The complex **2** was also synthesized electrolytically. The compound hat-$(CN)_6$ was reduced in acetone at -0.3 V (vs. SCE) in a 100 mL electrolysis cell, in which $(n\mathrm{Bu}_4\mathrm{N})\mathrm{PF}_6$ was used as the supporting electrolyte. The resultant green solution was added to a solution of $[\mathrm{Cu}(\mathrm{CH}_3\mathrm{CN})_4]\mathrm{PF}_6$ and dppe in acetone. The product corresponded to that obtained from the direct mixing of hat-$(CN)_6$, $[\mathrm{Cu}(\mathrm{CH}_3\mathrm{CN})_4]\mathrm{PF}_6$, and dppe.

Received: August 17, 1998
Revised version January 4, 1999 [Z12291IE]
German version: *Angew. Chem.* **1999**, *111*, 980 – 983

Keywords: copper · crystal engineering · host – guest chemistry · NMR spectroscopy · radicals

[1] J.-M. Lehn *Supramoleculer Chemistry*, VCH, Weinheim, **1995**.
[2] a) P. Baxter, J.-M. Lehn, A. DeCian, J. Fischer, *Angew. Chem.* **1993**, *105*, 92; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 69 – 71; b) V. J. Catalano, W. E. Larson, M. M. Olmstead, H. B. Gray, *Inorg. Chem.* **1994**, *33*, 4502 – 4509; c) T. J. Rutherford, O. Van Gijte, A. Kirsch-De Mesmaeker, F. R. Keene, *Inorg. Chem.* **1997**, *36*, 4465 – 4474; d) C. Moucheron, A. Kirsch-De Mesmaeker, *J. Am. Chem. Soc.* **1996**, *118*, 12834 – 12835; e) F. R. Keene, *Chem. Soc. Rev.* **1998**, *27*, 185 – 193.
[3] The data collections for **1** and **2** were made on a Rigaku RAXIS-IV imaging plate area detector with graphite monochromatic $\mathrm{Mo}_{\mathrm{K}\alpha}$ radiation. The data for **1** and **2** were collected at a temperature of $-30\,^{\circ}\mathrm{C}$ to a maximum 2θ value of 51.4 and 51.3°, respectively. A total of 12 and 14 oscillation images (6.00°) were collected, each being exposed for 8.0 and 18.0 min, respectively. A total of 9858 and 9073 reflections, respectively, were collected. The linear absorption coefficients, μ, for $\mathrm{Mo}_{\mathrm{K}\alpha}$ radiation are 7.4 and 8.0 cm^{-1}, respectively. The data were corrected for Lorentz and polarization effects. Crystal data for **1**: $\mathrm{C}_{106}\mathrm{H}_{88}\mathrm{N}_{12}\mathrm{Cu}_3\mathrm{S}_2\mathrm{O}_8\mathrm{F}_6\mathrm{P}_6$, M_{r}=2212.53, orthorhombic, space group $P2_12_12_1$, $a=24.545(3)$, $b=26.687(1)$, $c=16.0793(8)$ Å, $V=10532(1)$ Å^3, $Z=4$, $\rho_{\mathrm{calcd}}=1.395$ g cm^{-3}, $T=-30\,^{\circ}\mathrm{C}$, $2\theta_{\mathrm{max}}=51.4^{\circ}$, $R=0.073$, $R_{\mathrm{w}}=0.071$. Crystal data for **2**: $\mathrm{C}_{104}\mathrm{H}_{88}\mathrm{N}_{12}\mathrm{Cu}_3\mathrm{F}_{12}\mathrm{O}_2\mathrm{P}_8$, $M_{\mathrm{r}}=2204.33$, monoclinic, space group $C2/c$, $a=28.552(2)$, $b=15.777(4)$, $c=25.298(2)$ Å, $\beta=95.006(7)^{\circ}$, $V=11352(1)$ Å^3, $Z=4$, $\rho_{\mathrm{calcd}}=1.290$ g cm^{-3}, $T=-30\,^{\circ}\mathrm{C}$, $2\theta_{\mathrm{max}}=51.3^{\circ}$, $R=0.093$, $R_{\mathrm{w}}=0.135$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-107042 (**1**) and 107044 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[4] a) S. Ernst, P. Hänel, J. Jordanov, W. Kaim, V. Kasack, E. Roth, *J. Am. Chem. Soc.* **1989**, *111*, 1733 – 1738; b) W. Kaim, S. Kohlmann, *Inorg. Chem.* **1986**, *25*, 3442 – 3448; c) W. Kaim, S. Ernst, S. Kohlmann, P. Welkerling, *Chem. Phys. Lett.* **1985**, *118*, 431 – 434.
[5] K. Unoura, A. Iwase, H. Ogino, *J. Electroanal. Chem.* **1990**, *295*, 385 – 392.
[6] D. L. Caulder, R. E. Powers, T. N. Parac, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1940 – 1943; *Angew. Chem. Int. Ed.* **1998**, *37*, 1840 – 1843.
[7] a) A. Bianchi, K. Bowman-James, A. Garcia-España, *Supramolecular Chemistry of Anions*, VCH, New York, **1997**; b) P. D. Beer, D. Hesek, J. E. Kingston, D. K. Smith, S. E. Stokes, M. G. B. Drew, *Organometallics* **1995**, *14*, 3288; c) P. D. Beer, A. R. Graydon, A. O. M. Johnson, D. K. Smith, *Inorg. Chem.* **1997**, *36*, 2112 – 2118; d) K. T. Holman, M. M. Halihan, S. S. Jurisson, J. L. Atwood, R. S. Burkhalter, A. R. Mitchell, J. W. Steed, *J. Am. Chem. Soc.* **1996**, *118*, 9567 – 9576; e) S. Kitagawa, M. Kondo, S. Kawata, S. Wada, M. Maekawa, M. Munakata, *Inorg. Chem.* **1995**, *34*, 1455 – 1465; f) J. S. Fleming, K. L. V. Mann, C.-A. Carraz, E. Psillakis, J. C. Jeffery, J. A. McCleverty, M. D. Ward, *Angew. Chem.* **1998**, *110*, 1315 – 1318; *Angew. Chem. Int. Ed.* **1998**, *37*, 1279 – 1281.
[8] a) G. N. LaMar, J. W. D. Horrocks, R. H. Holm, *NMR of Paramagnetic Molecules*, Academic Press, New York, **1973**; b) I. Bertini, C. Luchinat, *NMR of Paramagnetic Molecules in Biological Systems*, The Benjamin/Cummings Publishing Company, Menlo Park, **1986**.
[9] The pseudo-contact term; $\delta_{\mathrm{pseudo\text{-}con}}$ is represented by Equation (1), where β, k, and S have the usual meaning, while R is a distance between a paramagnetic center and the observed nucleus, and θ is an angle between the molecular principal axis and the R vector. The R value was calculated to be 3.31 Å by using the slope of a linear plot of the observed chemical shift for PF_6^- against T^{-1}, and the anisotropic g values obtained from the ESR spectrum at 5.4 K.

