Self-Assembled Hydrogen-Bonded Dimeric Capsules with High Kinetic Stability**

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Calix[4]arenes substituted at their wide rim by four urea functions (general formula **3**) exist as hydrogen-bonded dimers[1, 2] in apolar solvents in the presence of a suitable guest, which is included in the molecular cavity thus formed (Figure 1). Although these capsules[3] are kinetically stable on the NMR time scale, their dissociation/recombination occurs within seconds. Rate constants of $k = 0.26\ s^{-1}$ for the dissociation/recombination process and $k = 0.47\ s^{-1}$ for the guest (benzene) exchange were determined in benzene by EXSY spectroscopy[4] for the dimer of a tetra-urea similar to **3a**, but less symmetric due to alternating methyl and pentyl ether groups. We were interested whether the (kinetic) stability of such capsules can be increased by structural modifications. This could be achieved, for instance, by additional attractive forces between the two calixarenes combined in the dimer, or by increasing the energy barrier for the dissociation process by steric hindrance (repulsive forces). We therefore synthesized the sterically crowded tetra-urea derivatives **3b–e** (Scheme 1) and we report herein their ability to form hydrogen-bonded dimers including the first detailed measurements of the rate of their guest exchange.[5, 6]

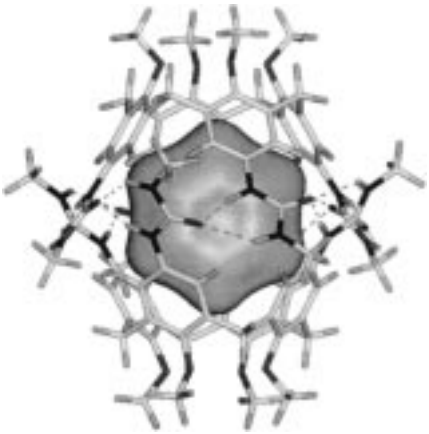
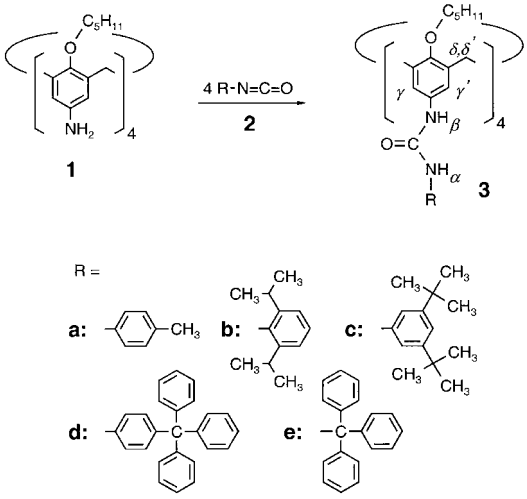


Figure 1. Tetra-urea dimer **3**/**3** with included benzene.



Scheme 1. Synthesis of the tetra-urea calixarene **3**.

Compounds **3** were synthesized by reaction of the corresponding isocyanate **2** with the tetraaminocalix[4]arene **1** (Scheme 1). The isocyanates used were commercially available (**2a, 2b**), or prepared from trityl chloride and potassium cyanate (**2e**),[7] or from the respective aniline and triphosgene (**2c, 2d**)[8] and used in situ. The structure of the tetra-ureas **3** follows unambiguously from their ^1H and ^{13}C NMR spectra in [D$_6$]DMSO where they exist in the monomeric form. It was further confirmed by elemental analysis and by mass spectra.

Homo- and heterodimerization of tetra-ureas **3a–e** was studied by ^1H NMR spectroscopy in [D$_6$]benzene, a solvent known also to be an excellent guest for the dimer (Table 1). It became apparent that the steric strain produced by R makes the formation of dimers with all partners impossible for **3b**, while **3e** forms no heterodimers with **3c** and no homodimers. Thus, for example, the ^1H NMR spectrum of **3e** (Figure 2a) shows only very broad signals, while a typical homodimer such as **3a**/**3a** or **3d**/**3d** (Figure 2b) shows well-defined, sharp signals among which especially the low-field-shifted NH signal at $\delta = 9.9$ is characteristic for the hydrogen-bonded R-NH groups in the dimer. Remarkably a 1:1 mixture of **3d** and **3e** shows (nearly) exclusively the presence of the heterodimers **3d**/**3e** (Figure 2c), easily identified by two pairs of doublets for the Ar-CH$_2$-Ar protons.[9] Evidently this situation, in which *all* urea groups are "saturated" by intermolecular hydrogen bonds is favored over a situation in which the molecules **3e** are unpaired, while **3d** forms (possibly more perfect) dimers.

