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NMR Studies of the Reversible Dimerization and Guest Exchange Processes of Tetra Urea Calix[4]arenes Using a Derivative with Lower Symmetry

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Abstract: The calix[4]arene derivative **3** substituted at the wider rim by four urea residues was prepared in three steps from the corresponding *tert*-butyl calix[4]arene **2a**. Due to the different ether residues attached to the narrow rim its constitution is C_{2v}-symmetrical, and the hydrogen bonded dimers **3·3** formed in benzene have C_2-symmetry. Thus, the ^{1}H NMR spectrum not only gives an unambiguous proof for the dimerization but also allows the determination of the exchange rates for four sets of protons by NOESY experiments. The rate constant for the dissociation/dimerization $k_d = 0.26 \pm 0.06$ s^{-1} is in reasonable agreement with the rate constant for the exchange of included and free benzene $k_e = 0.47 \pm 0.1$ s^{-1}. It was also shown that the formation of dimers is induced by the presence of suitable guest molecules like benzene.

Introduction

Self-organization is found as a general principle in nature, and consequently the self-assembly of suitably functionalized synthetic molecules to well defined supramolecular structures in two or three dimensions has become a topic of current interest.[1] Various examples of self-complementary molecules have been reported which form definite dimers in solution via hydrogen bonds or via apolar forces.[2] When this dimerization occurs between suitably curved, concave molecules, the formation of molecular containers can be achieved which are able to encapsulate smaller guest molecules in a reversible manner. The first example reported by Rebek and Mendoza[3] has been modified in numerous ways meanwhile.[4,5]

Calix[4]arene derivatives which are fixed in the cone conformation by O-alkylation offer a more or less preorganized cavity. They are easily available and may be functionalized in various ways by substitution at the wider rim.[6,7] The organiza-

tion of *N,N′*-dialkyl or -diaryl urea derivatives in the crystal lattice via hydrogen bonds between the NH- and C=O-functions[8] has inspired the attachment of urea functions to a calixarene skeleton[9] in order to obtain molecules **1** which are therefore simultaneuously equipped with hydrogen bond donor and acceptor sites. These molecules are self-complementary and able to associate via hydrogen bonds in apolar organic solvents.[10,11]

The formation of dimers **1·1** was first deduced from the ^{1}H NMR pattern.[10] The splitting of the signal of the aromatic protons of the calixarene skeleton into two *meta* coupled doublets and the large separation of the singlets for the NH-protons are especially characteristic. Additional evidence came from high field shifted signals of the guest included in the cavity of such dimers.[12,13] In polar solvents, like DMSO-d_6, only one singlet for the aromatic calixarene protons and two closely spaced singlets for the aromatic protons are found, indicating that no dimers are formed.

We could prove this dimerization of tetra urea calix[4]arenes **1** in apolar solvents independently by ^{1}H NMR spectroscopy,

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(13) For the first example of a definite dimer formed between different calix[4]arenes substituted at the wider rim by pyridine and carboxylic acid functions no inclusion of guest molecules was reported. Kok, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255–8258.
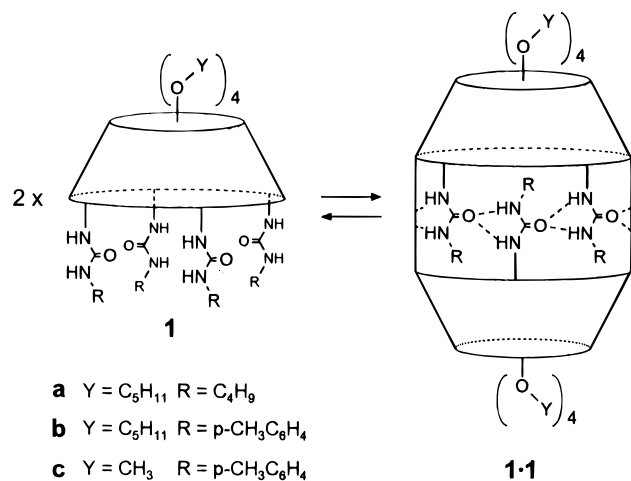

Figure 1. Schematic representation of the reversible dimerization of tetra urea calix[4]arenes **1**.

since a solution, containing two different urea derivatives, e.g., **1a** and **1b**, shows signals of the heterodimer **1a·1b** in addition to those of the homodimers **1a·1a** and **1b·1b**.[14] This demonstrates also that dimerization is a general phenomenon for urea derivatives of type **1**, which seems to be independent both from the ether residues Y attached to the phenolic oxygens and the residues R at the urea unit.[15] In addition we recently confirmed the dimerization for one example by single crystal X-ray analysis, which allowed for the first time an exact geometrical description of such a dimer.[16] A highly disordered guest molecule (benzene) was found in the cavity formed by the two calixarenes supporting the encapsulation properties of these self-assembled dimers, already suggested by Rebek et al.[12]

Due to their easy synthetic access (in comparison to the other hydrogen bonded capsules described in the literature) and to their nearly unlimited potential of modification, these dimers of urea calix[4]arenes may also gain some practical importance. Therefore a more detailed knowledge of their kinetic and thermodynamic stability is desirable. Obviously the dimers **1·1** are stable on the usual NMR time scale, and their monomeric form has not yet been observed in equilibrium with the dimer. For **1b** in CDCl$_3$ the dimer is the only species detectable by ^{1}H NMR down to concentrations of about 2 mM, while further dilution leads to ill defined associates. Rebek et al. were able to follow the appearance of an additional signal, attributed to benzene trapped in the cavity, as a function of time after the addition of benzene to a solution of the dimer **1·1** in *p*-xylene-d_{10}.[12] They estimated a half-life time of about 8 min for this uptake process which must be related somehow to the reversible dissociation of the dimer. An association constant of $K = 230$ M^{-1} was deduced for the encapsulation. Our own experiments show, on the other hand, that the formation of heterodimers is complete in less than 2 min after mixing two solutions containing the homodimers.

