Calix[4]arene-Based (Hemi)Carcerands and Carceplexes: Synthesis, Functionalization, and Molecular Modeling Study

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Abstract: The synthesis of 11 calix[4]arene-based carceplexes obtained by solvent or doped inclusion is reported. Carceplexes with amides, for example, DMF, NMP, and 1,5-dimethyl-2-pyrrolidinone, and sulfoxides, for example, DMSO and thiolane-1-oxide, were obtained by solvent inclusion. In these cases the yield of the carceplex decreases with increasing guest size. Potential guests that do not form carceplexes by solvent inclusion, such as 2-butanone and 3-sulfolene, could be incarcerated by doped inclusion with 1,5-dimethyl-2-pyrrolidinone as a solvent "doped" with 5–15 vol% of potential guest. The amide bridges of the carceplexes were converted into thioamide bridges in essentially quantitative yield by means of Lawesson's reagent in refluxing xylene. The dynamic properties of the incarcerated guests were examined by 2D NMR spectroscopy. Whereas for most guests a preference for one orientation inside the calix[4]arene-based (thia)carcerands was observed, for DMA, NMP, and ethyl methyl sulfoxide inside calix[4]arene-based (thia)carcerands *two different orientations* were present. The energy barriers for interconversion between the various orientations of DMA, NMP, and ethyl methyl sulfoxide inside calix[4]arene-based (thia)carcerands were determined with 2D EXSY NMR. The energy barriers are higher for the thiacarcerands than for the corresponding carcerands with amide bridges. This may be due to the stronger hydrogen-bond-donating character of the thioamide group. Furthermore, molecular modeling simulations indicate that in case of the thiacarcerand the cavity is smaller as a result of a smaller diametrical distance between the N*H* atoms. Our results demonstrate that molecular modeling can be used to estimate the energy barriers for interconversion; the calculated activation energies showed good quantitative agreement with the experimental values.

Keywords
calixarenes · carcerands · inclusion compounds · molecular devices · resorcinarenes

Introduction

The developments in microelectronics and data processing during the past twenty years have raised the demand for devices that combine a large data storage capacity with as small dimensions as possible. The smallest "storage device" is one molecule, a so-called *molecular switch*. Requirements for a molecular switch include thermal stability, different "read" and "write" tools, and durability. Furthermore, it should be possible to organize the switches in such a way that a molecular device can be constructed.

Various approaches towards molecular switches have been reported in the literature. The reversible ring closure of 1,2-diarylethenes has been used by Lehn et al. to obtain multifunctional molecules.[1] The open form can be converted almost quantitatively into a closed form by UV light ($\lambda = 365$ nm). The reverse process can be carried out both photochemically ($\lambda > 600$ nm) and thermally. The isomerism in thioxanthenes has been used by Feringa et al. to obtain chiroptical switches.[2] Light of different wavelengths was used to switch between M and a P isomer. The difference in chirality/helicity leads to a different response in the circular dichroism spectrum. The conversion of one isomer into the other depends on the wavelength and on the solvent. A switchable rotaxane with different stations, a so-called molecular shuttle, was reported by Stoddart et al.[3] The position of the bead can be switched both by quaternization of the amino groups and electrochemically. The activation energy for the bead to move from one station to the other was estimated to be 13 kcal mol^{-1} by means of coalescence measurements. Although the bead and the thread are not connected by covalent bonds, the different positions of the bead lead to different topological stereoisomers. Another approach towards a molecular switch uses the different oxidation states of anthraquinone, which can be converted electrochemically into the hydroquinone form and vice versa.[4, 5] A similar system was

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reported for bianthrone, which can be transformed from a quasiplanar form A into a rotated form B by photoexcitation, heat, pressure, or electrochemical means.[6]

Cram et al. have already shown that carcerands, obtained by combination of two resorcin[4]arenes, can permanently incarcerate guest molecules.[7] In contrast to the carcerands, hemicarcerands allow the exchange of included guests after synthesis of the host molecule. Owing to the symmetry of the cavity formed by the two resorcin[4]arene moieties different orientations of guests do not lead to different stereoisomers.[8] Our approach to a molecular switch combines the use of container molecules with a noncentrosymmetric (C_{4v}) cavity, for example, calix[4]arene-based carcerands, and self-assembled monolayers on gold surfaces in order to be able to address a specific number of molecules.[9] Previously a calix[4]arene-based carcerand with one incarcerated DMF molecule was isolated during the synthesis of a receptor molecule with a nanosize cavity.[10, 11]

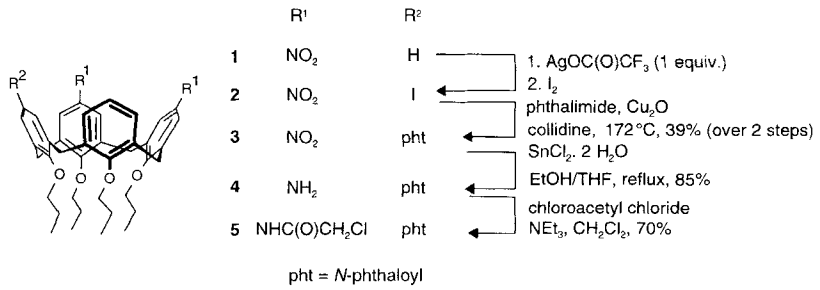
In this paper we report the full details of the synthesis of calix[4]arene-based (hemi)carcerands[12] obtained by combination of a calix[4]- and resorcin[4]arene. These molecules possess a noncentrosymmetric (C_{4v}) cavity and, therefore, *different orientations of incarcerated guests will lead to different diastereoisomers.* First, the synthesis and structural properties of calix[4]arene-based hemicarcerands will be discussed; the synthesis of carceplexes by solvent and doped inclusion will be presented as well as functionalization of calix[4]arene-based carceplexes *after* inclusion of a guest molecule. The properties of incarcerated guests have been examined by 2D NMR spectroscopy and by mass spectrometry. Through-space connectivities were determined with NOESY[13] and ROESY[14] experiments, whereas TOCSY (MLEV17)[15] and HMQC[16] measurements were used to establish through-bond connectivities, that is, H–H and H–C J-coupling, respectively. In addition, molecular mechanics calculations were used to study the properties of the various guests and carcerands. Finally, energy barriers for interconversion between different orientations of guests inside calix[4]arene-based carcerands were calculated and compared to experimental values.

Results and Discussion

Calix[4]arene-Based Hemicarcerands: Our first approach towards a molecular switch comprises the synthesis of a calix[4]arene-based hemicarcerand in which a calix[4]- and resorcin[4]arene moiety are connected by three bridges. This approach would allow the exchange of guests after synthesis of the host molecule. Hence, various hemicarceplexes would be available from one hemicarcerand.

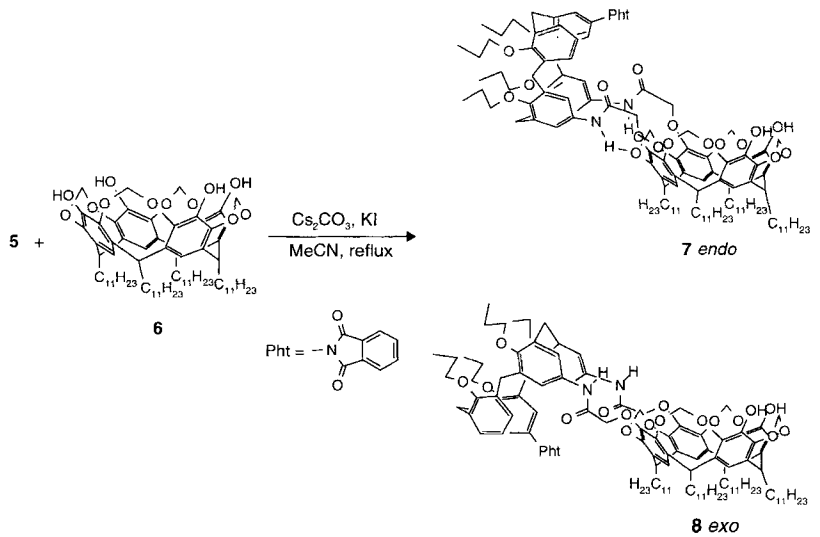
The most obvious synthetic route towards calix[4]arene-based carcerands is direct linking between the two building blocks. However, due to the flexibility of the calix[4]arene skeleton this does not lead to the expected product. We found that a diametrically substituted calix[4]arene exclusively reacts with two proximal positions of the resorcin[4]arene moiety.[10] Therefore, a stepwise method was used in which the two building blocks are first connected by two spacers.

Starting material for the calix[4]arene building block is 1,2-dinitrocalix[4]arene **1**. Iodination with one equivalent of $AgOC(O)CF_3$ and subsequent quenching with iodine resulted in a mixture of mono- (**2**) and diiodocalix[4]arene that could not be separated. This mixture was converted into the corresponding phthalimidocalix[4]arenes with phthalimide and Cu_2O in refluxing collidine,[17] which allows the separation of the two compounds.[18] Reduction of the nitro groups of **3** with $SnCl_2 \cdot 2H_2O$, leaving the phthalimido group intact, afforded 3-*N*-phthaloyl-1,2-diaminocalix[4]arene **4**. Subsequent reaction of **4** with chloroacetyl chloride gave the corresponding bis(chloroacetamido)calix[4]arene **5** in 70% yield (Scheme 1).



Scheme 1. Synthesis of bis(chloroacetamido)calix[4]arene **5**.

Reaction of calix[4]arene **5** and the known tetrahydroxycavitand **6** in refluxing acetonitrile with Cs_2CO_3 as a base under high dilution conditions yielded a number of products. The 1:1 *endo*-coupled product (**7**) was obtained in the highest yield (24–32%); the *exo*-coupled product **8** was isolated in 5–19% yield (Scheme 2). The conformation of **7** and **8** could easily be deduced from the characteristic resonances in the ^{1}H NMR spectra for the N*H* atoms at $\delta = 10.13$–9.24 and 8.37–8.24 corresponding to an *endo* and *exo*-orientation of the calix[4]arene moiety, respectively.[19]



Scheme 2. Synthesis of the 1:1 *endo*-coupled product **7** and the *exo*-coupled product **8**.

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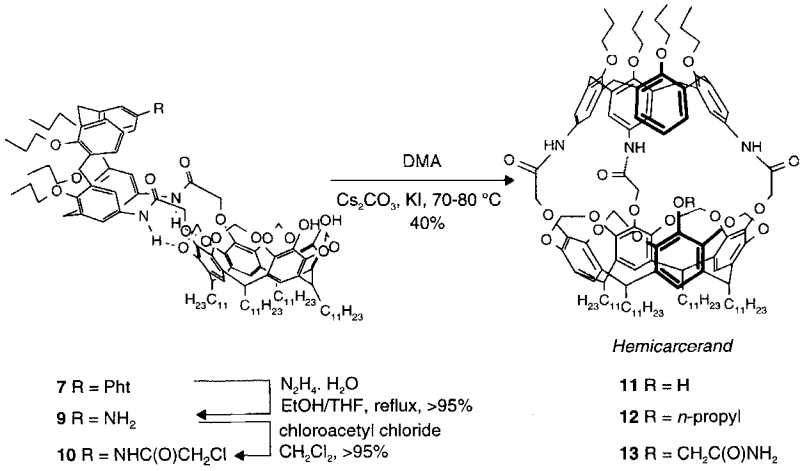
endo-Coupled compound **7** was used for the synthesis of calix[4]arene-based hemicarcerand **11**. After deprotection of the phthalimido group and subsequent reaction with chloroacetyl chloride, the monochloroacetamido derivative **10** was obtained in essentially quantitative yield. During the acylation of the amino groups the absence of base prevents alkylation or acylation on the free hydroxyl groups. Closure of the third bridge in DMA with Cs_2CO_3 as a base gave calix[4]arene-based hemicarcerand **11** in ca. 40% yield (Scheme 3). The hemicarcerand was isolated without an included DMA molecule, although from the calix[4]arene-based carcerands we know that DMA can occupy such a cavity (vide infra).



Scheme 3. Closure of the third bridge in DMA with Cs_2CO_3 to give calix[4]arene-based hemicarcerands.

In contrast to most of the hemicarcerands described by Cram et al.[7] calix[4]arene-based hemicarcerand **11** contains a free hydroxyl group, by means of which additional binding sites can be introduced. Simple *O*-alkylation of hemicarcerand **11** yielded hemicarcerands **12** and **13** in essentially quantitative yield. The ^{1}H NMR spectrum of **12** shows no signals below $\delta = 0$ that would indicate the self-inclusion of the *O*-propyl group. Therefore, it seems reasonable to assume that the *O*-propyl group can freely rotate around the Ar–O bond and is not preferentially oriented toward the cavity. Most likely this is also the case for the acetamido group of **13**. Although the alkylations were carried out in DMA, again both hemicarcerands **12** and **13** were obtained *without an incarcerated DMA molecule*.

The structure of hemicarcerand **11** in $CDCl_3$ solution was investigated by 2D ROE spectroscopy (at room temperature).[20] After full assignment of the 1D ^{1}H NMR spectrum by TOCSY and 2D ROESY measurements the relative distances between the equatorial ArCH_2Ar atoms and the *o*-Ar*H* (calix[4]arene) were used to determine the flexibility of the calix[4]arene skeleton.[21] The results indicate that the "free" aromatic unit of the calix[4]arene is in a flattened orientation, whereas the diametrically bridged aromatic units of the calix[4]arene are oriented parallel. CPK molecular models indicate that in this conformation the hemicarcerand does not possess an enforced but a cleft-like cavity. Furthermore, the extra binding sites introduced at the free hydroxyl group of the resorcin[4]arene moiety tend to rotate away from the cavity and, therefore, do not shield the entrance. Although several methods were applied to obtain hemicarceplexes, the inclusion of a guest molecule was not observed.[22]

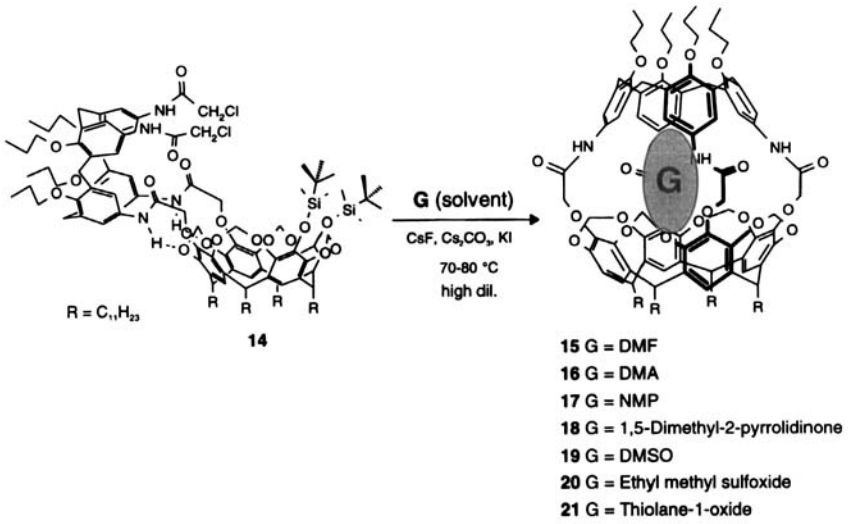
Therefore, we focused our attention on the synthesis and properties of calix[4]arene-based carcerands in which the calix[4]- and resorcin[4]arene moiety are connected by four bridges. In these molecules the flexibility of the calix[4]arene moiety is reduced and incarcerated guests will not be able to leave the cavity.

