Rate Acceleration through Dispersion Interactions: Effect of a Hemicarcerand on the Transition State of Inner Phase Decompositions of Diazirines**

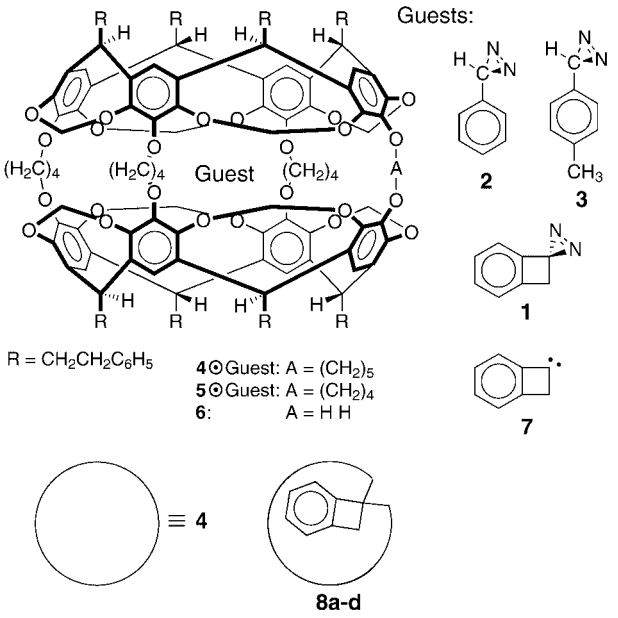
Ralf Warmuth,* Jean-Luc Kerdelhué, Sigifredo Sánchez Carrera, Kevin J. Langenwalter, and Neil Brown

In memory of Donald J. Cram

The concept of molecular container compounds and of single molecule incarceration has provided a novel way to address topics that are important to chemical and biological sciences,[1] such as reactive intermediates,[2–5] through-space phenomena,[6] templating,[7] stereoisomerism,[8] and catalysis.[9] In addition, the investigation of inner phase reactions allows one to probe the effect of a constrained, electron-rich environment on the transition states of a reaction.[10] Insight gained from such studies is expected to be very important for the design of novel catalysts and for the understanding of the stabilization of the transition state in enzyme-catalyzed reactions.[11] Recently, Rebek and co-workers demonstrated that bimolecular reactions can be strongly accelerated in the presence of a self-assembled molecular capsule.[9] The observed acceleration of Diels–Alder reactions was explained by the increased apparent concentration in the tetrameric ene–diene–capsule complex. Whether molecular containers can, like enzymes, stabilize transition states, and if so, which interactions play a role, still remains to be established.

Here, we show for the first time that inner phase reactions, such as the thermal decomposition of diazirines, can be strongly accelerated through dispersion interactions between the hemicarcerand shell and the transition state.

Our investigation of the thermal decomposition of aryldiazirines **1**–**3** in the inner phase of hemicarcerands **4**[12] and **5**[13] was initiated by an unexpected observation. The reaction of **6** with 1,5-pentanediol di-*p*-tosylate and Cs_2CO_3 in hexamethylphosphoramide (HMPA) in the presence of excess **1**,[14b] unexpectedly did not afford the hemicarceplex **4** ⊙ **1;** instead only four isomeric products **8a**–**d** were isolated, which evidently result from an innermolecular addition of **7** to an arene unit of the host **4**.[15] Thus within the reaction time (24–48 h), **1** must have decomposed thermally in the inner phase of **4**,[16] which is very surprising in light of the much higher thermal stability of neat **1**. Shortening of the reaction time



(2 h) gave a small amount of a new hemicarceplex (27%) in addition to **8a**–**d** (10%). The same hemicarceplex is formed in 80% yield if a solution of **4** and excess **1** in $CDCl_2CDCl_2$ ([D_2]TCE; TCE = 1,1,2,2,-tetrachloroethane) is stirred for 50 min at 0 °C (Figure 1a).[17]