We report here for the first time a detailed and systematic NMR study of these exchange processes which was possible using a dimer **3·3** with reduced symmetry in which the two calix[4]arene parts are distinguishable by NMR. In addition
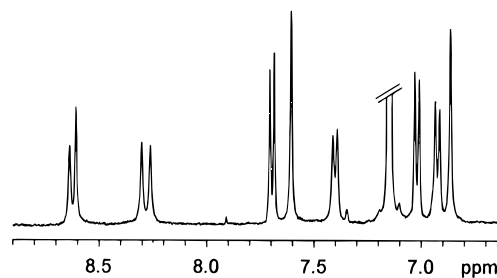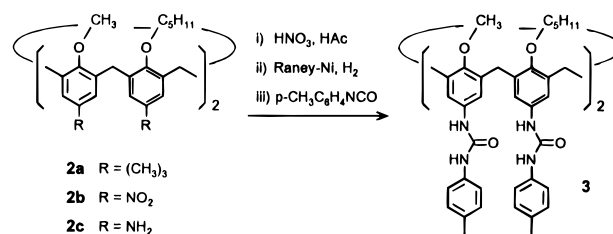

Figure 2. Partial ^{1}H NMR spectrum (400 MHz, 298 K) of **3** in benzene-d_6 containing ∼2% DMSO-d_6.

Scheme 1

we show that the dimerization of tetra urea calix[4]arenes is a template driven process

Results and Discussion

Synthesis and Characterization. Compound **3** was synthesized as previously described for compounds **1** by treatment of the corresponding amine **2c** with a slight excess of *p*-tolylisocyanate in chloroform at room temperature.[14] The coupling gave exclusively the tetra urea calix[4]arene **3** which was obtained in 89% yield as a colorless solid after recrystallization from chloroform/methanol. The amino derivative **2c** was obtained from the *tert*-butyl calixarene derivative **2a** in two steps. *Ipso* nitration of **2a** yielded the *p*-nitro calixarene **2b**. Reduction with hydrogen and Raney nickel in toluene gave the desired amino compound **2c** in high yield (Scheme 1).

The ^{1}H NMR spectrum of compound **3** in benzene-d_6, containing ∼2% DMSO-d_6, is in agreement with the monomeric, C_{2v}-symmetrical molecule.[17] Especially characteristic are the protons in the region of 8.7–6.7 ppm (Figure 2) where four singlets for the NH-protons and four doublets with *ortho* coupling for the protons of the tolyl residues were observed. The aromatic protons of the calixarene skeleton appeared as two singlets and in addition in the region between 4.4–3.1 ppm one pair of doublets was found for the protons of the bridging methylene groups.

Due to the fact that the methoxy groups can pass the annulus of a calix[4]arene the single molecule **3** could assume, in principle, the *partial cone* or *1,3-alternate* conformation with one or two inverted anisol units. Figure 2 clearly shows that monomeric **3** exists exclusively in the *cone* conformation, while for instance the tetranitro calix[4]arene **2b** is present as a mixture of 91% *partial cone* and 9% *cone* conformers in CDCl$_3$.[18]

General Symmetry Considerations. Calix[4]arenes **1** with four identical ether and urea groups have a C_{4v}-symmetrical constitution. Their dimers **1·1** are composed of pairs of enantiomers with opposite chirality due to the opposite direction

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(15) Dimerization has also been reported for some calix[4]arenes substituted by two urea residues at the wider rim. Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476–3481.

(16) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996** 2533–2534.

(17) The addition of small amounts of polar solvents to solutions in apolar solvents leads to the formation of monomeric species.

(18) Under similar conditions, also the monomeric form of the tetramethoxy urea derivative **1c** exists only in the *cone* conformation, and a recently described "conformational control through self-assembly" could not be observed as such in our experiments. Compare: Castellano, R. K.; Rudkevich, D. M.; Rebek, Jr., J. *J. Am. Chem. Soc.* **1996**, *118*, 10002–10003.
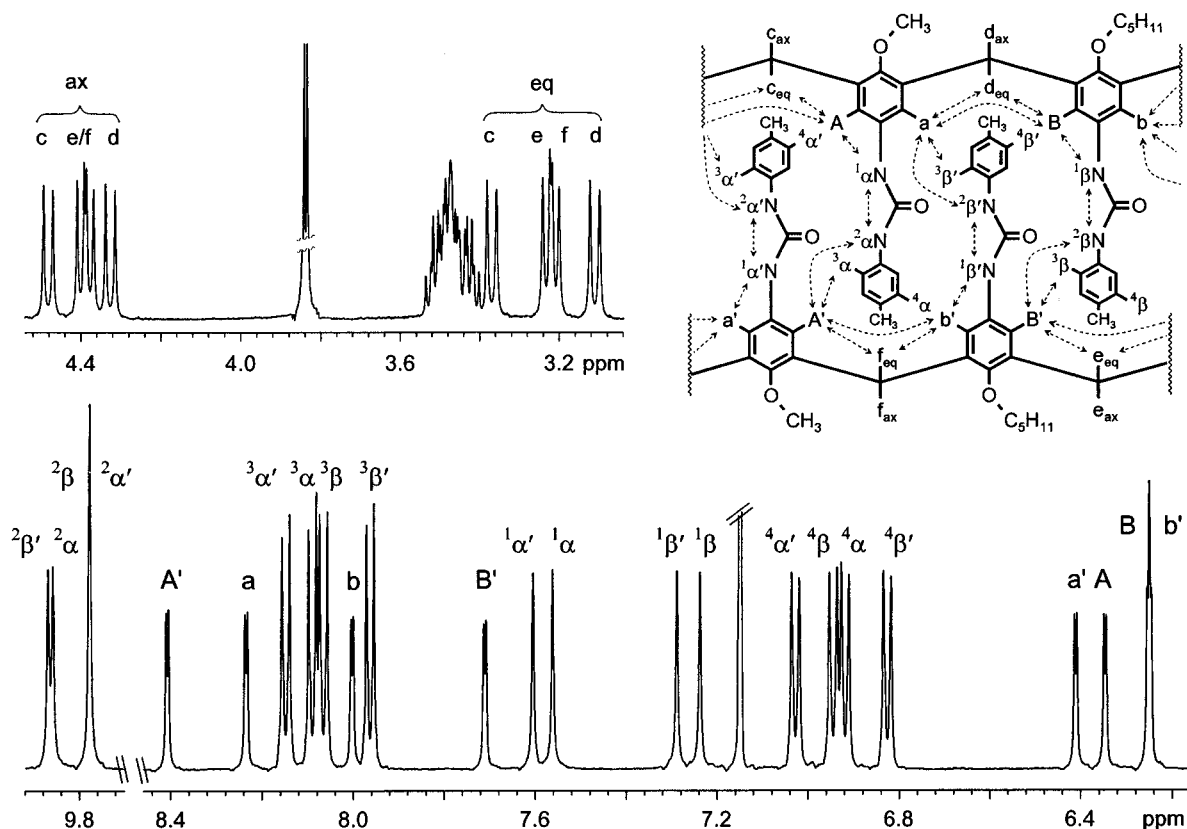
Figure 3. Partial ^{1}H NMR spectrum (500 MHz, 298 K) of **3** in benzene-d_6. The schematic formula shows the NOEs/ROEs ($\leftarrow - \rightarrow$) observed in the dimer **3·3** and the labeling scheme for the protons.