Table 1. Dimerization of tetra-ureas **3a–e**.[a]

Compound	**3a**	**3b**	**3c**	**3d**	**3e**
3a	+	0[b]	50[c]	39[c]	78[b]
3b	–	–	0[b]	0[b]	0
3c	+	–	+	31[c]	0[b]
3d	+	–	+	+	95[b]
3e	+	–	–	+	–

[a] For each pair the formation of dimers is indicated by +. Additionally, the amount of heterodimers present in a 1:1 mixture in [D$_6$]benzene at a total concentration of $c(\mathbf{3}) = 2.5$ mM is reported in %. [b] Plus one homodimer and one unpaired tetra-urea. [c] Plus two homodimers.

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

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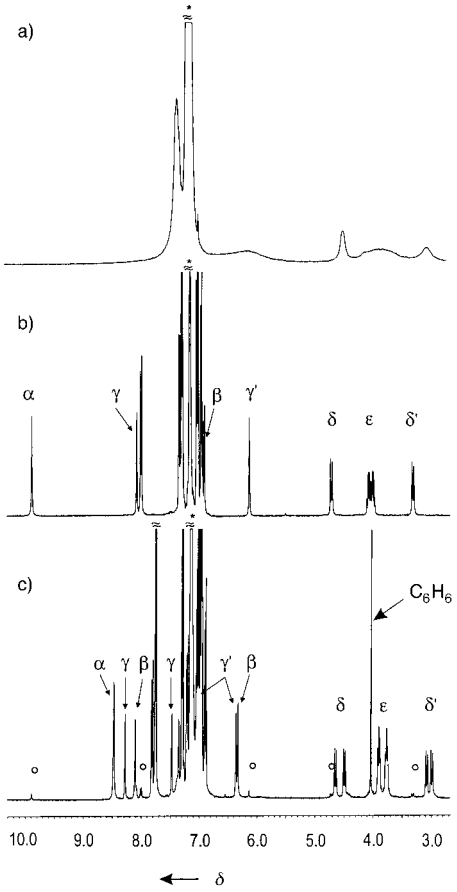

Figure 2. ^{1}H NMR spectra (400 MHz, [D$_6$]benzene, c(**3**) = 2.5 mM, 25 °C); a) irregular associate of **3e**; b) homodimer **3d**/**3d**; c) heterodimer **3d**/**3e**, prepared in C_6H_6, about 10 min after dissolution; signals for included benzene and a small amount of **3d**/**3d** (○) are labeled. Protons of the calixarene skeleton and the amide groups are marked as follows: α/β (NH), γ (ArH), δ (ArCH$_2$Ar), ε (OCH$_2$); see also Scheme 1.

If a 1:1 mixture of **3d** and **3e** is dissolved in benzene (ca. 12 h at 35 °C), evaporated, and the resulting white powder is dissolved in [D$_6$]benzene, the spectrum shown in Figure 2c results, in which the peak at $\delta = 4.03$ belongs to the included benzene. This peak[10] slowly (!) disappears with time, while the rest of the spectrum remains unchanged. This must be interpreted by an exchange of the nondeuterated guest benzene against [D$_6$]benzene present as solvent in large excess, a process which may be described by Equation (1). In principle the analogous behavior was found for the heterodimers **3a**/**3e**.

$$[\mathbf{3d}/C_6H_6/\mathbf{3e}] + C_6D_6 \longrightarrow [\mathbf{3d}/C_6D_6/\mathbf{3e}] + C_6H_6 \quad (1)$$

As Figure 3a shows for the example [**3d**/C_6H_6/**3e**], this disappearance of the guest signal follows first-order kinetics up to conversions of 90%. To our knowledge this is the first clear kinetic analysis of the guest–exchange process in such hydrogen-bonded capsules.[6] And this guest exchange which most probably is identical with the rate of a dissociation/recombination process[4] leads to half-life times of $\tau = 130$ min for [**3a**/C_6H_6/**3e**] and $\tau = 60$ h for [**3d**/C_6H_6/**3e**].

