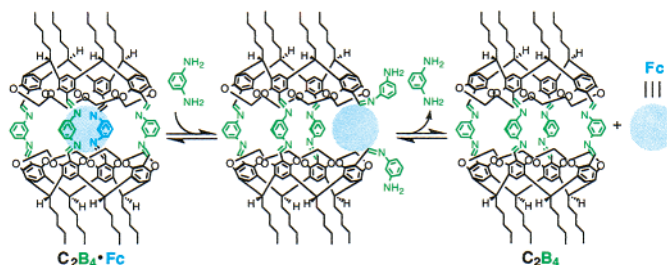


Dynamic Hemarcerands and
HemicarceplexesStephen Ro,[†] Stuart J. Rowan,[‡] Anthony R. Pease,[†] Donald J. Cram,[†] and
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ABSTRACT



The reversible nature of the imine bond formation in CDCl_3 solution has been exploited to exchange substituted for unsubstituted *m*-phenylenediamine (MPD) units in hemarcerand octaimines. Moreover, acid-catalyzed imine exchange has been shown to provide a novel mechanism whereby ferrocene (Fc) can be released as an entrapped guest from the hemicarceplex $\text{C}_2\text{B}_4\odot\text{Fc}$ dissolved in CDCl_3 to give the hemarcerand C_2B_4 when excess of both MPD and trifluoroacetic acid are present.

In 1991, one of us¹ reported a new class of container molecule² called *hemarcerands*. Guests can become imprisoned inside these molecular capsules to generate complexes known as *hemicarceplexes*. Although these complexes can be isolated under standard laboratory conditions, at higher temperatures, the “equatorial” portals in the hemicarceplexes open up sufficiently to let their imprisoned guests escape.

One of us^{1,3} has also identified two free energy terms that govern the stabilities of hemicarceplexes formed between hemarcerands and their guests—one is the *intrinsic binding*

which equates with the free energy of complexation and the other is *constrictive binding* which is commensurate with the free energy of activation for complex formation;⁴ it follows that the sum of these two terms corresponds to the free energy of activation (ΔG^\ddagger_a) of decomplexation.

According to computational studies carried out subsequently by Houk,⁵ the ingress of guests into hemarcerands and their egression out of hemicarceplexes is controlled by one or other of two slightly different conformational processes, i.e., gating by either a “sliding door” or “French door” mechanism. More recently, novel gating

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(4) The concept of *constrictive binding* as it relates to hemicarceplexes and their hemarcerands is analogous to the concept of *slippage* in the context of pseudorotaxanes and their dumbbell components. See: Ashton, P. R.; Baxter, I.; Fyfe, M. C. T.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, 120, 2297–2307.

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mechanisms have also been invoked⁶ to explain the exchange of guest molecules in Rebek's sportsballs,⁷ e.g., spherical dimeric supermolecules held together by multiple hydrogen bonds.^{8,9}

A recent foray we have made into the realm of molecular capsules was prompted by the notion that yet another mechanism might operate during the escape of guests from hemicarceplexes in which two cavitands are held together by dynamic covalent bonds.¹⁰ There are a number of reversible covalent bond-making and -breaking processes that lend themselves to doing reactions on molecular compounds under thermodynamic control. They include olefin metathesis,¹¹ as well as the formation, and sometimes also the exchange, of acetals,¹² borazaaromatic anhydrides,¹³ disulfides,¹⁴ esters,¹⁵ hydrazones,¹⁶ imines,¹⁷ and oximes.¹⁸ In this Letter, we describe how imine exchange (1) can be used to replace 5-substituted-*m*-phenylenediamine (5-substituted-MPD) units by unsubstituted ones (MPD) in hemicarcerand octaamines and (2) provides a "bar-opening/bar-closing" mechanism whereby ferrocene (**Fc**), entrapped in a hemicarceplex octaamine, can escape imprisonment from behind the diimine bars.