of the carbonyl groups. This directionality reduces the symmetry of each subunit to C_4. Interdigitation of the urea substituents converts the C_4 axis of each monomer to an overall S_8 axis for the dimer.

Calix[4]arene **3** has effective C_{2v} symmetry which consequently is reduced to C_2 when the urea substituents form an ordered circular array of hydrogen bonds with a definite orientation of the C=O groups. However, the lower symmetry of **3** prevents the formation of a meso dimer with an S_n axis. Thus the C_2 axis is the only symmetry element in the dimer, and, in particular, the two calixarene units are nonequivalent within the dimer.

This symmetry is entirely reflected by the ^{1}H NMR spectrum (Figure 3). The dimer **3·3** contains four different phenolic units. Each has two different aromatic protons. This leads to eight doublets with *meta* coupling for the protons a, a′, A, A′, b, b′, B, and B′ which can be clearly discerned in Figure 3. (For the exact assignment, see below.) Correspondingly for the protons of the NH groups directly connected to the calixarene skeleton the four singlets $^1\alpha$, $^1\alpha'$, $^1\beta$, and $^1\beta'$ are found in the region between 7.2 and 7.7 ppm, while the remaining NH resonances $^2\alpha$, $^2\alpha'$, $^2\beta$ and $^2\beta'$ appear as three signals around 9.7–9.9 ppm in the ratio 2:1:1. In the region of 3.1–4.5 ppm there are eight doublets found for the protons of the methylene bridges c, d, e, and f next to two singlets for the methoxy protons. The *p*-methyl groups of the four different urea residues give singlets in the ratio 1:2:1. The aromatic protons of these tolyl residues $^3\alpha$, $^3\alpha'$, $^3\beta$, and $^3\beta'$ appear as four pairs of *ortho* coupled doublets, showing the identity of both sides due to fast rotation around the aryl–nitrogen bond. The multiplet in the region ot 3.54–3.4 ppm is attributed to the O-CH$_2$ protons of the pentyl ether residues.

This NMR pattern unambiguously proves that **3** exists exclusively in form of dimers **3·3** which are stable on the NMR time scale.

^{1}H NMR Assignmemt of the Resonances of Calixarene 3. For the assignment the different protons in the dimer **3·3** are labeled as follows (Figures 3 and 4).

(a)Different letters are used for aromatic protons belonging to rings with different substituents: A/a refers to anisole rings and B/b to rings with a pentyl ether substituent.

(b)Capital and small letters are used to distinguish between nonequivalent protons in the same aromatic ring.

(c) A dash is used to differentiate between protons belonging to the two different calixarenes in the dimer.

This labeling convention is based on the fact that a phenol ether ring of a given type (e.g., an anisole ring) is facing two rings of different types in the opposite calixarene in the dimer (an anisole and a pentyloxy substituted ring). Capital letters are assigned to the protons pointing to a ring of the same type, and small letters are used for the protons pointing to a ring of the opposite type. The two calixarenes in the dimer differ by the orientation of their urea carbonyl groups. A dash is used for both aromatic protons of a phenol ether ring if the carbonyl group of the urea unit bound to it, is pointing to the side where an aromatic ring of the same type is located in the opposite calixarene.