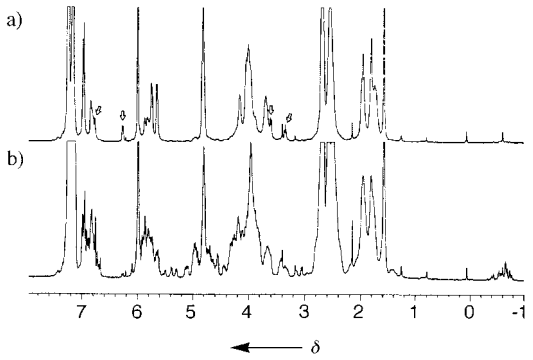


Figure 1. ^{1}H NMR spectra (400 MHz, 24 °C) of a) of **4** ⊙ **1** (80%) in [D_2]TCE and b) same solution as (a) after 16 h at 24 °C. Signals assigned to the protons of incarcerated **1** are marked with arrows.

We assign this new hemicarceplex to **4** ⊙ **1** based on the following features and observations. 1) The FAB mass spectrum shows signals for $[M^+ + 1]$ at *m*/*z* 2393 (54%), and for $[M^+ - \mathbf{1} + 1]$ at *m*/*z* 2263 (100%). 2) Brief irradiaton ($\lambda >$ 350 nm) completely decomposes the complex leading to the formation of **8a**–**d**. 3) In $CDCl_3$, the hemicarceplex decomposes within a few hours by the thermolysis of the guest (36%) and by decomplexation (64%) leading to **4** ⊙ $CDCl_3$[12] and free **1.** In [D_2]TCE, the dissociation of the hemicarceplex is almost completely suppressed, and **8a**–**d** are formed in about 90% yield (Figure 1b). 4) If **1** is thermolyzed in the presence of **4** ⊙ TCE[12] neither the addition products **8a**–**d** are formed nor is the decomposition rate of **1** affected. 5) The ^{1}H NMR spectrum displays signals at $\delta = 6.89$ (t, 1H), 6.36 (d, 1H), 3.62 (d, 1H), 3.43 (t, 1H), and 2.73 (s, 2H), which

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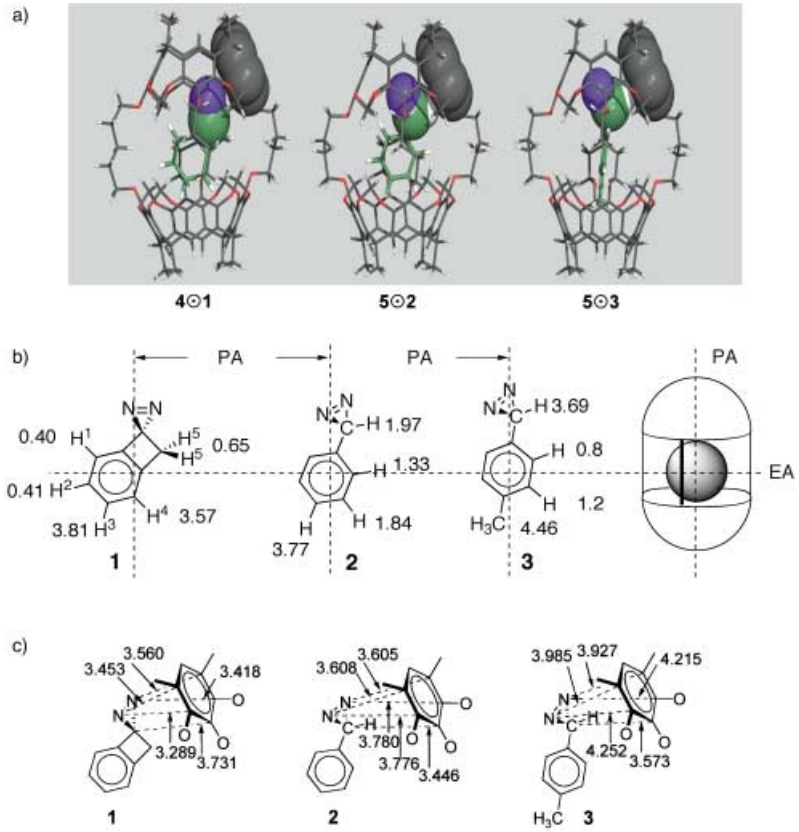
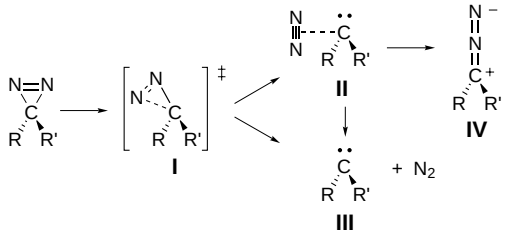


