4b: M.p. 98 – 100 °C (decomp); ^{1}H NMR (270 MHz, [D$_8$]THF, −90 °C): δ = 2.30 (s, 12H), 2.32 (s, 12H), 7.18, 7.74 (AA′BB′, J = 8.4 Hz, 16H), 7.25, 7.67 (AA′BB′, J = 8.4 Hz, 16H); ^{125}Te NMR (85.2 MHz, [D$_8$]THF, −90 °C): δ = 1063.4, 1263.4 (integration ratio 1:1); FAB-MS: m/z (%): 1437 (2) [M − CF_3SO_3]$^+$, 1111 (36) [M − **3** − CF_3SO_3]$^+$, 785 (64) [M − 2**3** − CF_3SO_3]$^+$, 329 (71) [**3**+H]$^+$, 312 (100) [**3** − O]$^+$; elemental analysis calcd for $C_{58}H_{56}F_6O_9S_2Te_4 \cdot H_2O$ (%): C 43.44, H 3.65; found: C 43.25, H 3.50.

4c: M.p. 94 – 97 °C (decomp); ^{1}H NMR (270 MHz, [D$_8$]THF, −90 °C): δ = 2.24 (s, 12H), 2.28 (s, 12H), 2.32 (s, 6H), 7.05 – 7.35 (m, 20H), 7.58 – 7.88 (m, 20H); ^{125}Te NMR (85.2 MHz, [D$_8$]THF, −90 °C): δ = 992.9, 1087.0, 1242.2 (integration ratio 1:2:2); FAB-MS: m/z (%): 1437 (1.4) [M − **3** − CF_3SO_3]$^+$, 1111 (15) [M − 2**3** − CF_3SO_3]$^+$, 785 (36) [M − 3**3** − CF_3SO_3]$^+$, 329 (76) [**3**+H]$^+$, 312 (100) [**3** − O]$^+$; elemental analysis calcd for $C_{72}H_{70}F_6O_{10}S_2Te_5 \cdot H_2O$ (%): C 44.82, H 3.76; found: C 44.87, H 3.69.

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Synthesis and Characterization of a Unimolecular Capsule**

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Host molecules that completely surround other molecules make use of either strong covalent bonds as in carcerands[1] and cryptophanes, [2] or weak hydrogen bonds as in self-assembling capsules.[3] The former type offers the kinetic stability needed to isolate reactive intermediates[4] and restrict molecular motions,[5] while the latter type shows the dynamic lability useful in recognition[6] and catalysis.[7] We describe

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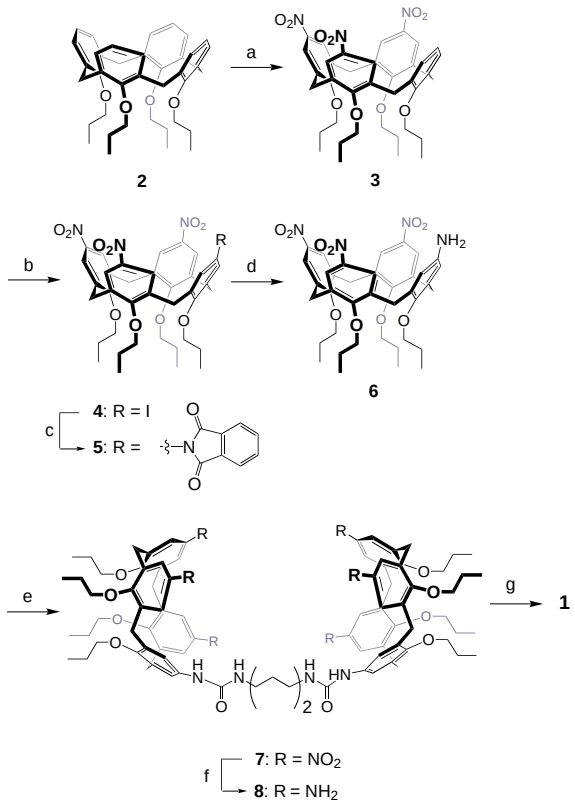
here a system of intermediate stability[8] that blends the characteristics of the two.