Calix[4]arene-Based Carcerands: Starting material for the calix[4]arene-based carcerands is the 1:1 *endo*-coupled product **14**.[10] This compound has been used for the synthesis of a receptor molecule with an enforced nanosize cavity in which two calix[4]arenes are coupled with two resorcin[4]arenes.[10, 23] Calix[4]arene-based carceplexes are formed by closing the final two bridges of **14**. Two different methods will be discussed that lead to calix[4]arene-based carceplexes, so-called *solvent* and *doped* inclusion.

Synthesis of Calix[4]arene-Based Carceplexes by Solvent Inclusion: The most straightforward method for the synthesis of calix[4]arene-based carceplexes comprises the closure of the final two bridges of 1:1 *endo*-coupled product **14** in an appropriate solvent. The *tert*-butyldimethylsilyl groups are removed in situ with CsF, and Cs_2CO_3 is used as a base. During the reaction one solvent molecule is permanently incarcerated. Solvents that can be used are amides and sulfoxides. Carceplexes with *N*,*N*-dimethylformamide (DMF) (**15**), *N*,*N*-dimethylacetamide (DMA) (**16**), dimethyl sulfoxide (DMSO) (**19**), and ethyl methyl sulfoxide (**20**) were obtained in essentially quantitative yields. Furthermore carceplexes with *N*-methyl-2-pyrrolidinone (NMP) (**17**), 1,5-dimethyl-2-pyrrolidinone (DNMP) (**18**), and thiolane-1-oxide (**21**) were obtained in 50, <5, and 16% yield, respectively (Scheme 4). The results clearly demonstrate that the yield of the carceplex decreases with increasing guest size.

The FAB mass spectra all show molecular ion peaks that correspond to the (carcerand + guest). Furthermore, the ^{1}H NMR spectra show a large upfield shift of 2–4 ppm for the hydrogen atoms of the incarcerated guests compared with the resonances of the free guests in $CDCl_3$ solution due to the shielding of the aromatic moieties of the calix[4]- and resorcin[4]arene moieties. Characteristic guest signals are found in the ^{1}H NMR spectra at values below $\delta = 0$; the ^{1}H NMR spectrum of ethyl methyl sulfoxide carceplex **20** is presented in Figure 1. Selected ^{1}H NMR data are depicted in Table 1. The ^{1}H NMR spectra of carceplexes **15–25** are consistent with a C_{4v} symmetry of the calix[4]arene-based carcerand; this means that rotation of the incarcerated guests around the *z*-axis is fast on the ^{1}H NMR chemical shift timescale.[24]

It is striking that in DMF carceplex **15** and DMA carceplex **16** the resonances for the NCH_3 atoms are separated by 1.5 ppm and ca. 2.3 ppm, respectively, whereas the difference between the corresponding absorptions for DMF and DMA in $CDCl_3$



Scheme 4. Carceplexes obtained in varying yields depending on guest size.

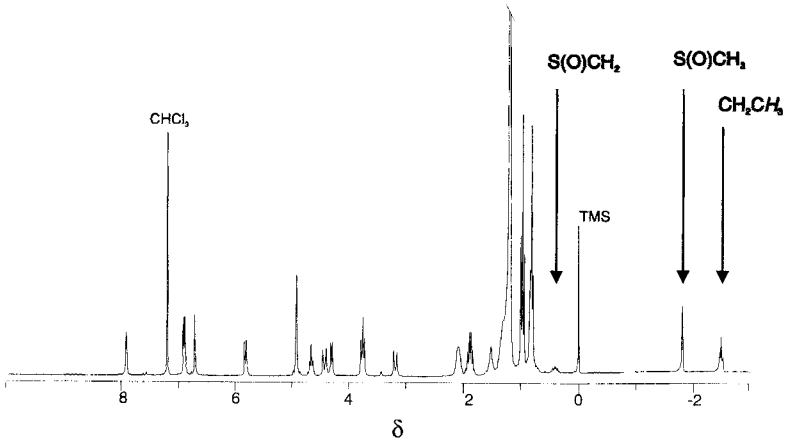


Figure 1. ^{1}H NMR spectrum ($CDCl_3$, 250 MHz) of ethyl methyl sulfoxide carceplex **20**.

solution is only ca. 0.2 ppm. This indicates that for the carceplexes there is a difference in environment for the *N*-methyl groups.

The 1 D ^{1}H NMR spectrum of 1,5-dimethyl-2-pyrrolidinone carceplex **19** shows two doublets for the *o*-Ar*H*NH as well as for the C(O)C$H_{a,b}$ hydrogen atoms, whereas those in carceplexes **15**–**18** exhibit singlets. This degeneracy is probably due to the chirality of the incarcerated guest. The C(O)$H_{a,b}$ protons in the 1,5-dimethyl-2-pyrrolidinone carceplex are diastereotopic and, hence, give two signals in the ^{1}H NMR spectrum. The relatively large difference in chemical shift of the signals for the C(O)C$H_{a,b}$ atoms, $\Delta\delta = 0.15$ ppm, indicates that the chiral center is near these hydrogen atoms. Similar degeneracy is observed for the *o*-Ar*H*NH atoms in ethyl methyl sulfoxide carceplex **20**. In this case the difference in resonances is ca. 0.1 ppm. Furthermore, TOCSY and ROESY experiments revealed that the resonances for the two C$H_{a,b}$SO atoms of incarcerated ethyl methyl sulfoxide are located at $\delta = 0.4$ and -1.05 ppm. In the ^{1}H NMR spectrum of free ethyl methyl sulfoxide in $CDCl_3$ solution the difference in chemical shift is < 0.1 ppm. In both carceplexes no splitting is observed for the protons of the methyleneoxy bridges of the resorcin[4]arene moiety.

The synthesis of calix[4]arene-based carceplexes by solvent inclusion is restricted to highly polar solvents, that is, amides and sulfoxides. In the 1:1 *endo*-coupled product there is a hydrogen bond between the N*H* atoms of the bridges and the *O*CH_2*O* atoms of the methyleneoxy bridges of the resorcin[4]arene moiety. This hydrogen bond must be broken in order to situate the calix[4]arene moiety above the resorcin[4]arene moiety. Furthermore, molecular modeling indicates that the N*H* atoms must point into the cavity of the carcerand. This is facilitated by a hydrogen-bond-accepting function of the guest. Therefore, only solvents that are highly polar and able to break or to form a hydrogen bond can be used during solvent inclusion.

Solvents that failed to give a carceplex include *N*-methyl-2-piperidone, *N*-ethyl-2-pyrrolidinone, 2-butanone, cyclopentanone, and acetonitrile. The first two solvents are too large, whereas the others do not form a carceplex because they lack the hydrogen-bond-accepting properties mentioned above.

Synthesis of Calix[4]arene-Based Carceplexes by Doped Inclusion: The limitation that calix[4]arene-based carceplexes can only be formed by solvent inclusion in highly polar solvents with a hydrogen bond accepting group, that is, amides and sulfoxides, is a disadvantage for the investigation of new carceplexes. Therefore, a method called *doped* inclusion was used, which allows the use of a larger variety of guests. The reaction conditions are similar to those applied during solvent inclusion but 1,5-dimethyl-2-pyrrolidinone, which itself is a poor template for the closure of the final two bridges (vide supra), is used as a solvent and potential guests are added in 5–15 vol%; this results in the selective formation of the carceplexes with the added guests (Scheme 5). This strategy had been demonstrated by Sherman et al.[25] for the synthesis of resorcin[4]arene-based (hemi)carcerands.

Whereas the synthesis of a calix[4]arene-based carceplex with 2-butanone failed by the solvent inclusion method (vide supra), 2-butanone carceplex **22** was obtained in 16% yield by doped inclusion.[26] Furthermore, carceplexes with 3-sulfolene (**23**), which is a solid, and [D_7]DMF (**24**) and [D_6]DMSO (**25**) were obtained in 26, 13, and 16% yield, respectively. By means of the doped inclusion method DMA carceplex **16** was obtained in 27% yield. Characteristic ^{1}H NMR data are summarized in Table 1. The ^{2}H spectra of [D_7]DMF carceplex **24** and [D_6]DMSO carceplex **25** are presented in Figure 2. Similar to the carceplexes obtained by solvent inclusion a large upfield shift is observed in the NMR spectra for the hydrogen and deuterium atoms of the incarcerated guests.

To investigate the templating ability of different guests competition experiments were carried out with 5 vol% DMA and 5 vol% of another guest in 1,5-dimethyl-2-pyrrolidinone. The yields of the different carceplexes were determined by integra-

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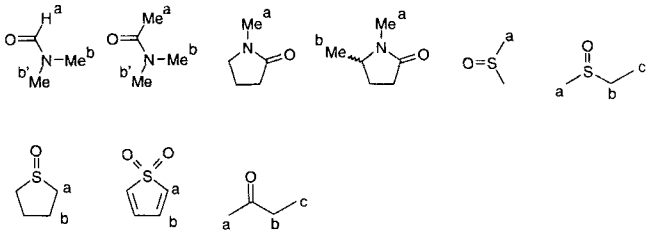
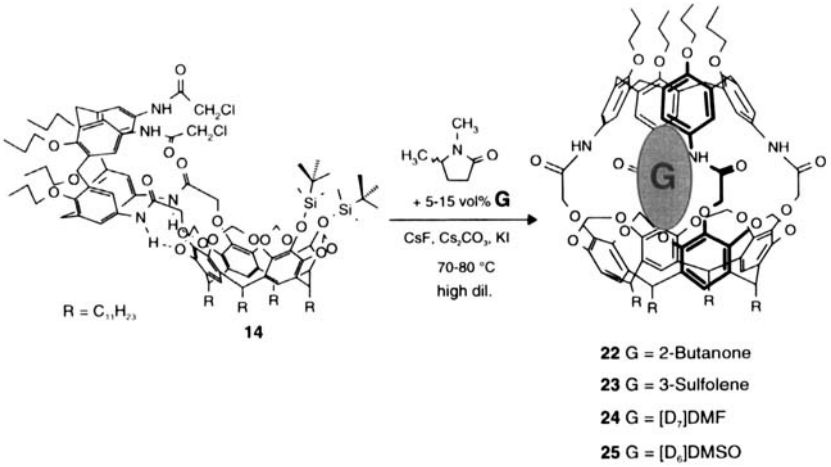
Table 1. Yields and selected 1D ^{1}H NMR data of calix[4]arene-based carceplexes **15–23**.



Guest	Method [a]	Yield (%)	H	δ ($CDCl_3$)	δ (carceplex)	$\Delta\delta$
DMF	A	quant.	a	8.1	4.84	3.26
			b	2.9	0.66	2.24
			b′	2.8	−0.88	3.86
DMA	A	quant.	a	2.1	−1.98	4.08
			b	2.9	1.3	1.6
			b′	2.8	−1.01	3.81
NMP	A	50	a [b]	2.3	−1.3	3.6
1,5-Dimethyl-2-pyrrolidinone	A	<5	a	2.7	−1.3	4.0
			b	1.01	0.18	0.83
DMSO	A	quant.	a	2.5	−0.8	3.3
Ethyl methyl sulfoxide	A	quant.	a	2.48	−1.81	4.29
			b	2.67	1.05	3.72
			b′		0.41	3.08
			c	1.27	−2.48	3.75
Thiolane-1-oxide	A	16	a	1.85–2.1	0.1	1.9 [c]
			b	2.3–2.5	−0.3	2.7 [c]
3-Sulfolene	B	26	a	3.7	0.18	3.52
			b	6.0	3.23	2.77
2-Butanone	B	16	a	2.10	−2.01	4.1
			b	2.45	0.39	2.06
			c	1.05	−2.85	3.85

[a] A: direct, B: doped. [b] Major conformer (263 K). [c] Average. [d] n.d.: not determined.



Scheme 5. Doped inclusion results in the selective formation of carceplexes with the added guests.

tion of characteristic signals in the ^{1}H NMR spectra. The results are summarized in Table 2.

From Table 2 it is clear that DMA is the best template for the carcerand synthesis. Since the carceplexes can only be formed when the guest occupies the calix[4]- and resorcin[4]arene cavity, the templating ability is comparable to an association strength between host and guest. Furthermore, the observed yields are a rough indication for the rate of carceplex formation. If this rate is slow, intermolecularly coupled products will be formed or the

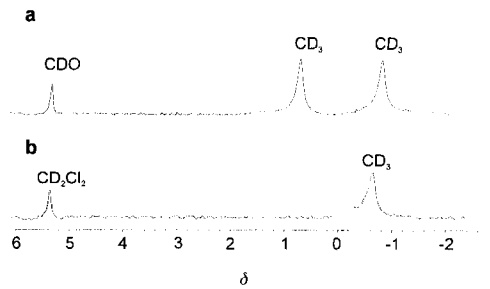


Figure 2. ^{2}H NMR spectra (CH_2Cl_2, 61.4 MHz) of a) [D_7]DMF carceplex **24** and b) [D_6]DMSO carceplex **25**.

Table 2. Templating ability of potential guests during the synthesis of calix[4]arene-based carceplexes by doped inclusion.

Guest	Templating ability [a]	Yield (%) [b]
DMA	100	27
DMSO	63	16 [c]
DMF	27	13 [c]
2-Butanone	27	16

[a] DMA is set at 100. [b] Isolated carceplex when only one guest is used during doped inclusion. [c] Yield of deuterated guests.

chloroacetamido groups of **14** will decompose.[27] Our results indicate that DMA provides the best solvation of the transition state during the closure of the final two bridges. This might be due to the guest polarity and to the size and shape of the guest.