Measuring the reaction rate at different temperatures allows one to derive the activation parameters. They are

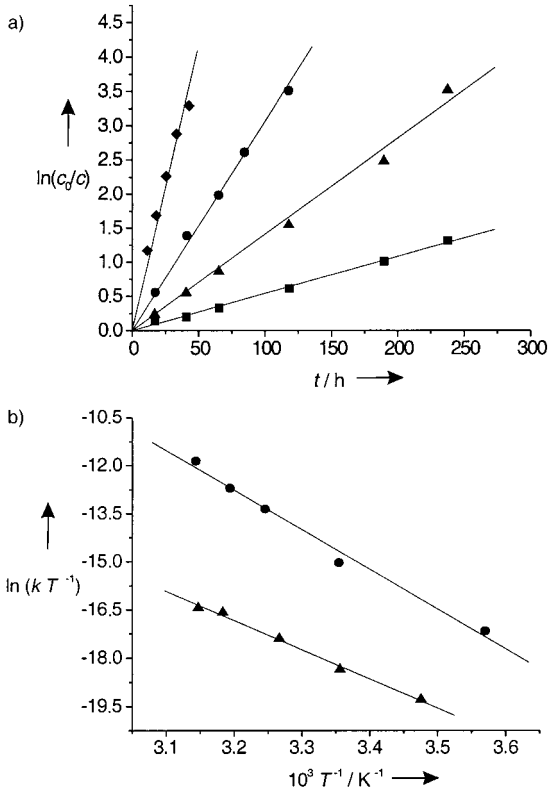

Figure 3. a) First-order plots for the disappearance of the guest signal of [**3d**/C_6H_6/**3e**] in C_6D_6 at 15 °C (■), 25 °C (▲), 33 °C (●), and 45 °C (◆); b) Eyring plots for [**3a**/C_6H_6/**3e**] (●) and [**3d**/C_6H_6/**3e**] (▲). The points are the average of at least three kinetic runs.

collected in Table 2; Eyring plots are shown in Figure 3b. A higher value for the activation enthalpy $\Delta H^{\neq}$ in **3a**/**3e** is overcompensated in **3d**/**3e** by the lower activation entropy $\Delta S^{\neq}$ which evidently is mainly responsible for the lower

Table 2. Activation parameters for the guest exchange for the heterodimers **3a**/**3e** and **3d**/**3e** in [D$_6$]benzene.

Complex	[**3a**/C_6H_6/**3e**]	[**3d**/C_6H_6/**3e**]
Temp. range [°C]	7–45	15–45
R	0.994	0.997
$\Delta H^{\neq}$ [kJ mol^{-1}]	103 (±6)	75 (±3)
$\Delta S^{\neq}$ [J K^{-1} mol^{-1}]	26 (±21)	−96 (±10)
$\Delta G^{\neq}$ [kJ mol^{-1}][a]	95 (±0.4)	104 (±0.6)

[a] at 25 °C.

exchange rate observed for the latter capsules. This can be understood by less perfect hydrogen bonds and a lower conformational freedom of the residues R in the sterically more strained dimer **3d**/**3e**.

If [**3d**/C_6H_6/**3e**] is dissolved in [D$_8$]toluene or [D$_{10}$]*p*-xylene the signal for the included benzene disappears with a similar rate, leading to $\Delta G^{\neq} = 107$ and 108 ± 0.5 kJ mol^{-1}, respectively. However, in contrast to [D$_6$]benzene the whole ^{1}H NMR spectrum changes with the same rate to show finally the spectrum of the homodimer **3d**/**3d**, most probably with the solvent included (Figure 4a–c). Evidently the overall process in this case must be formulated by Equation (2).

$$2[\mathbf{3d}/C_6H_6/\mathbf{3e}] + C_7D_8 \longrightarrow [\mathbf{3d}/C_7D_8/\mathbf{3d}] + 2\,\mathbf{3e} + 2\,C_6H_6 \quad (2)$$

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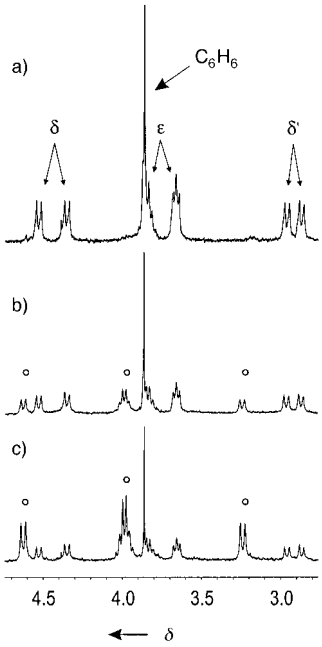

Figure 4. NMR-spectral changes observed for [**3d**/C_6H_6/**3e**] in [D_{10}]*p*-xylene at 25 °C at different times after dissolution; a) 10 min, b) 90 h, and c) 185 h. Not only the guest signal disappears, but also all signals for the heterodimer, while the signals of the homodimer **3d**/**3d** (○) appear. For the assignment of protons see Figure 2.