Calixarenes with urea substituents on their upper rims[9] dimerize through a cyclic array of complementary hydrogen-bond donors and acceptors ("upper rim" indicates the opening of a calixarene that is not functionalized with hydroxyl groups). The resulting systems feature well-defined cavities that reversibly encapsulate smaller molecules.[10] Connecting two of these calixarenes through their upper rims (to give, for example, **1**; Figure 1) requires special spacers: They must be long enough to reverse the direction of the divergent bonds of the adjacent urea substituents (arrows in Figure 1, **C1**), but short enough to minimize the loss of entropy due to restriction of freely rotating single bonds. Modeling suggested a hexamethylene spacer. This system allows several types of assembly: 1) intramolecular folding to the capsule **C1**, 2) assembly of dimers **1** · **1**, and 3) oligomerization to higher order systems $\mathbf{1}_n$ (Figure 1), which are either cyclic or linear.

The synthesis[11] of **1** followed well-practiced procedures developed by Reinhoudt et al.[12] for the selective functionalization of the upper rim of calix[4]arenes (Scheme 1). Nitration of the known tetrapropoxycalix[4]arene **2**[12a, 13] with 60% HNO_3 and acetic acid in CH_2Cl_2 afforded the trinitrocalixarene **3**[14] in 92% yield. Treatment of **3** in boiling chloroform with silver trifluoroacetate and iodine provided the monoiodinated species **4**. Copper-mediated aromatic substitution with phthalimide gave **5**,[15] which was deprotected by hydrazinolysis to the amine **6**. Two molecules of **6** were coupled with 1,6-diisocyanatohexane to form the covalently bound hexanitro dimer **7**[16] in 33% yield. Reduction of the six nitro functionalities with Raney Ni/H_2 (→**8**) followed by treatment with excess (*n*-heptyl)phenylisocyanate in CH_2Cl_2 afforded **1**.[17]



Scheme 1. Synthesis of **1**: a) 60% aq HNO_3, CH_3CO_2H, CH_2Cl_2, RT, 4 h, 92%; b) AgO_2CCF_3 (2 equiv), I_2 (2 equiv); $CHCl_3$, 60 °C→reflux, 82%; c) phthalimide (2 equiv), Cu_2O (2 equiv), 2,4,6-trimethylpyridine, reflux, 24 h, 45%; d) excess $H_2NNH_2 \cdot H_2O$, toluene/C_2H_5OH, reflux, 65%; e) O=C=N$(CH_2)_6$N=C=O (0.5 equiv), CH_2Cl_2, 12 h, 33%; f) Raney Ni, H_2, toluene/C_2H_5OH, reflux, 24 h, quant.; g) C_7H_{15}PhN=C=O (12 equiv), CH_2Cl_2, 4 h, 48%.

