Solvent Controls Synthesis and Properties of Supramolecular Structures

Yuji Tokunaga, Dmitry M. Rudkevich, Javier Santamaría, Göran Hilmersson, and Julius Rebek, Jr.*

Abstract: A template effect by solvent was found in the synthesis of self-assembled capsules. Use of aromatic solvents such as benzene, toluene, and *p*-xylene leads predominantly to the formation of the C-shaped molecules **3** and **6**, which form hydrogen-bonded dimeric capsules. This is the medium in which the solvent-occupied dimeric capsule enjoys the greatest stability, and the best solvated surfaces with properly filled niches are formed preferentially. The dimerization constant (K_D) value and a ΔG^0 value of >14.0 kcal mol^{-1} for the capsules **16** (**3**·**3**) were estimated for the first time in guest-exchange experiments. When solvents not suitable for dimerization ($CHCl_3$ and CH_2Cl_2) or those solvents that compete for hydrogen bonds (DMSO and THF) were employed, only statistical yields of the stereoisomers (C-, S-, and W-shaped) were observed. Experimental evidence is presented that the solvent molecules control the covalent bond formation through molecular recognition within the monomeric tetrahedral intermediate. It is proposed that solvation effects can be treated as a subset of molecular recognition events.

Keywords: hydrogen bonds · molecular recognition · solvent effects · supramolecular chemistry · template synthesis

Introduction

The synthesis of macrocyclic host polyethers, catenanes, rotaxanes, and other large ring systems is very often accompanied by template effects; either ions or neutral molecules can act as templating guests.[1] That the reaction solvent could act as a template was recognized only recently by Cram,[2] Sherman,[3] and Reinhoudt[4] during their syntheses of carceplexes, the covalently bound molecule within molecule[5] complexes. In these cases, solvent molecules control the synthesis through van der Waals or electrostatic interactions within the transition state, and by being objects of molecular recognition, the guest within the host. Thus, size–shape selectivities were found within a large series of solvent-templated syntheses and empty (solvent free) carcerands were not observed. Solvent was recently found to drive helical folding of hole-containing phenylacetylene oligomers.[6] Solvent participation of a specific sort was proposed for guest exchange within a deep, tube-shaped cavitand,[7] and in the reversible dimerization of tetramethoxycalix[4]arene ureas.[8] It is also at the heart of entropy-driven noncovalent dimerization of Cram's velcrands.[9] Solvent molecules can be reversibly and selectively encapsulated into hydrogen-bonded assemblies of self-complementary structures.[10] Here we report that in addition to covalent synthesis, solvent can also play a role in the synthesis of systems held together by only weak intermolecular forces. Solvents act as positive templates: the best-solvated shapes are formed preferentially in kinetically controlled reactions (Figure 1).[11, 12] We further propose that template effects involving solvents may be a more general feature of synthetic processes than previously recognized.

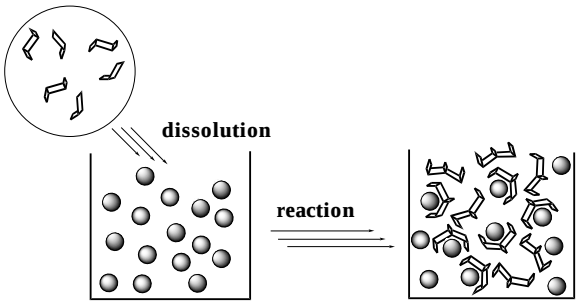


Figure 1. Schematic representation of the templation by solvent. Apparently, the reaction can be directed towards the most solvated shape.

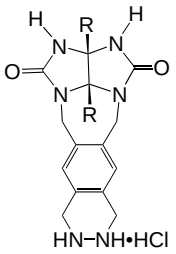
[*] Prof. J. Rebek, Jr., Dr. Y. Tokunaga, Prof. D. M. Rudkevich, Dr. J. Santamaría, Dr. G. Hilmersson
The Skaggs Institute for Chemical Biology
and The Department of Chemistry
The Scripps Research Institute, MB-26
10550 North Torrey Pines Rd., La Jolla, CA 92037 (USA)
Fax: (+1) 619-784-2876
E-mail: jrebek@scripps.edu

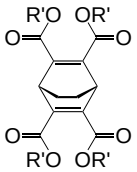
Results and Discussion

Synthesis and kinetics: The synthetic reaction, in which solvent recognition is implicated, involves the acylation of hydrazine derivatives **1a** or **1b** with the active tetraesters **2a** or **2b**

  0947-6539/98/0408-1449 $ 17.50+.25/0

(Scheme 1) in aprotic media. The reaction generally proceeds in high yield in a number of organic solvents and is complete within a few hours when **2a** is used or longer with the less



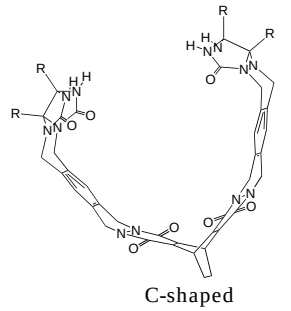


1a R = CO_2-*i*-C_5H_{11}
1b R = 4-(*n*-$C_6H_{13}O$)-C_6H_4

2a R' = C_6F_5
2b R' = 2,4,5-$Cl_3C_6H_2$

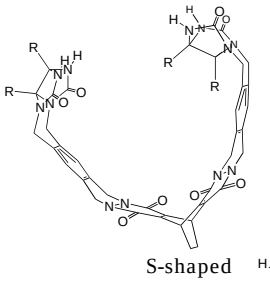
Scheme 1. Components for the final reaction in the synthesis of the C-, S-, and W-shaped isomers: hydrazines **1a** and **b** and tetraesters **2a** and **b**.

reactive **2b**. In the case of **1a**, **2a**, and **2b** the formation of all three isomers is observed: the C-shaped **3**, S-shaped **4**, and W-shaped **5** (Scheme 2 represents the corresponding energy-



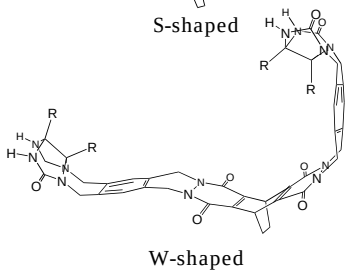
C-shaped

3 R = CO_2-*i*-C_5H_{11}
6 R = 4-(*n*-$C_6H_{13}O$)-C_6H_4



S-shaped

4 R = CO_2-*i*-C_5H_{11}
7 R = 4-(*n*-$C_6H_{13}O$)-C_6H_4



W-shaped

5 R = CO_2-*i*-C_5H_{11}

Scheme 2. Schematic representation of the energy-minimized structures of the three possible isomers: C-, S-, and W-shaped.

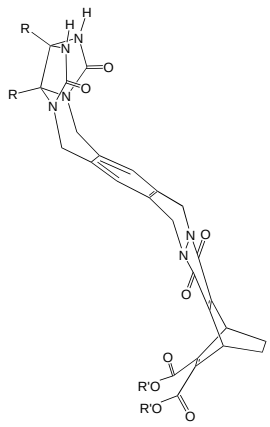
minimized structures[13]). The product distribution responds to specific features of the solvent (Table 1). In parallel experiments, compounds **3–5** were prepared by acylation of hydrazine **1a** with active diesters **8** and **9** in various organic

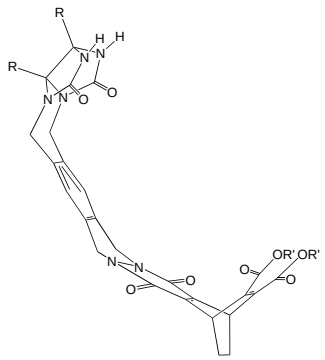
Table 1. The yields of the reaction **1** + **2a** and **17** + **2a** in different solvents.[a,b]

	Solvent	Yield [%][c]			Ratio			C/S
1 + **2a**		**3**	**4**	**5**	**3**	**4**	**5**	
	theory	25	50	25	1.0	2.0	1.0	0.50
	DMSO	31	44	25	1.4	1.8	1.0	0.78
	THF	25	46	29	0.9	1.6	1.0	0.56
	benzene	36	43	20	1.8	2.2	1.0	0.81
	toluene	41	41	17	2.4	2.4	1.0	1.0
	p-xylene	39	48	13	3.0	3.7	1.0	0.81
	$CHCl_3$	19	66	16	1.2	4.1	1.0	0.29
	CH_2Cl_2	23	62	15	1.5	4.1	1.0	0.37
17 + **2a**		**18**[d]	**19**[d]	**20**[d]	**18**	**19**	**20**	
	theory	25	50	25	1.0	2.0	1.0	0.50
	benzene	50	30	8	6.3	3.8	1.0	1.7
	$CHCl_3$	20	44	8	2.5	5.5	1.0	0.45

[a] Averaged data after at least two independent experiments; estimated error ± 5%. Total yield of the reaction **1** + **2a** is quantitative. Total yield of the reaction **17** + **2a** is 88% in benzene and 72% in $CHCl_3$. [b] All the reactions were performed with a 5 mM concentration of **2a**. [c] Determined by ^{1}H NMR. [d] Determined experimentaly after preparative column chromatography due to overlapping of the ^{1}H NMR.

solvents (Scheme 3). The diesters **8** and **9** were synthesized from hydrazine **1a** and approximately twofold excess of ester **2a**.





