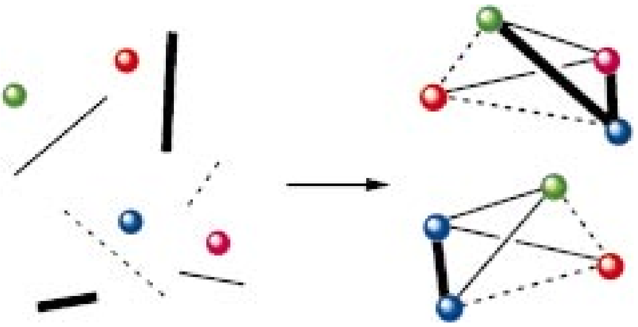
Combinatorial Libraries of Metal – Ligand Assemblies with an Encapsulated Guest Molecule**

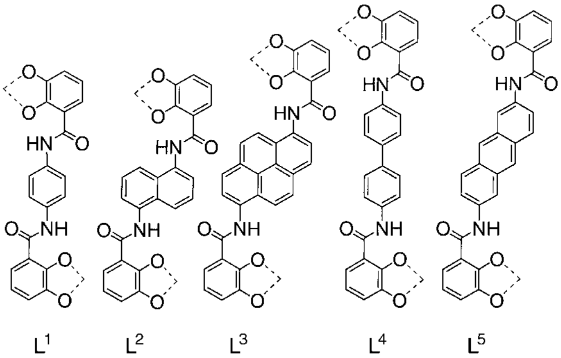
Marco Ziegler, J. J. Miranda, Ulla N. Andersen,
Darren W. Johnson, Julie A. Leary, and
Kenneth N. Raymond*

Remarkable self-assembled polyhedral structures of high symmetry are found in nature. In some cases, subunits are interchangeable and assemble in mixtures of different components to form a structure with higher functionality and complexity. For example, the multicatalytic protease complex in the archaebacterium *Thermoplasma acidophilum* consists of 14 identical protein subunits assembled in a cylindrical structure with D_7 symmetry,[1] whereas the proteasome in a higher organism, the yeast *Saccharomyces cerevisiae*, is made of pairs of seven different protein subunits assembled in a structure with C_7 symmetry.[2]

A number of synthetic coordination clusters of various sizes, stoichiometries, and symmetries has recently been described and reviewed.[3–5] We have shown that careful consideration of the geometric requirements of a particular symmetry and stoichiometry for a cluster leads to the controlled formation of M_4L_4 (T),[6] M_4L_6 (S_4 and T),[7, 8] M_6L_6 (D_3),[9] M_6L_8 (O), and M_8L_8 (D_{4d})[10] assemblies (with point symmetry noted). By combination of different subunits out of a pool of available ligands and metals, a large array of different assemblies (a library) can be obtained. Here we report the formation of libraries of tetrahedral M_4L_6 complexes (Scheme 1) and describe the synthesis and characterization of such assemblies made of combinations of various biscatecholate ligands (Scheme 2).[11] Each assembly is able to encapsulate a tetraalkylammonium cation as a guest in its cavity, as we have previously observed for the $Ga_4L^2_6$ coordination cluster.[8]



Scheme 1. A schematic representation of the generation of a supramolecular library consisting of 152496 possible tetrahedral M_4L_6 assemblies made from 10 different components with homoconfigurational metal centers.



Scheme 2. The biscatecholate ligands used in this study, which have varying linker units between the chelating groups.

The size of such a library increases rapidly with the number of different subunits used (Table 1). Including the possibility of having metal centers with Δ or Λ chirality, a total of 2488212 diasteromeric assemblies can theoretically be formed out of ten different subunits (six different ligands and four different metals) with a very broad probability distribution of species.[12] Ligand arrangements and statistical weights have been derived by using a computer program.[13]

Table 1. Number of different ligand combinations and total number of diastereomeric species formed for a homochiral M_4L_6 assembly made of different ligands L.