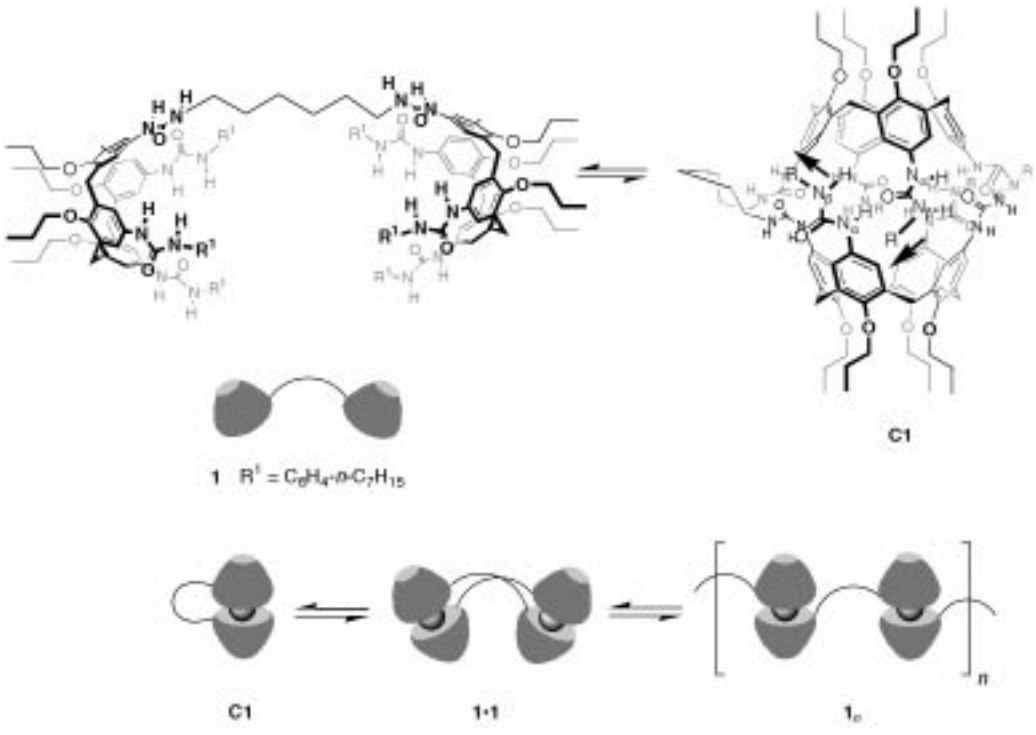


Figure 1. Bridged calixarene dimer **1** and the different options for its self-assembly.

Compound **1** and its complexes were characterized by a combination of ^{1}H NMR spectroscopy (Figure 2) and electrospray mass spectrometry (ESI-MS, Figure 3). The former method takes advantage of the downfield shifts of host NH resonances that signal hydrogen-bonded assemblies and the upfield shifts of guest resonances characteristic of encapsulation. The latter method takes advantage of ammonium salt guests: They are readily encapsulated and simultaneously provide ion labels for the complexes.[18] This method has been used to identify related encapsulation complexes,[19] and to characterize other weakly bound synthetic assemblies[20] in the gas phase.

The ^{1}H NMR spectrum of **1** in [D_6]DMSO (Figure 2a)

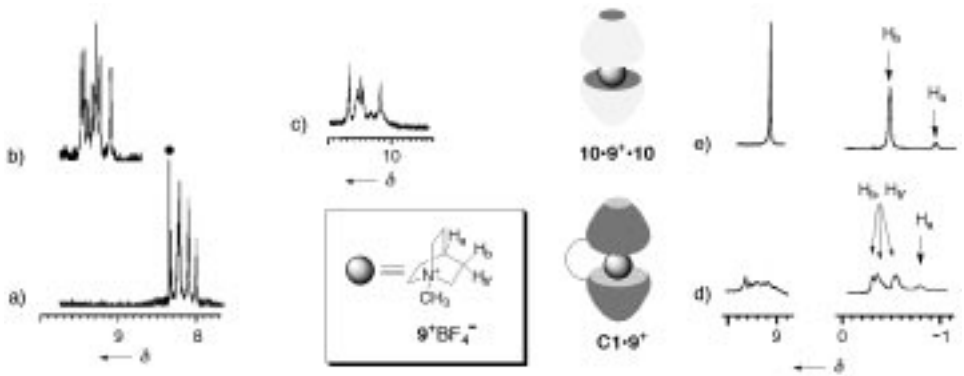


Figure 2. The downfield regions of the ^{1}H NMR spectra (600 MHz) of **1** a) in [D_6]DMSO (an extra peak for remaining $CHCl_3$ is marked with a dot) and b) in $CDCl_3$ with a downfield shift of the urea NH signals for the assembly. c) Portion of the spectrum of $\mathbf{11}_2\cdot\mathbf{1}$ in $CDCl_3$. The upfield and downfield regions of the ^{1}H NMR spectra (600 MHz, $CDCl_3$) of d) $\mathbf{C1}\cdot\mathbf{9}^+$ with separate signals for H_b and e) $\mathbf{10}\cdot\mathbf{9}^+\cdot\mathbf{10}$; these spectra show only a signal set of signals for $\mathbf{9}^+$.

shows the signals expected for an "open" system, that is, one in which no intramolecular hydrogen bonds compete with the solvent for the urea hydrogen atoms. The resonances for the urea NH protons adjacent to an aryl group appear as expected between $\delta = 8-9$ as five peaks in a 1:2:2:1:1 ratio of intensities. The urea hydrogen atom adjacent to the aliphatic tether appears upfield at $\delta = 5.79$. In contrast, in $CDCl_3$ (Figure 2b), a less competitive solvent, the urea NH signals shift downfield ($\Delta\delta \approx 1$), indicating a molecular assembly held together by a seam of hydrogen bonds. The relative simplicity and sharpness of these downfield signals suggested the formation of a discrete assembly rather than a polymer.[21] However, the rest of the NMR spectrum is broadened and cannot be clearly assigned to any one of the possible assemblies.