Initially TOCSY experiments were used to correlate protons belonging to the same spin system such as protons belonging to the same aromatic ring (e.g., A, a; B, b; etc.) or pairs of methylene protons in the calixarene skeleton. HMBC experiments were used as previously described to assign protons belonging to aromatic rings with different substituents.[19] In this case the carbon atoms bearing the ether residues show a three bond coupling to both the aromatic protons of the same ring and the α-protons in the aliphatic ether group. This experiment shows that the signals at 8.41, 8.23, 6.41, and 6.35 ppm belong

(19) Molins, M. A.; Nieto, P. M.; Sánchez, C.; Prados, P.; de Mendoza, J.; Pons, M. *J. Org. Chem.* **1992**, *57*, 6924–6931.
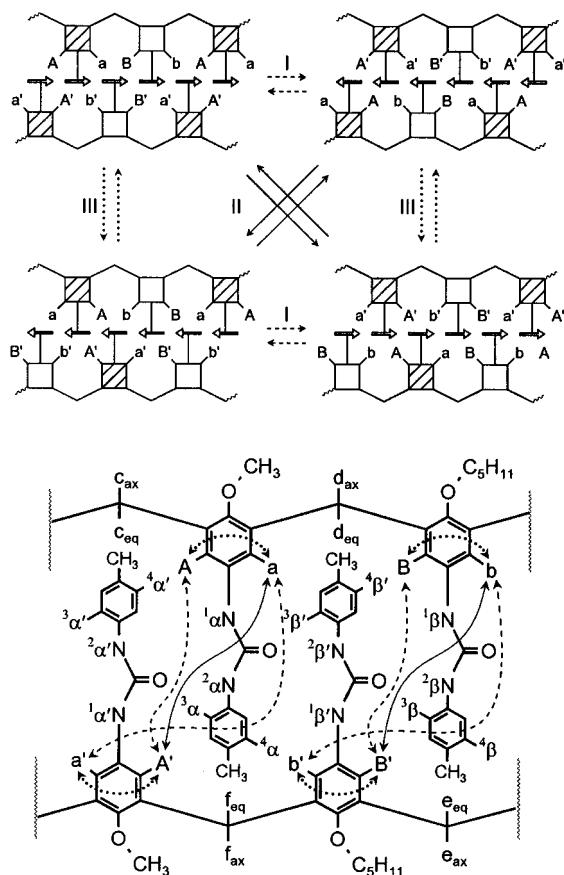
Figure 4. Schematic representation of the homomerization pathways for the dimer **3·3** (upper part). Observed exchange cross-peaks in NOESY experiments are indicated as arrows in the schematic formula of the dimer **3·3** (lower part).

to protons located in O-methylated phenolic units (A, a, A′, a′), while those at 8.01, 7.71, 6.26, and 6.24 ppm are resonances of protons in pentyl ether rings (B, b, B′, b′).

NOESY spectra show close contacts between aromatic protons in adjacent rings of the same calixarene (i.e., B-a, A-b, B′-a′, and A′-b′) and to those of the bridging methylene groups (i.e., A-c_{eq}-b, B-d_{eq}-a, B′-e_{eq}-a′, and A′-f_{eq}-b′). These NOEs and the information from TOCSY spectra provide the complete connectivity around each calixarene in the dimer. This could be extended to the urea substituents by consecutive correlations between aromatic-NH, NH-NH, and NH-tolyl protons. In order to complete the assignment it is necessary to establish the relative position of the two calixarene rings. This could be accomplished by the observation of a full set of ROE contacts between aromatic protons in the skeleton of one calixarene to both urea and tolyl protons from the opposite calixarene. All these connectivities are summarized in the schematic representation of the dimer **3·3** in Figure 3.

Homomerization of Dimers. The fact that the two calixarene units forming the dimer can be distinguished by NMR gives the unique chance to study in detail the dynamic exchange or regrouping processes at equilibrium in these dimers and to elucidate their mechanisms. For instance the aromatic protons of the anisole units, which are equivalent in the monomeric calix[4]arene **3**, are found in the four positions a, a′, A, and A′ in the dimer **3·3**. This allows, in principle, the study of three site exchange processes, namely a → a′, a → A, and a → A′, while the two different aromatic protons in dimers of calix[4]-arenes **1** allow the study of only one exchange process.

These exchange processes can be realized by the following pathways (Figure 4).

(I) The change of the direction of the C=O···HN hydrogen bonds transfers a → a′, A → A′, b → b′, etc. This process can occur either *within a dimer* by a more or less concerted rotation (flipping) of the urea moieties around the aryl-NH bonds or via *dissociation* of the dimer followed by *recombination*.

(II) The dissociation and recombination of the dimer occurs without a change in the direction of the carbonyl groups, but the two subunits are turned by 90° with respect to each other. This process transfers a → A′, A → a′, b → B′, etc.

(III) The dissociation and recombination occurs with a rotation of the subunits by 90° accompanied by a change in the direction of the carbonyl groups. This is formally a combination of the processes I and II and it transfers a → A, A → a, b → B, etc.

A fourth possibility for the recombination, namely the formation of the starting dimer, cannot be observed by NMR. Figure 4 summarizes all these possibilities.

Exchange information is normally obtained from EXSY experiments, which are identical to NOESY experiments. Therefore discrimination between exchange and cross-relaxation (NOE) cross-peaks which have the same sign, except for very small molecules, has to be exercised carefully. Rotating frame experiments provide a useful way of discriminating between exchange and direct cross-relaxation as the corresponding cross-peaks have opposite signs. Complications arise, however, from three spin effects and TOCSY transfer since both give rise to peaks of the same sign as those originating from exchange. Furthermore, differential off-resonance effects complicate the quantitative interpretation of cross-peak integrals. In the case of the dimer **3·3** cross-peaks from the process III correlate sites between which scalar coupling exists, and therefore TOCSY contamination of the exchange cross peaks cannot be neglected. Off-resonance ROESY[20] strongly attenuates TOCSY transfer and offset-dependent intensity variations. In this experiment spin-locking is carried out at an effective field which forms an angle Θ with the external magnetic field B_0. The cross-relaxation rate (σ) for this experiment is a linear combination of those effective in the laboratory frame σ_N (i.e., in NOE experiments, $\Theta = 0$) and in the on-resonance rotating frame σ_R (i.e., in ordinary ROE experiments, $\Theta = 90°$). For molecules outside the extreme narrowing condition σ_N and σ_R have different sign. Therefore, there is an angle for which the two contributions mutually cancel, and cross-relaxation is eliminated leaving only exchange cross-peaks. Figure 5 shows a comparison of NOESY, on-resonance and off-resonance ROESY ($\Theta = 35.6°$) spectra of dimer **3·3** in benzene-d_6 which demonstrates that the indicated cross peaks are in fact exchange cross-peaks.