$$\delta_{\mathrm{pseudo\text{-}con}}=\beta^2S(S+1)/9kTR^3(1-3\cos^2\theta)\,(g_{\parallel}^2-g_{\perp}^2) \qquad (1)$$

[10] Similar trapping behavior ($\delta=-133.3$ at room temperature) for the PF_6^- ion was observed in benzene, while the anion release occurs in acetone, in which relatively sharp signals centered at $\delta=-143.6$, close to that of free PF_6^-, were observed.
[11] a) J. T. Rademacher, K. Kanakarajan, A. W. Czarnik, *Synthesis* **1994**, 378 – 379; b) K. Kanakarajan, A. W. Czarnik, *J. Heterocycl. Chem.* **1988**, *25*, 1869 – 1870; c) J. C. Beeson, L. J. Fitzgerald, J. C. Gallucci, R. E. Gerkin, J. T. Rademacher, A. W. Czarnik, *J. Am. Chem. Soc.* **1994**, *116*, 4621 – 4622.
[12] This reagent was purchased from Aldrich Chemical Co.
[13] a) P. Hemmerich, C. Sigwart, *Experientia* **1963**, *15*, 448; b) G. Kubas, *Inorg. Synth.* **1979**, *19*, 90.

Noncovalent Assembly of a Fifteen-Component Hydrogen-Bonded Nanostructure

Katrina A. Jolliffe, Peter Timmerman,* and David N. Reinhoudt*

The design and synthesis of molecules that contain all the necessary information to organize themselves spontaneously into well-defined finite nanostructures provides one of the most important challenges in supramolecular chemistry.[1, 2] Strong coordinative and much weaker hydrogen bonds are possible interactions that can drive the assembly process. The reversible formation of helicates,[3, 4] grids,[5] cages,[6, 7] metallodendrimers,[8] or hydrogen-bonded rosettes,[9, 10] capsules,[11] spheres,[12] dendrimers,[13, 14] polymers,[15] and other architectures[16, 17] has been realized over the past decade. The major difficulty in this area is to control the assembly process whilst increasing the structural complexity of the assembly.[18–20]

We have previously reported the formation of assembly $\mathbf{1}_3\cdot(\mathrm{DEB})_6$ (DEB = 5,5-diethylbarbituric acid) that is held together by 36 hydrogen bonds.[21] We are currently investigating the formation of supramolecular libraries of noncovalent assemblies,[22] with the long-term objective of this work being to develop self-assembled nanostructures with binding properties that mimic those of natural antibodies.[23] Therefore, we have now investigated the assembly of tetramelamine derivatives **2**, in which two calix[4]arene units are covalently connected through a flexible linker X, with four equivalents of DEB. Variation of the size and chemical nature of the connector unit X creates chemical diversity in the resulting