Addition of cationic guests, for example *N*-methyl quinuclidinium ($\mathbf{9}^+$; counterion BF_4^-), to these NMR samples gave further evidence of capsule formation. Unlike neutral guests, the cation competes successfully with the solvent for entrance into the interior of the capsule due to cation–π interactions,[18] and new signals for the encapsulated ammonium ion of the $\mathbf{1}\cdot\mathbf{9}^+$ complex appear upfield at $\delta = -0.2$ to -0.4 (Figure 2d).

The ESI mass spectrum from a solution of **1** and $\mathbf{9}^+$ in $CHCl_3$ showed a base peak corresponding to $\mathbf{C1}\cdot\mathbf{9}^+$ (*m/z* 2902, Figure 3a). Comparison of the measured isotope pattern with those calculated for $\mathbf{C1}\cdot\mathbf{9}^+$ and $\mathbf{1}\cdot(\mathbf{9}^+)_2\cdot\mathbf{1}$ (inset of Figure 3a) confirms that the ion bears only one charge, and rules out larger assemblies such as $[\mathbf{1}\cdot\mathbf{9}^+]_n$, where $n = 2$. This result was also found for a highly concentrated sample of **1** (2×10^{-4} M), for which both NMR and ESI mass spectra were obtained. Accordingly, in the concentration range 5×10^{-3} M to 5×10^{-5} M, intramolecular formation of **C1** is preferred over the formation of intermolecular assemblies.[22]

It is unlikely that the ions observed for **1** originate from the fragmentation of oligomeric assemblies that may exist in solution. Rather, multiple MS experiments on heterodimer formation, guest selectivity, and collision-induced decomposition, which are described elsewhere,[19] reinforce the evidence that the capsule's structure in solution is retained in the gas phase.

The ^{1}H NMR spectrum, conclusively assigned to **C1**, illustrates the complexity generated by adding a simple alkyl bridge. The tether breaks the symmetry of the capsule, and all urea protons adjacent to the heptylphenyl groups are heterotopic.[23] A total of six downfield signals is expected.[24] However, the eight distinct signals visible (Figure 2b) declare that the symmetry of the capsule may not be so simple. Molecular modeling suggests the cavity of the capsule may be deformed by the tether, thereby reducing the symmetry. At present there is no strong