This is entirely in agreement with the fact that a mixture of **3d** and **3e** does not form heterodimers in toluene or *p*-xylene.[11] And this again can be understood by "assuming" that a less favorable guest (toluene/*p*-xylene vs. benzene) cannot be included in a sterically more strained capsule like **3d**/**3e**.[12] Further measurements extending probably to further dimers will be necessary to establish a complete picture.

Even more remarkable is the behavior of [**3d**/C_6H_6/**3e**] in [D_{12}]cyclohexane. After 18 h at 40 °C the signal at $\delta = 4.03$ still corresponds to *one* molecule of included C_6H_6 per heterodimer **3d**/**3e**, which shows that these capsules are *kinetically stable* under these conditions.[13] This means that in principle a suitable guest can be "permanently" included, and liberated at will by the addition of a hydrogen bond breaking agent.

Clearly the two molecules of dimers like **3d**/**3e** are not held together exclusively by a mechanical entanglement of the residues R attached to the urea functions (Figure 5). Hydrogen bonding (and probably guest inclusion[14]) still play an important role, since the dimer is rapidly destroyed by the addition of DMSO. A comparison of the half-life times for **3a**/**3a** (ca. 1 s),[4] **3a**/**3e** (130 min), and **3d**/**3e** (60 h) shows, however, that the steric crowding by the residues R plays a very decisive role for the kinetic stability[15] of these dimers in benzene. This increase by more than five orders of magnitude can hardly be explained in a different way. It should be possible to increase this steric strain and to obtain tetra-urea derivatives which dimerize under drastic conditions (e.g. high temperature, high pressure) to form dimers stable under standard conditions. The chemical modification of "preformed" dimers by the subsequent introduction of bulky groups at the residues R would be an alternative strategy.[16]

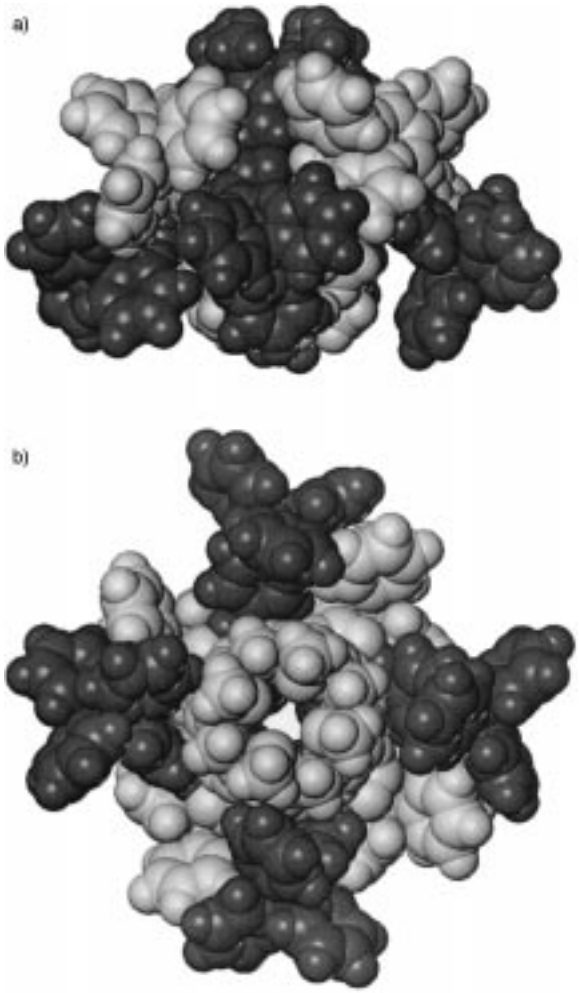

Figure 5. Space-filling representation of the heterodimer **3d** (dark)/**3e** (light) showing the mechanical entanglement of residues R. Methyl ether residues were used for simplicity. a) Side view, b) top view.