Figure 2. a) MM2 energy-minimized structures of **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**. Color code: O: red; H: white; N: blue; host C: gray; guest C: green. b) Hemicarcerand-induced upfield shifts (in ppm) of guest proton resonances in **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**. Guests **1**–**3** are shown in their preferred inner phase orientation with respect to the polar axis and the equatorially located axis of **4** and **5**. c) Calculated (MM2) atom–atom distances [in Å] between **1**–**3** and the host's arene unit that is facing the diazirine ring in **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**. PA = polar axis; EA = equatorial axis.

are assigned to the protons H2, H1, H4, H3, and H5 of incarcerated **1**, respectively (Figure 2b and Supporting Information). All this strongly supports that the new hemicarceplex is **4** ⊙ **1** and that **8a**–**d** are formed through an inner phase decomposition of **1**.

To quantify the effect of the hemicarcerand on the thermal stability of aryldiazirines, we measured the thermal decomposition rates of **4** ⊙ **1**, **5** ⊙ **2**,[5a,b] and **5** ⊙ **3** as well as of free **1**, **2**, and **3** at different temperatures. Arrhenius plots provided activation energies E_a and preexponential factors $\ln A$ from which $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $T\Delta S^{\ddagger}$ were calculated (Table 1 and Supporting Information). Remarkably, whereas **2** and **3** decompose as fast or slightly slower in the inner phase than in the bulk, the decomposition of **1** is 15-fold faster in the inner phase of **4**. An analysis of the activation parameters shows that this effect is enthalpic in nature.[18] Polarity effects cannot account for the large difference in the ratio between inner phase and bulk phase rates k_{IP}/k_{BP} (Table 1), since decomposition rates for diazirines are essentially insensitive to the solvent polarity.[19, 20]

Kinetic studies and ab initio calculations of the thermolysis of diazirines predict a C_1-symmetric diazirine-like transition state **I** with differently elongated C–N bonds which leads either to free carbene **III** or a carbene–nitrogen encounter complex **II**.[21, 22] The latter further reacts to **III** and/or diazomethane **IV** depending on the substituents R, R′, and the medium (Scheme 1).[21]



Scheme 1. Possible reaction channels for the decomposition of diazirines.

From the measured hemicarcerand-induced upfield shifts of the guest proton resonances we deduce preferred guest orientations (Figure 2b) in which all diazirine groups are located inside a polar cap of **4** or **5**. These orientations compare well with those obtained from force field calculations (Figure 2a).[23, 24] Thus, the increased thermal stability of **3** upon incarceration could be a result of a small steric effect as **3** approaches the transition state **I**. This is consistent with the unchanged stability of the less cavity-filling **2** and the increase in the number of van der Waals contacts (in parentheses) between the diazirine group and the arene groups of the hemicarcerand, which increase in the order **5** ⊙ **3** (16) ≫ **5** ⊙ **2** (3) > **4** ⊙ **1** (1). However, steric effects cannot explain the accelerated de-

Table 1. Activation parameters (E_a, $\ln A$, $\Delta G^{\ddagger}$) for the thermal decomposition of **1**–**3**, **4** ⊙ **1**, **5** ⊙ **2**, and **5** ⊙ **3**.[a]