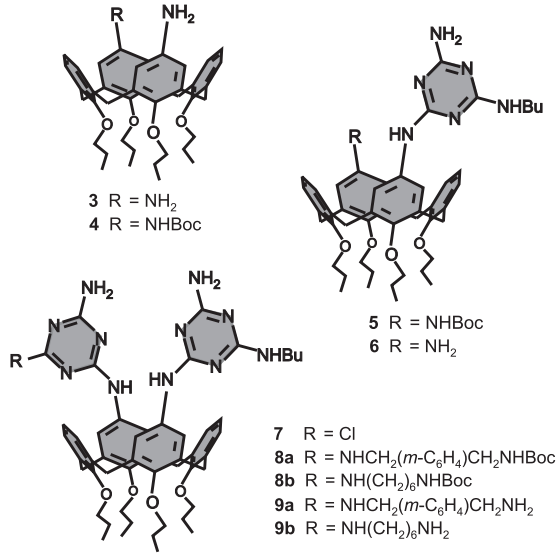
[*] Dr. P. Timmerman, Prof. Dr. Ir. D. N. Reinhoudt, Dr. K. A. Jolliffe
Laboratory of Supramolecular Chemistry and Technology
University of Twente
P.O. Box 217, NL-7500 AE Enschede (The Netherlands)
Fax: (+31) 53-489-4645
E-mail: smct@ct.utwente.nl

  1433-7851/99/3807-0933 $ 17.50+.50/0

cavities. Guest binding can be optimized in these cavities by using chemical evolution.[24]

Herein we report the first generation of such noncovalent assemblies $\mathbf{2}_3\cdot(\mathrm{DEB})_{12}$ that consist of 15 different components and are held together by 72 hydrogen bonds (Figure 1). The assemblies were fully characterized by 1D and 2D ^{1}H NMR spectroscopy and matrix-assisted laser-desorption time-of-flight (MALDI-TOF) mass spectrometry by using our recently developed Ag^+-labeling technique.[25]

The syntheses of the tetramelamine derivatives **2** were completed in ten steps starting from diamine **3**. Mono protection of **3** with *tert*-butylcarbamate (Boc) gives **4**, and subsequent reaction with cyanuric chloride, NH_3, and *n*-butylamine gives triazine **5**. Removal of the Boc group followed by another reaction with cyanuric chloride and NH_3 affords chlorotriazine **7**, which is converted into either **8a** or **8b** by reaction with mono-Boc protected *m*-xylylenediamine (**8a**) or mono-Boc protected 1,6-hexylenediamine (**8b**). Finally, removal of the Boc groups and reaction with an equimolar amount of **7** gives both tetramelamines **2a** and **2b** in overall yields of 26% and 32%, respectively.



The tetramelamines **2a** and **2b** form well-defined assemblies $\mathbf{2}_3\cdot(\mathrm{DEB})_{12}$ in the presence of four equivalents of DEB in $CDCl_3$. The ^{1}H NMR titration of both tetramelamines with DEB proves the 1:4 stoichiometry of the assemblies. At a ratio of **2**:DEB = 1:4 all the tetramelamine resonances are absent and the spectra exclusively exhibit signals for assemblies $\mathbf{2}_3\cdot(\mathrm{DEB})_{12}$ (Figure 2). Four singlets of equal intensity are observed for assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ at $\delta = 14.01$, 13.83, 13.42, and 12.86, which pairwise represent the C(O)NHC(O) protons (four different types, total of 24) of the various "floors" of the assembly (see Figure 1). Two singlets at $\delta =$ 8.40 and 8.25 correspond to the twelve ArN*H*Ar protons and resonances at $\delta = 7.67$ and 7.32 correspond to the aliphatic and benzylic N*H* protons, respectively. The addition of excess DEB does not change the ^{1}H NMR spectrum of the assembly, except for the additional broad signal at $\delta \approx 9$ that corresponds to free DEB (Figure 3).