Experimental Section

Kinetic studies: Samples for kinetic measurements were prepared by stirring a tetra-urea solution in dichloromethane and methanol (5–10%) with basic aluminum oxide (20-fold excess) for 1.5 h. After filtration and evaporation under reduced pressure, the residue was dried in vacuum for 6 h at 100 °C and finally kept in a desiccator over phosphorus pentoxide and potassium hydroxide. All solvents for kinetic measurements were stored over 4 Å molecular sieves. The kinetic runs were performed at 2–2.5 mM concentration of heterodimers with two pieces of molecular sieves present directly in the NMR tube. In a typical experiment **3e** (14.4 mg, 7.5 μmol) and **3d** (16.7 mg, 7.5 μmol) were stirred in benzene (5 mL) (p.a. grade) with molecular sieves for 12 h at 35 °C. A 1 mL portion of the solution was evaporated under reduced pressure, the residual heterodimer was dried in vacuum and then dissolved in [D_6]benzene (0.6 mL). From this solution, kept at constant temperature in a thermostatted bath or in the NMR spectrometer, spectra were recorded in suitable intervals to have 5–10 points over an 80% conversion range.

[**3d**/C_6H_6/**3e**]: ^{1}H NMR (400 MHz, [D_6]benzene, 295 K): $\delta = 8.470$ (s, 4H; NH), 8.467 (s, 4H; NH), 8.272 and 6.948 (dd, $^4J(H,H) = 2.4$ Hz, 8H; CH), 8.098 (s, 4H; NH), 7.806 and 7.203 (dd, $^3J(H,H) = 8.8$ Hz, 8H; CH), 7.747 (d, $^3J(H,H) = 8.2$ Hz, 24H; CH), 7.464 and 6.357 (dd, $^4J(H,H) = 2.3$ Hz, 8H; CH), 7.287 (d, $^3J(H,H) = 7.6$ Hz, 24H; CH), 7.024 (t, $^3J(H,H) = 7.6$ Hz, 24H; CH), 6.970 (d, $^3J(H,H) = 7.6$ Hz, 24H; CH), 6.885 (t, $^3J(H,H) = 7.0$ Hz, 12H; CH), 6.324 (s, 4H; NH), 4.636 and 3.070 (dd, $^2J(H,H) = 11.7$ Hz, 8H; Ar-CH_2-Ar), 4.483 and 2.983 (dd, $^2J(H,H) = 11.4$ Hz, 8H; Ar-CH_2-Ar), 4.030 (s, 6H; C_6H_6), 3.891 (t, $^3J(H,H) = 7.6$ Hz, 8H; OCH_2), 3.759 (t, $^3J(H,H) = 7.0$ Hz, 8H; OCH_2), 2.20–2.10 (m, 16H; CH_2), 1.50-1.40 (m, 16H; CH_2), 1.35–1.20 (m, 16H; CH_2), 1.012 (t, $^3J(H,H) = 7.0$ Hz, 12H; CH_3), 0.984 (t, $^3J(H,H) = 7.0$ Hz, 12H; CH_3).

See the Supporting Information for the syntheses and spectroscopic data of **3b**–**3e**.

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[4] O. Mogck, M. Pons, V. Böhmer, W. Vogt, *J. Am. Chem. Soc.* **1997**, *119*, 5706 – 5712.

[5] Rebek et al. report a half-life time of 8 min for the uptake of benzene in the dimer formed by a tetra-urea similar to **3a** in [D_{10}]*p*-xylene, but this refers to a very small concentration of benzene (probably about 1 mM) which is not reported exactly in ref. [1c].

[6] a) Recent kinetic studies concerning the guest exchange in hydrogen-bonded capsules of the "softball" type were described: J. Santamaria, T. Martin, G. Hilmersson, S. L. Craig, J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 8344 – 8347; b) for theoretical calculations concerning this guest exchange see: X. Wang, K. N. Houk, *Org. Lett.* **1999**, *1*, 591 – 594.

[7] K.-K. D. Ng, H. Hart, *Tetrahedron* **1995**, *51*, 7883 – 7906.

[8] H. Eckert, B. Foster, *Angew. Chem.* **1987**, *99*, 922 – 923; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 894 – 895.

[9] For heterodimers between tetratolyl- and tetratosyl-ureas see: R. K. Castellano, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 3657 – 3663.

[10] Integration of the initial spectrum proves the inclusion of one benzene molecule per dimer.

[11] The undimerized **3e** remains dissolved in toluene, while it precipitates from *p*-xylene.