Carceplexes were not obtained with *N,N*-dimethylthioformamide, *N,N*-dimethylthioacetamide, *N,N*-dimethylmethanesulfonamide, cyclopentanone, *N*-ethyl-*N*′-methylacetamide, or biacetyl. During the synthesis of resorcin[4]arene-based carcerands the largest templating effect was observed for pyrazine.[25] However, in the case of the calix[4]arene-based carcerands no carceplex with pyrazine was formed. As was also demonstrated by the solvent inclusion experiments, six-membered rings are too large to be incarcerated in calix[4]arene-based carcerands.

The importance of the hydrogen-bond-accepting ability of the guest has already been stressed. The presence of this hydrogen bond between the calix[4]arene-based carcerand and the incarcerated guests is nicely demonstrated by the relation between the chemical shift of the N*H* protons of the calix[4]arene-based carcerand versus the polarity parameter E_T^N of the incarcerated guests (Figure 3).[28]

Calix[4]arene-Based Thiacarceplexes: In order to extend the number of different calix[4]arene-based carcerands we investigated the possibility of altering the tumbling of incarcerated guests *after* inclusion. The obvious positions for modification of the calix[4]arene-based carceplexes are the amide bridges, since amides can easily be converted into thioamides. Calix[4]arene-based thiacarceplexes **26–30** were obtained as pure compounds in quantitative yield, without extensive purification, from the corresponding amide-bridged carceplexes by treatment with Lawesson's reagent[29] in xylene at 140 °C (Scheme 6).

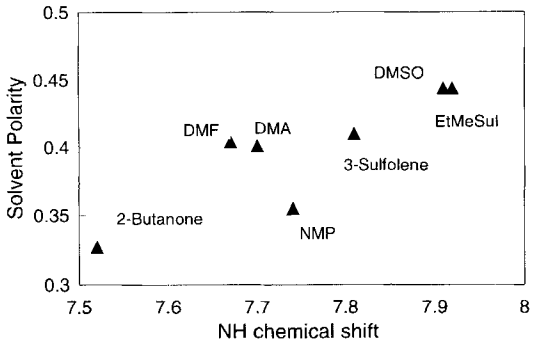
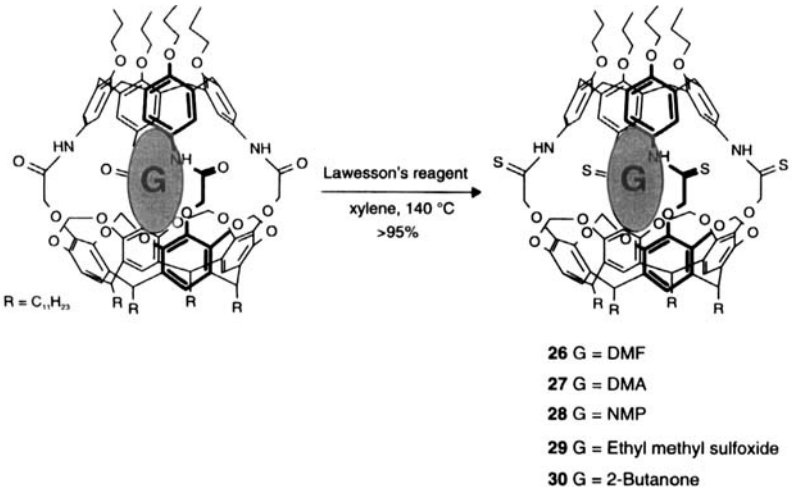


Figure 3. Solvent polarity, E_T^N, versus chemical shift of N*H* atoms in the ^{1}H NMR spectra of carceplexes **15**–**25**.



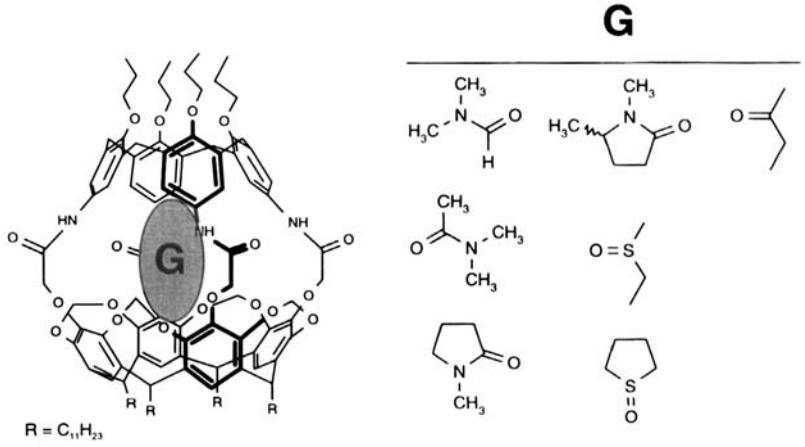
Scheme 6. Production of calix[4]arene-based thiacarceplexes **26**–**30** in quantitative yield from the corresponding amide-bridged carceplexes.

Thiacarceplexes **26**–**30** all show FAB mass spectra that correspond to complete conversion of the amide bridges into thioamides *without affecting the incarcerated guests*. This indicates that the guests are well shielded from the outside since amides[30] and ketones[31] are readily converted into the corresponding thio analogues, and sulfoxides can be reduced by Lawesson's reagent.[32] For the calix[4]arene-based thiacarceplexes **26**–**30** characteristic shifts of the N*H*-, *o*-Ar*H*NH (calix[4]arene moiety), and CH_2C(X) hydrogen atoms of the thiacarcerand are observed in the ^{1}H NMR spectra similar to those of the corresponding amide-bridged carceplexes. The largest shift is observed for the NH protons, which are shifted downfield by ca. 1.4 ppm. This is due to the stronger hydrogen-bond-donating ability of thioamides vs. amides,[33] the pK_a for formamide and thioformamide being 26.9 and 21.0, respectively.[33c] The *o*-Ar*H*NH (calix[4]arene moiety) and CH_2C(X) atoms show a downfield shift of 0.2 ppm due to the lower electronegativity of sulfur compared with oxygen. As is the case for amide-bridged carceplexes the chemical shift of the N*H* atoms in **26**–**30** varies with the polarity of the guest. For 2-butanone thiacarceplex **30** a chemical shift of $\delta = 9.1$ is found, whereas for ethyl methyl sulfoxide thiacarceplex **29** this shift is $\delta = 9.25$.

Orientation(s) and Tumbling of Guests Inside Calix[4]arene-Based (Thia)Carcerands: The orientation of the guests inside the calix[4]arene-based (thia)carceplexes **15**–**30** was determined by 2D NOESY and ROESY measurements (Scheme 7).[34] Whereas in most cases the preferential orientation was deduced from single experiments, in case of DMF, DMA, NMP, and thiolane-1-oxide the orientation was determined by measuring NOE build-up curves.[35] The exact orientation of 3-sulfolene could not be established. However, the presence of two singlets for the incarcerated guest, identified by HMQC spectroscopy, strongly suggests the conclusion that the symmetry of the guest is preserved upon incarceration. This means that the guest is oriented along the *z*-axis of the calix[4]arene-based carcerand, that is, with the sulfone group oriented toward the calix[4]- or resorcin[4]arene moiety.

In the ^{1}H NMR spectra of thiacarceplexes **26**–**30** the chemical shifts of the hydrogen atoms of the guests are similar to those of the corresponding amide-bridged carceplexes (vide supra). This indicates that the orientation of the guests does not change on conversion of the amide into thioamide bridges. This result was confirmed by 2D NOESY experiments.

On lowering the temperature of DMA (**16**, **17**) and NMP (**27**, **28**) (thia)carceplexes the presence of a second isomer corresponding to a different orientation of the guest inside the carcerand was observed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of DMA (thia)carceplexes **12** and **27** show two new resonances at $\delta = -1.3$ and -1.8. NOESY experiments showed that these signals originate from an isomer in which the acetyl group is positioned close to the resorcin[4]arene moiety. The ^{1}H NMR spectrum of NMP carceplex **28** sharpens on lowering the temperature. At a temperature below $-10\,^\circ$C two resonances are observed for the NCH_3 atoms at $\delta = -1.3$ and -1.7, respectively. Furthermore, two resonances are present for the N*H* atoms at $\delta = 7.87$ and 7.77. NOESY experiments revealed that the signal at $\delta = -1.3$ corresponds to the isomer in which the NCH_3 group is positioned close to the resorcin[4]arene moiety. For NMP thiacarceplex **28** the second



Scheme 7. Experimentally determined (preferred) orientations of guests inside calix[4]arene-based (thia)carcerands. Note: The incarcerated thiolane-1-oxide is somewhat tilted with respect to the long axis of the calix[4]arene-based carcerand.

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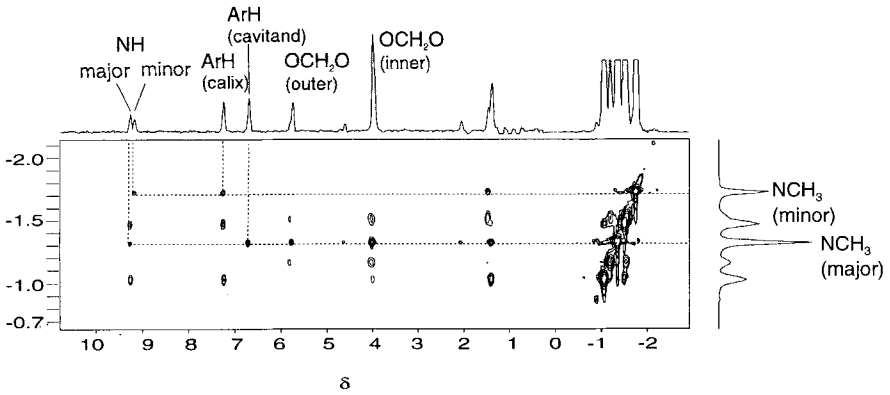

Figure 4. Part of the 2D NOESY spectrum (400 MHz) at −55 °C in $CDCl_3$ of NMP thiacarceplex **28** showing the presence of a major and minor conformer.

isomer is already observed at room temperature. There are two resonances for the N*H* protons, which correspond to the different orientations, as demonstrated by the 2D NOESY spectrum (see Figure 4). Whereas only one isomer was observed for ethyl methyl sulfoxide carceplex **20**, for the corresponding thiacarceplex **29** a second conformer was observed on lowering the temperature. At a temperature below −50 °C two new signals are present in the ^{1}H NMR spectrum at $\delta = -1.6$ and -3.0. Each signal shows a cross peak with one of the resonances of the incarcerated ethyl methyl sulfoxide at $\delta = -1.8$ and -2.6. Unfortunately, no NOE connectivities were observed between the resonances of this second conformer and the calix[4]arene-based thiacarcerand that would allow elucidation of the precise structure of this second isomer. The energy barriers for interconversion between the orientations were determined by 2D EXSY NMR (Table 3).

Table 3. Energy difference (ΔG°), rotational barriers ($\Delta G^\ddagger$), and exchange rates (k_{ex}) for interconversion between different orientations of guests inside calix[4]arene-based (thia)carceplexes determined by 2D EXSY NMR (400 MHz, $CDCl_3$).

Carceplex (bridge)	Guest	ΔG° (kcal mol^{-1})[a]	$\Delta G^\ddagger_{273}$ (kcal mol^{-1})	k_{ex} (s^{-1})
12 (amide)	DMA	0.7 [b]	12.7±0.5	395
27 (thioamide)	DMA	0.5 [c]	15.2±0.5	4.5
13 (amide)	NMP	0.4 [c]	15.7±0.5	1.6
28 (thioamide)	NMP	0.2 [d]/0.3 [c]	17.5±0.5	0.06
29 (thioamide)	Ethyl methyl sulfoxide	0.8 [d]	13.4±0.5 [d]	0.17

[a] Determined by integration of the ^{1}H NMR spectra. [b] 213 K. [c] 273 K. [d] 218 K.

The activation energy for interconversion between the different diastereoisomers of calix[4]arene-based (thia)carceplexes is higher for the NMP (thia)carceplexes than for the corresponding carceplexes with the incarcerated (smaller) DMA and ethyl methyl sulfoxide molecules. Furthermore, it is clear that conversion of the amide bridges of the calix[4]arene-based carcerand into thioamides increases the activation energy for interconversion between the various diastereoisomers. The reason for this may be the stronger hydrogen bond between the carcerand and the incarcerated guests in the case of the thioamides or a smaller cavity as indicated by molecular modeling calculations (vide infra).

Whereas for DMA (**16**, **27**), NMP (**18**, **28**), and ethyl methyl sulfoxide (**29**) (thia)carceplexes we observed different orientations of the incarcerated guests, in all other cases, that is, DMF (thia)carceplexes **15** and **26**, ethyl methyl sulfoxide carceplex **20**, 1,5-dimethyl-2-pyrrolidinone carceplex **18**, 2-butanone (thia)carceplexes **22** and **30**, and thiolane-1-oxide carceplex **21**, only one isomer could be detected in a temperature range from −50 to 120 °C. This indicates that probably the difference in Gibbs free energy between the different isomers is too large. The presence of other orientations that are in fast equilibrium with the observed structures, but that cannot be separately observed by ^{1}H NMR spectroscopy, cannot be totally excluded.

Energy Barriers for Rotation around the Amide Bonds of Incarcerated DMF and DMA: The stereoisomerism of amides such as DMF and DMA, due to hindered rotation around the N-C(O) bond, is well known and has been extensively studied both experimentally, by NMR spectroscopy in the gas phase[36] and in solution,[37] and theoretically.[37c, 38] Although the *N*-methyl groups are chemically equivalent, they are not magnetically equivalent. The energy barrier for DMF is larger than for DMA. This difference is mainly a result of destabilization of the ground state in DMA due to steric repulsion rather than by a difference in the energy of the transition state.[38c] The energy barriers increase when the solvent polarity or the hydrogen-bond-donating ability of the solvent increases.[37b, 37c, 38] In neat solution the Gibbs free energy barriers for rotation at 25 °C, $\Delta G^\ddagger_{298}$, for DMF and DMA are ca. 21 and 18 kcal mol^{-1}, respectively. The rotational barriers around the amide bonds of incarcerated DMF and DMA inside calix[4]arene-based (thia)carceplexes were determined by 2D EXSY NMR measurements (Table 4).