8 R = CO_2-*i*-C_5H_{11}
R' = C_6F_5

9 R = CO_2-*i*-C_5H_{11}
R' = C_6F_5

10 R = 4-(*n*-$C_6H_{13}O$)-C_6H_4
R' = 2,4,5-$Cl_3C_6H_2$

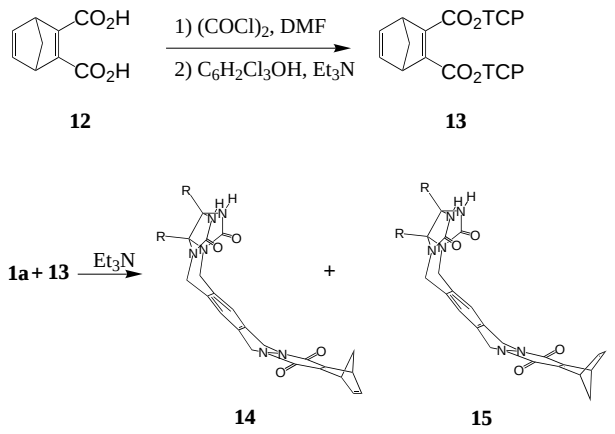
11 R = 4-(*n*-$C_6H_{13}O$)-C_6H_4
R' = 2,4,5-$Cl_3C_6H_2$

Scheme 3. Isolated intermediates: *E* isomers **8** and **10** and *Z* isomers **9** and **11** in the synthesis of the C-, S-, and W-shaped compounds.

Compounds **14** and **15** were prepared as model systems for the second stage of the synthesis of **3** and **4**; equimolar amounts of hydrazine **1a** and active ester **13** were employed. The latter was obtained by the activation of dicarboxylic acid **12** and its esterification with 2,4,5-trichlorophenol (Scheme 4). The C-shaped **6** and S-shaped **7** bisglycolurils were synthesized in a manner similar to that of compounds **3** and **4** from either **1b** and **2b**, or **1b** and diester **11** (Scheme 3).

In a typical template experiment, the solution of active ester and hydrazine (obtained from the corresponding hydrochloric salt and 5 equiv of Et_3N) in the designated solvent was

0947-6539/98/0408-1450 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 8



Scheme 4. Synthesis of model compounds **14** and **15**.

stirred at 20 °C. The product mixtures were analyzed by HPLC and high-resolution ^{1}H NMR spectroscopy. The results are presented in Tables 1 and 2.

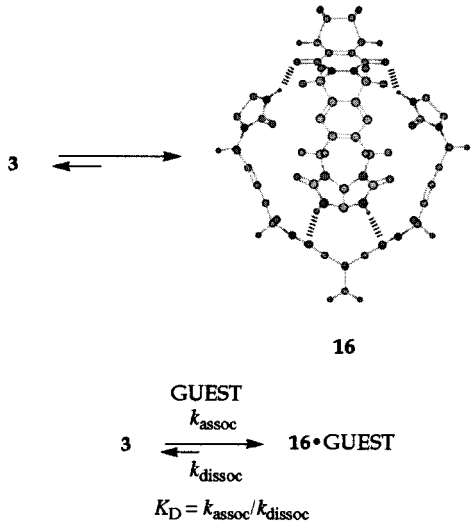
Table 2. The yields of the reaction between **1a** + **8**, **1a** + **9**, and **1b** + **11** in different solvents.[a, b, c]

	Solvent		Yield [%]	Ratio
(**1a** + **8**)		**4**	**5**	(**4/5**)
	theory	50	50	1.0
	DMSO	50	50	1.0
	benzene	62	38	1.6
	$CHCl_3$	65	35	1.9
(**1a** + **9**)		**3**	**4**	(**3/4**)
	theory	50	50	1.0
	DMSO	51	49	1.0
	benzene	64	36	1.8
	$CHCl_3$	36	64	0.56
(**1b** + **11**)		**6**	**7**	(**6/7**)
	theory	50	50	1.0
	benzene	63	37	1.7

[a] Averaged data after at least two independent experiments; estimated error ±5%. Total yield is quantitative. [b] All the reactions were performed with a 5 mM concentration of **1a**. [c] Determined by ^{1}H NMR in [D_6]DMSO.

Spectroscopic features: A unique property of glycolurils **3** and **6** is that they are self-complementary in hydrogen-bond donor and acceptor sites. Accordingly, they form dimeric capsules in solvents that compete poorly for hydrogen bonds. For example, the C isomer **3** in benzene or toluene forms a well-defined dimeric capsule **16** (Scheme 5), in which two solvent molecules are enclosed.[10, 13]

The ^{1}H NMR spectrum of **3** in [D_6]benzene is sharp and features, in particular, a concentration-independent ($5 \times 10^{-4} - 1.5 \times 10^{-2}$ M), downfield NH singlet at $\delta = 8.8$. The corresponding NH singlet in model (nondimeric) glycolurils is situated at approximately $\delta = 5.0$ in [D_6]benzene. The FTIR spectrum of **3** in benzene ($2 \times 10^{-5} - 1 \times 10^{-3}$ M) showed exclusively the hydrogen-bonded NH stretching absorption at 3229 cm^{-1}. This absorption appears at 3409 cm^{-1} for the nonassembled glycolurils. The dimerization constant K_D is far beyond the detection limits of ^{1}H NMR in [D_6]benzene ($> 10^7$ M^{-1}). Nevertheless, when [D_6]benzene solutions of **3**



Scheme 5. Self-assembly of compound **3** into hydrogen-bonded dimer **16** with guest molecule encapsulation. In the energy-minimized structure of **16** the chains are omitted for clarity.[13]

and **6** were mixed in a 1:1 ratio, three species (four sets of NH signals) were observed in the ^{1}H NMR spectrum in the ratio 8:7:4. These were assigned as homodimers **3**·**3** (**16**) and **6**·**6**, and the heterodimer **3**·**6**, respectively (Figure 2). Benzene solutions of **3** were analyzed by electrospray mass spectrometry (ESI-MS) and, in addition to the peak for **3** at 1268 daltons, a sizable (ca. 20%) peak corresponding to the

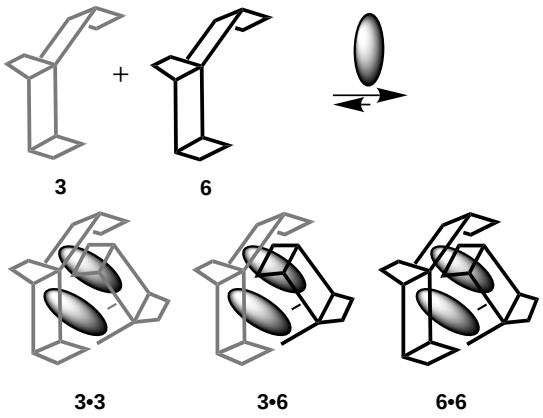


Figure 2. Homo- and heterodimerization of C-shaped isomers **3** and **6** in benzene.

dimer **16** was observed at 2535 daltons. In [D_{10}]*p*-xylene, the ^{1}H NMR spectrum of **3** is broader, but it possesses the same pattern of signals, and again, a downfield NH singlet at about $\delta = 8.8$.