Previously, one¹⁹ of us has described how the hemicarcerand octaamine **C₂B₄** can be made in 45% yield by condensing 2 equiv of the appropriate cavitand tetraaldehyde with 4 equiv of *m*-phenylenediamine (MPD) (Figure 1) in

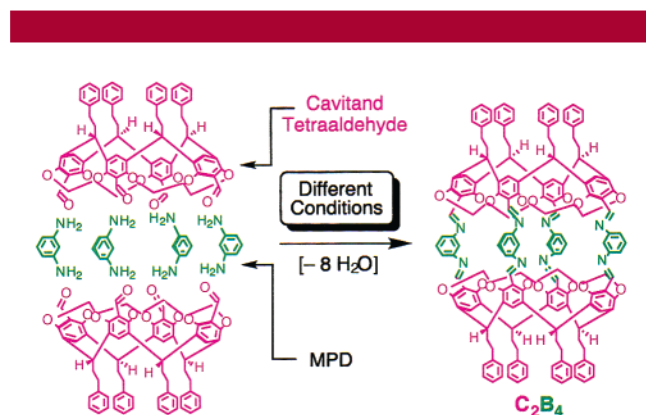


Figure 1. The preparation of hemicarcerand **C₂B₄** by eight successive imine condensations between two molecules of the cavitand tetraaldehyde with four molecules of MPD.

$\text{C}_5\text{H}_5\text{N}$ at $\sim 65^\circ\text{C}$ for 4 days. On the other hand, Kaifer et al.²⁰ have isolated **C₂B₄** in 39% yield by carrying out the same reaction in CH_2Cl_2 with added MgSO_4 at room temperature for 6 days. It occurred to us that, in addition to

(8) For additional recent examples of hydrogen-bonded supramolecular capsules, see: (a) Körner, S. K.; Tucci, F. C.; Rudkevich, M.; Heinz, T.; Rebek, J., Jr. *Chem. Eur. J.* **2000**, *6*, 187–195. (b) Grawe, T.; Schrader, T.; Gurrath, M.; Kraft, A.; Osterod, F. *Org. Lett.* **2000**, *2*, 29–32. (c) Kobayashi, K.; Shirasaka, T.; Yamaguchi, K.; Sakamoto, S.; Horn, E.; Furukawa, N. *Chem. Commun.* **2000**, 41–42. (d) Prins, L. J.; Huskens, J.; de Jong, F.; Timmermann, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498–502. (e) Shivanyuk, A.; Paulus, E. F.; Böhmer, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 2906–2909. (f) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 9818–9826. (g) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469–472.

acting as a water scavenger, the MgSO_4 is probably also catalyzing imine bond formation. When we repeated this reaction in CDCl_3 with MgSO_4 absent, but in the presence of a catalytic amount of trifluoroacetic acid (TFA), ^1H NMR spectroscopy indicated a near-quantitative conversion of the reactants to **C₂B₄** in less than 1 h. The efficiency of this reaction indicates that, most likely, it is being thermodynamically driven. In support of this hypothesis, we observed that the product undergoes slow hydrolysis during silica gel chromatography, leading to 55% yield of the pure **C₂B₄**. Unfortunately, however, the hemicarcerand octaamine, with phenethyl feet and *m*-phenylenediamine (**B**) bridging units, is not soluble in the millimolar concentration range in CDCl_3 , making detailed ^1H NMR spectroscopic analyses difficult. We decided that it would be more straightforward to address this problem, not by chemically modifying the feet of the cavitands but rather by introducing 5-substituted-MPD (**A**) bridging units. One of the attractions of using this approach to increase the solubility of the hemicarcerand is that a suitable ^1H NMR probe can be introduced (Figure 2) into

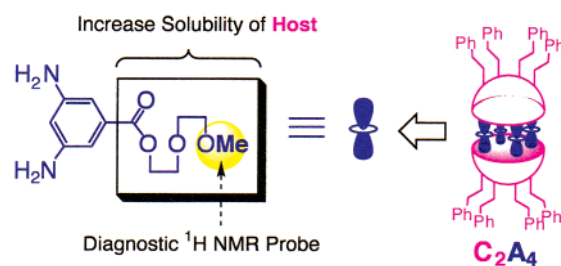


Figure 2. The 5-substituted-MPD employed in the synthesis of the hemicarcerand **C₂A₄** portrayed as a graphical representation.