	1[b] TCE[d]	**4** ⊙ **1**[c] TCE	**2**[b] TCE[d]	**5** ⊙ **2**[c] TCE	**3**[b] TCE[d]	**5** ⊙ **3**[c] TCE	**5** ⊙ **3**[c] THF
E_A	26.4 ± 0.2	24.5 ± 0.8	30.7 ± 0.5	27.4 ± 0.3	29.8 ± 0.2	27.4 ± 0.3	28.3 ± 0.4
$\ln A$	31.8 ± 0.3	31.4 ± 1.2	35.5 ± 0.7	30.9 ± 0.5	35.0 ± 0.2	30.6 ± 0.4	31.7 ± 0.6
$\Delta G^{\ddagger}$	25.0 ± 0.2[e]	23.3 ± 1.1[e]	26.6 ± 0.7[f]	26.5 ± 0.5[f]	26.1 ± 0.2[f]	26.7 ± 0.4[f]	26.9 ± 0.5[f]
$\Delta\Delta H^{\ddagger}$[g]	1.9		3.3		2.4		1.5
$\Delta(T\Delta S^{\ddagger})$[g]	0.2		3.2		3.0		2.3
$\Delta\Delta G^{\ddagger}$[g]	1.7		0.1		− 0.6		− 0.8
k_{IP}/k_{BP}[h]	15/1		1.2/1		1/2.4		1/3.2

[a] Standard errors were estimated by linear least-squares regression of Arrhenius plots. All energy values are in kcal mol^{-1}. [b] Determined by UV/Vis spectroscopy. [c] Determined by ^{1}H NMR spectroscopy. [d] Contained 5% CH_3COOH as carbene and diazomethane trap. [e] T = 313 K. [f] T = 345 K. [g] $\Delta\Delta X^{\ddagger} = \Delta X^{\ddagger}$(free guest) − $\Delta X^{\ddagger}$(incarcerated guest). [h] k_{IP} = inner phase rate constant; k_{BP} = bulk phase rate constant.

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composition of **1**. We propose that dispersion forces strongly stabilize the transition state for the decomposition of **1**. The inner phases of **4** and **5** are lined with eight electron-rich, highly polarizable arene groups. The elongated C–N bonds of the transition state **I** are more polarizable than the intact bonds in the ground state and are able to interact strongly with the host's arene units through dispersion forces. Earlier, Dougherty et al. showed the importance of dispersion interactions in biomimetic catalysis.[25]

In all three hemicarceplexes, the breaking C–N bonds will be located in close proximity to a highly polarizable arene unit of **4** and **5**, suitable for stabilization of the transition state through dispersion interactions. In agreement with this, the decomposition rate of free **1** slightly increases with increasing bulk phase polarizability (see Supporting Information).[20]

A reason why only the thermolysis of **1** but not that of **2** and **3** is strongly accelerated through London forces might lie in the different distances between the diazirine ring and the arene ring (shown as space-filling representation in Figure 2a), that is closest to and almost coplanar with it. The distances between the atoms of the diazirine ring and the O-substituted carbon atoms of the host's arene ring decrease in the order $\mathbf{5}\odot\mathbf{3} \gg \mathbf{5}\odot\mathbf{2} > \mathbf{4}\odot\mathbf{1}$ (Figure 2c) which is opposite to the observed stabilization of the transition state ($\mathbf{5}\odot\mathbf{3} < \mathbf{5}\odot\mathbf{2} \ll \mathbf{4}\odot\mathbf{1}$) and consistent with the strong distance dependence ($\propto R^{-6}$) of dispersion interactions.[26] Further insight into the specific interactions between host and transition state should come from QM/MM calculations, which are currently in progress.