In $CDCl_3$, however, compound **3** behaves quite differently. The FTIR spectrum of **3** ($5 \times 10^{-4} - 1.5 \times 10^{-2}$ M) showed, in addition to the hydrogen-bonded NH stretching absorption at 3250 cm^{-1}, the free NH band at 3439 cm^{-1}, the intensity of which increases upon further dilution. The corresponding ^{1}H NMR spectra showed the broad glycoluril NH resonance at approximately $\delta = 8.0$ (at $5 \times 10^{-4} - 1.5 \times 10^{-2}$ M). This indicates the formation of the dimeric assembly, since the

corresponding NH singlet in model (nondimeric) glycolurils is usually situated upfield of $\delta = 6.5$ in $CDCl_3$.[14] Nevertheless, the spectrum undergoes significant broadening upon dilution from 1.5×10^{-2} M to 5×10^{-5} M; the glycoluril NH signal is also broadened and shifted approximately $\delta = 0.2$ upfield. Apparently, other aggregates—cyclic or linear—are also present, which form and dissipate on the NMR time scale. The dimeric capsule **16** was not detected by ESI–MS in $CDCl_3$. When a 1.2×10^{-2} M $CDCl_3$ solution of **3** was titrated with [D_6]benzene, the glycoluril NH signal shifted approximately $\delta = 1.0$ downfield upon addition up to 14% (vol) of [D_6]benzene. The spectrum at that point closely resembled the one observed for the capsular form in pure [D_6]benzene. This indicates a higher relative affinity of capsule **16** for benzene vs. chloroform.[15] The spectra in CD_2Cl_2 were similar to those in $CDCl_3$.

In polar solvents such as DMSO, which compete well for hydrogen-bond donors, all three isomers (**3–5**) exist as monomeric species. The S-shaped **4** and **7** and the W-shaped isomer **5** do not assemble in apolar solvents. Their ^{1}H NMR spectra are broadened, with the glycoluril NH signals upfield of $\delta = 6.0$. Molecular modeling of various sorts indicates that these structures are incapable of forming reasonable dimeric structures.

Since the dimerization constant K_D for C-shaped **3** (Scheme 5) is too large for determination by ^{1}H NMR spectroscopic dilution experiments, only an approximate K_D value was estimated from the guest-exchange dissociation rate constant. The guest-exchange rate constant was determined by EXSY spectroscopy with the use of the initial-rate approximation.[16] From the EXSY experiments (mixing time 0.5 s) with 1:1 complexes **16**·(1*R*)-(+)-camphor or **16**·(1*R*)-(−)-camphorquinone in $CDCl_3$, the guest exchange was determined to be $0.07 \pm 0.02\,s^{-1}$ at 295 K. This sets a lower limit for the dissociation rate constant k_{dissoc} of **16**·guest, since the guest exchange may, in principle, proceed through the partial opening of the capsule. Assuming the association rate constant k_{assoc} of $2 \times 10^9\,M^{-1}s^{-1}$, typical for diffusion-controlled hydrogen-bond formation in $CHCl_3$,[17] an estimate of the dimerization constant K_D of $3 \times 10^{10}\,M^{-1}$ ($\Delta G^0 \approx 14.0$ kcal mol^{-1}) can be made.[18]

Mechanistic considerations: The sequence of reactions between **1** and **2**, leading to the isomers **3–5**, is lengthy: four covalent bonds are irreversibly formed, and processes involving the preassociation of the reactive components should be considered. Evidently, one amide bond forms slowly between **1** and **2**, then a rapid 6-membered cyclization makes the second amide bond and produces intermediates **8** or **9**. Repetition of the sequence at the remaining two esters of the centerpiece completes the process. The very first amide bond to be formed irreversibly determines whether isomer **8** or **9** is the intermediate (i.e., whether the glycoluril substituents (R) are *E* or *Z* with respect to the bridge of the centerpiece), but both isomers are reasonably expected to form in equal amounts. We were not able to follow the formation **8** and **9** quantitatively; however, the use of a truncated model system **13** treated with **1a** bears out the expectation: equal amounts of the corresponding *E* and *Z* isomers **14** and **15** are formed, independently of solvent (benzene, $CHCl_3$, etc.). This places an upper limit of 50% on the yield of the C-shaped subunit **3**, since it can only arise from the *Z* isomer. Accordingly, the template effect of solvent, if any, must operate at the second stage of the reaction, the partitioning of the *E* or *Z* isomers (Figure 3).

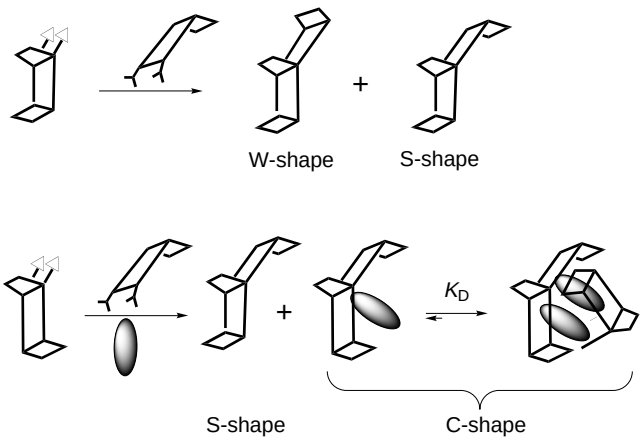


Figure 3. Sequence of reactions leading to the formation of the C-, S-, and W-shaped isomers.

Coupling and selectivity: We found that in those solvents that favor the formation of the dimeric capsule **16**, the reaction between **1** and **2** has a higher selectivity for the C-shaped isomer (Table 1). The expected (statistical) distribution of C-shaped **3**, S-shaped **4**, and W-shaped **5** isomers is 1:2:1, respectively. In competitive solvents like THF and DMSO, the distribution was close to the theoretical expectation. The portions of **3** in benzene, toluene, and *p*-xylene were 1.5–1.6 times higher, with the product distribution of **3**, **4**, and **5** reaching 2.4:2.4:1.0 in toluene. On the other hand, in $CHCl_3$ and CH_2Cl_2 the quantities of **3** were even lower than those expected statistically. Instead, these solvents favored the formation of the S-shaped compound **4**.

In the absence of other factors, reaction of **1a** with **9** is expected to give the C-shaped **3** and S-shaped **4** in equal amounts, and that with **8** is expected to give the S-shaped **4** and W-shaped **5** in equal amounts (Figure 3). To test the selectivity, compounds **8** and **9** were subjected to the second stage of the reaction in various media. When treated with 1 equivalent of **1a** in DMSO, both isomers **8** and **9** indeed gave the expected (1:1) ratios of **4**:**5** and **3**:**4**, respectively (Table 2). This is in good agreement with the distribution for the overall reaction in DMSO (Table 1). Unexpectedly, in $CHCl_3$ the *E* isomer **8** and **1a** reacted to give yields up to 65% of the S-shaped compound **4**. The same result holds for the reaction of *Z* isomer **9** and **1a**; again the S-shaped isomer is formed preferentially (64%). Apparently, the action of $CHCl_3$ disfavors the C-shaped or W-shaped products (Table 2). Either some fit of $CHCl_3$ into the transition state for the S-shaped product, or the inappropriate fit of $CHCl_3$ into the transition state leading the other products is responsible. The S-shaped isomer also has a uniquely compact low-energy conformation (Scheme 2) in which its internal cavity can be filled by the *iso*-pentyl esters of a glycoluril.

0947-6539/98/0408-1452 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 8

In benzene the product distribution was reversed and a yield of 64% was obtained for the C-shaped **3**. This is the medium in which the solvent-occupied dimeric capsule enjoys the greatest stability.

Analysis: These data suggest roles for a) solvent and b) hydrogen bonding in the reaction. It is hard to imagine a role for the solvent in the first stage of the reaction, as the stereocenters are remote from each other and are only connected by a single amide: no cavities are generated in the rate-determining step. The distributions of compounds **3–5** in different solvents were calculated from the data for the second stage and assuming that the first stage gives equal amounts of *Z* and *E* intermediates. Those numbers (Table 3) compare reasonably well with the experimental results of Table 1. They justify the premise that selection occurs in the second stage of the reaction.

Table 3. Estimated yield distribution (in %)[a] of compounds **3–5** in different solvents.

	3	**4**	**5**
DMSO			
total	31	44	25
from *E* isomer	0	25	25
from *Z* isomer	26	25	0
$CHCl_3$			
total	19	66	16
from *E* isomer	0	33	18
from *Z* isomer	18	32	0
benzene			
total	36	43	20
from *E* isomer	0	31	19
from *Z* isomer	32	18	0

[a] Calculated from the reactions **1a** + **2a**, **1** + **8** and **1** + **9**. [Total] = [**3**] + $[\mathbf{4}]_Z + [\mathbf{4}]_E + [\mathbf{5}]$, where [**3**], $[\mathbf{4}]_Z$, $[\mathbf{4}]_E$ and [**5**] correspond to the concentrations of isomers **3, 4,** and **5** produced from both *Z* and *E* isomers.

