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Dynamic Hemicarcerands and Hemicarceplexes

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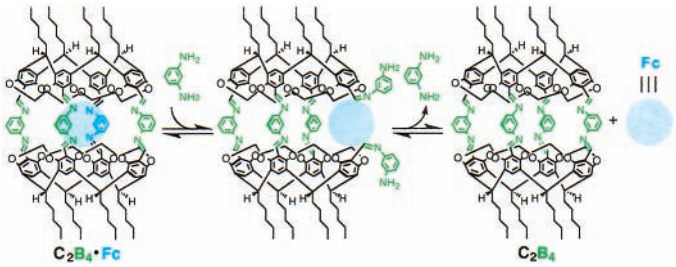
ABSTRACT



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 hemicarcerand 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 C_2B_4⊙Fc dissolved in $CDCl_3$ to give the hemicarcerand C_2B_4 when excess of both MPD and trifluoroacetic acid are present.

In 1991, one of us[1] reported a new class of container molecule[2] called *hemicarcerands*. 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 hemicarcerands 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 ($\Delta G^{\ddagger}_{d}$) of decomplexation.

According to computational studies carried out subsequently by Houk,[5] the ingression of guests into hemicarcerands 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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(1) (a) Cram, D. J.; Cram, J. M. In *Container Molecules and Their Guests*; Stoddart, J. F., Ed.; RSC: Cambridge, 1994; pp 149−216 and references therein.

(2) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967 and references therein.

(3) Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7765−7773.

(4) The concept of *constrictive binding* as it relates to hemicarceplexes and their hemicarcerands 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.

(5) Houk, K. N.; Nakamura, K.; Sheu, C.; Keating, A. E. *Science* **1996**, *273*, 627−629.

(6) Wang, X.; Houk, K. N. *Org. Lett.* **1999**, *1*, 591−594.

(7) (a) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647−1668. (b) de Mendoza, J. *Chem. Eur. J.* **1998**, *4*, 1373−1377. (c) Rebek, J., Jr. *Acc. Chem. Res.* **1999**, *32*, 278−286.

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mechanisms have also been invoked[6] 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 octaimines and (2) provides a "bar-opening/bar-closing" mechanism whereby ferrocene (**Fc**), entrapped in a hemicarceplex octaimine, can escape imprisonment from behind the diimine bars.

Previously, one[19] of us has described how the hemicarcerand octaimine $\mathbf{C_2B_4}$ 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

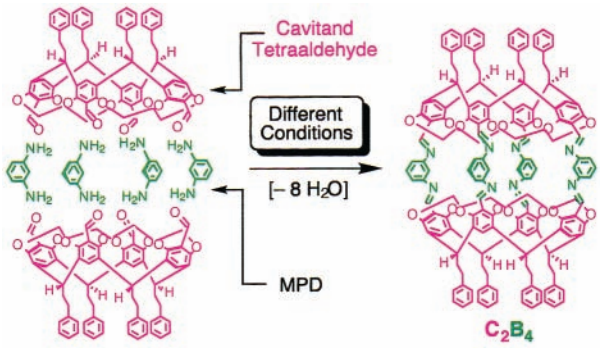


Figure 1. The preparation of hemicarcerand $\mathbf{C_2B_4}$ by eight successive imine condensations between two molecules of the cavitand tetraaldehyde with four molecules of MPD.

C_5H_5N at ~65 °C for 4 days. On the other hand, Kaifer et al.[20] have isolated $\mathbf{C_2B_4}$ 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 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), ^{1}H NMR spectroscopy indicated a near-quantitative conversion of the reactants to $\mathbf{C_2B_4}$ 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 $\mathbf{C_2B_4}$. Unfortunately, however, the hemicarcerand octaimine, with phenethyl feet and *m*-phenylenediimine (**B**) bridging units, is not soluble in the millimolar concentration range in $CDCl_3$, making detailed ^{1}H 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 ^{1}H NMR probe can be introduced (Figure 2) into

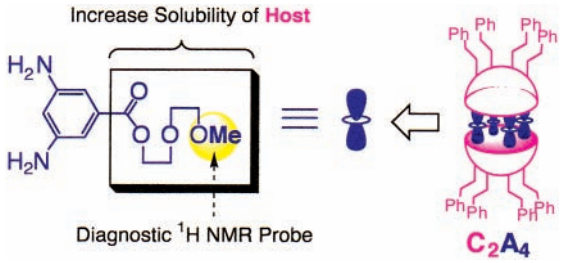


Figure 2. The 5-substituted-MPD employed in the synthesis of the hemicarcerand $\mathbf{C_2A_4}$ portrayed as a graphical representation.

the 5-substituent on **B** to give **A**. The 5-substituted-MPD (**A**), which was prepared[21] 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

(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.