Number of different ligands *n*	Number of ligand combinations	Total number of diastereomers
1	1	1
2	7	12
3	28	87
4	84	416
5	210	1475
6	462	4236

We chose to start with the simplest case: a mixture of two different ligands (L^2 and L^3) and one metal cation (Ga^{III}). This gives rise to twelve diastereomeric assemblies with ligand arrangements shown in Figure 1. We found that many, if not all, possible combinations of ligands and different spatial arrangements of a given number of components are indeed present in solution, and that they do not interconvert on the NMR time scale. The individual components of the library were characterized by NMR spectroscopy (Figure 2a) and ESI-FTICR MS[14] (Figure 3). The encapsulated guest molecule (Et_4N^+) is an ideal NMR probe to distinguish the different isomers formed since the large upfield shift of the proton resonances of Et_4N^+, which is indicative of encapsulation,[8] is strongly dependent on the number and spatial arrangment of aromatic rings present in the assembly. ESI has previously proven useful for characterizing multiply charged

---

[*] Prof. K. N. Raymond, M. Ziegler, J. J. Miranda, U. N. Andersen,
D. W. Johnson, Prof. J. A. Leary
Department of Chemistry
University of California
Berkeley, CA 94720-1460 (USA)
Fax: (+1) 510-486-5283
E-mail: raymond@socrates.berkeley.edu

[**] Coordination Number Incommensurate Cluster Formation, Part 17. Financial support of this work was provided by NSF CHE-9709621 and a NATO-NSF exchange grant SRG 951516. We thank the Miller Foundation for a fellowship to M.Z. Part 16: R. M. Yeh, M. Ziegler, D. W. Johnson, A. J. Terpin, K. N. Raymond, *Inorg. Chem.* **2001**, in press.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

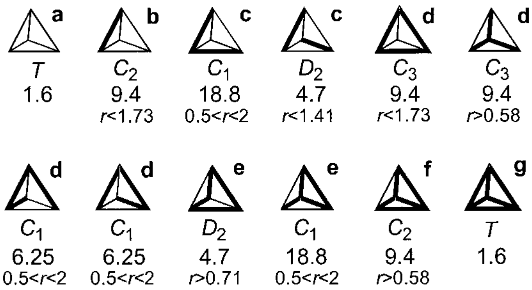


Figure 1. All possible arrangements (diastereomers) of two different ligands in a tetrahedral assembly with homoconfigurational metal centers. Isobaric species are labeled with the same letter. Underneath each species are noted 1) the point group symmetry, 2) the statistical weight (%) assuming a 1:1 ratio of ligands, and 3) the ratio r of lengths of the two ligands required to form the assembly.

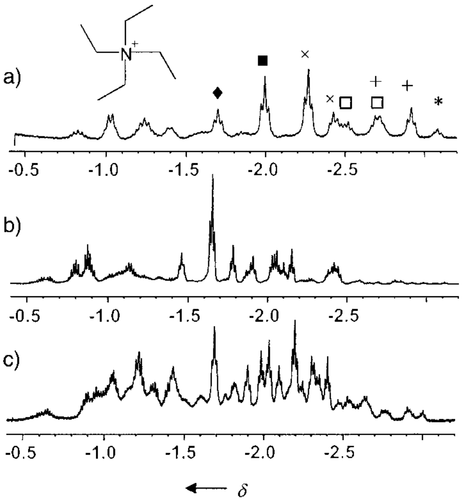


Figure 2. NMR spectra of encapsulated Et_4N^+ in libraries of $[Ga_4L_6 \supset Et_4N)]^{11-}$ complexes. The methyl resonances of various species are marked and assigned as follows: a) L^2:$L^3 = 2$:1 ◆ $Ga_4L^2_6$; ■ $Ga_4L^2_5L^3$; × $Ga_4L^2_4L^3_2$; □ $Ga_4L^2_3L^3_3$ (four diastereomers); + $Ga_4L^2_2L^3_4$ (two diastereomers); * $Ga_4L^2L^3_5$ b) L^1:L^2:$L^3 = 1$:4:1, c) L^1:L^2:L^3:$L^4 = 1$:4:1:1.