In conclusion, our investigations show that inner phase reaction rates can be strongly altered through the interplay of rate-accelerating dispersion interactions between the transition state and the highly polarizable arene units of the surrounding hemicarcerand and steric effects due to the constrained environment. This suggests that even larger rate enhancements are possible for reactions with very negative activation volumes, such as Diels–Alder reactions or Cope and Claisen rearrangements.[27] Moreover, our studies indicate that properly aligned tryptophan or tyrosine side chains in the active site of an enzyme might account for a stabilization of the transition state by up to 1–2 kcal mol^{-1} per formed or broken bond in an enzyme-catalyzed reaction.[11a]

Experimental Section

5 ⊙ **3**: *p*-Tolyldiazirine **3** (0.110 mL) was added by syringe to a suspension of **6** (150 mg, 0.068 mmol), 1,4-butanediol dimesylate (130 mg, 0.53 mmol), and Cs_2CO_3 (700 mg) in dry HMPA (8 mL). The suspension was stirred for four days under argon in the dark at room temperature. The reaction was quenched by the addition of brine (40 mL). The precipitate was filtered off, washed with water (2 × 10 mL) and methanol (2 × 10 mL), and dried at high vacuum. The crude product was dissolved in the minimum amount of chloroform and purified by column chromatography (silica gel, chloroform). Concentration of the product fraction gave **5** ⊙ **3** (54 mg, 33 % yield) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$, 24 °C): δ = 7.27–7.12 (m, 40H), 6.89 (s, 4H; aryl-*H*), 6.77 (s, 4H; aryl-*H*), 5.98, 5.94 (AB system, $^3J_{A,B}$(H,H) = 8 Hz, 4H; aryl-*H*, **3**), 5.71 (d, ^3J(H,H) = 6.8 Hz, 4H; OCH_{outer}HO), 5.66 (d, ^3J(H,H) = 6.8 Hz, 4H; OCH_{outer}HO), 4.89 (t, ^3J(H,H) = 7.6 Hz, 4H; C$H_{methine}$), 4.88 (t, ^3J(H,H) = 7.6 Hz, 4H; C$H_{methine}$), 4.36 (d, ^3J(H,H) = 6.8 Hz, 4H; OCH_{inner}HO), 4.10 (d, ^3J(H,H) = 6.8 Hz, 4H; OCH_{inner}HO), 3.97 (br s, 8H; OCH_2CH_2), 3.88 (br s, 8H; OCH_2CH_2), 2.76–2.63 (m, 16H), 2.56–2.42 (m, 16H; 1.84 (br s, 16H), –1.68 (s, 1H; C$H_{methine}$, **3**) – 2.12 (s, 3H; CH_3, **3**); LR FAB-MS (NBA matrix): *m*/*z*: 2383 (100) [M^++2], 2354 (78) [M^+ – N_2+1], 2351 (56) [M^+ – **3**+2]; C,H,N analysis calcd (%) for $C_{152}H_{144}N_2O_{24}$: C 76.62, H 6.09, N 1.18; found: C 76.49, H 5.91, N 0.95.

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Supramolecular Cluster Catalysis: Benzene Hydrogenation Catalyzed by a Cationic Triruthenium Cluster under Biphasic Conditions**

Georg Süss-Fink,* Matthieu Faure, and Thomas R. Ward

Dedicated to Professor Lord Lewis of Newnham

Organometallic catalysis most often proceeds through a catalytic cycle that involves the coordination of the substrate, either by ligand substitution or by oxidative addition, transformation of the coordinated substrate, and liberation of the product, either by decoordination or by reductive elimination.[1] Classical examples that have been studied in great detail are the hydrogenation of olefins with Wilkinson's catalyst[2] and the carbonylation of methanol with rhodium iodide (Monsanto Process).[3] The complete characterization of the intermediates of the latter process and the proposal of a well-established catalytic cycle represents one of the triumphs of organometallic chemistry.[4]

In all these reactions, the elementary steps of the catalytic process are believed to occur within the first coordination sphere of the organometallic catalyst.[5] We now have reasons to believe that organometallic catalysts may transform a substrate without prior coordination, the interactions between both partners entirely relying on weak intermolecular contacts. Although hydrogen transfer from a catalyst molecule to a substrate via a merely hydrogen-bonded catalyst–substrate complex has already been considered as the mechanism of ketone transfer hydrogenation reactions,[6] catalytic transformations by host–guest interactions and molecular recognition are generally accepted only in enzymatic catalysis.[7]