(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) Jacopozzi, P.; Dalcanale, 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.

(10) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455−2463.

(11) (a) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101−1103. (b) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599−1600.

(12) Davies, A. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 591−594.

(13) Comina, P. J.; Philp, D.; Kariuki, B. M.; Harris, K. D. M. *Chem. Commun.* **1999**, 2279−2280.

(14) Tam-Chang, S.-W.; Stehouwer, J. S.; Hao, J. *J. Org. Chem.* **1999**, *64*, 334−335.

(15) (a) Rowan, S. J.; Sanders, J. K. M. *Chem. Commun.* **1997**, 1407−1408. (b) Brady, P. A.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3237−3253. (c) Rowan, S. J.; Reynolds, D. J.; Sanders, J. K. M. *J. Org. Chem.* **1999**, *64*, 5804−5814.

(16) Cousins, G. R. L.; Poulsen, S.-A.; Sanders, J. K. M. *Chem. Commun.* **1999**, 1575−1576.

(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.; Nazarpack-Kandlousy, N.; Ryabov, A. D.; Eliseev, A. V. *J. Phys. Org. Chem.* **1999**, *12*, 357−363.

of $\mathbf{C_2B_4}$ in the presence of a catalytic amount of TFA to afford $\mathbf{C_2A_4}$ as a pale yellow solid in 45% yield after silica gel chromatography.

Following addition of 4 equiv of MPD[22] to 1 equiv of $\mathbf{C_2A_4}$ in $CDCl_3$,[23] ^{1}H NMR spectroscopy indicates (Figure 3) that imine exchange takes place with time in such a manner that **A** bridging units in $\mathbf{C_2A_4}$ are replaced by **B** bridging units.[24] Initially, peaks for $\mathbf{C_2A_4}$ 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.

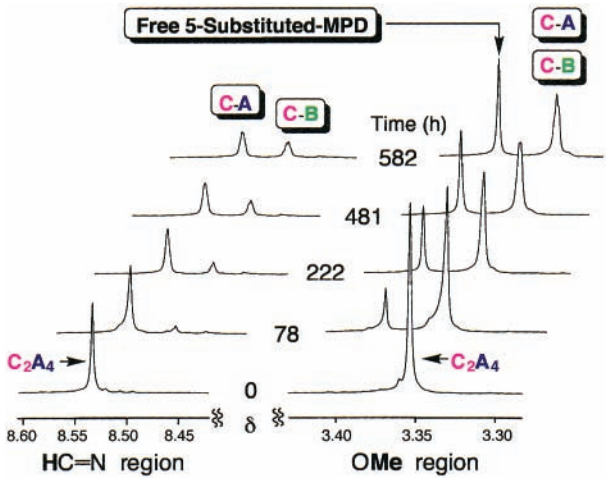


Figure 3. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) recorded with time. The exchange of **A** for **B** reaches an equilibrium after 582 h in which some or all of the species shown in Figure 5 are present. The boxed descriptors refer to signals arising from methoxy and imine protons in the bridging units **A** and **B** in the hemicarcerands $\mathbf{C_2A_{4-n}B_n}$.

It should be noted that the peaks at δ 3.36 and 8.53 also become progressively broadened with time, reflecting the fact that they arise from the multicomponent mixture of hemicarcerands shown in Figure 4. Indeed, a FAB mass spectrum recorded on the equilibrated reaction mixture revealed peaks with *m*/*z* values of 2418, 2565, 2711, and 2859 for the hemicarcerands $\mathbf{C_2B_4}$, $\mathbf{C_2AB_3}$, $\mathbf{C_2A_2B_2}$ (two regioisomers presumably), and $\mathbf{C_2A_3B}$ with the relative intensities of 48, 79, 100, and 64, respectively.

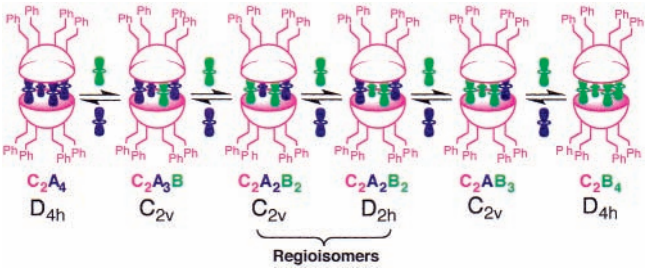


Figure 4. Equilibrium established between the different hemicarcerands in the series $\mathbf{C_2A_{4-n}B_n}$, where $n = 0$, 1, 2, 3, or 4.