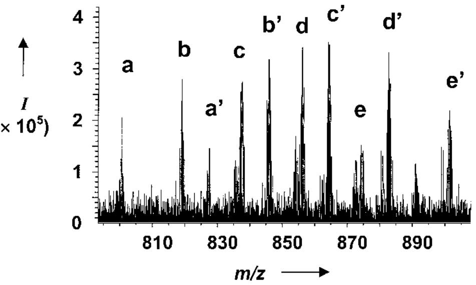


Figure 3. Electrospray ionization Fourier transform ion cyclotron resonance mass spectra (ESI-FTICR-MS) of a library formed with ligands L^2 and L^3 in 1:1 ratio: a: $[Ga_4L^2L^2_5 \supset (Et_4N)]Na_7{}^{4-}$; b: $[Ga_4L^2_2L^3_4 \supset (Et_4N)]Na_7{}^{4-}$; c: $[Ga_4L^2_3L^3_3(Et_4N)]Na_7{}^{4-}$; d: $[Ga_4L^2_4L^3_2 \supset (Et_4N)]Na_7{}^{4-}$; e) $[Ga_4L^2_5L^3 \supset (Et_4N)]Na_7{}^{4-}$. In the species denoted with prime, a sodium cation is exchanged by Et_4N^+. I = intensity in arbitrary units.

coordination compounds in solution.[15, 16] FTICR detection allowed us, for the first time, to analyze libraries of such negatively charged supramolecules with very high resolution and mass accuracy.

The binary library described above represents the true thermodynamic equilibrium: while boiling for several days no change in composition of the library was observed. Furthermore, when an aqueous solution of $[Ga_4L^2_6 \supset (Et_4N)]^{11-}$ and another solution containing $[Ga_4L^3_6 \supset (Et_4N)]^{11-}$ were mixed and heated for several hours at 60 °C the very same library formed. Time-dependent NMR studies of L^1/L^2, L^1/L^3, and L^2/L^3 mixtures revealed the kinetics of this process. The assignment of NMR peaks of newly appearing species was based on the assumption that ligands are exchanged stepwise and with equal probability for each ligand [Eqs. (1) and (2)].

$$A_nB_{6-n} \underset{k'}{\overset{k}{\rightleftharpoons}} A_nB_{5-n} + B \qquad (1)$$

$$A_nB_{6-n} \underset{k'}{\overset{k}{\rightleftharpoons}} A_{n-1}B_{6-n} + A \qquad (2)$$

We compared the actual concentration of species present with the concentration predicted by a first-order statistical model[17] for the ligand-exchange process and found that the experimental data were in good agreement with such a model. Figure 4 shows the measured data for a L^2/L^3 mixture and the calculated values according to the model with $k = 1.5(3) \times 10^{-4}\,s^{-1}$ (60 °C in D_2O solution, pD 7.5). Similar rates of $0.8(2) \times 10^{-4}\,s^{-1}$ and $0.6(3) \times 10^{-4}\,s^{-1}$ were obtained for the ligand-exchange process of L^1/L^2 and L^1/L^3 mixtures, respectively.