Tetramelamine **2a** exhibits a characteristic difference in assembly behavior compared to bismelamines **1**.[26] Whereas assembly of bismelamines **1** with DEB displays positive cooperativity, the formation of assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ shows negative cooperativity.[27] At a ratio of **2a**:DEB < 1:3 the ^{1}H NMR spectrum mainly exhibits broad resonances, which is

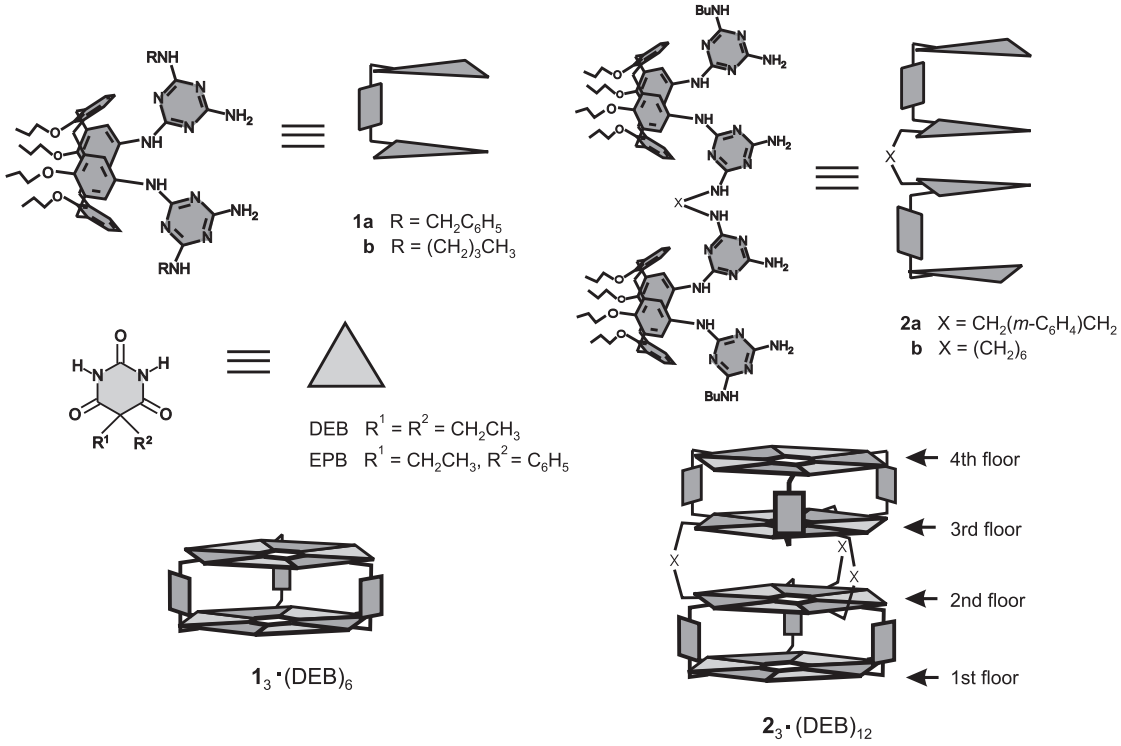


Figure 1. Schematic representation of the aggregates $\mathbf{1}_3\cdot(\mathrm{DEB})_{12}$ and $\mathbf{2}_3\cdot(\mathrm{DEB})_{12}$.

  1433-7851/99/3807-0934 $ 17.50+.50/0

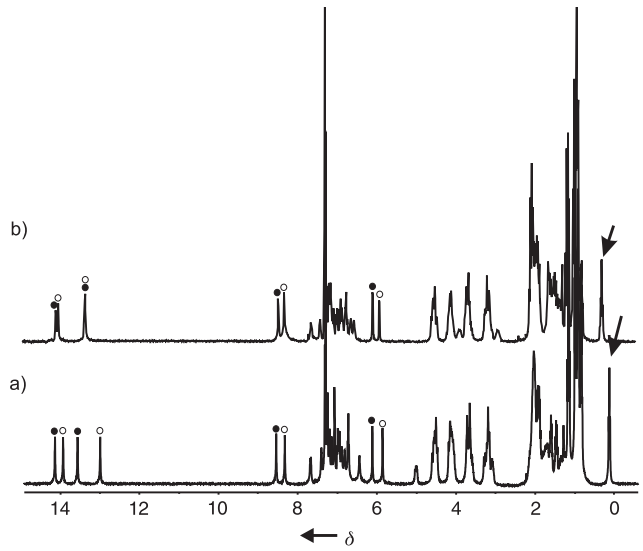


Figure 2. ^{1}H NMR spectra (400 MHz) of assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ (a) and assembly $\mathbf{2b}_3\cdot(\mathrm{DEB})_{12}$ (b) in $CDCl_3$ at room temperature. ● indicates first and fourth floor resonances, ○ indicates second and third floor resonances; the arrows on the right mark half of the DEB methyl resonances on the second and third floor.