Rate Constants. The rate constants were derived from NOESY experiments according to the method described by Abel et al.[21] in which the matrix containing measured peak volumes (**A**) is related to the matrix containing all pairwise exchange and cross-relaxation rates (**L**) by the equation

$$\mathbf{A} = \mathbf{P}e^{(\mathbf{L}t_m)}$$

where t_m is the mixing time and **P** is an array containing the relative populations of each site. Therefore **L** is defined to be

$$\mathbf{L} = \frac{1}{t_m} \ln(\mathbf{A}\mathbf{P}^{-1})$$

(20) Desvaux, H.; Berthault, P.; Birlirakis, N.; Goldman, M. *J. Magn. Reson.* **1994**, *108*, 219−229.
(21) Abel, E. W.; Coston, T. P. J.; Orrell, K. G.; Sik, V.; Stephenson, D. *J. Magn. Reson.* **1986**, *70*, 34−53.
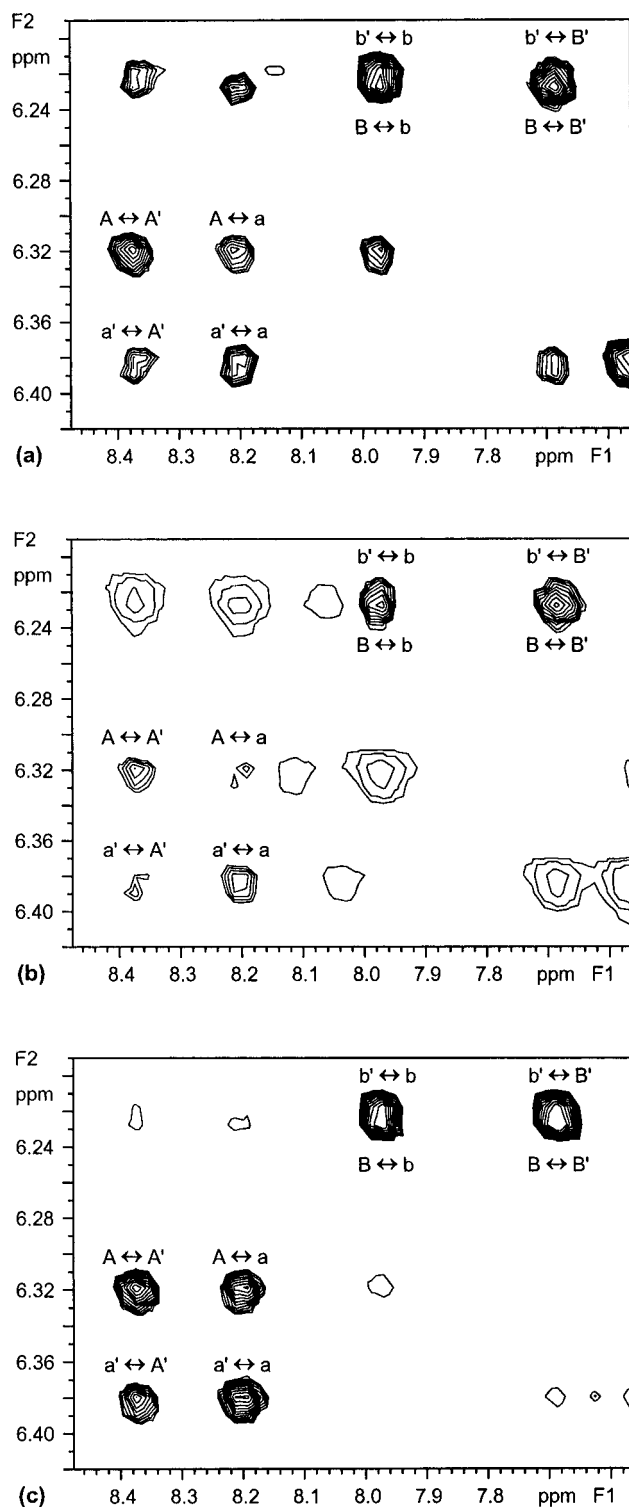
Figure 5. Partial 2D NMR spectra (500 MHz, 298 K) of **3** in benzene-d_6, $t_m = 300$ ms: NOESY (a), ROESY (b), and off-resonance ROESY ($\Theta = 35.6°$) (c). Negative cross-peaks in (b) arising from cross-relaxation are plotted with a reduced number of contours.

Table 1. Rate Constants $k_I - k_{III}$ for the Three Observable Homomerization Pathways of Dimers **3·3** in Benzene-d_6 Derived from NOESY Experiments with Different Mixing Times t_m (500 MHz, 298 K)

entry	t_m [ms]	k_I [s^{-1}]	k_{II} [s^{-1}]	k_{III} [s^{-1}]
1[a]	200	0.054 ± 0.004	0.041 ± 0.004	0.053 ± 0.003
2[a]	1000	0.059 ± 0.004	0.069 ± 0.004	0.054 ± 0.003
3[b]	500	0.151 ± 0.013	0.078 ± 0.010	0.038 ± 0.005
4[b]	1000	0.149 ± 0.040	0.073 ± 0.008	0.051 ± 0.008
5[c]	300	0.074 ± 0.009	0.072 ± 0.006	0.056 ± 0.005
6[c]	500	0.069 ± 0.025	0.065 ± 0.015	0.059 ± 0.028
7[c]	1000	0.075 ± 0.007	0.073 ± 0.007	0.063 ± 0.007
8[c,d]	500	0.064 ± 0.012	0.080 ± 0.026	0.066 ± 0.022
av		0.066[e]	0.069	0.055