Table 4. Activation energies for rotation around the amide bond of DMF and DMA inside calix[4]arene-based (thia)carcerands.

	$\Delta G^\ddagger_{298}$ (kcal mol^{-1})	
	DMF	DMA
Pure [a]	20.9	18.1
Carceplex	23.1	20.0
Thiacarceplex	24.0	20.5

[a] Taken from ref. [37].

The energy barriers for rotation around the amide bond of DMF and DMA inside calix[4]arene-based (thia)carceplexes **15**, **16** and **26**, **27** are larger than for the neat amides. Furthermore, the activation energies for the thiacarceplexes **26** (DMF) and **27** (DMA) are higher than for the corresponding amide-bridged carceplexes **15** (DMF) and **16** (DMA). This behavior is probably caused by steric repulsion due to incarceration of the guests. The larger barriers for the thiacarceplexes might indicate that the cavity inside the calix[4]arene-based thiacarceplexes is

smaller than for the corresponding amide-bridged carceplexes. It is known that the energy barriers for rotation around the amide bond of amides increases as the solvent polarity or hydrogen-bond-donating character of the solvent increases (vide supra). Therefore, the increased energy barrier for the thiacarceplexes might also be due to the increased hydrogen-bond-donating character of the thioamide bridges compared to the amide bridges.

Extrusion of SO_2 and Butadiene from the 3-Sulfolene Carceplex: The extrusion of SO_2 and butadiene from 3-sulfolene takes readily place on heating at 100–130 °C.[39] The activation enthalpy ($\Delta H^{\neq}$) and entropy ($\Delta S^{\neq}$) for dissociation are 33.6 kcal mol^{-1} and 8.9 cal mol^{-1} K^{-1}, respectively.[406]

The extrusion of SO_2 or butadiene from 3-sulfolene carceplex **23** was investigated by electron impact mass spectrometry.[41] The probe was loaded with a sample of carceplex **23** and the temperature of the probe was gradually increased. At a probe temperature above 170–180 °C SO_2 was detected and above 215 °C butadiene was detected. The SO_2 and butadiene can only originate from the 3-sulfolene carceplex. Since the carceplex exhibits a melting point >300 °C it is unlikely that the calix[4]arene-based carcerand is destroyed at this temperature (170–215 °C).[42] Therefore, the SO_2 and butadiene can only originate from the incarcerated 3-sulfolene and should leave the carcerand through the side portals formed by the bridges between the calix[4]- and resorcin[4]arene moiety. Additional evidence for the extrusion of SO_2 and butadiene from 3-sulfolene carceplex **23** results from field desorption mass spectrometry (FD MS). At a temperature below ca. 180 °C only 3-sulfolene carceplex **23** is observed, whereas above 180 °C empty carcerand is detected (Figure 5). These results are in good agreement

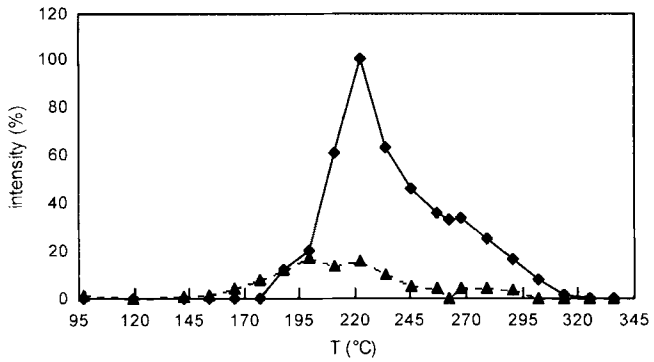

Figure 5. Desorption curves during field desorption mass spectrometry of 3-sulfolene carceplex **23**, showing the carceplex [*m*/*z* 2148 and 2171 (+ Na^+)] and empty carceplex **23** [*m*/*z* 2030 and 2053 (+ Na^+)]. ◆ = empty carcerand; ▲ = carcerand + 3-sulfolene.

with the electron impact mass spectrometry experiments. A carcerand containing either butadiene or SO_2 is not observed.[43] This indicates that under the conditions applied only empty carcerand is formed.[447]

The mass spectrometric experiments with 3-sulfolene carceplex **23** indicate that incarcerated 3-sulfolene exhibits a higher thermal stability than pure 3-sulfolene. The reason for this increased stability might be an increase in recombination rate for the products in the carcerand compared with that of free sulfolene in solution. In the latter case the extrusion product can freely dissociate, whereas for the carceplex they are restricted to the cavity of the carcerand.

Molecular Modeling Study of Calix[4]arene-Based (Thia)-Carceplexes: *Strategy for Investigating Calix[4]arene-Based (Thia)carceplexes:* The key step in the molecular modeling study of calix[4]arene-based (thia)carceplexes **15**–**30** is a systematic search of all possible orientations of the guests inside the (thia)carcerands. Due to the fourfold symmetry of the calix[4]arene-based (thia)carcerand only a limited number of structures must be considered. After rotation of the guest and subsequent energy minimization a set of structures was obtained that corresponds to the global and local energy minima. From these structures information concerning the calix[4]arene-based (thia)carceplexes can be obtained. This includes the ability of the calix[4]arene-based (thia)carcerand to adapt the cavity size with respect to the size of the guest. Since the NH hydrogen atoms are pointing into the cavity forming a hydrogen bond to the guest the average distance between the diametrical (across the cavity) N*H* atoms and between the Ar*C*NH atoms was calculated.[45] From the local energy minima the energy barrier(s) for interconversion between the various stereoisomers was(were) calculated by the conjugated peak refinement (CPR)[46] algorithm implemented as the TRAVEL (trajectory refinement algorithm) module in CHARMM. This algorithm is able to find true saddle points between two (local) energy minima on the adiabatic potential energy surface of systems with a large degree of freedom. The CPR algorithm has been successfully applied for the calculation of the energy barriers for the interconversion between different calix[4]arene conformers[47] and for the isomerization around the amide bond in proline.[48] Furthermore, it has been used to study the dynamic behavior of a hemispherand sodium complex.[49, 50]

Cavity Size: For carceplexes **15**–**23** the average diametrical distances between the various N*H* atoms and the different Ar*C*NH atoms of the calix[4]arene moiety were calculated as a parameter that describes the ability of the carcerand to adapt the cavity size to that of the guest size. The diametrical distances between the N*H* atoms and between the Ar*C*NH atoms of the calix[4]arene moiety are plotted against the size of the guest[51] in Figure 6.

From Figure 6a it is clear that the distance between the N*H* atoms does not significantly change for incarcerated molecules, the volumes of which are smaller than that of NMP. However, incarcerated NMP and 1,5-dimethyl-2-pyrrolidinone force the N*H* atoms of the bridges more outward. This indicates that the calix[4]arene-based carcerand adapts the cavity size by variation of the diametrical distance between the N*H* atoms. Figure 6b shows that the distance between the Ar*C*NH atoms is only increased when 1,5-dimethyl-2-pyrrolidinone is included. The calculated distance is close to that for a calix[4]arene in a perfect cone conformation, that is, ca. 7.9–8.0 Å.[52] This may be the reason for the fact that larger guests do not form a carceplex because it is not possible to push the aromatic moieties of the calix[4]arene further outward. Since this limit is not reached for guests smaller than 1,5-dimethyl-2-pyrrolidinone it is likely that

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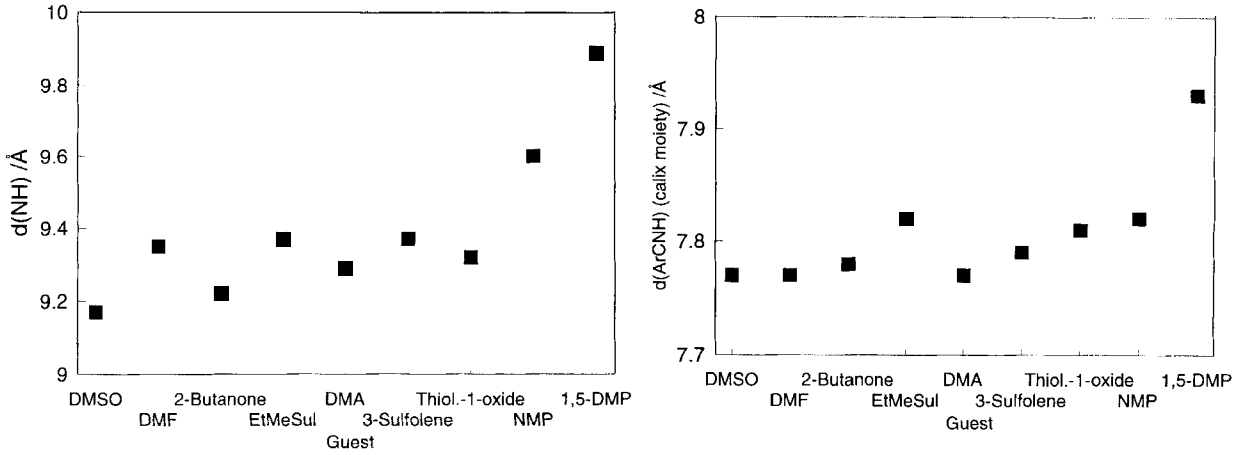

Figure 6. a) Calculated average distances between diametrical N*H* atoms of carceplexes **15–25**; b) Calculated average distances between diametrical ArCNH atoms of carceplexes **15–25**

in these cases the calix[4]arene moiety still possesses some flexibility resulting in a fast equilibrium between different pinched cone conformers.

The calculated average diametrical distances between the N*H* atoms and between the Ar*C*NH atoms of calix[4]arene-based thiacarceplexes **25–30** are shown in Table 5. The largest distance between the N*H* atoms is observed for NMP, whereas the smallest is found for DMA. The distance between the N*H* atoms in the amide-bridged carceplexes is significantly smaller in the thiacarceplexes. This is probably a result from the larger sulfur atoms compared with the oxygens situated at the outside of the thiacarcerand that force the N*H* atoms more into the cavity. The distance between the Ar*C*NH atoms does not change significantly, indicating that the conversion of the amide bridges into thioamides does not affect the geometry of the calix[4]arene moiety. The smaller distance between the N*H* atoms may be a reason for the higher energy barrier for interconversion between the different stereoisomers (vide supra).

Table 5. Calculated average diametrical distances between the N*H* atoms and between the Ar*C*NH atoms of the calix[4]arene moiety for energy-minimized structures of different guests inside calix[4]arene-based thiacarceplexes compared with the corresponding carceplexes with amide bridges.

Guest	d_{NH} (Å)	Δd_{NH} (Å)[a]	d_{ArCNH} (Å)	Δd_{ArCNH} (Å)[a]
DMF	8.72	0.64	7.81	0.04
DMA	8.56	0.73	7.81	−0.01
NMP	8.85	0.75	7.85	0.03
2-Butanone	8.58	0.64	7.76	−0.01
Ethyl methyl sulfoxide	8.78	0.59	7.79	0.03

[a] d(carceplex) − d(thiacarceplex).

Calculation of Energy Barriers: Analysis of the structures obtained after the systematic search of all possible orientations of the guest inside the calix[4]arene-based (thia)carcerands revealed that for most guests the experimentally observed orientation corresponds to the lowest energy, whereas in the other cases the structure with the second lowest energy corresponds to the experimental structure.

The global and local energy minima of the orientations of guests inside calix[4]arene-based (thia)carcerands were used to calculate the energy barrier for interconversion between the various orientations. The results of the calculations are summarized in Table 6.[53]

For DMF and DMSO the energy barrier for rotation around one short axis of the carcerand is low (3.6 and 4.3 kcal mol^{-1}, respectively). The preference for one orientation of DMF inside the calix[4]arene-based carcerand is most likely due to the difference in energy between the two orientations. For DMSO the calculated energy barrier corresponds to the observed fast rotation of the guest molecules inside the carcerand. This was also indicated by the ^{1}H NMR spectrum since only one signal was found for the guest molecule. The energy barriers for ethyl methyl sulfoxide and 2-butanone are not larger than for DMA. This indicates that the preference for one orientation, as observed by 2D NMR spectroscopy, probably does not result from a high energy barrier for interconversion. More likely, this

Table 6. Calculated (ΔE_{calc}) and experimental ($\Delta G_T^{\ddagger}$) energy barriers for interconversion between different orientations of guests inside calix[4]arene-based (thia)carcerands.

Guest	Carceplex		Thiacarceplex	
	ΔE_{calc} (kcal mol^{-1})	$\Delta G_{273}^{\ddagger}$ (kcal mol^{-1})	ΔE_{calc} (kcal mol^{-1})	$\Delta G_T^{\ddagger}$ (kcal mol^{-1})
DMF	3.6	n.o. [a]	8.6	n.o.
DMA	9.8	12.7 [c]	15.5	15.2 [c]
NMP	13.0	15.7 [c]	14.0	17.5 [c]
1,5-Dimethyl-2-pyrrolidinone	19.4	n.o. [a]	n.d. [b]	n.d. [b]
DMSO	4.3	n.o. [a]	n.d. [b]	n.d. [b]
Ethyl methyl sulfoxide	12.7	n.o. [a]	14.9	13.4 [d]
2-Butanone	7.9	n.o. [a]	10.0	n.o. [a]

[a] n.o.: not observed, that is, only one isomer present. [b] n.d.: not determined. [c] $T = 273$ K. [d] $T = 228$ K.

preference is a consequence of the energy difference between the different orientations.

The extra methyl group of 1,5-dimethyl-2-pyrrolidinone compared with NMP results in an increase in the (calculated) activation energy of ca. 6.4 kcal mol^{-1}. The calculated energy barrier for 1,5-dimethyl-2-pyrrolidinone is 19.4 kcal mol^{-1}. Only one orientation was observed with 2D NMR spectroscopy. This is, however, most likely due to the difference in energy between the different orientations and not due to a high energy barrier for interconversion.

It was shown that conversion of the amide bridges into thioamides leads to an increase in energy barrier for interconversion between the various stereoisomers corresponding to different orientations of the guests (vide supra). The increase in energy barrier for interconversion between the various stereoisomers found experimentally is indeed reproduced by the molecular modeling calculations (Table 6). Although the differences between the calculated and experimental values range from 3.5 to 0.3 kcal mol^{-1} for NMP and DMA, respectively, the trend in the calculated energy barriers is similar to the experimentally determined values. The calculations do not predict an extremely high (>20 kcal mol^{-1}) or an extremely low (<10 kcal mol^{-1}) activation energy. For DMF thiacarceplex **26** and 2-butanone thiacarceplex **30** only one stereoisomer was observed with 2D NMR spectroscopy. This is probably due to a too large energy difference between different orientations but also the energy barrier for interconversion may be too low to detect a second orientation of the guest inside calix[4]arene-based thiacarceplexes **26** and **30**.