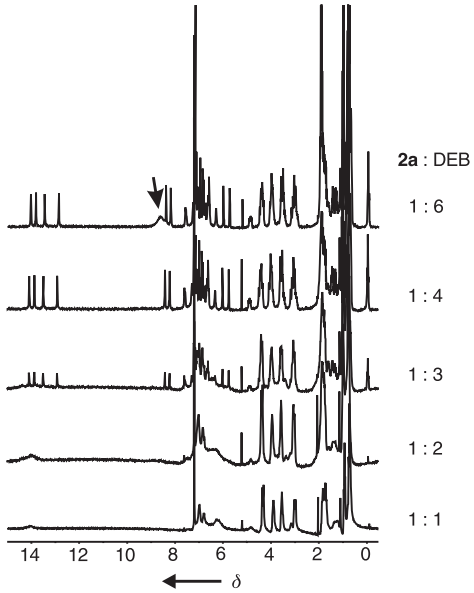


Figure 3. ^{1}H NMR titration of tetramelamine **2a** with DEB in $CDCl_3$ at room temperature. The arrow in the upper spectrum marks the resonance corresponding to the unbound DEB.

indicative of the formation of a nondefined assembly (Figure 3). Only at a ratio of **2a**:DEB > 1:3 does the assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ start to form. This negative cooperativity leads to a lower stability of $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ than expected from the melting point index $I_{\mathrm{Tm}} = \mathrm{HB}/(N-1)$ for hydrogen-bonded aggregates, where HB = number of particles in the aggregate.[28] This index predicts an increased stability for assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ (5.1) relative to $\mathbf{1}_3\cdot(\mathrm{DEB})_6$ (4.5). However, experiments in which assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ was mixed with either bismelamine **1a** or **1b** clearly show that the stability order is reversed. In both cases only assembly $\mathbf{1}_3\cdot(\mathrm{DEB})_6$ is formed at the expense of $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$. The reduced stability of $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ is most probably related to the inward curvature of the two rosette planes as observed in the X-ray crystal structure of assembly $\mathbf{1}_3\cdot(\mathrm{DEB})_6$ (interplanar distance is 3.2 Å in the center and 3.5 Å at the outside).[21] Formation of the second double rosette in assembly $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ may therefore be much less favorable because of incomplete filling of the space in between the two double rosettes.

Interestingly, both $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$ and $\mathbf{2b}_3\cdot(\mathrm{DEB})_{12}$ assemble stereoselectively in one of the two possible (sss and ses)

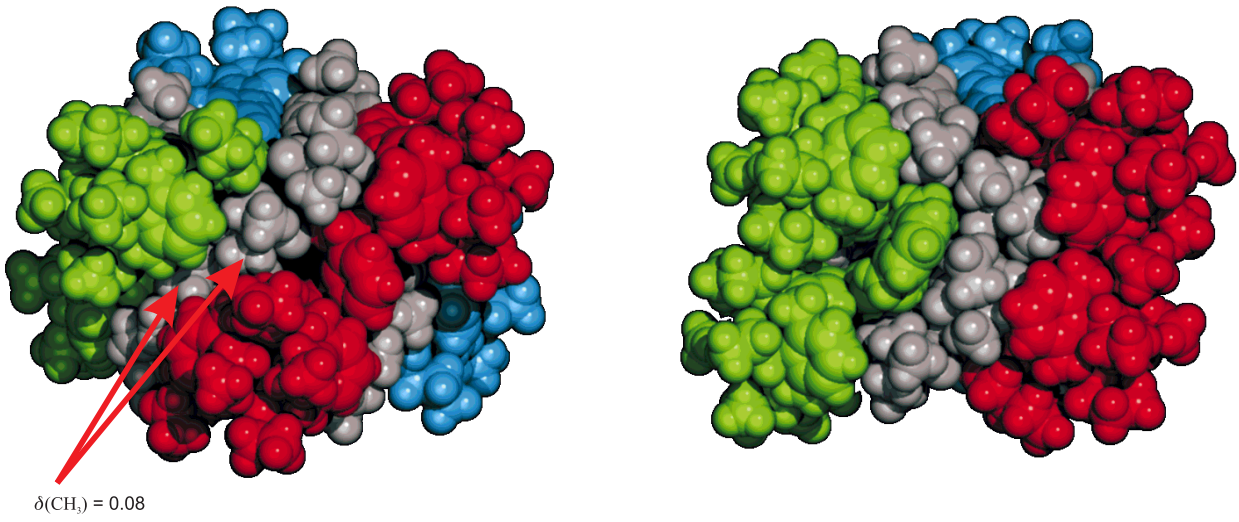


Figure 4. Energy-minimized structures (Quanta/CHARMm 3.3) of the sss (I) and the ses (II) diastereoisomeric forms of $\mathbf{2a}_3\cdot(\mathrm{DEB})_{12}$.