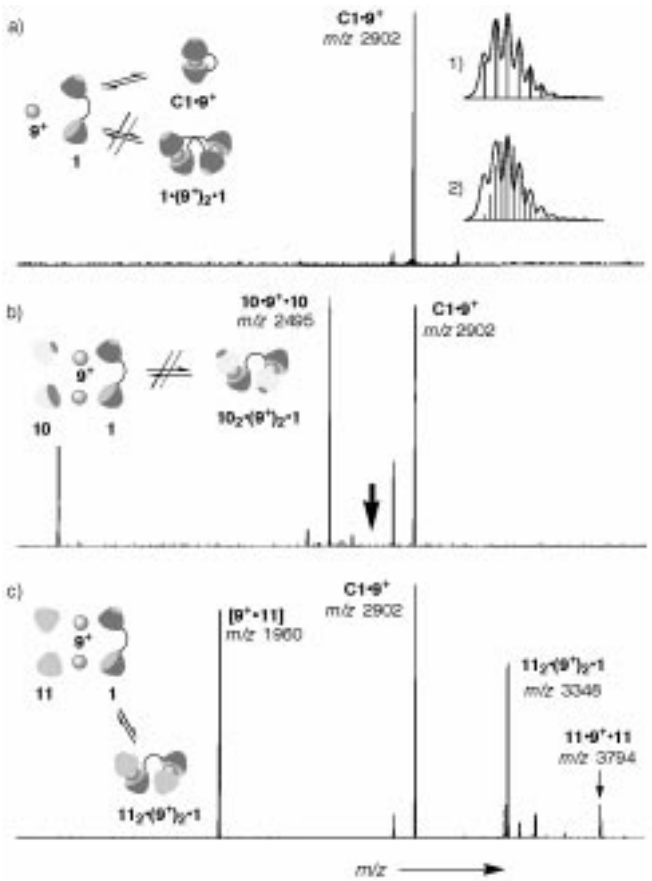


Figure 3. ESI mass spectra of solutions in $CHCl_3$ of a) **1** (2.5×10^{-5} M) with $\mathbf{9}^+BF_4^-$ (7.5×10^{-5} M) (the insets show the measured isotope pattern and those calculated for $\mathbf{C1}\cdot\mathbf{9}^+$ (1) and $\mathbf{1}\cdot(\mathbf{9}^+)_2\cdot\mathbf{1}$ (2)), (b) **1** (2.5×10^{-5} M) and **10** (5×10^{-5} M) with $\mathbf{9}^+BF_4^-$ (2.5×10^{-4} M), and c) **1** (2.5×10^{-5} M) and **11** (5×10^{-5} M) with $\mathbf{9}^+BF_4^-$ (2.5×10^{-4} M).

evidence for this in the NMR spectrum, but the broadened guest signals of encapsulated $\mathbf{9}^+$ may reflect such a loss of symmetry (Figure 2d).[23] The symmetric calixarene complex $\mathbf{10}\cdot\mathbf{9}^+\cdot\mathbf{10}$ shows a much simpler spectrum for both the host and the guest (Figure 2e). Deuterium labeling of the methyl

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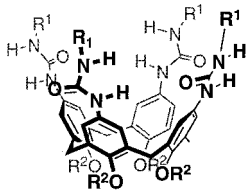
group of $\mathbf{9}^+$ led to the assignments for the visible guest signals as shown (Figure 2).

The effects of the tether on the stability of the capsule were addressed through competition experiments with other urea-substituted calixarenes. Studies of Böhmer et al.[25] had shown that simple calixarene dimers such as $\mathbf{10}\cdot\mathbf{10}$ disproportionate to form heterodimeric species in the presence of similar calixarene dimers, and do so in an entropically driven (statistical) manner. What is expected for **C1** in the presence of, say, **10**? Intuition hints that heterodimerization is disfavored because it leads to a reduction in the number of



10 $R^1 = p\text{-}C_6H_4CH_3$, $R^2 = n\text{-}C_3H_7$

11 $R^1 = p\text{-Ts}$, $R^2 = n\text{-}C_{10}H_{21}$

particles. In the experiment, a 1:1 mixture of **10** and **1** gave *no* new signals for other assemblies such as $\mathbf{10}_2\cdot\mathbf{1}$ in the ^{1}H NMR spectrum. Nor did the ESI mass spectrum of this mixture with $\mathbf{9}^+$ as a label show a peak corresponding to $\mathbf{10}_2\cdot(\mathbf{9}^+)_2\cdot\mathbf{1}$ (*m/z* 2699, arrow in Figure 3b); only signals for the two homodimers were observed.

In contrast, the sulfonylurea derivative **11** (*p*-Ts = *p*-toluenesulfonyl) in the presence of **1** gave a dumbbell system; four new peaks ($\delta = 10.5-10.8$) from the NH protons adjacent to the sulfonyl group of the heterotrimer $\mathbf{11}_2\cdot\mathbf{1}$ replace the signals of **C1** in the NMR spectrum (Figure 2c). The ESI mass spectrum of this mixture, again with $\mathbf{9}^+$ as the guest, showed an intense signal for the dumbbell-like structure $\mathbf{11}_2\cdot(\mathbf{9}^+)_2\cdot\mathbf{1}$ (*m/z* 3348, Figure 3c). Arylurea and sulfonylurea calixarenes such as **10** and **11** are known to prefer the heterodimers because of the well-matched acid/base properties of their hydrogen bonding sites.[23]

In summary, a combination of ^{1}H NMR spectroscopy and ESI mass spectrometry shows that **1** exists as primarily the intramolecularly assembled capsule **C1**. Its encapsulation behavior and stability toward denaturants indicates that the addition of even a simple aliphatic tether can have profound effects on the shape of the calixarene cavity. It may be possible to apply these findings to create an optically active cavity—the goal of our current efforts.