Conclusion

In this paper we have presented a new approach towards a molecular switch, which uses calix[4]arene-based (hemi)-carcerands. These container molecules, obtained by combination of a calix[4]- and resorcin[4]arene, possess a noncentrosymmetric cavity and therefore, different incarcerated guest molecules lead to different stereoisomers. It was shown that a calix[4]arene-based *hemicarcerand*, in which the calix[4]- and resorcin[4]arene moieties are coupled by three bridges, can be obtained by a stepwise coupling of the two building blocks. Additional functional groups could be introduced at the free hydroxyl group of the resorcin[4]arene moiety. Dynamic NMR experiments revealed that calix[4]arene-based hemicarcerands do not possess an enforced cavity. This is most likely the reason why no complexes could be obtained. On the other hand, calix[4]arene-based *carcerands*, obtained by linking a calix[4]- and resorcin[4]arene by four bridges can (permanently) incarcerate one guest molecule. Two methods were presented to obtain calix[4]arene-based carceplexes. Amides and sulfoxides can be incarcerated by solvent inclusion, whereas potential guests that cannot be used as a solvent could be incarcerated by doped inclusion. Conversion of the amide bridges of the carceplexes into thioamides was shown to be a valuable tool for altering the rotation properties of incarcerated guests after synthesis of the carceplex. Rotational barriers for interconversion between the different orientations of incarcerated DMA, NMP, and ethyl methyl sulfoxide were determined by 2D EXSY NMR experiments. The results show that the energy barriers for interconversion between different orientations of guests inside calix[4]-arene-based (thia)carcerands is higher for the thiacarceplexes compared with the corresponding amide-bridged carceplexes. Molecular modeling was used to study the behavior of the incarcerated guests. Comparison between calix[4]arene-based carcerands and thiacarcerands revealed that the cavity is smaller for the latter. This is most likely a reason for the increased energy barriers. Furthermore, the difference in hydrogen-bond-donating ability of the thioamide and amide bridges could play a role. Good quantitative agreement was found between the calculated and experimentally determined activation energies. The results demonstrate that molecular mechanics calculations can be a useful tool for investigating, and predicting, the properties of incarcerated guests inside calix[4]arene-based (thia)-carcerands.

Experimental Section

General: All experiments were carried out under an inert Ar atmosphere. All solvents used for the synthesis of the carceplexes were freshly distilled prior to use. Amides were distilled from $MgSO_4$, sulfoxides from BaO, hexane (referring to petroleum ether with b.p. 60–80 °C) and CH_2Cl_2 from $CaCl_2$, 2-butanone and ethyl acetate (EtOAc) from K_2CO_3, and THF from sodium/benzophenone ketyl. Triethylamine (NEt_3) was distilled from P_2O_5 and stored over KOH pellets. NMR spectra were recorded on a Bruker AC250 (^{1}H NMR 250 MHz) or a Varian Unity 400 (^{1}H NMR 400 MHz) spectrometer in $CDCl_3$ unless stated otherwise. Residual solvent protons were used as internal standard and chemical shifts are given relative to tetramethylsilane (TMS). FAB and electron impact mass spectra were measured on a Finnigan MAT 90 spectrometer with *m*-nitrobenzyl alcohol (NBA) as a matrix. Field desorption mass spectra were recorded on a Jeol JMS SX/SX102A four-sector mass spectrometer, coupled to a Jeol MS-MP7000 data system. FD emitters (10 μm tungsten wire) containing carbon microneedles with an average length of 30 μm were used. The samples were dissolved in chloroform and then loaded onto the emitters with dipping technique. An emitter current of 0–15 mA was used to desorb the samples. Melting points were determined with a Reichert melting point apparatus and are uncorrected. Flash chromatography was performed on silica gel (SiO_2, E. Merck, 0.040–0.063 mm, 230–240 mesh). Preparative thin-layer chromatography (TLC) was performed on precoated silica plates (E. Merck, Kieselgel 60 F_{254}, 2 mm). For dropwise additions a perfuser was used. The presence of solvents in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Dinitrocalix[4]arene **1**,[54] tetrahydroxycavitand **6**,[10] and 1:1 *endo*-coupled product **14**[10] were prepared following literature procedures.

Synthesis

Calix[4]arene-Based Hemicarcerands

5,11-Dinitro-17-phthalimido-25,26,27,28-tetrapropoxycalix[4]arene (3): A suspension of dinitrocalix[4]arene **1** (1.50 g, 2.21 mmol) and $AgOC(O)CF_3$ (0.50 g, 2.27 mmol) in $CHCl_3$ (150 mL) was refluxed for 2 h. After the mixture was cooled to room temperature, I_2 was added until a deep purple color remained and the mixture was stirred for an additional 30 min. After filtration over Hyflo the solvent was evaporated and the residue taken up in EtOAc (100 mL). The organic layer was washed with ca. 5% $NaHSO_3$ (25 mL), H_2O (25 mL), and brine (25 mL) and dried over Na_2SO_4. After evaporation of the solvent a mixture (1.70 g) of 5-iodo-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (**2**) and 5,11-diiodo-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene was obtained, which was used without further purification. The presence of **2** was confirmed by FAB mass spectrometry, $m/z = 808.2$ (M^+, calcd. 808.2). The mixture of mono- and diiodocalix[4]arene (1.70 g), phthalimide (0.77 g, 5.2 mmol) and Cu_2O (0.50 g, 3.5 mmol) in collidine (40 mL) was refluxed for 24 h. After the mixture was cooled to room temperature CH_2Cl_2 (50 mL) was added. The mixture was washed with 2N HCl (2 × 50 mL), 2N NaOH (2 × 50 mL), H_2O (50 mL), and brine (50 mL) and subsequently dried over Na_2SO_4. The crude reaction product was purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc 98/2) to give pure **3**. Yield

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0.71 g (39%, starting from **1**); m.p. 259–260 °C (CH_2Cl_2/MeOH); ^{1}H NMR: δ = 7.95–7.9 (m, 2H; Pht), 7.75–7.70 (m, 4H; Pht + $ArNO_2$), 7.44 and 7.33 (2d, J = 2.8 Hz, 4H; $ArHNO_2$), 6.92 and 6.89 (2d, J = 2.5 Hz, 4H; ArH-Pht), 6.55–6.50 (m, 2H; ArH), 6.45–6.40 (m, 1H; ArH), 4.55–4.45 and 3.35–3.20 [2 × 3d (1:2:1), 4H; $ArCH_2Ar$], 4.07–3.77 (m, 8H; OCH_2), 2.05–1.9 (m, 8H; OCH_2CH_2), 1.28–0.94 (m, 12H; CH_3); ^{13}C NMR: δ = 167.1 (C=O), 162.1, 161.8, 142.8, 137.0, 136.5, 136.1, 134.8, 134.6, 134.2, 132.9, 131.7, 128.7, 128.0, 127.1, 126.2, 126.0, 124.8, 124.2, 123.8, 126.6, 123.3, 122.6, 77.3 (OCH_2), 31.1 ($ArCH_2Ar$), 23.3 (OCH_2CH_2), 10.5, 10.3 and 10.1 (CH_3); MS (FAB): m/z = 827.2 (M^+, calcd. 827.3). Anal. $C_{48}H_{49}N_3O_{10}$, 0.25 H_2O: calcd. C, 68.94; H, 5.92; N, 5.02; found: C, 68.64; H, 5.93; N, 5.02.

5,11-Diamino-17-phthalimido-25,26,27,28-tetrapropoxycalix[4]arene (4): A mixture of **3** (0.50 g, 0.60 mmol) and $SnCl_2 \cdot 2H_2O$ (1.35 g, 6.0 mmol) in EtOH (50 mL) was refluxed until no starting material could be detected by TLC. The reaction mixture was poured onto crushed ice and after adjustment of the pH to 9–10 with 2N NaOH and addition of CH_2Cl_2 (50 mL) the mixture was filtered over Hyflo. The filtrate was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic layers were washed with 2N NaOH (15 mL), H_2O (15 mL), and brine (15 mL) and subsequently dried over Na_2SO_4. The solvents were evaporated and the residue dried in vacuo. The crude product was used without further purification. Yield 0.38 g (82%); m.p. 145–148 °C; ^{1}H NMR: δ = 7.90–7.85 and 7.75–7.7 (2m, 4H; Pht), 6.85 and 6.84 (2d, J = 2.6 Hz, 4H; Ar*H*Pht), 6.65–6.6 (m, 3H; ArH), 6.11 and 6.09 (2d, J = 2.8 Hz, 2H; Ar*H*NH_2), 5.95 (s, 2H; Ar*H*NH_2), 4.55–4.25 and 3.2–2.9 (2 × 4d; 8H; $ArCH_2Ar$), 3.9–3.55 (m, 8H; OCH_2), 2.15–1.8 (m, 8H; OCH_2CH_2), 1.10–0.95 (m, 12H; CH_3); ^{13}C NMR: δ = 166.1 (C=O), 158.1, 152.2, 150.9, 140.5, 137.6, 137.1, 135.4, 134.4, 134.3, 132.7, 130.7, 129.4, 128.1, 123.4, 122.0, 117.3, 116.8, 76.8 (OCH_2), 76.4 (OCH_2), 31.2 ($ArCH_2Ar$), 23.5, 23.2, 23.0, 22.8, 10.9, 10.3, 9.8, 9.7; MS (FAB): m/z = 768.1 (M^+, calcd. for $C_{48}H_{53}N_3O_6$ 767.9).

5,11-Bis(chloroacetamido)-17-phthalimido-25,26,27,28-tetrapropoxycalix[4]arene (5): To a solution of **4** (0.36 g, 0.44 mmol) and NEt_3 (1.4 mL, 10 mmol) in dry CH_2Cl_2 (15 mL) was added chloroacetyl chloride (0.35 mL, 4.4 mmol) and the reaction mixture was stirred for 45 min. After dilution with CH_2Cl_2 (25 mL) the organic layer was washed with 2N HCl (2 × 15 mL), 2N NaOH (2 × 15 mL), H_2O (15 mL), and brine (15 mL) and subsequently dried over Na_2SO_4. The reaction mixture was purified by column chromatography (SiO_2, EtOAc/hexane 1/1) to give pure **5**. Yield 0.30 g (70%); m.p. 189–192 °C (171–173 °C phase transition); ^{1}H NMR: δ = 8.06 and 8.01 (2s, 2H; NH), 7.9–7.85 and 7.8–7.7 (2m, 4H; Pht), 6.88 and 6.85 [2d, J = 2.4 Hz, 4H; Ar*H*NHC(O)], 6.75–6.55 (m, 7H; ArH), 4.5–4.4 and 3.2–3.1 (2ABq, J = 12.1 Hz, 8H; $ArCH_2Ar$), 4.09 (s, 2H; CH_2Cl), 3.96 (s, 2H; CH_2Cl), 3.95–3.75 (m, 8H; OCH_2), 2.0–1.85 (m, 8H; CH_2), 1.1–0.95 (m, 12H; CH_3); ^{13}C NMR: δ = 167.6 (C=O), 164.1 (C=O), 163.5 (C=O), 156.7, 156.1, 154.1, 135.8, 135.5 (2x), 135.2, 135.1, 135.0, 134.8, 134.6, 134.2, 131.8, 130.7, 130.3, 128.6, 128.3, 126.5, 126.3, 125.2, 123.5, 122.4, 122.1, 120.9, 120.7, 77.3 (OCH_2), 77.2 (OCH_2), 77.0 (OCH_2), 76.7 (OCH_2), 42.9 (CH_2Cl), 31.1 ($ArCH_2Ar$), 31.0 ($ArCH_2Ar$), 23.3, 23.2, 23.1, 10.4, 10.2; MS (FAB): m/z = 921.3 (M^+, calcd. 920.9). Anal. $C_{52}H_{55}Cl_2N_3O_8$, 2.5 H_2O: calcd. C, 64.66; H, 6.26; N, 4.35; found: C, 64.60; H, 5.86; N, 4.23.

41,59-Dihydroxy-19-phthalimido-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16*H*,21*H*,28*H*,34*H*-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1*H*,8*H*,47*H*,49*H*-[1,3]benzodioxocino[9′,8′:4,5][1,3]benzodioxocino[9,10-*d*][1,3]dioxocino-[4,5-l_1][1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10*H*,36*H*)-dione (7,8): In a typical experiment a solution of **5** (0.42 g, 0.46 mmol) in acetonitrile (50 mL) was added dropwise (125 μL min^{-1}) to a mixture of tetrahydroxycavitand **6** (1.67 g, 1.37 mmol), Cs_2CO_3 (0.60 g, 1.84 mmol) and a spatula full of KI in refluxing acetonitrile (260 mL). The reaction mixture was refluxed for another 14 h and subsequently evaporated to dryness. The residue was taken up in CH_2Cl_2 (100 mL) and washed with 2N HCl (30 mL), H_2O (30 mL), and brine (30 mL) and subsequently dried over Na_2SO_4. After evaporation of the solvent the crude mixture was purified by column chromatography (SiO_2 60H, EtOAc/hexane 40/60–50/50).