  1433-7851/99/3807-0935 $ 17.50+.50/0

diastereomeric forms,[29, 30] as indicated by the presence of one single set of proton signals for both assemblies. Evidence as to which of the two diastereomers is formed comes from the presence of the strongly upfield-shifted resonance at $\delta = 0.08$ ($\mathbf{2a}_3 \cdot (\mathrm{DEB})_{12}$) or $\delta = 0.25$ ($\mathbf{2b}_3 \cdot (\mathrm{DEB})_{12}$), which represents half of the methyl groups of DEB (namely, 18H) that are located in the two middle floors of the assembly. Gas-phase MM calculations (Quanta/CHARMm 3.3)[31] show that in the sss isomer half of the methyl protons on the second floor point right into the face of one of the calix[4]arene aromatic rings on the third floor (Figure 4), which causes the upfield shift. The same type of interaction is not possible in the corresponding ses isomer as the same aromatic rings are much more remote.

The hydrogen-bonded nanostructures were also characterized by MALDI-TOF mass spectrometry using Ag^+-labeling.[25] 5-Ethyl-5-phenylbarbituric acid (EPB) was used for this purpose instead of DEB because of the lack of a binding site for the Ag^+ ion in the assemblies with DEB. Samples prepared by mixing assemblies $\mathbf{2a}_3 \cdot (\mathrm{EPB})_{12}$ and $\mathbf{2b}_3 \cdot (\mathrm{EPB})_{12}$ with 1.5 equivalents of $AgCF_3COO$ in $CHCl_3$ show intense signals at $m/z = 8585.2$ (calcd for $C_{468}H_{546}N_{96}O_{60} \cdot {}^{107}Ag^+ = 8583.1$) and at $m/z = 8525.3$ (calcd for $C_{462}H_{558}N_{96}O_{60} \cdot {}^{107}Ag^+ = 8523.1$), respectively, for the corresponding monovalent Ag^+ complexes (Figure 5). Signals corresponding to

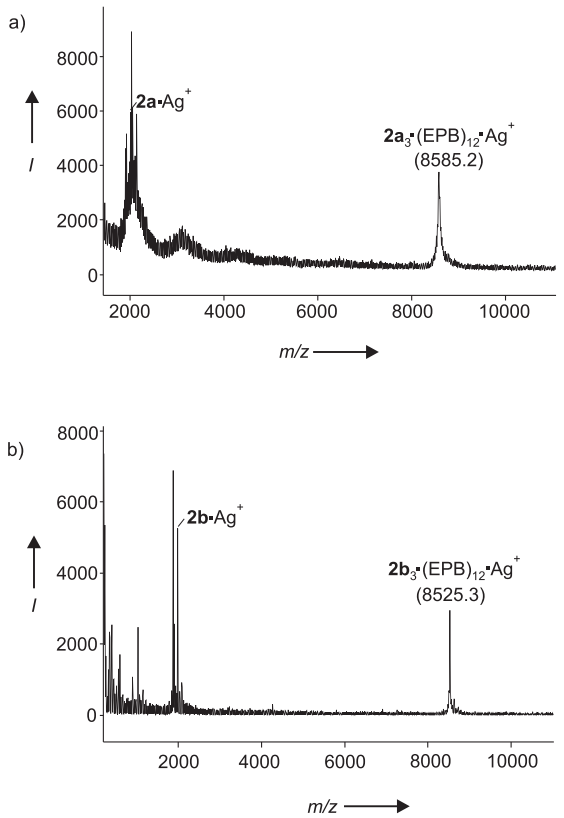


Figure 5. MALDI-TOF mass spectra of the Ag^+ complexes of assembly $\mathbf{2a}_3 \cdot (\mathrm{EPB})_{12}$ (a) and assembly $\mathbf{2b}_3 \cdot (\mathrm{EPB})_{12}$ (b). Matrix = 2,5-dihydroxybenzoic acid.

more highly charged or fragmented Ag-complexed assemblies were not observed.

Both tetramelamines **2** and bismelamines **1** show a high degree of self sorting.[32] Mixtures of **2a** and **1a**, in a ratio of 1:2, with a slight excess of DEB exclusively show the formation of the homomeric assemblies $\mathbf{2a}_3 \cdot (\mathrm{DEB})_{12}$ and $\mathbf{1a}_3 \cdot (\mathrm{DEB})_6$. Formation of heteromeric assemblies $\mathbf{2a}_2 \cdot \mathbf{1a}_2 \cdot (\mathrm{DEB})_{12}$ and $\mathbf{2a} \cdot \mathbf{1a}_4 \cdot (\mathrm{DEB})_{12}$ are not observed. Similar results were obtained for tetramelamine **2b**. Self sorting has been observed before in dynamic covalent libraries of macrocycles[32] and in metal-coordinated helicates.[33, 34]

When equal amounts of **2a** and **2b** were mixed with DEB the formation of heteromeric assemblies containing both tetramelamines was observed. This indicates that supramolecular library formation with different tetramelamines is indeed possible. The second generation of assemblies with specific binding sites in the connector unit X, such as metalloporphyrins, is currently under investigation.