The initial stage of the reaction, in benzene at 5×10^{-3} M, between **1b** and *Z* isomer **11** (structurally similar to **9** and more soluble, Scheme 3) was followed by HPLC. A 1.4-fold higher initial rate of formation of C-shaped product **6** was observed compared with the S-shaped product **7** (Figure 4). This is in a fairly good agreement with the data from Table 2 obtained by ^{1}H NMR spectroscopy at the end of the reaction.

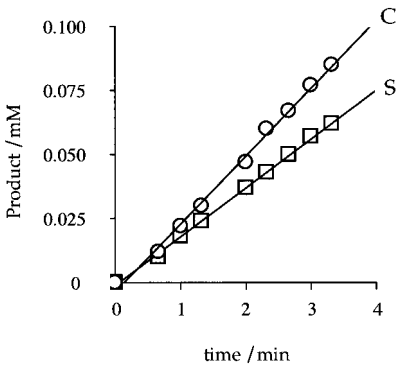
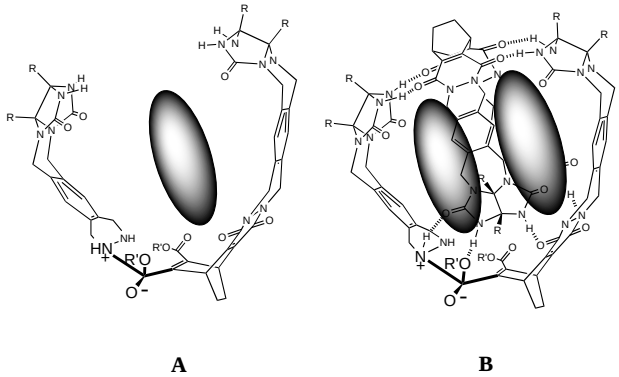


Figure 4. Production of the C- and S-shaped compounds **6** and **7**, respectively, from **1b** and **11** at 5×10^{-3} M in benzene. Data taken by HPLC from the initial stage of the reaction.

Formally, the reaction between **1b** and **11** is a second-order parallel reaction, and $d[\mathbf{6}]/d[\mathbf{7}] = k_6/k_7 = [\mathbf{6}]/[\mathbf{7}]$, where k_6 and k_7 are the corresponding rate constants.

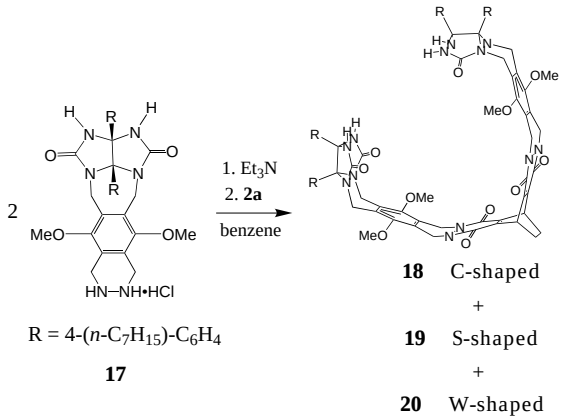
The curvature and the concave shapes of the *E* or *Z* intermediate invite solvation. When benzene, toluene, or *p*-xylene are present, they can be recognized by and fit well within the *Z* intermediate. Subsequently, the remaining exposed surface of the solvent attracts the reactant **1**, and lends stability to the reversibly formed zwitterionic tetrahedral intermediate on the pathway to the C-shaped product (Scheme 6A); $k_6 > k_7$. We propose that one of these solvent molecules fits well—and much better than $CHCl_3$ or CH_2Cl_2—within the monomeric form **3** (or **6**), since it is known that two of these molecules are nicely accommodated inside the dimeric capsular form.[10]



A **B**

Scheme 6. Possible tetrahedral intermediates of the reaction between **1** and **2**; A: monomeric intermediate associated with solvent molecule; B: templated complex.

To estimate the affinity of the monomeric C-shaped molecule **3** (or **6**) towards aromatic solvents is experimentally difficult; the monomer cannot be detected. On the other hand, the C-shaped molecule **18** obtained from tetraester **2a** and dimethoxyglycoluril **17**[19] (Scheme 7) does not form a capsule and can be used as a model for the effects of aromatic solvents. Computer modeling[13] indicates that the methoxy groups in **18** prevent hydrogen bonding within the capsular dimeric structures. The ^{1}H NMR spectrum of **18** in $CDCl_3$ is



R = 4-(*n*-C_7H_{15})-C_6H_4

17

18 C-shaped
+
19 S-shaped
+
20 W-shaped

Scheme 7. Reaction between hydrazine **17** and tetraester **2a**.

sharp and possesses, in particular, the glycoluril NH singlet at $\delta = 6.0$ (6×10^{-3} M concentration), indicating that it is in the monomeric state. Titration of this solution with [D_6]benzene resulted in downfield shift of the NH signal to $\delta = 6.8$ ($\approx 35\%$ *v*/*v* in $CDCl_3$); the spectrum became broader upon titration. The ^{1}H NMR spectra in pure [D_6]benzene or [D_8]toluene were very broad and showed the NH signal at $\delta \approx 7.0$. Interestingly, at concentrations higher than 5×10^{-3} M the solution formed gels. Such a gelation of aromatic solvents by the monomeric C-shaped **18**, combined with the ^{1}H NMR studies, indicates the presence of an intermolecular hydrogen-bonded network that involves affinity between gelator and solvent.[20] Accordingly, we were unable to obtain direct evidence of interactions between the monomeric subunit and aromatic solvent.

Alternatively, or even in addition, the autocatalytic (templated) pathway involving the hydrogen-bonded tetrahedral intermediate is possible (Scheme 6B).[21, 14] In such a case, $d[\mathbf{6}]/d[\mathbf{7}] = (k_{\mathbf{6}} + k_{cat}K_D^{-1/2}K_T[\mathbf{6}\cdot\mathbf{6}]^{1/2})/k_{\mathbf{7}}$, where K_D is a dimerization constant of **6** into capsule [**6**·**6**], K_T is a termolecular constant for the formation of templated complex [**1**·**11**·**6**], and k_{cat} is a catalytic rate constant. The ratio [**6**]/[**7**] should not be constant with respect to time, since the product concentration increases. Nevertheless, we detected only slight (ca. 20%) deviations in the [**6**]/[**7**] ratio with time at concentrations from 1×10^{-3} to 5×10^{-3} M.

To test this hypothesis, 0.25, 2.0, or 0.8 equivalents of **3** were added to the reaction mixtures at 1×10^{-3} and 5×10^{-3} M concentration, respectively. Compound **3** has approximately the same shape and size as the product **6**, and the only difference resides in the substituents (*iso*-pentyl instead *p*-hexyloxyphenyl) on the periphery of the glycoluril functions. We used **3** in the reaction of **6** for pure experimental reasons; the corresponding chemical shifts and the HPLC retention times for **3**, **6**, and **7** are quite different, so it was easy to integrate the ^{1}H NMR spectra and HPLC traces cleanly. At the same time, compounds **3** and **6** form a heterodimeric complex (Figure 2), so the nature of the autocatalysis, if any exists, should be unaffected as it involves replication of the shape. However, a) only a slight (<20%) rate acceleration was found, and b) no changes in the [**6**]/[**7**] ratio were observed.

Even though negligible autocatalysis was detected in our hands, the following must be taken into consideration. Since the dimerization constant K_D of **3** (or **6**) in benzene is extremely high ($K_D = 3 \times 10^{10}\,M^{-1}$ in $CDCl_3$ and roughly two orders of magnitude higher in benzene), the concentration of monomeric species **3** (template) and its complex (Scheme 6B) must be extremely low. For example, when 5×10^{-4} M of the template **3** (or **6**) is produced (e.g., ca. 20% conversion at 5×10^{-3} M), only approximately 2.9×10^{-8} M of the template is available in its monomeric form for (auto)catalysis. At the same time, and perhaps more importantly, since neither reactant is complementary to the product,[14] the termolecular constant K_T is expected to be very low, that is, the concentration of the catalytic termolecular complex [**1**·**11**·**6**] is insignificant.[22]

Further support for benzene templation was obtained from the reaction between tetraester **2a** and glycoluril **17**[19] performed both on an analytical and preparative scale (Scheme 7). As shown above, the C-shaped product **18** does not form a self-assembled dimer due to steric clashes introduced by the methoxy functions. The C-shaped isomer **18** was formed preferentially in benzene (50% yield) and the S-shaped **19** slightly dominated in $CHCl_3$ (Table 1). If, again, the *E* and *Z* isomers are equally formed in the initial reaction, then the 50% yield of **18** indicates that practically all of the *Z* isomer reacts to give **18**. A unanticipated result, indeed. This implies that the transition state and the intermediate (Scheme 6A) of the reaction are monomeric.[23]