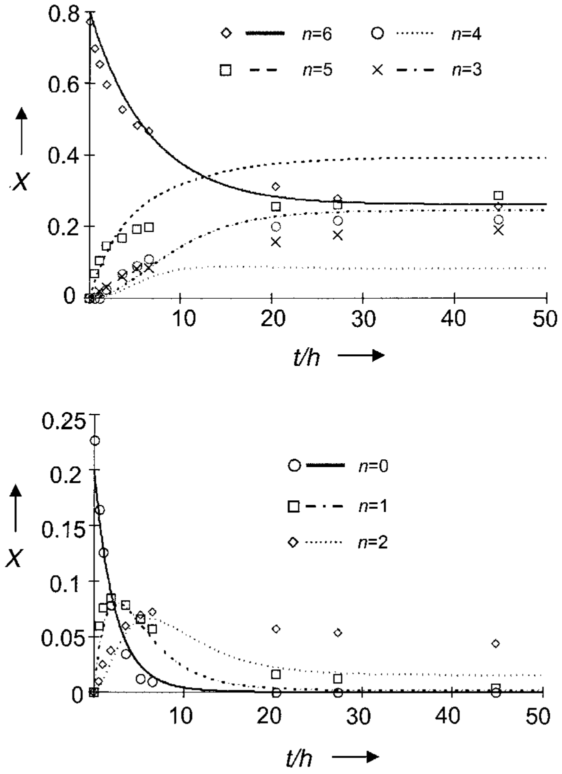


Figure 4. Time-dependent concentration of different species ($x = 1$ mole fraction) $[Ga_4L^2_nL^3_{6-n} \supset (Et_4N)]^{11-}$ as determined by NMR spectroscopy (points) and calculated according to a statistical model (lines) from a mixture containing pure $[Ga_4L^2_6 \supset (Et_4N)]^{11-}$ and $[Ga_4L^3_6 \supset (Et_4N)]^{11-}$ in a 4:1 ratio initially (D_2O solution at pD 7.5 at 60 °C).

Mixtures of ligands L^1/L^2, L^1/L^3, L^2/L^4, and L^3/L^4 formed very similar libraries. The ligands L^1 and L^4 incorporate into a tetrahedral assembly even though $[Ga_4L^1_6 \supset (Et_4N)]^{11-}$ or

$[Ga_4L^4_6 \supset (Et_4N)]^{11-}$ are not observed; these ligands prefer to form the corresponding entropically favored $[Ga_2L_3]^{6-}$ assemblies.[18] Interestingly, a library made of ligands L^2 and L^5 was kinetically stable at room temperature for several weeks, but thermodynamically unstable forming pure $[Ga_4L^2_6 \supset (Et_4N)]^{11-}$ and $[Ga_4L^5_6 \supset (Et_4N)]^{11-}$ complexes upon boiling in water or DMSO for several hours.

Using a mixture of ligands L^1, L^2, and L^3, 28 possible combinations of ligands and a total of 87 diastereomers can be formed (Table 1). NMR spectra show that a wide distribution of species is indeed obtained (Figure 2b), however, the complexity and number of isomers present does not allow unambiguous assignment of NMR peaks of the structures present. Figure 5 shows the mass spectral data of a library containing metal complexes of the composition $[Ga_4L^1_xL^2_yL^3_z \supset (Et_4N)]^{11-}$. The statistically most probable combinations for x, y, and z (Table 2) are observed.[19] A mass scale expanded segment (Figure 5) shows the spectrum of the $[Ga_4L^1L^2_4L^3E \supset (Et_4N)]Na_7^{4-}$ species, which deviates less than 10 ppm from the calculated isotope distribution. Since all combinations of ligands differ in their masses, the high resolution and high mass accuracy of the FTICR instrument makes it uniquely possible to assign the peaks in the spectrum and consequently provide exact information about the elemental composition of the ion cluster in question. Mixtures of four (Figure 2c) or more ligands gave libraries with a very large number of species, which we have not yet been able to fully characterize. Given research in the area of ESI of metal–ligand complexes which shows comparability between solid-, solution-, and gas-phase structures,[20–24] there is a precedent for the data described here. We find both stereochemical differentiation and metal-coordinated dendrimer composition in the gas phase that reflects the solution conformation as well as mass spectral data of single crystals which again reflect the isolated and purified product. Retention of solution-phase structure has been shown for metal ion bipyridine complexes[23] and various metal macrocycle complexes.[24] An error of 10 ppm for the mass spectral data is in excellent agreement with theory and although attachment of alkali metal ions is observed in the gas phase, there has been no evidence of ligand clustering. When combined with the NMR data, the overall structure, coordination number, and composition of the complexes are reliably determined.