the 5-substituent on **B** to give **A**. The 5-substituted-MPD (**A**), which was prepared²¹ in two steps in 70% overall yield from 3,5-dinitrobenzoic acid, was condensed in CHCl_3 with the same cavitand tetraaldehyde as that used in the synthesis

(9) For molecular capsules formed by metal-ion coordination, see: (a) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature* **1995**, *378*, 469–471. (b) Jacopozi, P.; Dalcanales, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613–615. (c) Olenyuk, B.; Fechtenkötter, A.; Stang, P. J. *J. Chem. Soc., Dalton. Trans.* **1998**, 1707–1728.

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(17) (a) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363–1366. (b) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913–1916.

(18) Polyakov, V. A.; Nelen, M. I.; Nazarpak-Kandlousy, N.; Ryabov, A. D.; Eliseev, A. V. *J. Phys. Org. Chem.* **1999**, *12*, 357–363.

of **C₂B₄** in the presence of a catalytic amount of TFA to afford **C₂A₄** as a pale yellow solid in 45% yield after silica gel chromatography.

Following addition of 4 equiv of MPD²² to 1 equiv of **C₂A₄** in CDCl₃,²³ ¹H NMR spectroscopy indicates (Figure 3) that imine exchange takes place with time in such a

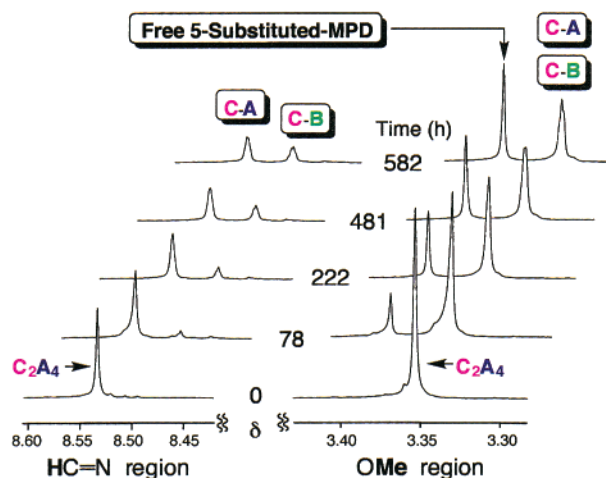


Figure 3. Partial ¹H NMR spectra (400 MHz, CDCl₃, 300 K) recorded with time. The exchange of **A** for **B** reaches an equilibrium after 582 h in which some or all of the species shown in Figure 5 are present. The boxed descriptors refer to signals arising from methoxy and imine protons in the bridging units **A** and **B** in the hemicarcerands **C₂A₄–nB_n**.

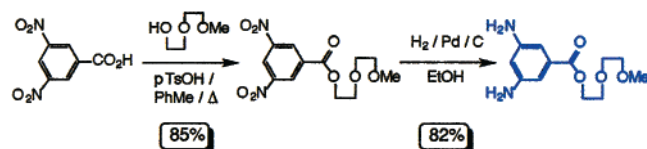
manner that **A** bridging units in **C₂A₄** are replaced by **B** bridging units.²⁴ Initially, peaks for **C₂A₄** are observed at δ 3.36 and 8.53 for the methoxy and imine protons, respectively. After some hours, additional peaks appear centered on δ 3.39 (well-resolved) and 8.49 (broad) for methoxy (in free released 5-substituted-MPD) and imine (in hemicarcerands containing **B** bridging units) protons, respectively.

It should be noted that the peaks at δ 3.36 and 8.53 also become progressively broadened with time, reflecting the

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(21) A solution of 3,5-dinitrobenzoic acid in PhMe was heated under reflux with diethylene glycol methyl ether in the presence of a catalytic amount of *p*-TsOH. The ester was isolated in 85% yield. Subsequent reduction (H₂ over Pd/C in EtOH) of the nitro groups in the ester gave (82%) the 5-substituted-MPD.



(22) The final concentration of **C₂A₄** in CDCl₃ was always maintained at 3 mM. All samples were sealed and monitored for their proton signals on a 400 MHz NMR spectrometer at 300 K.