Conclusions

Template effects are frequently observed on a macroscopic level. For example, equally sized emulsion droplets can serve as templates around which titania, silica, and zirconia materials are assembled into highly ordered structures.[24] In the systems described here the solvent recognizes and thereby controls the product structure on a molecular level. It can even prevent collapse of self-assembled aggregates.[25] The reactions described in the present work provide a means by which the influence of such a weak and delicate noncovalent effect as solvation can be studied. In addition to commonly known solvent effects, the concepts of preorganization, size–shape selectivity, and goodness of fit should be considered when choosing a solvent for a reaction. Decades ago, Kobuke et al. observed *endo* selectivities of methyl-substituted dienophiles in Diels–Alder reactions with cyclopentadiene.[26] In this case the diene was used as a solvent and apparently provided for a more favorable transition state for the *endo* vs. *exo* reaction. Perhaps CH/π interactions were involved or even other specific contacts involving solvent size and shape. Another close analogy is the work of Reinhoudt et al. on the synthesis of large hydrophobic surfaces by combination of calix[4]arene and resorcinarene building blocks.[27] Exploring multiple S_N2 alkylation reactions in polar aprotic solvents (acetonitrile, DMF, etc.), the Reinhoudt group attributed the *endo* selectivity in the yield distribution to specific interactions of the functional groups in the calixarene (and resorcinarene) framework. We propose that in addition, solvent size and shape are responsible: the best solvated surface, with properly filled niches, is formed preferentially. As previously mentioned, this is also the case in solvent-templated syntheses of covalently bound carcerands.[2–4] Similar solvent effects may also be in control of the spectacular hexameric assembly of resorcinarenes through sixty hydrogen bonds recently described by Atwood.[28] We suspect that whether in synthetic or natural systems, molecular solvation plays an active rather than passive role in processes forming covalent bonds.

Experimental Section

General: Melting points (m.p.) were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with TMS as the internal standard at 22 °C on Bruker DRX600 (600 MHz) or Bruker AM300 (300 MHz) spectrometers. ^{13}C

0947-6539/98/0408-1454 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 8

NMR spectra were recorded on a Bruker DRX 600 (150 MHz) spectrometer. FTIR spectra were recorded at 22 °C in thin film, $CDCl_3$, and [D_6]benzene on a Perkin–Elmer Paragon 1000PC FT-IR spectrometer. The fast atom bombardment (FAB) positive ion mass spectra were obtained on a VG ZAB-VSE double-focusing high-resolution mass spectrometer equipped with a cesium-ion gun. The HPLC analysis was performed with Waters 600 HPLC with a reverse-phase column (Beckman C_{18} column, 4.6 mm i.d. × 250 mm, 5 μm, flow rate 1 mL min^{-1}). A linear gradient of H_2O/MeOH 9:1 to MeOH/Et_3N 99:1 over 30 min was used. The detection wavelength was 340 nm. The integration and calculation for all the peaks were performed with Waters 820 Baseline software. All solvents used were dried and stored over molecular sieves. All the chemicals were of reagent grade and were used without purification. Column chromatography was performed with silica gel (Merck; 0.040–0.063 mm). All reactions were carried out in a nitrogen atmosphere. Compounds **1a**,[10] **1b**,[29] **2a**,[29] **3**,[10] **8**,[29] **9**,[29] and **17**–**20**[19] were prepared according to literature procedures. Molecular mechanics (MM2* and Amber* forcefield) calculations of structures **3**–**5**, their complexes with benzene and chloroform, and the zwitterionic intermediates (Scheme 6) were performed with MACROMODEL 5.5.[13]

EXSY experiments: The EXSY spectra of complexes **16**·(1*R*)-(+)-camphor and **16**·(1*R*)-(−)-camphorquinone were recorded at 295 K at 600 MHz with the phase-sensitive NOESY pulse sequence supplied with the Bruker software. TPPI was used to obtain quadrature detection in F_1. Each of the 480 F_1 increments resulted from the accummulation of 16 scans. The relaxation delay was 2.4 s. The mixing time was 500 ms. Before Fourier transformation, the FIDs were multiplied by a π/2 shifted square-sine bell function in both the F_2 and the F_1 domain. The data file was zero-filled, resulting in a spectrum of 4 K × 1 K real data points, with a resolution of 1.75 Hz/point in F_2 and 7.03 Hz/point in F_1. The rate constants were obtained from the analysis of the crosspeak (I_{AB}, I_{BA}) to diagonal peak intensities (I_{AA}, I_{BB}) and the molar fractions (X_A, X_B) of the different compounds giving rise to the exchange peaks: see Equations (1)–(4) and ref. [30]

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \tag{1}$$

$$k = k_1 + k_{-1} \tag{2}$$

$$k = \frac{1}{\tau_m} \ln \frac{r+1}{r-1} \tag{3}$$

$$r = 4 X_A X_B (I_{AA} + I_{BB})(I_{AB} + I_{BA}) - (X_A - X_B)^2 \tag{4}$$

Template experiments: In a typical templation experiment, a solution of ester **2a** (or **2b**) and hydrazine **1a, 1b**, or **17**, or esters **8**, **9**, or **11** and hydrazine **1a or b** (and an additive **3** if used) in the appropriate dry solvent and 5 equiv of Et_3N was stirred at 20 °C for 10 h, then evaporated in vacuo. The residue was redissolved in [D_6]DMSO and analysed by high-resolution ^{1}H NMR spectroscopy (600 MHz); the area $\delta = 6.0–4.0$ was used for integration (see Figure 5). In the cases of compounds **18**–**20**, the reaction was additionally run on a preparative scale. For the reaction **1b** and **11** in benzene, the product formation was followed in equal time intervals (after quenching with large amount of MeOH) by reverse-phase HPLC (H_2O/MeOH 9:1, MeOH/Et_3N 99:1). The corresponding retention times for the S-shaped compound **7** and C-shaped compounds **6** and **3** were 24.0, 26.0, and 15.5 min, respectively. Anthracene (retention time 14.5 min) was used as the internal standard for integration. All measurements were performed at least in duplicate, and good reproducibility was observed.

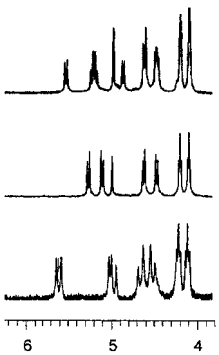


Figure 5. Portions of the ^{1}H NMR spectra of the S-shaped isomer **4** (top), C-shaped isomer **3** (middle), and W-shaped isomer **5** (bottom), used for the product distribution determination, in [D_6]DMSO.

Active ester 2b: Dicyclohexylcarbodiimide (DCC, 3.49 g, 16.9 mmol) was added to the suspension of the corresponding tetraacid[10] (954 mg, 3.38 mmol), 2,4,5-trichlorophenol (5.34 g, 27.0 mmol), and DMAP (82.6 mg, 0.68 mmol) in dichloroethene (50 mL) at RT. After being stirred for 30 h, the reaction mixture was filtered and the filtrate was concentrated. Purification of the residue by column chromatography (hexane/benzene, 1:1) gave active ester **2b** as a white solid (after trituration with hexane). Yield 2.28 g (67 %); m.p. 246–248 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.98$ (s, 4H; CH_2), 5.05 (s, 2H; CH), 7.42 (s, 4H; arom), 7.56 (s, 4H; arom); ^{13}C NMR ($CDCl_3$): $\delta =$ 24.7 (CH_2), 42.0 (CH), 125.6 (C=C), 126.3 (arom), 131.7 (arom), 131.9 (arom), 132.4 (arom), 142.5 (arom), 145.3 (arom), 161.3 (C=O); FTIR (thin film): $\tilde{\nu} = 3090–2980$ (CH, CH_2), 1745 (C=O), 1211, 1180 cm^{-1} (C-O-C); MS-FAB: *m/z*: 853/855/857 [M^++Na − 5Cl] (calcd 855). The product was additionaly characterized as tetrakis(*p*-methoxybenzylamide) after its reaction with *p*-methoxybenzylamine and Et_3N in $CHCl_3$, followed by evaporation and recrystallization from MeOH. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.56$ (s, 4H; CH_2), 3.77 (s, 12H; OMe), 4.38 (d, ^3J(H,H) = 5.7 Hz, 8H; CH_2Ar), 4.57 (s, 2H; CH), 6.82, 7.23 (2 × d, ^3J(H,H) = 8.0 Hz, 16H; arom), 8.89 (t, ^3J(H,H) = 5.7 Hz, 4H; NH); HRMS-FAB: *m/z*: 891.2334 [M^++Cs] (calcd for $C_{44}H_{46}N_4O_8$ 891.2370).