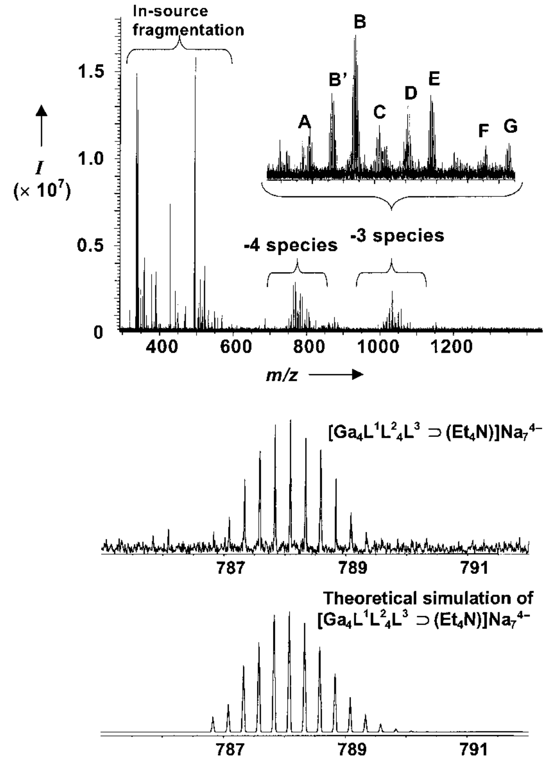


Figure 5. ESI-MS spectra of various $[Ga_4L^1_xL^2_yL^3_z \supset (Et_4N)]Na_{12}$ species where the ligands were mixed in the following initial ratio: L^1:L^2:L^3 = 1:4:1 (assignment according to Table 2).

Table 2. Statistically most abundant and experimentally observed masses in a single run of a 1:4:1 mixture of ligands L^1, L^2, and L^3 forming a library of $[Ga_4L^1_xL^2_yL^3_z \supset (Et_4N)]^{11-}$ complexes. All other possible species have calculated probabilities lower than 3% and have not been observed in the ESIMS spectra.

x	y	z	Probability [%]	Peaks assigned (Figure 5)
2	4	0	8.2	A
1	5	0	13.2	B (B′ with Na^+ exchanged by H^+)
2	3	1	8.2	C
0	6	0	8.8	D
1	4	1	13.2	E
0	5	1	13.2	F
1	3	2	8.2	G
0	4	2	8.2	not observed

A statistical distribution of compounds is also obtained when different metal cations, such as mixtures of In^{III}/Ga^{III} are used with the same ligand. Given the similarity in size and charge of the metals used, this is anticipated, but it underlines again the principle of obtaining a mixture of self-assembled compounds containing all possible combinations of subunits.

The term "virtual" dynamic combinatorial library[25] has been proposed for the formation of labile assemblies where out of many possible (virtual) structures only certain species form, which is the foundation for recognition associated with self-assembly processes. We demonstrate here that a "real" supramolecular dynamic combinatorial library with many assemblies simultaneously being present in solution is made from labile ligands and metals forming kinetically inert assemblies with an encapsulated guest molecule. The investigation of the kinetics and thermodynamics of self-assembly processes involving different subunits reveals insight into how diversity and complexity in molecular assemblies is achieved. We are currently investigating such libraries for screening of supramolecular hosts encapsulating small molecules.

Experimental Section

All NMR spectra were measured with a Bruker 500-MHz spectrometer. Chemical shifts are reported as in ppm downfield from tetramethylsilane (TMS). Mass spectral data were acquired using a Bruker ApexII 7 Tesla actively shielded FTICR mass spectrometer equipped with an Analytica electrospray source (off axis probe). Sample solutions were 300 pmol μL^{-1} in methanol with Na^+ as counterions. Hexapole storage time: 0.5 s; capillary exit voltage: 100 V.

Bis(bidentate) catecholamide ligands (Scheme 2) were synthesized according to previously published procedures.[26] Libraries were obtained following a simple procedure: H_4-L^2 (33.1 mg, 0.077 mmol), H_4-L^3 (39.0 mg, 0.077 mmol), Et_4NCl, (4.3 mg, 0.026 mmol), and $[Ga(acac)_3]$ (acac = acetylacetonate) (37.1 mg, 0.102 mmol) were suspended in methanol (20 mL). A 0.5 N NaOH solution (620 µL) in H_2O was added slowly, and a clear solution was obtained. After the mixture had been stirred for 2 h, the solvent was reduced to 4 mL, and excess acetone was added to precipitate the product, which was collected by ultracentrifugation, washed with acetone and dried (quantitative yields). The same library was obtained by mixing solutions of $[Ga_4L^2_6 \supset (Et_4N)]^{11-}$ and $[Ga_4L^3_6 \supset (Et_4N)]^{11-}$ at pD 7.5 after heating for several hours at 60 °C.