[12] MD simulations in vacuo (Tripos force field, M. Clark, R. D. Cramer, N. van Opdenbusch, *J. Comp. Chem.* **1989**, *10*, 982 – 1012; 300 K, 200 ps) on dimers with included benzene led to the following cavity sizes (energy-minimized average structures) expressed by the distance of the two calix[4]arene mean planes defined by the four methylene carbons: **3d/3d** 10.0 Å, **3e/3e** 8.4 Å, **3d/3e** 9.8 Å. The hydrogen bonds characterized by the distance between nitrogen (N_I attached to the calixarene, N_{II} attached to the urea-residues) and the carbonyl oxygen are $N_I \cdots O = 2.55$ and 3.02 Å, $N_{II} \cdots O = 2.52$ and 2.98 Å in **3d/3e** and $N_I \cdots O = 2.62$, $N_{II} \cdots O = 2.48$ Å in **3d/3d**. Thus, the distinctly smaller cavity explains that homodimers **3e/3e** are not formed in benzene, while the slight difference in size between **3d/3d** and **3d/3e** together with less favorable hydrogen-bond distances might explain that also heterodimers are impossible with larger guests such as toluene or p-xylene.

[13] If in a control experiment [**3a**/C_6H_6/**3a**] is treated with C_6D_{12} or C_6H_{12} under the same conditions, the signal of included C_6H_6 (at $\delta = 3.88$ in C_6D_{12}) disappears completely, being replaced by a signal at $\delta = -1.44$ for included C_6H_{12} in the latter case.

[14] For a recent example of guest-controlled dimerization see: A. Shivanyuk, V. Böhmer, E. F. Paulus, *Angew. Chem.* **1999**, *111*, 3091 – 3094; *Angew. Chem. Int. Ed.* **1999**, *38*, 2906 – 2909.

[15] This means a high value for the free energy of activation ΔG^{+}; compare the "constrictive binding" defined by Cram for (hemi)-carceplexes: "Container Molecules and Their Guests": D. J. Cram, J. M. Cram in *Monographs in Supramolecular Chemsitry* (Ed.: J. F. Stoddart), Royal Society of Chemistry, Cambridge, **1994**.

[16] These procedures would be analogous to the formation of rotaxanes by "slipping" or by "threading + capping".

A Supramolecular Enzyme Mimic That Catalyzes the 15,15′ Double Bond Scission of *β,β*-Carotene**

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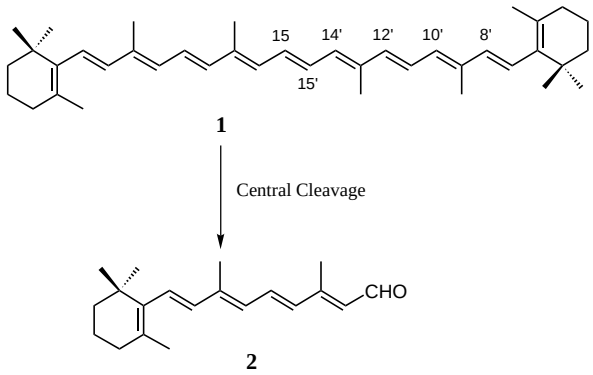
Dedicated to Professor Albert Eschenmoser on the occasion of his 75th birthday

The enzymes (carotene dioxygenases, CDOs) that cleave *β,β*-carotene **1** to provide retinal **2** as a precursor for retinol (vitamin A) are of significance to animal and human nutrition.[1] To date two modes of cleavage of **1** have been proposed: 1) the more recently discovered excentric cleavage which yields apocarotenals, which can be degraded to **2** by *β*-oxidation, and 2) the central cleavage of **1** which gives retinal **2** directly (Scheme 1).[2, 3] The CDO enzymes responsible for



Scheme 1.

catalyzing these reactions have been neither purified nor are their respective co-factors known. Results concerning central cleavage suggest that the enzyme involved places its active site's metal complex directly above the C(15)=C(15′) bond.[4, 5] The fact that this CDO controls the regiospecific cleavage of one C=C bond out of a possible six within the substrate is an intriguing and challenging one.

To mimic such a regioselective system the following strategy was employed. a) The synthesis of a receptor for **1** for which the binding constant K_a for **1** is orders of magnitude greater than that for retinal **2** was necessary in order to prevent product inhibition. b) The introduction of a reactive metal center which is capable of cleaving *E*-configured, conjugated double bonds to aldehydes. c) The use of a co-

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