***endo*-Coupled 7**: Yield 0.28 g (29%); m.p. 214–215 °C; ^{1}H NMR: δ = 10.13 and 9.24 (2s, 2H; NH), 7.75–7.7 and 7.55–7.50 (2m, 4H; Pht), 7.55 and 7.15 (2d, J = 2.2 Hz, 2H; Ar*H*Pht), 6.96 (s, 2H; ArH), 6.93 (s, 2H; ArH), 6.9–6.85 [m, 1H; ArH (calix)], 6.71 (s, 2H; ArH), 6.03 (d, J = 3.5 Hz, 1H; ArH), 6.6–6.55 (m, 1H; ArH), 6.50 and 6.26 (2d, J = 2.4 Hz, 4H; ArH), 6.42 (d, J = 7.5 Hz, 1H; ArH), 6.0–5.9 [m, 4H; OCH_2O (outer)], 4.75–4.35 [m, 16H; $CHC_{11}H_{23}$ + $ArCH_2Ar$ + OCH_2O (inner) + $CH_2C(O)$], 4.2–3.85 (m, 2H; OCH_2), 3.77 (t, J = 7.0 Hz, 2H; OCH_2), 3.66 (t, J = 7.0 Hz, 4H; OCH_2), 3.25–3.15 (m, 4H; $ArCH_2Ar$), 2.2–2.05 (m, 8H; $CHCH_2$), 1.05–0.85 (m, 8H; OCH_2CH_2), 1.4–1.05 (m, 72H; CH_2), 1.0–0.8 (m, 24H; CH_3); ^{13}C NMR: δ = 167.0 (C=O), 166.8 (C=O), 156.9, 155.2, 154.3, 152.6, 147.9, 147.6, 147.0, 146.8, 144.7, 144.4, 142.2, 142.0, 141.9, 141.1, 141.0, 140.4, 140.3, 138.8, 138.6, 138.2, 138.0, 137.1, 136.1, 135.6, 135.1, 134.4, 133.9, 132.0, 131.6, 126.0, 125.2, 123.2, 77.2 and 77.1 ($ArOCH_2$), 36.9, 31.9 ($ArCH_2Ar$), 29.8, 29.7, 29.4, 27.9, 23.4, 23.2, 22.9, 22.7, 14.1, 10.6, 10.1, 9.9; MS (FAB): m/z = 2065.8 ([M+H]$^+$, calcd. 2065.3). Anal. $C_{128}H_{165}N_3O_{20}$, 1.50 H_2O: calcd. C, 73.51; H, 8.10; N, 2.00; found: C, 73.13; H, 7.90; N, 1.73.

***exo*-Coupled 8**: Yield 0.19 g (19%); m.p. 198–200 °C; ^{1}H NMR: δ = 8.37 and 8.24 (2s, 2H; NH), 7.8–7.77 and 7.55–7.5 (2m, 4H; Pht), 7.02 (s, 1H; ArH), 7.08 (s, 1H; ArH), 6.86 (d, J = 2.3 Hz, 2H; ArH), 6.77 (s, 2H; ArH), 6.7–6.5 (m, 3H; ArH), 6.52 (s, 2H; ArH), 6.48 (s, 1H; ArH), 6.18 (s, 1H; ArH), 5.85–5.75 [m, 3H; OCH_2O (outer)], 5.58 [d, J = 6.5 Hz, 1H; OCH_2O (outer)], 4.6–4.2 [m, 16H; $CHC_{11}H_{23}$ + $ArCH_2Ar$ + OCH_2O (inner) + $CH_2C(O)$], 3.85–3.71 (m, 8H; OCH_2), 3.2–2.95 (m, 4H; $ArCH_2Ar$), 2.1–2.0 (m, 8H; $CHCH_2$), 1.9–1.85 (m, 8H; OCH_2CH_2), 1.5–1.15 (m, 72H; CH_2), 1.1–0.9 (m, 12H; CH_3), 0.85–0.75 (m, 12H; CH_3); ^{13}C NMR: δ = 167.5 (C=O), 166.8 (C=O), 166.4, 156.3, 156.0, 154.1, 153.4, 148.1, 147.7, 147.7, 147.0, 146.7, 144.0, 143.8, 142.3, 142.1, 142.0, 141.2, 139.8, 139.0, 138.5, 138.4, 138.2, 136.6, 136.2, 135.7, 135.3, 134.8, 134.2, 133.9, 131.9, 131.0, 130.6, 128.2, 126.6, 125.3, 123.4, 121.4, 119.6, 115.5, 115.2, 109.6, 99.9 (OCH_2O), 77.2 and 76.8 ($ArOCH_2$), 73.3 [$OCH_2C(O)$], 60.4, 36.9, 32.0 ($ArCH_2Ar$), 30.0, 29.8, 29.7, 29.4, 27.9, 23.4, 23.3, 23.2, 23.1, 22.7, 14.1, 10.5, 10.4, 10.3, 10.1; MS (FAB): m/z = 2065.8 ([M+H]$^+$, calcd. 2065.3). Anal. $C_{128}H_{165}N_3O_{20}$, H_2O: calcd. C, 73.78; H, 8.08; N, 2.02; found: C, 73.63; H, 8.19; N, 1.87.

19-Amino-41,59-dihydroxy-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16*H*,21*H*,28*H*,34*H*-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1*H*,8*H*,47*H*,49*H*-[1,3]benzodioxocino[9′,8′:4,5][1,3]benzodioxocino[9,10-*d*][1,3]dioxocino-[4,5-l_1][1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10*H*,36*H*)-dione (*endo*-9): A solution of **7** (0.22 g, 0.11 mmol) and hydrazine monohydrate (0.30 mL, 6.2 mmol) in a mixture of EtOH (30 mL) and THF (15 mL) was refluxed for 4 h. After evaporation of the solvents the crude mixture was taken up in CH_2Cl_2 (100 mL), washed with 2N HCl (25 mL), H_2O (25 mL), 1N NaOH (25 mL), H_2O (25 mL), and brine (25 mL) and subsequently dried over Na_2SO_4. After evaporation of the solvent and drying in vacuo **12** was isolated in essentially quantitative yield. M.p. > 300 °C; ^{1}H NMR: δ = 8.89 (brs, 2H; NH), 6.84 [s, 2H; ArH (cavitand)], 6.8–6.4 (m, 7H; ArH), 6.05–5.8 [m, 6H; OCH_2O (outer) + Ar*H*NH_2], 4.7–4.55 [m, 6H; $CHC_{11}H_{23}$ + $CH_2C(O)$], 4.5–4.25 [m, 10H; $ArCH_2Ar$ + OCH_2O (inner) + $CH_2C(O)$], 3.8–3.55 (m, 4H; OCH_2), 3.55–3.4 (m, 4H; OCH_2), 3.4–3.15 (m, 2H; $ArCH_2Ar$), 3.15–2.9 (m, 2H; $ArCH_2Ar$), 2.3–2.05 (m, 8H; $CHCH_2$), 2.05–1.75 (m, 8H; OCH_2CH_2), 1.6–1.2 (m, 72H; CH_2), 1.05–0.75 (m, 24H; CH_3); ^{13}C NMR: δ = 77.2 (OCH_2), 31.9 ($ArCH_2Ar$), 29.7, 29.4, 22.7, 14.1; MS (FAB): m/z = 1935.0 ([M+H]$^+$, calcd. for $C_{120}H_{163}N_3O_{18}$ 1935.6), 1958.0 ([M+Na]$^+$, calcd. for $C_{120}H_{163}N_3O_{18}Na$ 1958.5).

19-Chloroacetamido-41,59-dihydroxy-14,30,62,63-tetrapropoxy-1,47,49,57-tetraundecyl-16*H*,21*H*,28*H*,34*H*-13,31:51,55-dimethano-2,46:3,45:11,15:17,21:23,27:29,33-hexametheno-1*H*,8*H*,47*H*,49*H*-[1,3]benzodioxocino[9′,8′:4,5][1,3]benzodioxocino[9,10-*d*][1,3]dioxocino[4,5-l_1]-[1,3,6,36,9,33]benzotetraoxadiazacyclooctatriacontine-9,35(10*H*,36*H*)-dione (*endo*-10): To a solution of **9** (0.20 g, 0.10 mmol) in CH_2Cl_2 (20 mL) was added chloroacetyl chloride (0.12 mL, 1.5 mmol) and the reaction mixture was stirred for 90 min at room temperature. The mixture was subsequently diluted with CH_2Cl_2 (100 mL), washed with 1N HCl (2 × 20 mL), H_2O (2 × 25 mL), 1N NaOH (15 mL), H_2O (20 mL), and brine and dried over Na_2SO_4. After removal of the solvent and additional drying in vacuo, **10** was obtained in essentially quantitative yield. An analytically pure sample was obtained after column chromatography (SiO_2, EtOAc/hexane 1/1). M.p. 214–215 °C (CH_2Cl_2/MeOH); ^{1}H NMR: δ = 9.34, 8.90, and 7.67 (3s, 3H; NH), 7.42, 7.23, and 6.92 (3s, 3H; ArH), 6.84 and 6.82 [2s, 2H; ArH (cavitand)], 6.75–6.65 (m, 3H; ArH), 6.56 and 6.54 [2s, 2H; ArH (cavitand)], 6.21 and 6.06 (2s, 2H; ArH), 5.9–5.8 [m, 4H; OCH_2O (outer)], 4.7–4.5 (m, 8H; $ArCH_2Ar$ + $CHCH_2$), 4.5–3.75 [m, 18H; OCH_2O (inner) + $CH_2C(O)$ + CH_2Cl + OCH_2], 3.15–3.0 (m, 4H; $ArCH_2Ar$), 2.2–2.0 (m,

8H; $CHCH_2$), 2.0–1.75 (m, 8H; OCH_2CH_2), 1.3–1.0 (m, 72H; CH_2), 1.2–0.95 (m, 12H; CH_3), 0.8–0.75 (m, 12H; CH_3); ^{13}C NMR: $\delta = 31.9$ ($ArCH_2Ar$), 29.7, 29.4, 27.9, 22.7, 14.1, 10.6; MS (FAB): $m/z = 2011.7$ ($[M+H]^+$, calcd. 2011.2). Anal. $C_{122}H_{164}ClN_3O_{19}$, $2H_2O$: calcd. C, 71.58; H, 8.27; N, 2.05; found: C, 71.18; H, 8.17; N, 1.97.

Hemicarcerand 11: A solution of **10** (0.10 g, 0.50 mmol) in DMA (40 mL) was added dropwise (80 μL min^{-1}) to a suspension of Cs_2CO_3 (0.16 g, 0.50 mmol) and a catalytic amount of KI in DMA (50 mL) at 70–80 °C. The mixture was stirred for another 8–10 h whereupon 2N HCl (3 mL) was added. After the solution was concentrated to ca. 5 mL the crude product was taken up in CH_2Cl_2 (100 mL), washed with 2N HCl (25 mL), H_2O (2 × 25 mL), and brine (25 mL) and dried over Na_2SO_4. After evaporation of the solvent the crude mixture was purified by preparative TLC (SiO_2, CH_2Cl_2/THF 90/10 v/v). Yield 40 mg (40%); m.p. 280–283 °C; ^1H NMR: $\delta = 7.72$ (brs, 1H; NH), 7.33 (brs, 2H; NH), 7.02, 6.93, 6.90, and 6.75 (4s, 8H; ArH), 6.7–6.65 (m, 2H; ArH), 6.50 (s, 1H; ArH), 6.40 (s, 2H; ArH), 5.9–5.85 [m, 4H; OCH_2O (outer)], 4.81 [s, 2H; $OCH_2C(O)$], 4.65–4.45 (m, 10H; $CHC_{11}H_{23}$ + $CH_2C(O)$], 4.40 and 4.33 (2d, $J = 12.2$ Hz, 4H; $ArCH_2Ar$), 4.25 [d, $J = 7.0$ Hz, 2H; OCH_2O (inner)], 4.19 [d, $J = 6.5$ Hz, 2H; OCH_2O (inner)], 3.85–3.7 (m, 4H; OCH_2), 3.7–3.5 (m, 4H; OCH_2), 3.15 (d, $J = 12.1$ Hz, 2H; $ArCH_2Ar$), 3.08 (d, $J = 12.4$ Hz, 2H; $ArCH_2Ar$), 2.25–1.95 (m, 8H; $CHCH_2$), 1.9–1.75 (m, 8H; OCH_2CH_2), 1.35–1.1 (m, 72H; CH_2), 1.0–0.85 (m, 12H; CH_3), 0.8–0.65 (m, 12H; CH_3); ^{13}C NMR: $\delta = 77.2$ (OCH_2), 31.9 ($ArCH_2Ar$), 29.7, 29.4, 27.9, 22.7, 14.1; MS (FAB): $m/z = 1998.9$ ($[M+H+Na]^+$, calcd. 1998.6); $m/z = 1975.0$ (M^+, calcd. 1974.6). Anal. $C_{122}H_{162}N_3O_{19}$, $CHCl_3$: calcd. C, 70.56; H, 7.85; N, 2.01; found: C, 70.48; H, 7.56; N, 2.01.

***O*-Propyl-Hemicarcerand 12**: A solution of hemicarcerand **11** (10 mg, 5 μmol), K_2CO_3 (50 mg, 0.4 mmol), *n*-propyl iodide (0.5 mL, 5 μmol), and a catalytic amount of KI in DMA (10 mL) was stirred at 70–80 °C for 18 h. The reaction mixture was evaporated to dryness and the residue taken up in CH_2Cl_2 (25 mL), washed with 1N HCl (2 × 10 mL), H_2O (10 mL), and brine (10 mL) and subsequently dried over Na_2SO_4. After evaporation of the solvent and trituration with MeOH *O*-propyl hemicarcerand **12** was obtained in essentially quantitative yield. M.p. > 300 °C; ^1H NMR: $\delta = 7.67$ (brs, 1H; NH), 7.17 (brs, 2H; NH), 6.99 (s, 2H; ArH), 6.90 and 6.52 (2d, $J = 2.6$ Hz, 4H; Ar*H*NH), 6.95–6.9 (m, 2H; ArH), 6.73 (s, 2H; ArH), 6.7–6.65 (m, 3H; ArH), 5.85 and 5.79 [2d, $J = 6.9$ Hz, 4H; OCH_2O (outer)], 4.82 [s, 2H; $OCH_2C(O)$], 4.67 [s, 4H; $CH_2C(O)$], 4.65–4.4 (m, 4H; $CHCH_2$), 4.42 (d, $J = 12.0$ Hz, 2H; $ArCH_2Ar$), 4.36 (d, $J = 12.2$ Hz, 2H; $ArCH_2Ar$), 4.22 and 4.12 [2d, $J = 6.8$ Hz, 4H; OCH_2O (inner)], 3.85–3.7 (m, 6H; $ArOCH_2$), 3.7–3.5 (m, 4H; $ArOCH_2$), 3.17 (d, $J = 12.3$ Hz, 2H; $ArCH_2Ar$), 3.10 (d, $J = 12.6$ Hz, 2H; $ArCH_2Ar$), 2.3–2.05 (m, 8H; $CHCH_2$), 1.9–1.75 (m, 8H; OCH_2CH_2), 1.5–1.1 (m, 72H; CH_2), 1.15–0.95 (m, 15H, CH_3), 0.9–0.75 (m, 12H, CH_3); MS (FAB): $m/z = 2040.6$ ($[M+Na]^+$, calcd. for $C_{125}H_{168}N_3O_{19}Na$ 2040.6).