Received: October 15, 1998 [Z12514IE]
German version: *Angew. Chem.* **1999**, *111*, 983 – 986

Keywords: hydrogen bonds · nanostructures · noncovalent interactions · supramolecular chemistry

[1] J.-M. Lehn, *Supramolecular Chemistry, Concepts and Perspectives*, VCH, Weinheim, **1995**.
[2] G. M. Whitesides, J. P. Mathias, C. T. Seto, *Science* **1991**, *254*, 1312 – 1319.
[3] U. Koert, M. M. Harding, J.-M. Lehn, *Nature* **1990**, *346*, 339 – 342.
[4] C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005 – 2062.
[5] G. S. Hanan, D. Volkmer, U. S. Schubert, J.-M. Lehn, G. Baum, D. Fenske, *Angew. Chem.* **1997**, *109*, 1929 – 1931; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1842 – 1844.
[6] M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, *378*, 469 – 471.
[7] P. Jacopozzi, E. Dalcanale, *Angew. Chem.* **1997**, *109*, 665 – 669; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 613 – 615.
[8] W. T. S. Huck, F. C. J. M. Van Veggel, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1304 – 1306; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1213 – 1215.
[9] a) G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen, D. M. Gordon, *Acc. Chem. Res.* **1995**, *28*, 37 – 44; b) M. Mascal, N. M. Hecht, R. Warmuth, M. H. Moore, J. P. Turkenburg, *Angew. Chem.* **1996**, *108*, 2348 – 2350; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2204 – 2206; c) A. Marsh, M. Silvestri, J.-M. Lehn, *Chem. Commun.* **1996**, 1527 – 1528; d) S. V. Kolotuchin, S. C. Zimmerman, *J. Am. Chem. Soc.* **1998**, *120*, 9092 – 9093.
[10] A. Zafar, J. Yang, S. J. Geib, A. D. Hamilton, *Tetrahedron Lett.* **1996**, *37*, 2327 – 2330.
[11] M. M. Conn, J. Rebek Jr., *Chem. Rev.* **1997**, *97*, 1647 – 1668.
[12] J. L. Atwood, L. R. MacGillivray, *Nature* **1997**, *389*, 469 – 472.
[13] S. C. Zimmerman, F. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science* **1996**, *271*, 1095 – 1098.
[14] W. T. S. Huck, R. Hulst, P. Timmerman, F. C. J. M. Van Veggel, D. N. Reinhoudt, *Angew. Chem.* **1997**, *109*, 1046 – 1049; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1006 – 1008.
[15] R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe, E. W. Meijer, *Science* **1997**, *278*, 1601 – 1604.
[16] M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee, N. Khazanovich, *Nature* **1993**, *366*, 324 – 327.
[17] R. W. Saalfrank, I. Bernt, E. Uller, F. Hampel, *Angew. Chem.* **1997**, *109*, 2596 – 2599; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2482 – 2485.
[18] J. P. Mathias, E. E. Simanek, C. T. Seto, G. M. Whitesides, *Angew. Chem.* **1993**, *105*, 1848 – 1851; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1766 – 1769.
[19] D. P. Funeria, J.-M. Lehn, G. Baum, D. Fenske, *Chem. Eur. J.* **1997**, *3*, 99 – 104.