S-shaped isomer 4: This compound was isolated after the template experiments (see above) in various solvents and purified by preparative TLC (MeOH/AcOEt/$CHCl_3$, 10:25:65). M.p. > 265 °C (decomp); ^{1}H NMR (300 MHz, [D_6]DMSO): $\delta = 0.83–0.98$ (m, 24H; alkyl), 1.23 (s, 2H; CH_2), 1.40–1.70 (m, 12H; alkyl), 4.09 (t, ^3J(H,H) = 6.6 Hz, 4H; OCH_2), 4.19 (t, ^3J(H,H) = 6.6 Hz, 4H; OCH_2), 4.46 (2 × d, ^2J(H,H) = 15.6 Hz, 4H; CH_2), 4.61 (2 × d, ^2J(H,H) = 15.6 Hz, 4H; CH_2), 4.85 (d, ^2J(H,H) = 15.4 Hz, 2H; CH_2), 4.97 (s, 2H; CH), 5.24 (dd, ^2J(H,H) = 15.4 Hz, 4H; CH_2), 5.52 (d, ^2J(H,H) = 15.4 Hz, 2H; CH_2), 7.44 (s, 2H; arom), 7.45 (s, 2H; arom), 8.47 (s, 2H; NH), 8.50 (s, 2H; NH); FTIR (thin film): $\tilde{\nu} = 3242$ (NH), 2951 (CH, CH_2), 1713 (C=O), 1626 cm^{-1} (C=O); FAB-MS: *m/z*: 1399 [M^++Cs] (calcd for $C_{64}H_{74}O_{16}N_{12}$ 1399).

W-shaped compound 5: This compound was isolated after the template experiments (see above) in various solvents and purified by preparative TLC (MeOH/AcOEt/$CHCl_3$, 10:25:65). M.p. > 280 °C (decomp); ^{1}H NMR (300 MHz, [D_6]DMSO): $\delta = 0.83–0.95$ (m, 24H; alkyl), 1.23 (s, 2H; CH_2), 1.43–1.73 (m, 12H; alkyl), 4.10 (t, ^3J(H,H) = 6.7 Hz, 4H; OCH_2), 4.19 (t, ^3J(H,H) = 6.7 Hz, 4H; OCH_2), 4.48 (d, ^2J(H,H) = 15.2 Hz, 4H; CH_2), 4.61 (d, ^2J(H,H) = 15.2 Hz, 4H; CH_2), 4.91 (d, ^2J(H,H) = 15.3 Hz, 4H; CH_2), 4.96 (s, 2H; CH), 5.51 (d, ^2J(H,H) = 15.3 Hz, 4H; CH_2), 7.46 (s, 4H; arom), 8.50 (s, 4H; NH); FTIR (thin film): $\tilde{\nu} = 3251$, 3214 (NH), 2951 (CH, CH_2), 1714 (C=O), 1626 cm^{-1} (C=O); FAB-MS: *m/z*: 1399 [M^++Cs] (calcd for $C_{64}H_{74}O_{16}N_{12}$ 1399).

C-shaped isomer 6: This compound was isolated after the template experiments (see above) in various solvents and purified by preparative TLC (THF/$CHCl_3$, 1:3). M.p. 249–251 °C (decomp); ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 0.84$ (t, ^3J(H,H) = 6.7 Hz, 12H; alkyl), 1.20–1.36 (m, 24H; alkyl), 1.54–1.62 (m, 8H; alkyl), 3.79 (t, ^3J(H,H) = 6.4 Hz, 4H; OCH_2), 3.82 (t, ^3J(H,H) = 6.4 Hz, 4H; OCH_2), 4.04 (d, ^2J(H,H) = 15.6 Hz, 4H; CH_2), 4.65 (d, ^2J(H,H) = 15.6 Hz, 4H; CH_2), 4.97 (s, 2H; CH), 5.06 (d, ^2J(H,H) = 15.7 Hz, 4H; CH_2), 5.31 (d, ^2J(H,H) = 15.7 Hz, 4H; CH_2), 6.60 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 6.73 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 6.88 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 6.93 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 7.44 (s, 4H; arom), 8.05 (s, 4H; NH); ^{1}H NMR (600 MHz, [D_6]benzene): $\delta = 0.8–1.0$ (m, 12H; alkyl), 1.20–1.60 (m, 32H; alkyl), 3.29 (t, ^3J(H,H) = 6.4 Hz, 4H; OCH_2), 3.51 (t, ^3J(H,H) = 6.4 Hz, 4H; OCH_2), 3.81 (d, ^2J(H,H) = 16.0 Hz, 4H; CH_2), 4.12 (d, ^2J(H,H) = 16.0 Hz, 4H; CH_2), 4.52 (s, 2H; CH), 5.77 (d, ^2J(H,H) = 16.0 Hz, 4H; CH_2), 6.60 (d, ^2J(H,H) = 16.0 Hz, 4H; CH_2), 6.63 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 6.69 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 6.95 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 7.83 (d, ^3J(H,H) = 8.8 Hz, 4H; arom), 8.26 (s, 4H; arom), 8.52 (s, 4H; NH); FTIR (thin film): $\tilde{\nu} = 3423$ (NH), 3264 (NH), 2929 (CH, CH_2), 1694 (C=O), 1629 cm^{-1} (C=O); HRMS-FAB: *m/z*: 1647.6584 [M^++Cs] (calcd for $C_{88}H_{98}N_{12}O_{12}Cs$ 1647.6482).

S-shaped compound 7: This compound was isolated after the template experiments (see above) in various solvents and purified by preparative TLC (THF/$CHCl_3$, 1:3). Pale yellow foam; ^{1}H NMR (600 MHz, [D_6]DMSO): $\delta = 0.83–0.86$ (m, 12H; alkyl), 1.22–1.63 (m, 32H; alkyl), 3.76–3.85 (m, 8H; OCH_2), 4.04 (d, ^2J(H,H) = 15.6 Hz, 4H; CH_2), 4.64 (d, ^2J(H,H) = 15.6 Hz, 4H; CH_2), 4.86 (d, ^2J(H,H) = 15.6 Hz, 2H; CH_2), 4.98 (s, 2H; CH), 5.17 (d, ^2J(H,H) = 15.6 Hz, 2H; CH_2), 5.24 (d, ^2J(H,H) = 15.6 Hz, 2H; CH_2), 5.53 (d, ^2J(H,H) = 15.6 Hz, 2H; CH_2), 6.57–6.63 (m,

4H; arom), 6.70–6.76 (m, 4H; arom), 6.85–6.95 (m, 8H; arom), 7.44 (s, 2H; arom), 7.46 (s, 2H; arom), 8.03 (s, 2H; NH), 8.07 (s, 2H; NH); FTIR (thin film) $\tilde{\nu}$ = 3402 (NH), 3248 (NH), 2930, 2859 (CH, CH_2), 1697 (C=O), 1629 cm^{-1} (C=O); HRMS-FAB: *m/z*: 1647.6587 [M^++Cs] (calcd for $C_{88}H_{98}N_{12}O_{12}Cs$ 1647.6482).

***E* and *Z* isomers 10 and 11**: A solution of active ester **2b** (713 mg, 0.713 mmol) in THF (2 mL) was added to a mixture of hydrazine salt (327 mg, 0.476 mmol) and Et_3N (241 mg, 2.38 mmol) in THF (2.5 mL). After stirring for 10 h, the solvent was removed. Column chromatography of the residue (THF/$CHCl_3$, 3:1) gave the *Z* isomer **11** (187 mg, 31%) and the corresponding *E* isomer **10** (THF/$CHCl_3$, 1:1; 155 mg, 26%). The stereochemistry was assigned by subsequent conversion of **11** into **6**.

*E isomer **10***: ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 0.85 (t, ^3J(H,H) = 6.7 Hz, 6H; CH_3), 1.23–1.47 (m, 12H; alkyl), 1.55–1.77 (m, 8H; alkyl), 3.79 (t, ^3J(H,H) = 6.4 Hz, 2H; OCH_2), 3.82 (t, ^3J(H,H) = 6.4 Hz, 2H; OCH_2), 4.07 (d, ^2J(H,H) = 15.6 Hz, 2H; CH_2), 4.66 (d, ^2J(H,H) = 15.6 Hz, 2H; CH_2), 4.94 (d, ^2J(H,H) = 15.5 Hz, 2H; CH_2), 5.00 (s, 2H; CH), 5.59 (d, ^2J(H,H) = 15.5 Hz, 2H; CH_2), 6.61 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 6.74 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 6.89 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 6.94 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 7.50 (s, 2H; arom), 7.82 (s, 2H; arom), 8.08 (s, 1H; NH), 8.09 (s, 1H; NH); FTIR (thin film): $\tilde{\nu}$ = 3422 (NH), 2954, 2930 (CH, CH_2), 1773, 1728, 1698, 1631 (C=O), 1224 cm^{-1} (C-O-C); FAB-MS: *m/z*: 1389, 1391 [M^++Cs] (calcd 1389).