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[14] **3**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.81-7.79$ (m, 3H), 7.23 (s, 2H), 6.36 (s, 4H), 4.49 (t, $J = 15.0$ Hz, 4H), 4.06–3.97 (m, 2H), 3.95–3.89 (m, 2H), 3.87 (t, $J = 6.0$ Hz, 2H), 3.76 (t, $J = 6.0$ Hz, 2H), 3.33 (t, $J = 15.0$ Hz, 4H), 1.93–1.85 (m, 8H), 1.09–1.02 9 (m, 6H), 0.99–0.94 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.7$, 161.3, 155.7, 142.7, 142.3, 137.4, 135.7, 135.4, 135.0, 133.0, 132.6, 128.4, 124.6, 124.0, 123.6, 122.6, 31.6, 31.0, 29.7, 27.3, 23.3, 22.6, 14.1, 10.5, 10.3, 10.0; HR-MS calcd for $C_{40}H_{45}N_3O_{10}Cs^+$ [M+Cs$^+$]: 860.2159, found: 860.2194.

[15] **5**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.81-8.78$ (m, 6H), 8.68–8.65 (m, 2H), 8.40 (s, 2H), 7.61 (s, 2H), 5.51 (dd, $J = 3.5$ Hz, 13.6 Hz, 4H), 5.11–5.08 (m, 2H), 4.83–4.78 (m, 6H), 4.34 (d, $J = 12.3$ Hz, 4H), 2.95–2.87 (m, 8H), 2.08–1.94 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.6$, 162.4, 143.5, 142.7, 136.7, 135.5, 134.1, 133.3, 131.4, 126.4, 126.3, 124.5, 124.0, 123.9, 123.5, 77.8, 77.5, 77.4, 31.0, 23.2, 23.1, 109.4, 10.3, 9.9; HR-MS calcd for $C_{48}H_{54}N_4O_6Cs^+$ [M+Cs$^+$]: 915.3098, found: 915.3127.

[16] **7**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.64-7.60$ (br s, 16H), 4.46 (dd, $J = 1.2$, 24.0 Hz, 8H), 4.16–4.14 (m, 8H), 3.81–3.82 (m, 8H), 3.35–3.23 (m, 12H), 1.91–1.79 (m, 16H), 1.28–1.24 (m, 8H), 1.07–0.81 (m, 24H); HR-MS calcd for $C_{88}H_{104}N_{10}O_{22}Cs^+$ [M+Cs$^+$]: 1785.6381, found: 1785.6510.

[17] **1**: ^{1}H NMR (600 MHz, [D$_6$]DMSO, DMSO): $\delta = 8.29$ (s, 2H), 8.20 (s, 2H), 8.19 (s, 4H), 8.07 (s, 4H), 7.97 (s, 2H), 7.24 (d, $J = 6.0$ Hz, 4H), 7.19 (d, $J = 4.2$ Hz, 8H), 7.02 (d, $J = 6.0$ Hz, 4H), 6.28 (d, $J = 4.2$ Hz, 8H), 6.89 (s, 4H), 6.81 (s, 4H), 6.72 (s, 2H), 6.69 (s, 2H), 5.79 (s, 2H), 4.32 (t, $J = 6.9$ Hz, 8H), 3.79–3.76 (m, 12H), 3.72 (br s, 4H), 3.36–3.30 (m, 28H), 3.30–3.16 (m, 6H), 3.08 (dd, $J = 1.8$, 27 Hz, 4H), 2.98–2.96 (m, 4H), 2.54–2.46 (m, 14H), 2.00–1.85 (m, 8H), 1.49–1.47 (m, 8H), 1.24–1.22 (m, 20H), 1.00–0.94 (m, 6H), 0.85–0.81 (m, 6H); MS calcd for $C_{172}H_{230}N_{16}O_{16}Cs^+$ [M+Cs$^+$]: 2908, found: 2908.