  1433-7851/99/3807-0936 $ 17.50+.50/0

[20] M. Fujita, S.-Y. Yu, T. Kusukawa, H. Funaki, K. Ogura, K. Yamaguchi, *Angew. Chem.* **1998**, *110*, 2192 – 2196; *Angew. Chem. Int. Ed.* **1998**, *37*, 2082 – 2085.
[21] P. Timmerman, R. H. Vreekamp, R. Hulst, W. Verboom, D. N. Reinhoudt, K. Rissanen, K. A. Udachin, J. Ripmeester, *Chem. Eur. J.* **1997**, *3*, 1823 – 1832.
[22] M. Crego Calama, R. Fokkens, N. M. M. Nibbering, P. Timmerman, D. N. Reinhoudt, *Chem. Commun.* **1998**, 1021 – 1022.
[23] P. Timmerman, D. N. Reinhoudt, *Adv. Mater.* **1999**, *11*, 71 – 74.
[24] A. V. Eliseev, M. I. Nelen, *Chem. Eur. J.* **1998**, *4*, 825 – 834.
[25] K. A. Jolliffe, M. Crego Calama, R. Fokkens, N. M. M. Nibbering, P. Timmerman, D. N. Reinhoudt, *Angew. Chem.* **1998**, *110*, 1294 – 1297; *Angew. Chem. Int. Ed.* **1998**, *37*, 1247 – 1251.
[26] R. H. Vreekamp, J. P. M. Van Duynhoven, M. Hubert, W. Verboom, D. N. Reinhoudt, *Angew. Chem.* **1996**, *108*, 1306 – 1309; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1215 – 1218.
[27] Positive cooperativity in assemblies $\mathbf{1}_3 \cdot (\mathrm{DEB})_6$ means that formation of the first rosette strongly favors formation of the second rosette. Evidence for this comes from ^{1}H NMR spectra recorded on samples with **1**:DEB < 1:2, which exclusively exhibit resonances for free **1** and assembly $\mathbf{1}_3 \cdot (\mathrm{DEB})_6$ and none for any intermediate species. Negative cooperativity in assembly $\mathbf{2a}_3 \cdot (\mathrm{DEB})_{12}$ means that formation of the first double rosette disfavors formation of the second double rosette.
[28] M. Mammen, E. E. Simanek, G. M. Whitesides, *J. Am. Chem. Soc.* **1996**, *118*, 12614 – 12623.
[29] We adopt the staggered/eclipsed nomenclature to describe the relative orientation of the melamines in the different floors.[30] We refer to the various isomeric assemblies as diastereoisomers rather than as conformers, since their interconversion involves the disruption of (hydrogen) bonds. Eight possible diastereomeric assemblies can be formed, but because of the strong preference for a staggered orientation in assembly $\mathbf{1}_3 \cdot (\mathrm{DEB})_6$[21] we expect only the D_3-symmetric, all-staggered (sss) and the C_{3h}-symmetric, staggered-eclipsed-staggered (ses) diastereomers to be formed. The sss diastereomer is present as a racemic mixture of two enantiomers (we adopt the M/P descriptors to describe these), whereas the ses diastereomer is achiral.
[30] J. P. Mathias, E. E. Simanek, G. M. Whitesides, *J. Am. Chem. Soc.* **1994**, *116*, 4326 – 4340.
[31] The strong preference for formation of the sss isomer was confirmed by these studies, which calculate an energy difference of about 5 kcal mol^{-1} between the two diastereomers.
[32] S. J. Rowan, D. G. Hamilton, P. A. Brady, J. K. M. Sanders, *J. Am. Chem. Soc.* **1997**, 2578 – 2579.
[33] R. Kramer, J.-M. Lehn, A. Marquis-Rigualt, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5394 – 5398.
[34] D. L. Caulder, K. N. Raymond, *Angew. Chem.* **1997**, *109*, 1508 – 1510; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1440 – 1442.

Discovery of Novel Catalysts for Alkene Epoxidation from Metal-Binding Combinatorial Libraries**

Matthew B. Francis and Eric N. Jacobsen*

The quest for practical routes to chiral intermediates has inspired extensive research activity in the field of asymmetric catalysis, which has resulted in the development of numerous useful, highly enantioselective reactions. The vast majority of effective catalysts discovered thus far are metal complexes bearing specific ligands that direct the outcome of the catalytic reaction through control of the steric and electronic properties of the metal center. While progress has been made in elucidating the nature of these interactions, the identification of this finely tuned match between the metal ion and its coordination environment remains difficult and continues to limit the pace of reaction discovery.

Research directed toward the development of new systems for asymmetric catalysis can be divided into two phases. In the initial lead discovery phase effort is directed toward screening a wide variety of metal complexes with the goal of identifying a novel catalyst system for the reaction of interest. This is typically followed by a lead optimization stage wherein a highly enantioselective and reactive system is sought through systematic variation of the ligand components and reaction conditions. In the latter context, combinatorial chemistry has already emerged as a powerful tool: useful chiral catalysts have been obtained through the synthesis and analysis of parallel libraries of structural analogues based on a previously identified design motif.[1] However, despite the utility of combinatorial chemistry for the efficient investigation of systems that involve numerous interrelated variables, the application of such strategies to catalyst lead discovery remains underexplored. We reported recently the application of metal-binding combinatorial libraries to the identification of coordination complexes.[2] Herein we describe the successful elaboration of this strategy to the discovery of novel catalyst leads for a reaction of synthetic interest, namely the asymmetric epoxidation of olefins with hydrogen peroxide.

Because of the extreme sensitivity of oxidation systems to the exact coordination environment around the metal center[3] an ideal library design for the discovery of epoxidation catalysts—and selective catalysts in general—should consist of the widest possible variety of metal ions bound by an assortment of ligands, providing diverse coordination environments. Our initial approach to such a library design is depicted in Scheme 1. The general structural motif involves

[*] Prof. E. N. Jacobsen, M. B. Francis
Department of Chemistry and Chemical Biology and
Institute of Chemistry and Cellular Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-496-1880
E-mail: jacobsen@chemistry.harvard.edu

[**] Financial support has been provided by the Harvard University Institute of Chemistry and Cellular Biology, Versicor, and ArQule. M.B.F. acknowledges the National Science Foundation for a predoctoral fellowship.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/99/3807-0937 $ 17.50+.50/0