^{a} $c(3) = 7.3$ mg mL^{-1}, freshly prepared. ^{b} Solution of a stored for 3 months. ^{c} $c(3) = 6.3$ mg mL^{-1}, freshly prepared and sealed. ^{d} XD-NOESY experiment. ^{e} Calculated without entries 3 and 4.

intensity of the cross-peaks used to quantify the rates of exchange. A control XD-NOESY[22] experiment in which the urea NH protons were removed from the relaxation pathways showed that indeed the rates obtained by the full relaxation plus exchange matrix method are pure exchange rates, not affected by cross-relaxation. In a XD-NOESY experiment selected resonances are inverted in the middle of the relaxation time, and, therefore, cross-relaxation to these protons is effectively suppressed. The intensities of the exchange cross-peaks are different in NOESY and XD-NOESY experiments with the same mixing time, but the rates extracted by the method of Abel et al. were effectively the same (Table 1).

Rate constants for the three exchange processes calculated from different experiments are collected in Table 1. Comparing these values it must be considered that the experimental error for k_{II} should be slightly higher, since the cross peaks from which this rate was derived fall closer to the diagonal. Therefore, with the exception of entries 3 and 4 of k_I (*vide infra*) it can be stated that all three exchange processes occur with the same rate of $k_{I-III} = 0.065 \pm 0.015$ s^{-1}. This can be explained only as the result of a single mechanism, the dissociation of the dimer, and its statistical recombination. Keeping in mind that a fourth combination possibility exists, the overall rate constant for this dissociation/dimerization process must be 4 x $k_{I-III} = k_d = 0.26 \pm 0.06$ s^{-1}.

Experiments 3 and 4 led to a higher value for k_I while k_{II} and k_{III} remain unchanged. It seems reasonable to assume that in these cases the proton exchange additionally occurs via the reorientation of the C=O···HN hydrogen bonds within the dimer. This process might be catalyzed by traces of water accumulated in the sample during storage, which is indicated also by the broadening of the NH-peaks.

Guest Exchange. When normal benzene is added to a solution of **3·3** in benzene-d_6 a signal appears at 4.22 ppm, which is attributed to benzene included in the cavity of the dimer. We were able to prove the origin of this signal by the observation of an exchange cross-peak with "free" benzene (at 7.15 ppm) in a NOESY experiment. This allows also the estimation of the exchange rate (k_e) of benzene in and out of the cavity. The value of $k_e = 0.47 \pm 0.1$ s^{-1} is comparable with the rate constant for the dissociation/recombination process of the dimer **3·3** and is much higher than the rate for the uptake of the guest under the conditions reported by Rebek et al.[12] This probably reflects the different concentration of the guest in a mixed solvent system as compared to the pure solvent.

A simple experiment shows that the presence of a suitable guest can even be decisive for the dimerization. In solvents of

The matrix logarithm requires diagonalization of the original matrix and taking the logarithm of the eigenvalues. This method avoids the acquisition of a series of experiments with different mixing times, and it corrects for the effects of spin-difussion or the effect of cross-relaxation on the observed exchange rates. Separation of exchange and NO effects is very important for this molecule as the protons that allow the monitorization of the exchange processes show strong NOE contacts and composite NOE-exchange pathways are expected to affect the

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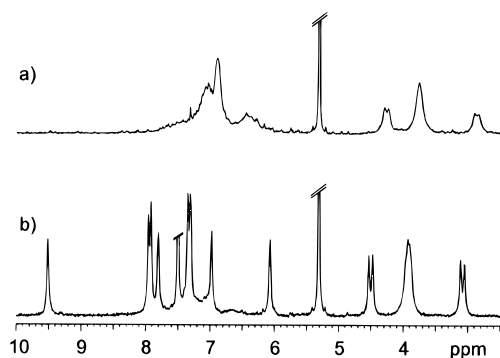
Figure 6. Partial ^{1}H NMR spectra (200 MHz, 298 K) of **1b** in CD$_2$Cl$_2$ (a) and after the addition of ∼5% benzene-d_6 (b).

the wrong size or shape, such as CD$_2$Cl$_2$, just ill defined associates of **1b** are present, as indicated by broad signals in the ^{1}H NMR spectrum. The addition of small amounts of a suitable guest molecule like benzene-d_6, however, induces the formation of dimers **1b·1b**, as shown in Figure 6.[23]

Conclusion

The C_{2v}-symmetrical tetra urea calix[4]arene **3** was synthesized and shown to self-assemble in benzene to C_2-symmetrical hydrogen bonded dimers **3·3** in which the two calix[4]arenes are nonequivalent. Therefore it is possible to follow by NOESY in this particular dimer three exchange processes between four sets of protons, which have been unambiguously assigned by a combination of NOESY, TOCSY, HMBC, and ROESY experiments. Consequently a distinction can be made between homomerization within the undissociated dimer and via dissociation/dimerization. In contrast, a C_{4v}-symmetrical urea derivative **1** forming a S_8-symmetrical dimer **1·1** allows only a single exchange process to be followed, and a distinction between different homomerization pathways is impossible.

It could be shown that the homomerization occurs in dry solution exclusively via dissociation/dimerization. The rate for this process is in reasonable agreement with the rate observed for the exchange between free and included benzene molecules. In addition it was demonstrated that the presence of a suitable guest can induce the dimerization under certain conditions.

From a methodological point of view, the use of a molecule with reduced symmetry combines the advantages achieved by a heterodimer formed from two different urea calixarenes avoiding, however, the drawback of the simultaneous presence of different dimers. Similarly, the direct measurement of the exchange of a given solvent has an obvious advantage over encapsulation studies in solvent mixtures. The use of experiments which allow for distinguishing unequivocally among cross-relaxation (NOESY), coherence transfer (TOCSY), and exchange (EXSY) peaks demonstrates the possibility to study exchange processes in complex systems. Finally, our results demonstrate the advantages of using a full relaxation plus exchange matrix to derive exchange rates uncontaminated by cross-relaxation.