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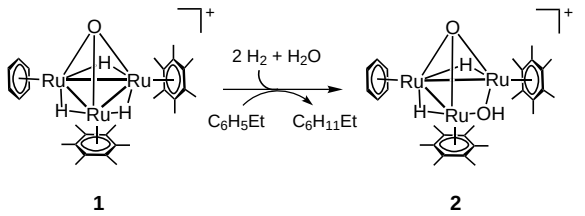
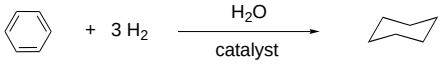
The water-soluble organometallic cluster cation **1** (see Scheme 1), accessible from $[(\eta^6\text{-}C_6H_6)Ru(H_2O)_3]^{2+}$ with $[(\eta^6\text{-}C_6Me_6)_2Ru_2(\mu_2\text{-}H)_3]^+$ in aqueous solution and isolated as the BF_4^- salt,[8] was found to catalyze the hydrogenation of aromatic substrates under biphasic conditions. An unusually high catalytic activity of **1** was observed for the hydrogenation of ethylbenzene. From the reaction mixture the cluster cation **2** could be isolated as the BF_4^- salt (Scheme 1).[9]



1 **2**

Scheme 1. Hydrolyis of the closed cluster cation **1** to give the open cluster cation **2** during the hydrogenation of ethylbenzene to ethylcyclohexane under biphasic conditions (no free C_6H_{12} or C_6Me_6 detected).

Cation **2**, dissolved in water, catalyzes the hydrogenation of aromatic compounds with higher activity than cation **1**: The reaction proceeds with a catalyst/substrate ratio of 1/1000 under hydrogen pressure (60 bar) at 110 °C with vigorous stirring of the biphasic system. For benzene, the reaction is almost complete within 15 min, the catalytic turnover number (TON) being 911, corresponding to a catalytic turnover frequency (TOF) of 3644 h^{-1}. Cation **2** can be recovered unaltered as the BF_4^- salt after a catalytic run from the aqueous phase and reused. Under identical conditions, cation **1** catalyzes the hydrogenation of benzene with a TOF of 289 h^{-1} (Scheme 2).



Scheme 2. Hydrogenation of benzene to cyclohexane catalyzed by **1**-BF_4 or by **2**-BF_4 (catalyst/substrate 1:1000, 60 bar H_2, 110 °C) in water (TOF 289 h^{-1} for **1** and 3544 h^{-1} for **2**, respectively).

Although a large number of organometallic complexes are known to catalyze the hydrogenation of olefins or acetylenes, only very few complexes are reported to catalyze the hydrogenation of aromatic compounds (TOF given in parantheses): $[(\eta^6\text{-}C_6Me_6)_2Ru_2(\mu_2\text{-}H)(\mu_2\text{-}Cl)_2]Cl_2$ (241 h^{-1}),[10] $[(\eta^5\text{-}C_5Me_5)_2Rh_2(\mu_2\text{-}Cl)_2]$ (11 h^{-1}),[11] $[(\eta^3\text{-}C_3H_5)Co(P(OMe)_3)_3]$ (0.7 h^{-1}),[12] $[RuH_2(\eta^2\text{-}H_2)_2(PCy_3)_2]$ (1.6 h^{-1}),[13] $[Nb(OC_6HPh_4\text{-}2,3,5,6)_2Cl_3]$ in combination (1:3) with BuLi (409 h^{-1}),[14] $[(\eta^6\text{-}C_6H_6)_4Ru_4(\mu_3\text{-}H)_4]Cl_2$ in water (376 h^{-1})[15] or in ionic liquids (364 h^{-1}),[16] and $[(\eta^6\text{-}C_6H_6)_2Ru_2(\mu_2\text{-}Cl_2)Cl_2]$ (1998 h^{-1}) in water.[17] The hydrogenation of arenes falls in general within the domain of heterogeneous catalysis: Millions of tons of benzene are hydrogenated per year to give cyclohexane using Raney nickel as the heterogeneous catalyst; the so-called IFP (Institut Français du Petrole) process[18] using nickel and cobalt salts in combination with triethylaluminum seems destined to take over.[19]

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