*Z isomer **11***: M.p. 285 °C (decomp); ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 0.85 (t, ^3J(H,H) = 6.7 Hz, 6H; CH_3), 1.23–1.47 (m, 12H; alkyl), 1.55–1.65 (m, 6H; alkyl), 1.74–1.80 (m, 2H; alkyl), 3.79 (t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2), 3.82 (t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2), 4.06 (d, ^2J(H,H) = 15.5 Hz, 2H; CH_2), 4.65 (d, ^2J(H,H) = 15.5 Hz, 2H; CH_2), 4.99 (s, 2H; CH), 5.16 (d, ^2J(H,H) = 15.5 Hz, 2H; CH_2), 5.36 (d, ^2J(H,H) = 15.5 Hz, 2H; CH_2), 6.61 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 6.74 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 6.89 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 6.95 (d, ^3J(H,H) = 8.8 Hz, 2H; arom), 7.48 (s, 2H; arom), 7.79 (s, 2H; arom), 8.07 (s, 1H; NH), 8.08 (s, 1H; NH); FTIR (thin film): $\tilde{\nu}$ = 3248 (NH), 2957, 2915 (CH, CH_2), 1695 (C=O), 1629 (C=O), 1230 cm^{-1} (C-O-C); MS-FAB: *m/z*: 1389, 1391 [M^++Cs] (calcd 1389).

Active ester 13: Oxalyl chloride (1.46 g, 11.5 mmol) and catalytic amount of DMF was added to a suspension of the diacid **12** (93.8 mg, 0.52 mmol) in dichloroethane (5 mL). The mixture was stirred for 3 h, diluted with benzene and evaporated to give the corresponding bischloroanhydride. Et_3N (475 mg, 4.69 mmol) was added to a solution of the latter and 2,4,5-trichlorophenol (463 mg, 2.35 mmol) in dichloroethane (5 mL). After being stirred over night at RT, the reaction mixture was diluted with ethyl acetate. The organic phase was washed with H_2O, 10% aq $KHSO_4$, and brine, then dried and concentrated. Purification of the residue by column chromatography (hexane/benzene, 1:1) gave active ester **13** (256 mg, 91%) as a colorless solid. M.p. 99–100 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.29 (d, ^2J(H,H) = 7.1 Hz, 1H; CH_2), 2.51 (d, ^2J(H,H) = 7.1 Hz, 1H; CH_2), 4.21 (s, 2H; CH), 7.05 (s, 2H; CH), 7.34 (s, 2H; arom), 7.56 (s, 2H; arom); ^{13}C NMR ($CDCl_3$): δ = 54.5 (CH_2), 73.9 (CH), 125.8 (C=C), 126.5 (arom), 130.9 (arom), 131.5 (arom), 132.1 (arom), 143.0 (arom), 145.7 (arom), 154.5 (CH=CH), 161.6 (C=O); FTIR (thin film): $\tilde{\nu}$ = 3090–2980 (CH, CH_2), 1740 (C=O), 1216 cm^{-1} (C-O-C); HRMS-FAB: *m/z*: 538.8777 [M^+] (calcd for $C_{21}H_{10}Cl_6O_4$ 538.8761).

Hydrazides 14 and 15: A solution of active ester **13** (24.4 mg, 0.045 mmol) was added to a solution of hydrazine hydrochloride **1a**[10] (25.6 mg, 0.045 mmol) in Et_3N (22.9 mg, 0.23 mmol) and $CHCl_3$ or benzene (5 mL). After stirring for 1.5 h, the organic layer was washed with H_2O and brine, dried, and concentrated. The residue was purified by preparative TLC ($CHCl_3$/MeOH/AcOEt, 3:1:2) to give equal amounts of hydrazides **14** and **15** as yellow foams. The stereochemistry was not assigned.

The more polar compound: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.98 (m, 12H; alkyl), 1.47–1.71 (m, 6H; alkyl), 2.28 (br s, 2H; CH_2), 4.14–4.30 (m, 2H; CH), 4.41 (d, ^2J(H,H) = 16.0 Hz, 2H; CH_2), 4.83 (d, ^2J(H,H) = 16.0 Hz, 2H; CH_2), 5.00 (d, ^2J(H,H) = 16.0 Hz, 2H; CH_2), 5.33 (d, ^2J(H,H) = 16.0 Hz, 2H; CH_2), 5.79 (br s, 2H; NH), 6.89 (s, 2H; arom), 7.33 (s, 2H; CH); FTIR (thin film): $\tilde{\nu}$ 3419 (NH), 3260 (NH), 2952 (CH, CH_2), 1731 (C=O), 1713 (C=O), 1616, 55, 1454, 1265 cm^{-1} (C–N); HRMS-FAB: *m/z*: 673.2995 [M^+] (calcd for $C_{35}H_{41}N_6O_8$ 673.2986).

The less polar compound: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.97 (m, 12H; alkyl), 1.45–1.70 (m, 6H; alkyl), 2.30 (br s, 2H; CH_2), 4.13–4.31 (m, 2H; CH), 4.40 (d, ^2J(H,H) = 15.9 Hz, 2H; CH_2), 4.82 (d, ^2J(H,H) = 15.9 Hz, 2H; CH_2), 5.06 (d, ^2J(H,H) = 15.9 Hz, 2H; CH_2), 5.26 (d, ^2J(H,H) = 15.9 Hz, 2H; CH_2), 5.89 (br s, 2H; NH), 6.87 (s, 2H; arom), 7.33 (s, 2H; CH); FTIR (thin film): $\tilde{\nu}$ = 3392 (NH), 3260 (NH), 2952 (CH, CH_2), 1731 (C=O), 1714 (C=O), 1617, 1555, 1454, 1263 cm^{-1} (C–N); HRMS-FAB: *m/z*: 673.2989 [M^+] (calcd for $C_{35}H_{41}N_6O_8$ 673.2986).

Acknowledgments: We are grateful to the Skaggs Foundation and the National Institutes of Health for support, and to the Lucille P. Markey Charitable Trust and The NIH Shared Instrumental grant 1 S10 RR07273–01 for the ESI-MS facilities. We thank Prof. F. de Jong and Prof. M. R. Ghadiri for advice on kinetics, Dr. R. S. Meissner for the preliminary titrations and Dr. S. Mecozzi for providing volume calculations. The Ministerio de Educación y Cultura (Spain) provided fellowship support to J.S., and the Knut and Alice Wallenberg Foundation provided fellowship support to G.H.

Received: December 12, 1997 [F928]

[1] a) C. J. Pederson, *J. Am. Chem. Soc.* **1967**, *89*, 7017– 7036; b) C. J. Pederson, *Angew. Chem.* **1988**, *100*, 1053–1059; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021–1027; c) L. Mandolini, *Pure Appl. Chem.* **1986**, *58*, 1485–1492; d) S. Capobianchi, G. Doddi, G. Ercolani, J. W. Keyes, P. Mencarelli, *J. Org. Chem*. **1997**, *62*, 7015–7017; e) D. B. Amabilino, J. F. Stoddart, *Chem. Rev.* **1995**, *95*, 2725–2828; f) F. Vögtle, T. Dünnwald, T. Schmidt, *Acc. Chem. Res.* **1996**, *29*, 451–460; g) S. Anderson, H. L. Anderson, J. K. M. Sanders, *ibid*. **1993**, *26*, 469–475; h) R. Hoss, F. Vögtle, *Angew. Chem.* **1994**, *106*, 389–398; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 375–384. For template effects in self-assembly see: i) B. Hasenknopf, J.-M. Lehn, B. O. Kneisel, G. Baum, D. Fenske, *ibid*. **1996**, *108*, 1987–1990 and **1996**, *35*, 1838–1840; j) D. Philp, J. F. Stoddart, *ibid*. **1996**, *108*, 1242–1286 and **1996**, *35*, 1154–1196; k) R. G. Chapman, J. C. Sherman, Tetrahedron **1997**, *53*, 15911–15945. See also reviews by D. H. Busch, J.-P. Sauvage, J. F. Stoddart, and J. K. M. Sanders, in *Comprehensive Supramolecular Chemistry*, *Vol. 9* (Eds.: J.-P. Sauvage, M. W. Hosseini), Pergamon, **1996**.