(23) The CDCl₃ employed in all the ¹H NMR experiments was stored over K₂CO₃ for 24 h prior to its use.

(24) No indication of diimine exchange was detected by ¹H NMR spectroscopy when simple anilines, such as *p*-toluidine and 3,5-di-*tert*-butylaniline, were added to CDCl₃ solutions of **C₂A₄**.

fact that they arise from the multicomponent mixture of hemicarcerands shown in Figure 4. Indeed, a FAB mass

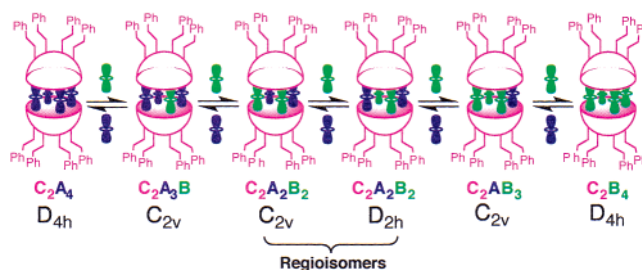


Figure 4. Equilibrium established between the different hemicarcerands in the series **C₂A_{4–n}B_n**, where $n = 0, 1, 2, 3$, or 4.

spectrum recorded on the equilibrated reaction mixture revealed peaks with m/z values of 2418, 2565, 2711, and 2859 for the hemicarcerands **C₂B₄**, **C₂AB₃**, **C₂A₂B₂** (two regioisomers presumably), and **C₂A₃B** with the relative intensities of 48, 79, 100, and 64, respectively.

To account for these experimental observations, we propose a mechanism that involves the stepwise opening of diimine bridging units as a result of imine exchange with the free diamines present in solution. The first step from **C₂A₄** to **C₂A₃B** in this proposed mechanism is shown in Figure 5.

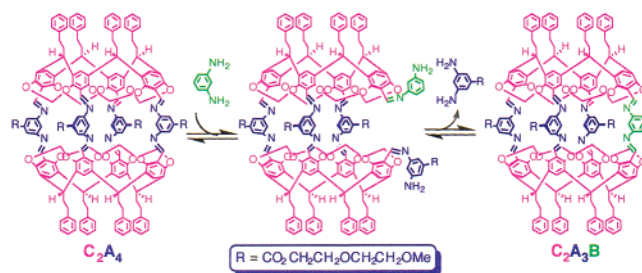


Figure 5. The first step in the proposed imine exchange mechanism that allows **C₂A₄** to be converted into **C₂A₃B**, **C₂A₂B₂** (two regioisomers), **C₂AB₃**, and **C₂B₄**.

To obtain evidence for such a “bar-opening/bar-closing” mechanism, we decided to explore if it is operational during the decomplexation of a hemicarceplex to give a hemicarcerand and its previously imprisoned guest. To carry out this experiment, we selected the known¹⁹ hemicarceplex **C₂B₄⊙Fc** because (1) its decomplexation using a gating mechanism has been studied previously,¹⁹ (2) its pentyl feet enhance its solubility in CDCl₃, and (3) the ferrocene (**Fc**) proton resonances, when both complexed and uncomplexed, appear as sharp singlets in ¹H NMR spectra at δ 3.66 and 4.16, respectively. Moreover, the **Fc** resonance peaks do not overlap with any signals arising from the hemicarcerand or hemicarceplex. Previously, one of us reported¹⁹ that the half-

life for the escape of **Fc** from **C₂B₄⊙Fc** is 19.6 h at 112 °C in C₂D₂Cl₄ while Kaifer et al.²⁰ report a *t*_{1/2} of >300 h in CD₂Cl₂ at 25 °C.