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 $\mathbf{C_2A_4}$ to $\mathbf{C_2A_3B}$ in this proposed mechanism is shown in Figure 5.

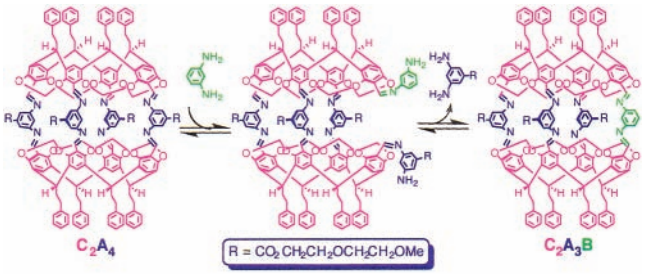


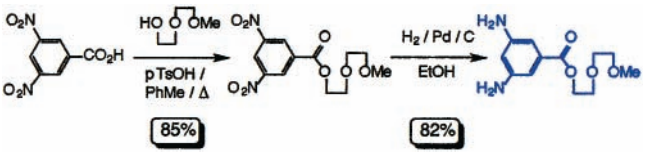
Figure 5. The first step in the proposed imine exchange mechanism that allows $\mathbf{C_2A_4}$ to be converted into $\mathbf{C_2A_3B}$, $\mathbf{C_2A_2B_2}$ (two regioisomers), $\mathbf{C_2AB_3}$, and $\mathbf{C_2B_4}$.

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 known[19] hemicarceplex $\mathbf{C_2B_4}\odot\mathbf{Fc}$ because (1) its decomplexation using a gating mechanism has been studied previously,[19] (2) its pentyl feet enhance its solubility in $CDCl_3$, and (3) the ferrocene (**Fc**) proton resonances, when both complexed and uncomplexed, appear as sharp singlets in ^{1}H 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 reported[19] that the half-

(19) Quan, M. L.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2754−2755.

(20) Mendoza, S.; Davidov, P. D.; Kaifer, A. E. *Chem. Eur. J.* **1998**, *4*, 864−870.

(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 (H_2 over Pd/C in EtOH) of the nitro groups in the ester gave (82%) the 5-substituted-MPD.



(22) The final concentration of $\mathbf{C_2A_4}$ in $CDCl_3$ 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 $CDCl_3$ employed in all the ^{1}H NMR experiments was stored over K_2CO_3 for 24 h prior to its use.

(24) No indication of diimine exchange was detected by ^{1}H NMR spectroscopy when simple anilines, such as *p*-toluidine and 3,5-di-*tert*-butylaniline, were added to $CDCl_3$ solutions of $\mathbf{C_2A_4}$.

life for the escape of **Fc** from C_2B_4⊙**Fc** is 19.6 h at 112 °C in $C_2D_2Cl_4$ while Kaifer et al.[20] report a $t_{1/2}$ of >300 h in CD_2Cl_2 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 $CDCl_3$) on the Half-Life ($t_{1/2}$) of Escape of **Fc** from C_2B_4⊙**Fc** at Room Temperature in $CDCl_3$

entry	equiv of C_2B_4⊙**Fc**	equiv of MPD	TFA (μL)	$t_{1/2}$ (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 C_2B_4⊙**Fc** in $CDCl_3$ at room temperature in a sealed NMR tube. When 4 μL (entry 2) and 8 μL (entry 3) of 1% TFA (v/v) in $CDCl_3$ were added to the C_2B_4⊙**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 Dynafit[25] 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 C_2B_4⊙**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 C_2B_4⊙**Fc** occurs fastest in the presence of an excess of MPD and an acid catalyst.

If we consider C_2B_4⊙**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 C_2B_4⊙**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 C_2B_4⊙**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 C_2B_4⊙**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 C_2B_4⊙**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 C_2B_4⊙**Fc** to open and close *essentially one at a time*, allowing the guest (**Fc**) to escape and hence produce the hemicarcerand C_2B_4. 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 C_2A_4 and C_2B_4. 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, ^{1}H and ^{13}C NMR spectroscopic and FAB mass spectrometric data for 5-substituted-MPD and hemicarcerand C_2A_4, and kinetic curves fitted for liberation of ferrocene from hemicarceplex C_2B_4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Kuzmic, P. *Anal. Biochem.* **1996**, *237*, 260−273.