***O*-Acetamido-Hemicarcerand 13**: A solution of hemicarcerand **11** (10 mg, 5 μmol), K_2CO_3 (50 mg, 0.4 mmol), α-bromoacetamide (50 mg, 0.4 mmol), and a catalytic amount of KI in DMA (10 mL) was stirred at 70–80 °C for 18 h. The reaction mixture was evaporated to dryness and the residue taken up in CH_2Cl_2 (25 mL), washed with 1N HCl (2 × 15 mL), H_2O (10 mL), and brine (10 mL), and subsequently dried over Na_2SO_4. After evaporation of the solvent and trituration with MeOH, *O*-acetamido-hemicarcerand **13** was obtained in essentially quantitative yield. M.p. > 300 °C; ^1H NMR: $\delta = 7.70$ (brs, 1H; NH), 7.40 (brs, 2H; NH), 7.02, 6.98, 6.85, 6.77, and 6.75 (5s, 10H; ArH), 6.68 (s, 1H; ArH), 6.41 (s, 2H; ArH), 5.90 [d, $J = 6.8$ Hz, 4H; OCH_2O (outer)], 4.81 [s, 2H; $OCH_2C(O)$], 4.65 [s, 4H; $CH_2C(O)$], 4.7–4.5 (m, 4H; $CHCH_2$), 4.42 (d, $J = 12.1$ Hz, 2H; $ArCH_2Ar$), 4.38 (d, $J = 12.0$ Hz, 2H; $ArCH_2Ar$), 4.25–4.15 (m, 4H; OCH_2O), 3.9–3.8 (m, 4H; $ArOCH_2$), 3.7–3.5 (m, 4H; $ArOCH_2$), 3.43 (s, 2H; NH_2), 3.21 (d, $J = 12.0$ Hz, 2H; $ArCH_2Ar$), 3.10 (d, $J = 12.3$ Hz, 2H; $ArCH_2Ar$), 2.25–1.95 (m, 8H; $CHCH_2$), 1.9–1.7 (m, 8H; OCH_2CH_2), 1.4–1.1 (m, 72H; CH_2), 1.05–0.85 (m, 12H; CH_3), 0.85–0.75 (m, 12H; CH_3); MS (FAB): $m/z = 2055.7$ ($[M+Na]^+$, calcd. for $C_{124}H_{165}N_4O_{20}Na$ 2055.6); $m/z = 2030.8$ ($[M-H]^-$, calcd. for $C_{124}H_{164}N_4O_{20}$ 2030.8).

Calix[4]arene-Based Carceplexes

General Procedure for Solvent Inclusion: In a typical experiment a solution of 1:1 *endo*-coupled compound **14** (60 mg, 26 μmol) in the "guest–solvent" (25 mL) (in the case of DMSO, ethyl methyl sulfoxide, and thiolane-1-oxide ca. 5 mL THF was added as a co-solvent) was added dropwise over a period of 6–11 h to a mixture of Cs_2CO_3 (0.21 g, 0.64 mmol), CsF (0.10 g, 0.66 mmol), and a catalytic amount of KI in deoxygenated "guest–solvent" (25 mL) at 70–80 °C. The reaction mixture was stirred at 70–80 °C for another 10–14 h. After cooling to room temperature the mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2 (100 mL), washed with 2N HCl (25 mL), H_2O (2 × 25 mL), and brine (25 mL) and dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by trituration with MeOH or by preparative TLC (SiO_2, THF/CH_2Cl_2 10/90 v/v). The carceplexes showed typical R_f values of 0.7–0.8.

15,31,66,67-Tetrapropoxy-46,54,55,56-tetraundecyl-17*H*,23*H*,29*H*,35*H*-4,20:42,26-bis(epoxyethanimino)-3,43-(epoxymethanoxy)-2,44:14,32:48,52-trimethano-12,16:18,22:24,28:30,34-tetramethano-9*H*,46*H*,54*H*-bisbenzo-[4,5][1,3]dioxocino[9,10-*d*:10′,9′-k_1][1,3,6,36,9,13]tetraoxadiazacyclooctatriacontine-10,36,62,69(11*H*,37*H*)-tetrone + DMF (15) was obtained in essentially quantitative yield; m.p. > 300 °C (CH_2Cl_2/MeOH); ^1H NMR: $\delta = 7.67$ (s, 4H; NH), 6.96 (s, 8H; *o*-NHArH), 6.75 (s, 4H; *m*-OArH), 5.75 [d, $J = 7.0$ Hz, 4H; OCH_2O (outer)], 4.84 [s, 8H; $CH_2C(O)$], 4.81 (s, 1H; CHO), 4.63 (t, $J = 8.0$ Hz, 4H; $CHC_{11}H_{23}$), 4.43 and 3.18 (ABq, $J = 12.0$ Hz, 8H; $ArCH_2Ar$), 3.99 [d, $J = 7.0$ Hz, 4H; OCH_2O (inner)], 3.74 (t, $J = 7.5$ Hz, 8H; $ArOCH_2$), 2.2–2.0 (m, 8H; $CHCH_2$), 1.88 (2t, $J = 7.6$ Hz, 8H; OCH_2CH_2), 1.4–1.1 [m, 72H; $CHCH_2(CH_2)_9$], 0.98 (t, $J = 7.5$ Hz, 12H; CH_3), 0.82 (t, $J = 6.5$ Hz, 12H; CH_3), 0.66 (s, 3H; CH_3 *trans* to carbonyl), −0.93 (s, 3H; CH_3 *cis* to carbonyl); ^{13}C NMR: $\delta = 166.7$ (C=O), 152.9, 145.4, 141.4, 130.7, 121.4, 113.5, 99.4 (OCH_2O), 70.5 [$OCH_2C(O)$]; MS (FAB): $m/z = 2126.1$ ($[M+Na]^+$, calcd 2126.5). Anal. $C_{127}H_{170}N_5O_{21}$, $1.5H_2O$: calcd. C, 71.58; H, 8.23; N, 3.29; found: C, 71.38; H, 8.16; N, 3.25. Karl-Fischer titration: calcd for $1.5H_2O$: 1.27; found: 1.20.

DMA Carceplex 16 was obtained in essentially quantitative yield; m.p. > 300 °C (CH_2Cl_2/MeOH); ^1H NMR: $\delta = 7.70$ (s, 4H; NH), 6.94 (s, 8H; *o*-NHArH), 6.72 (s, 4H; *m*-OArH), 5.75 [d, $J = 7.0$ Hz, 4H; OCH_2O (outer)], 4.85 [s, 8H; $CH_2C(O)$], 4.64 (t, $J = 8.0$ Hz, 4H; $CHC_{11}H_{23}$), 4.42 and 3.18 (ABq, $J = 12.0$ Hz, 8H; $ArCH_2Ar$), 4.09 [d, $J = 7.0$ Hz, 4H; OCH_2O (inner)], 3.74 (t, $J = 7.6$ Hz, 8H; $ArOCH_2$), 2.2–2.0 (m, 8H; $CHCH_2$), 1.88 (2t, $J = 7.6$ Hz, 8H; OCH_2CH_2), 1.4–1.1 [m, 75H; $CHCH_2(CH_2)_9$ + CH_3 *trans* to carbonyl], 0.98 (t, $J = 7.5$ Hz, 12H; CH_3), 0.82 (t, $J = 6.5$ Hz, 12H; CH_3), −1.01 (brs, 3H; CH_3 *cis* to carbonyl), −1.98 [s, 3H; $C(O)CH_3$]; ^{13}C NMR: $\delta = 166.8$ (C=O), 153.3, 145.4, 141.6, 130.8, 122.1, 113.6, 98.2 (OCH_2O), 70.1 [$OCH_2C(O)$]; MS (FAB): $m/z = 2030.8$ ($[M-DMA]^+$, calcd 2030.6). Anal. $C_{128}H_{173}N_5O_{21}$, $1.75H_2O$: calcd. C, 71.52; H, 8.28; N, 3.26; found: C, 71.52; H, 8.34; N, 3.26. Karl-Fischer titration: calcd. for $1.75H_2O$: 1.47. Found: 1.40.

NMP Carceplex 17 was isolated after preparative TLC in 50% yield; m.p. > 300 °C; ^1H NMR: (400 MHz, 263 K) $\delta = 7.87$ and 7.77 (2s, 4H; NH), 6.97 (s, 8H; *o*-NHArH), 6.74 and 6.68 (2s, 4H; *m*-OArH), 5.81 and 5.76 [2d, $J = 7.2$ Hz, 4H; OCH_2O (outer)], 4.91 and 4.87 [2s, 8H; $CH_2C(O)$], 4.7–4.6 (m, 4H; $CHC_{11}H_{23}$), 4.41, 4.39 and 3.19 (2ABq, $J = 12.0$ Hz, 8H; $ArCH_2Ar$), 4.09 [d, $J = 6.8$ Hz, 4H; OCH_2O (inner)], 3.72 (t, $J = 7.6$ Hz, 8H; $ArOCH_2$), 2.1–2.0 (m, 8H; $CHCH_2$), 1.9–1.8 (m, 8H; OCH_2CH_2), 1.55 (m, 2H; 5-CH_2 minor isomer), 1.46 (t, $J = 6.6$ Hz, 2H; 5-CH_2 major isomer), 1.4–1.1 [m, 72H; $CHCH_2(CH_2)_9$], 0.96 (t, $J = 7.5$ Hz, 12H; CH_3), 0.82 (t, $J = 6.8$ Hz, 12H; CH_3), −0.99 (pentet, $J = 7.0$ Hz, 2H; 4-CH_2 major isomer), −1.17 (t, $J = 8.0$ Hz, 2H; 3-CH_2 minor isomer), −1.32 (s, 3H; NCH_3 major isomer), −1.48 (t, $J = 7.4$ Hz, 2H; 3-CH_2 major isomer), −1.5 (m, 2H; 4-CH_2 minor isomer), −1.73 (s, 3H; NCH_3 minor isomer); ^{13}C NMR: $\delta = 166.9$ (C=O), 153.3, 145.6, 141.8, 131.3, 122.0, 113.6, 98.6 (OCH_2O), 70.5 [$OCH_2C(O)$]; MS (FAB): $m/z = 2152.0$ ($[M+Na]^+$, calcd 2152.3). Anal. $C_{129}H_{173}N_5O_{21}$, $1.25H_2O$: calcd. C, 71.98; H, 8.22; N, 3.25; found: C, 71.73; H, 8.15; N, 3.26. Karl-Fischer titration: calcd for $1.25H_2O$: 1.05; found: 1.08.

1,5-Dimethyl-2-pyrrolidinone Carceplex 18 was obtained in ≤5% after preparative TLC; m.p. > 300 °C; ^1H NMR: $\delta = 7.72$ (s, 4H; NH), 7.01 and 6.98 (2d, $J = 2.3$ Hz, 8H; *o*-NHAr*H*), 6.73 (s, 4H; *m*-OArH), 5.77 [d, $J = 7.0$ Hz, 4H; OCH_2O (outer)], 4.94 and 4.79 [2d, $J = 14.7$ Hz, 8H; $CH_2C(O)$], 4.63 (t, $J = 8.0$ Hz, 4H; $CHC_{11}H_{23}$), 4.44 and 3.15 (ABq, $J = 11.8$ Hz, 8H; $ArCH_2Ar$), 4.29 [d, $J = 7.0$ Hz, 4H; OCH_2O (inner)], 3.75

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(t, J = 7.6 Hz, 8H; ArOCH_2), 2.1–2.0 (m, 8H; CHCH_2), 1.90 (2t, J = 7.6 Hz, 8H; OCH$_2$CH_2), 1.3–1.0 [m, 72H; CHCH$_2$(CH_2)$_9$], 0.95 (t, J = 7.6 Hz, 12H; CH$_3$), 0.82 (t, J = 6.7 Hz, 12H; CH$_3$), −0.25 to −0.2 [m, 3H; CHCH_3 (guest)], −1.2 to −1.6 [m, 5H; CH$_2$ and CH (guest)], −1.48 (s, 3H; NCH$_3$); ^{13}C NMR: δ = 168.3 (C=O), 147.7, 137.0, 116.5 (*o*-NHAr*C*), 108.2, 93.4 (OCH$_2$O), 77.2 (O*C*H$_2$CH$_2$), 65.5 [*C*H$_2$C(O)], 30.9 (Ar*C*H$_2$Ar), 25.9, 23.5, 21.9, 16.9, 7.9; MS (FAB): m/z = 2166.6 ([M + Na]$^+$, calcd. for $C_{130}H_{175}N_5O_{21}$Na 2166.7).

DMSO Carceplex 19 was isolated in essentially quantitative yield; m.p. > 300 °C; ^{1}H NMR: δ = 7.92 (s, 4H; NH), 6.89 (s, 8H; *o*-NHAr*H*), 6.72 (s, 4H; *m*-OArH), 5.78 [d, J = 7.0 Hz, 4H; OCH$_2$O (outer)], 4.88 [s, 8H; CH_2C(O)], 4.62 (t, J = 8.0 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.41 and 3.17 (ABq, J = 12.1 Hz, 8H; ArCH$_2$Ar), 4.20 [d, J = 7.0 Hz, 4H; OCH$_2$O (inner)], 3.74 (t, J = 7.5 Hz, 8H; ArOCH_2), 2.15–2.0 (m, 8H; CHCH_2), 1.90 (2t, J = 7.6 Hz, 8H; OCH$_2$CH_2), 1.45–1.05 [m, 72H; CHCH$_2$(CH_2)$_9$], 0.97 (t, J = 7.3 Hz, 12H; CH$_3$), 0.85–0.8 (m, 12H; CH$_3$), −0.76 [s, 6H; S(O)CH_3]; ^{13}C NMR: δ = 167.4 (C=O), 153.5, 145.9, 140.8, 139.1, 136.3, 130.8, 130.0, 123.1 and 113.6 (ArC), 77.2 (O*C*H$_2$CH$_2$), 69.3 [*C*H$_2$C(O)], 36.9, 36.1, 31.9 (Ar*C*H$_2$Ar), 29.9, 29.8, 29.7, 29.4, 27.9, 23.2, 22.7, 14.1, 10.3; MS (FAB): m/z = 2131.6 ([M + Na]$^+$, calcd. for $C_{126}H_{170}N_4O_{21}$SNa 2131.7), 2106.7 ([M − 2H]$^-$, calcd. for $C_{126}H_{168}N_4O_{21}$S 2106.6).