Experimental Section

NMR Procedures. NMR spectra were recorded on Varian VXR-500 or on Bruker AM400 and AC200 spectrometers at 298 K with the solvents as internal lock and internal references (^{1}H NMR: benzene-d_6, 7.15 ppm; CD$_2$Cl$_2$, 5.32 ppm). Recycle times for all 2D experiments were chosen to be at least three times the longest T_1 value for the

relevant protons. Spectra were recorded in phase sensitive mode using the method of States et al.[24] with 1024 points in F2 and from 256 to 512 points in F1. Spectra were zero filled to 1024 × 2048 and processed with a Gaussian apodization in both dimensions.

Integration of the signals was carried out using the built in routines present in the VNMR software package. Before calculating the rates, cross-peak volumes were symmetrized by averaging volumes measured at both sides of the diagonal. The integral of the diagonal peak for the aromatic proton b could not be determined accurately because of signal overlapping, and, therefore, an average of the remaining diagonal peaks was used instead. Overlapping cross-peaks between protons which have contributions from processes I and III were divided in a way such that the ratio of the volumes assigned to the two components were the same as the average ratios determined for the same processes in the rest of the well resolved peaks. All cross-peaks corresponding to type II processes were assigned the same volume which was the average of the best resolved peaks of this type in the same spectrum. All rates are an average of four to six calculations in which the experimental peak-volumes have been randomly modified within a 10% limit which is an estimate of the integration errors, after averaging both sides of the diagonal. Signal-to-noise issues have been addressed by adding to the experimental value a small random number with a normal distribution with a variance equal to the one obtained from the integration of 50 empty regions around the area where cross peaks have been measured.

Rates of exchange of benzene in and out of the cavity were determined at 298 K from NOESY experiments with mixing times of 300 and 500 ms, respectively, in a sample of 5.4 mg mL^{-1} of **3** in a mixture of 77% benzene-H$_6$ and 23% benzene-d_6. Solvent suppression was carried out using a Sklenar-Bax read pulse to avoid saturation of the solvent signal.[25]

Syntheses. Compound **2a** was prepared following the procedure described in the literature for similar compounds.[26]

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(methyloxy)-26,28-bis-(pentyloxy)calix[4]arene 2a. Methyl iodide (5 mL, 84 mmol) was reacted with 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-(pentyloxy)calix[4]arene (4g, 5.06 mmol) in DMF with NaH as a base. The white solid obtained from the reaction was recrystallized from CHCl$_3$/MeOH to give pure 2a (3.48 g, 84%): mp 141−142 °C; the ^{1}H NMR spectra in CDCl$_3$ and DMSO-d_6 show just very broad, nondescriptive signals of a mixture of different conformers; MS (FD) 817.4 (M$^+$, calcd 817.2).

5,11,17,23-Tetranitro-25,27-bis(methyloxy)-26,28-bis(pentyloxy)-calix[4]arene 2b. Compound **2a** (2 g, 2.45 mmol) was dissolved in dry CH$_2$Cl$_2$ (250 mL). A mixture of fuming nitric acid (15 mL, 360 mmol) and glacial acetic acid (15 mL, 260 mmol) was added with vigorous stirring at room temperature. After 1−2 h, when the color of the solution had changed from black-violet to orange-yellow, water (150 mL) was added, and stirring continued for 15 min. The organic layer was then washed with water (3 × 150 mL), dried over Na$_2$SO$_4$, and evaporated to dryness. The resulting residue was dissolved in CHCl$_3$ (50 mL), and MeOH (150−200 mL) was added to precipitate a crude product. The material was recrystallized from CHCl$_3$/MeOH to give pure pale yellow solid **2b** (1.68 g, 89%) as a mixture of two conformers (91% *partial cone*, 9% *cone*): mp 255−257 °C dec; ^{1}H NMR 200 MHz (CDCl$_3$) δ_{pc} 8.24 (s, 2H, ArH), 8.19 (s, 2H, ArH), 7.83 (d, 2H, ArH, J = 2.6 Hz), 7.19 (d, 2H, ArH, J = 2.5 Hz), 4.07 (d, 2H, ArCH$_2$Ar, *ax*, J = 14.2 Hz), 3.93 (s, 3H, OCH$_3$), 3.91−3.65 (m, 8H, ArCH$_2$Ar and OCH$_2$), 3.33 (d, 2H, ArCH$_2$Ar, *eq*, J = 14.3 Hz), 3.01 (s, 3H, OCH$_3$), 1.99−1.87 (m$_{br}$, 4H, CH$_2$), 1.52−1.34 (m$_{br}$, 8H, CH$_2$), 0.95 (t, 6H, CH$_3$, J = 6.8 Hz) ppm; δ_c 8.19 (s, 4H, ArH), 7.12 (s, 4H, ArH), 4.41 (d, 4H, ArCH$_2$Ar, *ax*, J = 13.8 Hz), 3.97 (s, 6H, OCH$_3$) ppm, the signals for the remaining protons are superimposed by signals originating from the *partial cone* conformation; MS (FD) 772.8 (M$^+$, calcd 772.8). Anal. Calcd for C$_{40}$H$_{44}$N$_4$O$_{12}$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.05; H, 5.92; N, 7.11.