Received: October 2, 2000 [Z 15897]

---

[1] J. Lowe, D. Stock, R. Jap, P. Zwickl, W. Baumeister, R. Huber, *Science* **1995**, *268*, 533.

[2] M. Groll, L. Ditzel, J. Löwe, D. Stock, M. Bochtler, H. D. Bartunik, R. Huber, *Nature* **1997**, *386*, 463.

[3] M. Fujita, *Chem. Soc. Rev.* **1998**, *27*, 417.

[4] a) D. L. Caulder, K. N. Raymond, *J. Chem. Soc. Dalton Trans.* **1999**, 1185; b) D. L. Caulder, K. N. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975.

[5] S. Leininger, B. Olenyuk, P. J. Stang, *Chem. Rev.* **2000**, *100*, 853.

[6] C. Brückner, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1937; *Angew. Chem. Int. Ed.* **1998**, *37*, 1837.

[7] T. Beissel, R. E. Powers, T. N. Parac, K. N. Raymond, *J. Am. Chem. Soc.* **1999**, *121*, 4200.

[8] D. L. Caulder, R. E. Powers, T. N. Parac, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1940; *Angew. Chem. Int. Ed.* **1998**, *37*, 1840.

[9] D. W. Johnson, J. Xu, R. W. Saalfrank, K. N. Raymond, *Angew. Chem.* **1999**, *111*, 3058; *Angew. Chem. Int. Ed.* **1999**, *38*, 2882.

[10] J. Xu, K. N. Raymond, *Angew. Chem.* **2000**, *39*, 2745; *Angew. Chem. Int. Ed.* **2000**, *112*, 2857.

[11] A combinatorial library of hydrogen-bonded tetramers was recently characterized by ESIMS: F. Hof, C. Nuckolls, J. Rebek, Jr., *J. Am. Chem. Soc.* **2000**, *122*, 4251.

[12] Six ligands with four metals can give 16710 different arrangements for a total of 152496 diastereomers. If the possibility of heteroconfigurational metal centers is considered, 2488212 possible diastereomers can be formed: 152496 for $\Delta\Delta\Delta\Delta/\Lambda\Lambda\Lambda\Lambda$ (T), 840420 for $\Delta\Delta\Lambda\Lambda$ (S_4), and 1495296 for $\Delta\Delta\Delta\Lambda/\Lambda\Lambda\Lambda\Delta$ (C_3). With six different ligands in equimolar amounts and one metal cation, 4236 homoconfigurational diastereomers can be formed, out of which 3590 each has a probability of 0.02572 % to form, 540 form with a probability of 0.01286 %, and all others (106) have an abundance of 0.006 % or below. For the $\Delta\Delta\Lambda\Lambda$ assemblies, out of 12006 possible diastereomers, 11340 (94.5 %) have a probability (0.0086 %) to be formed; for the $\Delta\Lambda\Lambda\Lambda$ assemblies, out of 15576 diastereomers, 15540 have an abundance of 0.00643 % each.

[13] A pool of k different components can form n-assemblies in k^n different ways. The invariance under all symmetry transformations of the point group of the n assembly can be used to sort out identical structures in order to draw and calculate the statistical weight of all n assemblies.

[14] M. G. Marshall, C. L. Hendrickson, G. S. Jackson, *Mass Spectrom. Rev.* **1998**, *17*, 1.

[15] S. Konig, C. Brückner, K. N. Raymond, J. A. Leary, *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1099.

[16] G. Hopfgartner, F. Vilbois, C. Piguet, *Rapid Commun. Mass Spectrom.* **1999**, *13*, 302.