In the present investigation, we have observed (Table 1)

Table 1. A Comparison of the Effects of Different Amounts of MPD and TFA (1%, v/v, in CDCl₃) on the Half-Life (*t*_{1/2}) of Escape of **Fc** from **C₂B₄⊙Fc** at Room Temperature in CDCl₃

entry	equiv of C₂B₄⊙Fc	equiv of MPD	TFA (μL)	<i>t</i> _{1/2} (h)
1	1	0	0	>4000
2	1	0	4	1500
3	1	0	8	1400
4	1	4	4	380
5	1	8	4	330
6	1	4	8	180

a half-life of >4000 h (entry 1) for the decomplexation of **C₂B₄⊙Fc** in CDCl₃ at room temperature in a sealed NMR tube. When 4 μL (entry 2) and 8 μL (entry 3) of 1% TFA (v/v) in CDCl₃ were added to the **C₂B₄⊙Fc** solution, the half-life for the decomplexation dropped to 1500 and 1400 h, respectively. These *t*_{1/2} values emerge from a treatment of the reaction which assumes a mechanism whereby a single bar is opened as a result of the hydrolysis of one of the eight imine bonds present in the hemicarceplex. A full kinetic treatment of the data using Dynafit²⁵ suggest that the hydrolysis step is rate-limiting. When 4 equiv of MPD and 4 μL of TFA are present in the reaction mixture, a synergistic effect comes into play and *t*_{1/2} falls down (entry 4) to 380 h. When the amount of MPD is doubled to 8 equiv, then a further small decrease in the half-life (*t*_{1/2} = 330 h) is observed (entry 5). Finally, when the amount of acid is doubled to 8 μL, the half-life of **C₂B₄⊙Fc** drops (entry 6) to 180 h. Once again, a full kinetic treatment of these data established that the “bar-opening” step, as illustrated in the graphical abstract, is rate-determining. It follows that the release of **Fc** from **C₂B₄⊙Fc** occurs fastest in the presence of an excess of MPD and an acid catalyst.

If we consider **C₂B₄⊙Fc** to be a four-bar gate, then the likelihood of more than one bar on the gate being dislodged at any one time ready for its possible replacement becomes

more and more, and yet more, remote in relation to the other three bars. It follows that the hemicarceplex can be converted into the hemicarcerand without any serious risk of the two cavitands parting company.

In the case of a single bar-opening mechanism, at least three different processes can be identified. One involves the simple hydrolysis of one of the imine bonds in **C₂B₄⊙Fc** with hydronium ions to produce a formyl derivative which can either revert back to the hemicarceplex or release the guest **Fc** to give the hemicarcerand. In this case, the half-life of **C₂B₄⊙Fc** will depend on the concentration of the hydronium ion, i.e., the amount of adventitious water which is inevitably present in the reaction mixture. When MPD is also present, the formyl derivative will be converted into an intermediate, similar to that illustrated in Figure 5. Yet another process would involve direct imine exchange between **C₂B₄⊙Fc** and MPD to give the bis(*m*-aminoanilidene) intermediate. If this direct process is slower than the hydrolysis-followed-by-imine-exchange process, then the small decrease in the half-life of **C₂B₄⊙Fc** with an increasing concentration of MPD or TFA is not unexpected.

In summary, reversible imine exchange and/or reversible imine hydrolysis make it possible for the diimine bridges (**B**) in the hemicarceplex **C₂B₄⊙Fc** to open and close *essentially one at a time*, allowing the guest (**Fc**) to escape and hence produce the hemicarcerand **C₂B₄**. Reversible imine exchange also provides a means whereby unsubstituted and substituted *m*-phenylenediamine (**A** and **B**) bridging units can replace each other *essentially one at a time* in the hemicarcerands **C₂A₄** and **C₂B₄**. These observations demonstrate the power of dynamic chemistry—i.e., the stepwise breaking and remaking of dynamic covalent bonds—(1) to convert a hemicarceplex into a hemicarcerand and (2) to modify the constitution of a hemicarcerand without either the hemicarceplex or hemicarcerand falling apart into its component cavitands in the process.

Acknowledgment. We are grateful to the NIH and UCLA for generous financial support.

Supporting Information Available: Experimental procedures, ¹H and ¹³C NMR spectroscopic and FAB mass spectrometric data for 5-substituted-MPD and hemicarcerand **C₂A₄**, and kinetic curves fitted for liberation of ferrocene from hemicarceplex **C₂B₄**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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