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5,11,17,23-Tetraamino-25,27-bis(methyloxy)-26,28-bis(pentyloxy)-calix[4]arene 2c. The tetranitro compound **2b** (1 g, 1.29 mmol) was dissolved in toluene (150 mL) and hydrogenated in the presence of Raney nickel at room temperature. After the hydrogen uptake was complete, the catalyst was filtered off and washed with warm toluene. Then the toluene solution was evaporated in vacuum to give the pure tetraamino calixarene **2c** (735 mg, 87%): mp 147−148 °C dec; ^{1}H NMR 200 MHz (CDCl$_3$) δ 6.47 (s$_{br}$, 4H, ArH), 5.79 (s$_{br}$, 4H, ArH), 4.19 (d$_{br}$, 4H, ArCH$_2$Ar, *ax*, J = 11.5 Hz), 3.85−3.15 (m$_{br}$, 18H, NH$_2$, OCH$_3$, OCH$_2$), 2.93 (d$_{br}$, 4H, ArCH$_2$Ar, *eq*, J = 11.4 Hz), 1.92−1.71 (m$_{br}$, 4H, CH$_2$), 1.59−1.31 (m$_{br}$, 8H, CH$_2$), 0.98−0.84 (m$_{br}$, 6H, CH$_3$) ppm; MS (FD) 652.75 (M$^+$, calcd 652.9).

5,11,17,23-Tetrakis(*N′-p*-tolyl-*N*-ureido)-25,27-bis(methyloxy)-26,28-bis(pentyloxy)calix[4]arene 3. To a solution of **2c** (340 mg, 0.52 mmol) in dry CHCl$_3$ (30 mL) *p*-tolylisocyanate (295 mg, 2.2 mmol) was added, and the mixture was kept under argon at 40 °C for 2 h. The solution was then concentrated under reduced pressure. MeOH was added to precipitate essentially pure **3** (561 mg, 91%). The material was recrystallized from CHCl$_3$/MeOH: mp 223−224 °C; ^{1}H NMR 500 MHz (benzene-d_6) δ 9.87 (s, 2H, NH), 9.86 (s, 2H, NH), 9.77 (s, 4H, NH), 8.41 (d, 2H, ArH, J = 2.4 Hz), 8.23 (d, 2H, ArH, J = 2.4 Hz), 8.15 (d, 4H, ArH, J = 8.5 Hz), 8.09 (d, 4H, ArH, J = 8.7 Hz), 8.06 (d, 4H, ArH, J = 8.6 Hz), 8.01 (d, 2H, ArH, J = 2.5 Hz), 7.96 (d, 4H, ArH, J = 8.4 Hz), 7.71 (d, 2H, ArH, J = 2.5 Hz), 7.61 (s, 2H, NH), 7.56 (s, 2H, NH), 7.29 (s, 2H, NH), 7.24 (s, 2H NH), 7.03 (d, 4H, ArH, J = 8.5 Hz), 6.94 (d, 4H, ArH, J = 8.6 Hz), 6.92 (d, 4H, ArH, J = 8.7 Hz), 6.83 (d, 4H, ArH, J = 8.4 Hz), 6.41 (d, 2H, ArH, J = 2.5 Hz), 6.35 (d, 2H, ArH, J = 2.5 Hz), 6.26 (d, 2H, ArH, J = 2.4 Hz), 6.24 (d, 2H, ArH, J = 2.5 Hz), 4.48 (d, 2H, ArCH$_2$Ar, *ax*, J = 11.6 Hz), 4.39 (d, 2H, ArCH$_2$Ar, *ax*, J = 11.6 Hz), 4.37 (d, 2H, ArCH$_2$Ar, *ax*, J = 11.7 Hz), 4.32 (d, 2H, ArCH$_2$Ar, *ax*, J = 11.8 Hz), 3.84 (s, 6H, OCH$_3$), 3.83 (s, 6H, OCH$_3$), 3.53−3.41 (m, 8H, OCH$_2$), 3.37 (d, 2H, ArCH$_2$Ar, *eq*, J = 11.8 Hz), 3.23 (d, 2H, ArCH$_2$Ar, *eq*, J = 11.8 Hz), 3.21 (d, 2H, ArCH$_2$Ar, *eq*, J = 11.7 Hz), 3.11 (d, 2H, ArCH$_2$Ar, *eq*, J = 11.8 Hz), 1.97 (s, 12H, ArCH$_3$), 1.94 (s, 6H, ArCH$_3$), 1.90 (s, 6H, ArCH$_3$), 1.92−1.81 (m, 8H CH$_2$), 1.33−1.28 (m, 16H CH$_2$), 0.94−089 (m, 12H, CH$_3$) ppm; ^{1}H NMR 200 MHz (98% benzene-d_6, 2% DMSO-d_6) δ 8.65 (s, 2H, NH), 8.62 (s, 2H, NH), 8.32 (s, 2H, NH), 8.28 (s, 2H, NH), 7.7 (d, 4H, ArH, J = 7.7 Hz), 7.61 (s, 4H, ArH), 7.41 (d, 4H, ArH, J = 7.5 Hz), 7.02 (d, 4H, ArH, J = 7.8 Hz), 6.93 (d, 4H, ArH, J = 8.0 Hz), 6.87 (s, 4H, ArH), 4.35 (d, 4H, ArCH$_2$Ar, *ax*, J = 12.5 Hz), 3.94 (s, 6H, OCH$_3$), 3.57−3.44 (m, 4H, OCH$_2$), 3.17 (d, 4H, ArCH$_2$Ar, eq, J = 12.3 Hz), 2.10 (s, 6H, ArCH$_3$), 2.07 (s, 6H, ArCH$_3$), 1.81−1.62 (m, 4H, CH$_2$), 1.47−1.21 (m, 8H, CH$_2$), 0.84 (t, 6H, CH$_3$, J = 6.8 Hz) ppm. Anal. Calcd for C$_{72}$H$_{80}$N$_8$O$_8$: C, 72.95; H, 6.8; N, 9.45. Found: C, 73.13; H, 7.16; N, 9.34.