[17] In this model with ligands A and B, we assume that the rate-limiting step is the dissociation of a ligand and that the dissociation rate k ($k \ll k'$) is identical for both ligands. The probability of incorporating a ligand is then proportional to the molar fraction of A (denoted a) and B (denoted b) in the solution. a and b are constant and equal to the molar fraction of total A and B initially present. The equilibrium can then be expressed in terms of the linear differential equations [Eqs. (3)–(8)], which are used to trace the concentration curves (Figure 4)

$$\frac{d}{dt}[A_6] = k\left[-b[A_6] + \frac{1}{6}a[A_5B]\right] \tag{3}$$

$$\frac{d}{dt}[A_5B] = k\left[\frac{1}{3}a[A_4B_2] + b[A_6] - \left(\frac{5}{6}b + \frac{1}{6}a\right)[A_5B]\right] \tag{4}$$

$$\frac{d}{dt}[A_3B_3] = k\left[\frac{2}{3}a[A_2B_4] + \frac{2}{3}b[A_4\mathrm{B}_2] - \left(\frac{1}{2}b + \frac{1}{2}a\right)[A_3B_3]\right] \tag{5}$$

$$\frac{d}{dt}[A_4B_2] = k\left[\frac{5}{6}a[A_3B_5] + \frac{1}{2}b[A_3\mathrm{B}_3] - \left(\frac{1}{3}b + \frac{2}{3}a\right)[A_2B_4]\right] \tag{6}$$

$$\frac{d}{dt}[AB_5] = k\left[a[B_6] + \frac{1}{3}b[A_2\mathrm{B}_4] - \left(\frac{1}{6}b + \frac{1}{6}a\right)[AB_5]\right] \tag{7}$$

$$\frac{d}{dt}[B_6] = k\left[-a[B_6] + \frac{1}{6}b[AB_5]\right] \tag{8}$$

[18] D. L. Caulder, K. N. Raymond, *Angew. Chem.* **1997**, *109*, 1508; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1439.

[19] We did not observe the $y = 4$, $z = 2$ combination, even though we had detected this species in the binary mixture previously.

[20] S. P. Gaucher, J. A. Leary, *Anal. Chem.* **1998**, *70*, 3009.

[21] J. Kriesel, S. Koenig, M. Freitas, A. Marshall, J. A. Leary, T. D. Tilley, *J. Am. Chem. Soc.* **1998**, *120*, 12207.

[22] U. N. Andersen, S. Koenig, M. A. Freitas, A. G. Marshall, J. A. Leary, *J. Am. Soc. Mass Spectrom.* **1998**, *10*, 352.

[23] T. D. Burns, T. G. Spence, M. A. Mooney, L. A. Posey, *Chem. Phys. Lett.* **1996**, *258*, 669.

[24] K. Wang, G. W. Gokel, *J. Org. Chem.* **1996**, *61*, 4693.

[25] J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455.

[26] T. N. Parac, D. L. Caulder, K. N. Raymond, *J. Am. Chem. Soc.* **1998**, *120*, 8003.

Shape Selectivity in Hydrocarbon Conversion[**]

Merijn Schenk, Berend Smit,* Thijs J. H. Vlugt, and Theo L. M. Maesen

Molecular sieves with three-dimensional framework structures find many applications in catalysis.[1, 2] A comprehensive and fundamental understanding of the product selectivity associated with these catalytic processes remains a formidable challenge of considerable practical significance.[3] Herein we focus on conversion reactions of alkanes. We demonstrate that molecular sieves favor the formation of reaction intermediates that have a shape commensurate with their pore shape.

---

[*] Prof. Dr. B. Smit, M. Schenk, Dr. T. J. H. Vlugt
Department of Chemical Engineering
Universiteit van Amsterdam
Nieuwe Achtergracht 166, 1018 WV Amsterdam (The Netherlands)
Fax: (+31) 20-525-5604
E-mail: smit@its.chem.uva.nl

Dr. T. L. M. Maesen
Zeolyst International, PQ R&D Center
Conshohocken, PA 19428-2240 (USA)

[**] These investigations were supported in part by the Netherlands Research Council for Chemical Sciences (CW) with financial aid from the Netherlands Technology Foundation and by the Netherlands Organization for Scientific Research (NWO) through PIONIER. We would like to thank Christa Roemkens, Rob van Veen, Henk Schenk, Daan Frenkel, David Dubbeldam, and Marcello Rigutto for their comments on our manuscript.

1433-7851/01/4004-0736 $ 17.50+.50/0