, B. C. Gibb, *Supramol. Chem.* **2008**, *20*, 141–147; e) C. L. D. Gibb, B. C. Gibb, *Tetrahedron* **2009**, *65*, 7240–7248.

[19] a) R. Warmuth, M. A. Marvel, *Angew. Chem.* **2000**, *112*, 1168–1171; *Angew. Chem. Int. Ed.* **2000**, *39*, 1117–1119; b) R. Warmuth, M. A. Marvel, *Chem. Eur. J.* **2001**, *7*, 1209–1220.

[20] X. Liu, J. Sun, R. Warmuth, *Tetrahedron* **2009**, *65*, 7303–7310.

[21] J. W. Gillard, R. Fortin, H. E. Morton, C. Yoakim, C. A. Quesnelle, S. Daignault, Y. Guindon, *J. Org. Chem.* **1988**, *53*, 2602–2608.

[22] S. Mecozzi, J. Rebek, *Chem. Eur. J.* **1998**, *4*, 1016–1022.

[23] T. A. Robbins, C. B. Knobler, D. R. Bellew, D. J. Cram, *J. Am. Chem. Soc.* **1994**, *116*, 111–122.

[24] N. Guex, M. C. Peitsch, *Electrophoresis* **1997**, *18*, 2714–2723; (http://www.expasy.org/spdbv/).

[25] D. J. Cram, M. T. Blanda, K. Paek, C. B. Knobler, *J. Am. Chem. Soc.* **1992**, *114*, 7765–7773.

[26] Due to the small concentration of **1b·12** in the sample it was impossible to determine if **1b·12** rearranged exclusively to **1b·5** or in part to **1b·4**.

[27] Solvent-filled **1b** did not result from dissociation of **1b·6**, **1b·7** or **1b·8** in $(CD_3)_2SO$, but from oligomeric species formed as byproducts during the assembly of **1b·6** in D_2O.

[28] a) M. S. Platz, *Adv. Carbene Chem.* **1998**, *2*, 133; b) J. Wang, G. Burdzinski, T. L. Gustafson, M. S. Platz, *J. Am. Chem. Soc.* **2007**, *129*, 2597–2606.

[29] a) R. Warmuth, S. Makowiec, *J. Am. Chem. Soc.* **2007**, *129*, 1233–1241; b) K. Wolinski, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260; c) J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865; d) J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1997**, *78*, 1396; e) G. Buntkowsky, W. Hoffmann, T. Kupka, G. Pasterna, M. Jaworska, H. M. Vieth, *J. Phys. Chem. A* **1998**, *102*, 5794–5801.

[30] Photolysis samples were not rigorously dried and contained between 50–300 mM H_2O.

[31] a) R. Warmuth, *Chem. Commun.* **1998**, 59–60; b) J.-L. Kerdelhué, K. J. Langenwalter, R. Warmuth, *J. Am. Chem. Soc.* **2003**, *125*, 973–986; c) Z. Lu, R. A. Moss, R. R. Sauers, R. Warmuth, *Org. Lett.* **2009**, *11*, 3866–3869.

[32] I. Novak, *J. Chem. Inf. Model.* **2005**, *45*, 334–338.

[33] The fact that the injected sample was aerated, excludes that the signals assigned to **1b·5** are due to **1b·4**, which has the same mass as **1b·5**, but is expected to react with dissolved oxygen within seconds.
[34] Compared to **1b·8**, the yield of **1b·5** was smaller, if the photolysis was carried out in the presence of atmospheric oxygen, suggesting trapping of **1b·4**. Due to the complexity of the photolysis mixtures under these conditions and the instability of the expected oxidation products, a positive identification of the latter was not possible.

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