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[21] The large number of NH protons in different chemical environments cause polymeric "calixarene polycaps" to give very broad signals in the downfield region of the ^{1}H NMR spectra; see R. K. Castellano, D. M. Rudkevich, J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 7122 – 7127.
[22] A denaturation by DMSO titrations was done to help determine the driving force for the formation of **C1**. Thus, [D$_6$]DMSO was added to a solution of **1** in $CDCl_3$ until the "melting point" of the assembly was reached (i.e., the assembly is in a 1:1 ratio with the dissociated monomer in solution). The approximate melting point of **C1** was determined to be 2 vol % [D$_6$]DMSO, which is roughly equivalent to the melting points measured for other calixarene systems (see references [9, 10]). In as little as 10 % DMSO, **1** exists solely as the dissociated monomer. This indicates that not enthalpy, but entropy is driving the intramolecular formation of **C1**. For a description of this technique, see M. Mammen, E. E. Simanek, G. M. Whitesides, *J. Am. Chem. Soc.* **1996**, *118*, 12614 – 12623.
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[24] Only the more strongly hydrogen bound $N_\beta H$ protons adjacent to the aryl groups, as opposed to the $N_\alpha H$ protons adjacent to the calixarene, are shifted to this region in $CDCl_3$; see also J. Scheerder, Dissertation, University of Twente, **1995**, pp. 110 – 111.
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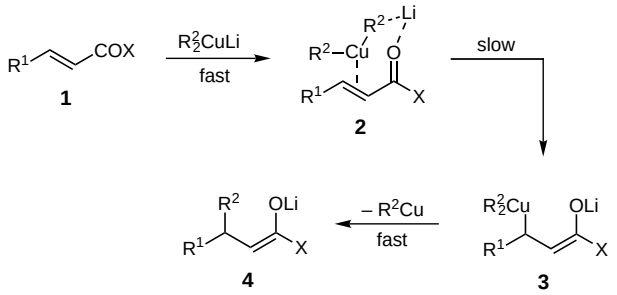
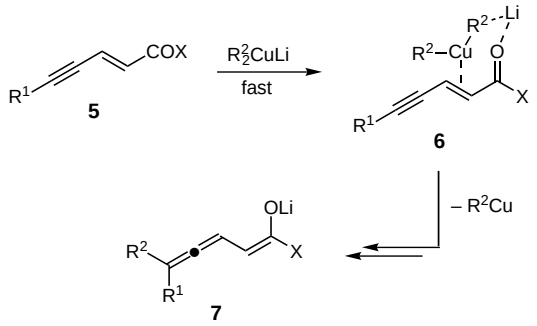
The Mechanism of 1,4- and 1,6-Cuprate Additions: The First Determination of Activation Parameters**

Johannes Canisius, Andreas Gerold, and Norbert Krause*

Michael additions of organocuprate reagents are among the most reliable methods for regio- and stereoselective coupling of C–C bonds. In addition to the classical 1,4-cuprate additions to enones, enoates, and acetylenic esters, recently 1,6-, 1,8-, 1,10-, and 1,12-additions to acetylenic Michael acceptors have been intensively studied.[1] The discovery of these new reaction classes, as well as advances in stereoselective cuprate additions,[2] has led to an increasing interest in the structure of organocuprate reagents[3] and the mechanisms of their reactions. Low-temperature NMR spectroscopy has been particularly well suited for mechanistic studies of these reactions,[1, 4–6] and has provided evidence for the intermediacy of π complexes **2** in the 1,4-cuprate addition to enones and enoates **1**.[4, 5] Further along the reaction pathway to product **4**, the rate-limiting step is likely an oxidative addition resulting in the formation of the σ copper(III) species **3**; this reaction pathway is in agreement with quantum-chemical calculations,[7] and recently evidence for copper(III) intermediates in biological systems has been obtained experimentally.[8]



Interestingly, 1,6-cuprate additions to electron acceptor substituted enynes **5** also result in π complexes **6** with coordination of the cuprate to the C–C double bond, even though the transfer of the alkyl moiety R^2 occurs at the acetylenic carbon atom.[6] The similarity between the π complexes **2** and **6** presumably leads to further analogies in the reaction pathways of the 1,4- and 1,6-additions, in which several short-lived intermediates take part in the formation of the 1,6-addition product **7** from the π complex **6**.[1, 6] To obtain



information about the rate-determining step of these reactions, we have performed a direct kinetic study for 1,4-additions of organocuprates to enones and 1,6-additions to enynes and determined the first set of activation parameters for these reactions.[9] These measurements indicate not only the analogies between the two reaction mechanisms, but also allow a comparison of the reactivity of various Michael acceptors.

Enone **8** and enynoate **9** were chosen as model substrates for the kinetic studies; qualitative studies had shown that these two Michael acceptors have comparable reactivities towards cuprates, allowing the kinetic measurements to be

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