[2] a) J. A. Bryant, M. T. Blanda, M. Vincenti, D. J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 2167–2172; b) J. C. Sherman, C. B. Knobler, D. J. Cram, *ibid.* **1991**, *113*, 2194–2204; c) D. J. Cram, M. E. Tanner, C. B. Knobler, *ibid.* **1991**, *113*, 7717–7727.

[3] a) R. G. Chapman, N. Chopra, E. D. Cochien, J. C. Sherman, *J. Am. Chem. Soc.* **1994**, *116*, 369–370; b) R. G. Chapman, J. C. Sherman, *ibid.* **1995**, *117*, 9081–9082; c) N. Chopra, J. C. Sherman, *Supramol. Chem.* **1995**, *5*, 31–37; d) K. Nakamura, C. Sheu, A. E. Keating, K. N. Houk, J. C. Sherman, R. G. Chapman, W. L. Jorgensen, *J. Am. Chem. Soc.* **1997**, *119*, 4321–4322; e) N. Chopra, J. C. Sherman, *Angew. Chem.* **1997**, *109*, 1828–1830; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1727–1729.

[4] a) P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven, D. N. Reinhoudt, *Angew. Chem.* **1994**, *106*, 2437–2440; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2345–2348; b) A. M. A. van Wageningen, P. Timmerman, J. P. M. van Duynhoven, W. Verboom, F. C. J. M. van Veggel, D. N. Reihoudt, *Chem. Eur. J.* **1997**, *3*, 639–654.

[5] This phrase first appeared as a title of a lecture by D. J. Cram.

[6] J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, *Science* **1997**, *277*, 1793–1796.

[7] D. M. Rudkevich, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 9911–9912.

[8] R. K. Castellano, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1996**, *118*, 10002–10003.

[9] a) D. J. Cram, H.-J. Choi, J. A. Bryant, C. B. Knobler, *J. Am. Chem. Soc.* **1992**, *114*, 7748–7765; b) J. R. Moran, J. L. Ericson, E. Dalcanale, J. A. Bryant, C. B. Knobler, D. J. Cram, *ibid.* **1991**, *113*, 5707–5714.

[10] a) R. S. Meissner, J. Rebek, Jr., J. de Mendoza, *Science* **1995**, *270*, 1485–1488; b) R. S. Meissner, X. Garcias, S. Mecozzi, J. Rebek, Jr., *J. Am. Chem. Soc*. **1997**, *119*, 77–85.

[11] Recently, Sanders et al. described *thermodynamically* controlled covalent macrocyclizations by predisposition of building blocks in a reaction mixture, see: S. J. Rowan, D. G. Hamilton, P. A. Brady,

0947-6539/98/0408-1456 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 8

J. K. M. Sanders, *J. Am. Chem. Soc.* **1997**, *119*, 2578–2579 and references therein. No solvent effect was discussed.

[12] Part of this work was published as a preliminary communication: Y. Tokunaga, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1997**, *109*, 2770–2773; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2656–2659.

[13] F. Mohamadi, N. G. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440–467.

[14] D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1997**, *109*, 877–879; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 846–848.

[15] A rough calculation indicates that the capsule is some 3 kcal mol^{-1} more stable in benzene than in chloroform.

[16] A. Kumar, G. Wagner, R. R. Ernst, K. Wütrich, *J. Am. Chem. Soc.* **1981**, *103*, 3654–3658.

[17] G. G. Hammes, A. C. Park, *J. Am. Chem. Soc.* **1968**, *90*, 4151–4157. With this approach, the K_D value of 3.2×10^9 M^{-1} in $CDCl_3$ for smaller glycoluril-based dimers (tennis balls) was determined from EXSY measurements. T. Szabo, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 6193–6194.

[18] In benzene, the K_D value must be at least two orders of magnitude higher. Direct EXSY experiment in [D_6]benzene is difficult, since benzene competes with camphor and camphorquinone for the cavity; the formation of several complexes was detected by ^{1}H NMR spectroscopy.

[19] J. Kang, G. Hilmersson, J. Santamaría, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 3650–3656.

[20] a) M. A. Aoki, K. Nakashima, S. Tsutsui, S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1993**, 347–354; b) K. Hanabusa, Y. Matsumoto, T. Miki, T. Koyama, H. Shirai, *J. Chem. Soc. Chem. Commun.* **1994**, 1401–1402; c) H. T. Stock, N. J. Turner, R. McCague, *J. Chem. Soc. Chem. Commun.* **1995**, 2063–2064; d) G. T. Crisp, J. Gore, *Synth. Commun.* **1997**, *27*, 2203–2215.

[21] The role of hydrogen bonding in stabilization and/or break-down of the tetrahedral zwitter-ionic intermediate has been discussed; see: a) C.-W. Su, J. Watson, *J. Am. Chem. Soc.* **1974**, *96*, 1854–1857; b) L. Wang, H. Zipse, *Liebigs Ann.* **1996**, 1501–1509; c) H. Zipse, L. Wang, K. N. Houk, *ibid.* **1996**, 1511–1522.

[22] This may be the case when no autocatalysis is observed in potentially autocatalytic systems. Thus, $k_{cat}K_D^{-1/2}K_T[\mathbf{6}\cdot\mathbf{6}]^{1/2} \approx 0$, even at high values of k_{cat}. In known nonenzymatic self-replicating systems based on oligonucleotides and peptides, there should be a very similar situation when K_D is very high and K_T is low. See: a) G. von Kiedrowski, *Angew. Chem.* **1986**, *98*, 932–934; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 932–935; b) G. von Kiedrowski, B. Wlotzka, J. Helbing, *ibid.* **1989**, *28*, 1235–1237; c) J. T. Goodwin, D. G. Lynn, *J. Am. Chem. Soc.* **1992**, *114*, 9197–9198; d) D. H. Lee, J. R. Granja, J. A. Martinez, K. Severin, M. R. Ghadiri, *Nature* **1996**, *382*, 525–528; e) K. Severin, D. H. Lee, J. A. Martinez, M. R. Ghadiri, *Chem. Eur. J.* **1997**, *3*, 1017–1024. However, since those systems operate in water, the values of K_D must be still several orders of magnitude lower than in our case. This means that the dimer dissociation rates in their case must be much faster, so the catalyst is not inhibited. For the kinetic analysis of templated self-replicating systems that are based on molecular recognition see: a) J. S. Nowick, Q. Feng, T. Tjivikua, P. Ballester, J. Rebek, Jr., *J. Am. Chem. Soc.* **1991**, *113*, 8831–8839; b) D. N. Reinhoudt, D. M. Rudkevich, F. de Jong, *ibid.* **1996**, *118*, 6880–6889.

[23] In another experiment, the reaction between **1** and **2a** was performed in benzene, *p*-xylene, and chloroform in the presence of 1 equiv of 1-adamantanecarboxyamide that is known to be a good guest for dimeric **16**.[10] The enhanced yields of **3** were observed in benzene and *p*-xylene, but not in chloroform, wherein the carboxamide is not encapsulated.

[24] See for example: A. Imhof, D. J. Pine, *Nature* **1997**, *389*, 948–951, and references therein.

[25] a) E. E. Simanek, M. Mammen, D. M. Gordon, D. Chin, J. P. Mathias, C. T. Seto, G. M. Whitesides, *Tetrahedron* **1995**, *51*, 607–619; b) E. E. Simanek, M. I. M. Wazeer, J. P. Mathias, G. M. Whitesides, *J. Org. Chem.* **1994**, *59*, 4904–4909. See also ref. [27c].

[26] Y. Kobuke, T. Fueno, J. Furukawa, *J. Am. Chem. Soc.* **1970**, *92*, 6548–6553. See also: M. Nishio, Y. Umezawa, M. Hirota, Y. Takeuchi, *Tetrahedron* **1995**, *51*, 8665–8701.

[27] a) P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom, F. C. J. M. van Veggel, W. P. van Hoorn, D. N. Reinhoudt, *Chem. Eur. J.* **1995**, *1*, 132–143; b) I. Higler, P. Timmerman, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1996**, *61*, 5920–5931; c) I. Higler, W. Verboom, F. C. J. M. van Veggel, F. de Jong, D. N. Reinhoudt, D. N. *Liebigs Ann./Recueil* **1997**, 1577–1586.

[28] L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469–472.

[29] Y. Tokunaga, J. Rebek, Jr., *J. Am. Chem. Soc.*, **1998**, *120*, 66–69.

[30] C. L. Perrin, T. J. Dwyer, *Chem. Rev.* **1990**, *90*, 935–967.