Ethyl Methyl Sulfoxide Carceplex 20 was obtained in essentially quantitative yield; m.p. > 300 °C; ^{1}H NMR: δ = 7.91 (s, 4H; NH), 6.88 (d, 8H; *o*-NHAr*H*), 6.70 (s, 4H; *m*-OArH), 5.80 [d, J = 7.0 Hz, 4H; OCH$_2$O (outer)], 4.90 [s, 8H; CH_2C(O)], 4.64 (t, J = 7.9 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.40 and 3.17 (ABq, J = 12.0 Hz, 8H; ArCH$_2$Ar), 4.29 [d, J = 7.0 Hz, 4H; OCH$_2$O (inner)], 3.75 (t, J = 7.5 Hz, 8H; ArOCH_2), 2.1–1.95 (m, 8H; CHCH_2), 1.88 (2t, J = 7.6 Hz, 8H; OCH$_2$CH_2), 1.35–1.0 (m, 72H; CHCH$_2$(CH_2)$_9$), 0.97 (t, J = 7.5 Hz, 12H; CH$_3$), 0.82 (t, J = 6.7 Hz, 12H; CH$_3$), 1.05 and 0.42 [q, J = 6 Hz, 2H; S(O)CH$_2$], −1.81 [s, 3H; S(O)CH_3], −2.49 (t, J = 7.2 Hz, 3H; CH$_2$CH_3); ^{13}C NMR: δ = 167.3 (C=O), 153.6, 146.0, 145.9, 141.0, 139.3, 139.2, 136.3, 130.8, 123.3, 98.4 (OCH$_2$O), 77.2 (O*C*H$_2$CH$_2$), 68.8 [*C*H$_2$C(O)] 36.8, 31.9 (Ar*C*H$_2$Ar), 31.0 [S(O)CH$_3$], 29.8, 29.7, 29.4, 27.9, 23.2, 22.7, 14.1, 10.3, 4.6 [S(O)CH$_2$*C*H$_3$]; MS (FAB): m/z = 2146.1 ([M + Na]$^+$, calcd. for $C_{127}H_{172}N_4O_{21}$SNa 2145.8).

Thiolane-1-oxide Carceplex 21 was isolated in 16% yield after preparative TLC; m.p. > 300 °C; ^{1}H NMR: δ = 7.82 (s, 4H; NH), 6.95 (s, 8H; *o*-NHAr*H*), 6.74 (s, 4H; *m*-OArH), 5.79 [d, J = 7.1 Hz, 4H; OCH$_2$O (outer)], 4.92 [s, 8H; CH_2C(O)], 4.63 (t, J = 8.0 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.43 and 3.18 (ABq, J = 12.1 Hz, 8H; ArCH$_2$Ar), 4.13 [d, J = 7.0 Hz, 4H; OCH$_2$O (inner)], 3.75 (t, J = 7.4 Hz, 8H; ArOCH_2), 2.15–2.0 (m, 8H; CHCH_2), 1.96–1.87 (m, 8H; OCH$_2$CH_2), 1.5–1.2 [m, 72H; CHCH$_2$(CH_2)$_9$], 0.96 (t, J = 7.4 Hz, 12H; CH$_3$), 0.82 (t, J = 6.3 Hz, 12H; CH$_3$), 0.0 to −0.1 (m, 2H; CH$_2$), −0.25 to −0.4 [m, 2H; S(O)CH$_2$], −0.55 to −0.7 [m, 4H; CH$_2$ + S(O)CH$_2$]; ^{13}C NMR: δ = 145.2, 139.4, 136.0, 116.2 (*o*-NHAr*C*), 108.5, 95.5 (OCH$_2$O), 77.2 (O*C*H$_2$CH$_2$), 64.1 [*C*H$_2$C(O)], 31.9 (Ar*C*H$_2$Ar), 29.7, 29.4, 22.7, 14.1; MS (FAB): m/z = 2157.8 ([M + Na]$^+$, calcd. for $C_{128}H_{174}N_4O_{21}$SNa 2157.8).

Doped Inclusion: General Procedure: In a typical experiment a solution of **14** (60 mg, 26 μmol) in a mixture of 1,5-dimethyl-2-pyrrolidinone (25 mL) and the potential guest (5–15 vol%) was added dropwise over a period of 6–9 h to a mixture of CsF (0.10 g, 0.66 mmol), Cs_2CO_3 (0.21 g, 0.64 mmol), and a catalytic amount of KI in a mixture of 1,5-dimethyl-2-pyrrolidinone (25 mL) and the potential guest (5–15 vol%) at 70–80 °C and stirred for another 10–13 h. After cooling to room temperature the mixture was concentrated in vacuo. The residue was taken up in CH_2Cl_2 (100 mL) and washed with 2N HCl (25 mL), H_2O (2 × 25 mL), and brine (25 mL) and dried over Na_2SO_4. After evaporation of the solvent the crude product was purified by preparative TLC (SiO_2, THF/CH_2Cl_2 10/90 v/v). The carceplexes showed typical R_f values of 0.7–0.8.

2-Butanone Carceplex 22 was isolated in 16% yield; m.p. > 300 °C; ^{1}H NMR: δ = 7.52 (s, 4H; NH), 6.90 (s, 8H; *o*-NHAr*H*), 6.70 (s, 4H; *m*-OArH), 5.82 [d, J = 7.0 Hz, 4H; OCH$_2$O (outer)], 4.89 [s, 8H; CH_2C(O)], 4.62 (t, J = 8.0 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.41 and 3.16 (ABq, J = 12.0 Hz, 8H; ArCH$_2$Ar), 4.02 [d, J = 6.7 Hz, 4H; OCH$_2$O (inner)], 3.74 (t, J = 6.6 Hz, 8H; ArOCH_2), 2.1–1.95 (m, 8H; CHCH_2), 1.95–1.85 (m, 8H; OCH$_2$CH_2), 1.5–1.2 [m, 72H; CHCH$_2$(CH_2)$_9$], 0.96 (t, J = 7.5 Hz, 12H; CH$_3$), 0.82 (t, J = 6.3 Hz, 12H; CH$_3$), 0.39 [q, J = 6.4 Hz, 2H; C(O)CH_2CH$_3$], −2.03 [s, 3H; C(O)CH_3], −2.86 [t, J = 6.7 Hz, 3H; C(O)CH$_2$CH_3]; ^{13}C NMR: δ = 77.2 (ArOCH$_2$), 29.7; MS (FAB): m/z = 2125.5 ([M + Na]$^+$, calcd. for $C_{127}H_{172}N_4O_{21}$Na 2125.6).

3-Sulfolene Carceplex 23 was isolated in 26% yield;[55] m.p. > 300 °C; ^{1}H NMR: δ = 7.81 and 7.72 (2s, 4H; NH), 6.96 (s, 8H; *o*-NHAr*H*), 6.74 (s, 4H; *m*-OArH), 5.81 [m, 4H; OCH$_2$O (outer)], 4.96 [s, 8H; CH_2C(O)], 4.62 (t, J = 8.0 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.43 and 3.20 (ABq, J = 12.5 Hz, 6H; ArCH$_2$Ar + = CH), 4.27 and 4.21 [2d, J = 6.7 Hz, 8H; OCH$_2$O (inner)], 3.75 (t, J = 7.5 Hz, 8H; ArOCH_2), 2.1–1.95 (m, 8H; CHCH_2), 1.95–1.85 (m, 8H; OCH$_2$CH_2), 1.5–1.2 [m, 72H; CHCH$_2$(CH_2)$_9$], 1.04 (t, J = 7.6 Hz, 12H; CH$_3$), 0.89 (t, J = 6.3 Hz, 12H; CH$_3$), 0.18 (s, 4H; SO$_2$CH$_2$); ^{13}C NMR: δ = 125.1, 122.6, 113.6, 99.6 (OCH$_2$O), 77.2 (O*C*H$_2$CH$_2$), 31.9 (Ar*C*H$_2$Ar), 29.7, 29.4, 23.2, 22.7, 14.1, 10.3; MS (FAB): m/z = 2171.0 ([M + Na]$^+$, calcd. for $C_{128}H_{170}N_4O_{22}$S 2171.6).

[D$_7$]DMF Carceplex 24 was isolated in 13% yield; m.p. > 300 °C; ^{1}H NMR: δ = 7.74 (s, 4H; NH), 7.03 (s, 8H; *o*-NHAr*H*), 6.81 (s, 4H; *m*-OArH), 5.82 [d, J = 7.0 Hz, 4H; OCH$_2$O (outer)], 4.88 [s, 8H; CH_2C(O)], 4.70 (t, J = 8.2 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.48 and 3.25 (ABq, J = 12.0 Hz, 8H; ArCH$_2$Ar), 4.06 [d, J = 6.7 Hz, 4H; OCH$_2$O (inner)], 3.82 (t, J = 7.5 Hz, 8H; ArOCH_2), 2.1–1.95 (m, 8H; CHCH_2), 1.95–1.85 (m, 8H; OCH$_2$CH_2), 1.5–1.2 [m, 72H; CHCH$_2$(CH_2)$_9$], 1.04 (t, J = 7.6 Hz, 12H; CH$_3$), 0.89 (t, J = 6.3 Hz, 12H; CH$_3$); ^{13}C NMR: δ = 152.1, 145.3, 141.4, 139.4, 136.4, 121.4, 77.2 (ArOCH$_2$), 31.9 (Ar*C*H$_2$Ar), 29.7, 29.4, 23.2, 22.7, 14.1, 10.3; ^{2}H NMR (CH_2Cl_2): δ = 5.2 [C(O)D], 0.4 (NCD$_3$) and −0.8 (NCD$_3$); MS (FAB): m/z = 2134.1 ([M + Na]$^+$, calcd. for $C_{127}D_7H_{164}N_5O_{21}$Na 2134.8).

[D$_6$]DMSO Carceplex 25 was isolated in 16% yield; m.p. > 300 °C; ^{1}H NMR: δ = 7.95 (s, 4H; NH), 6.94 (s, 8H; *o*-NHAr*H*), 6.76 (s, 4H; *m*-OArH), 5.82 [d, J = 7.1 Hz, 4H; OCH$_2$O (outer)], 4.92 [s, 8H; CH_2C(O)], 4.68 (t, J = 7.8 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.43 and 3.21 (ABq, J = 12.0 Hz, 8H; ArCH$_2$Ar), 4.24 [d, J = 7.0 Hz, 4H; OCH$_2$O (inner)], 3.80 (t, J = 7.5 Hz, 8H; ArOCH_2), 2.1–1.95 (m, 8H; CHCH_2), 1.95–1.85 (m, 8H; OCH$_2$CH_2), 1.5–1.2 [m, 72H; CHCH$_2$(CH_2)$_9$], 1.04 (t, J = 7.4 Hz, 12H; CH$_3$), 0.87 (t, J = 6.3 Hz, 12H; CH$_3$); ^{13}C NMR: δ = 163.0, 154.2, 145.9, 139.1, 136.7, 131.2, 123.5, 77.2 (OCH$_2$CH$_2$), 31.9 (Ar*C*H$_2$Ar), 29.7, 29.4, 22.7, 14.1; ^{2}H NMR (CH_2Cl_2): δ = −0.8 (CD_3); MS (FAB): m/z = 2137.7 ([M + Na]$^+$, calcd. for $C_{126}D_6H_{164}N_4O_{21}$SNa 2137.7).

General Procedure for the Synthesis of Calix[4]arene-Based Thiacarceplexes 26–30: In a typical experiment a mixture of carceplex (10 mg) and Lawesson's reagent (10 mg) was heated at 140 °C in xylene (10 mL, dried over 4 Å molecular sieves) for 2 h. After cooling to room temperature the reaction mixture was filtered over silica and eluted with hexane (100 mL) to remove xylene followed by THF/CH_2Cl_2 (150 mL, 15/85 v/v) to collect the crude product. After concentrating under reduced pressure the crude products were triturated with MeOH to obtain pure thiacarceplexes in essentially quantitative yield. Another work-up procedure comprises evaporation of xylene after cooling to room temperature and subsequent trituration with MeOH.

15,31,66,67-Tetrapropoxy-46,54,55,56-tetraundecyl-17*H*,23*H*,29*H*,35*H*-4,20:42,26-bis(epoxyethanimino)-3,43-(epoxymethanoxy)-2,44:14,32:48,52-trimethano-12,16:18,22:24,28:30,34-tetramethano-9*H*,46*H*,54*H*-bisbenzo-[4,5][1,3]benzodioxocino[9,10-*d*:10′,9′-*k*$_1$][1,3,6,36,9,13]tetraoxadiaza-cyclooctatriacontine-10,36,62,69(11*H*,37*H*-tetrathione + DMF (26): M.p. 216–220 °C (dec); ^{1}H NMR: δ = 9.12 (s, 4H; NH), 7.26 (s, 8H; *o*-NHArH), 6.75 (s, 4H; *m*-OArH), 5.75 [d, J = 6.8 Hz, 4H; OCH$_2$O (outer)], 5.06 [s, 8H; CH_2C(S)], 4.86 (s, 1H; CHO), 4.64 (t, J = 7.8 Hz, 4H; C*H*C$_{11}$H$_{23}$), 4.50 and 3.26 (ABq, J = 12.0 Hz, 8H; ArCH$_2$Ar), 3.94 [d, J = 6.8 Hz, 4H; OCH$_2$O (inner)], 3.82 (t, J = 6.5 Hz, 8H; ArOCH_2), 2.1–2.0 (m, 8H; CHCH_2), 1.92 (2t, J = 6.5 Hz, 8H; OCH$_2$CH_2), 1.5–1.05 [m, 72H; CHCH$_2$(CH_2)$_9$], 1.00 (t, J = 7.3 Hz, 12H; CH$_3$), 0.82 (t, J = 6.1 Hz, 12H; CH$_3$), 0.63 (s, 3H; NCH$_3$ *trans* to carbonyl), −0.93 (s, 3H; NCH$_3$ *cis* to carbonyl); ^{13}C NMR: δ = 136.2, 74.1 (OCH$_2$CH$_2$), 31.9 (Ar*C*H$_2$Ar), 29.6, 29.3, 14.2, 10.2; MS (FAB): m/z = 2189.5 ([M − H + Na]$^+$, calcd. for $C_{127}H_{170}N_5O_{17}S_4$Na 2190.0).

DMA Thiacarceplex 27: M.p. > 265 °C (dec); ^{1}H NMR: δ = 9.14 (s, 4H; NH), 7.19 (s, 8H; *o*-NHArH), 6.73 (s, 4H; *m*-OArH), 5.72 [d, J = 6.8 Hz, 4H; OCH$_2$O (outer)], 5.08 [s, 8H; CH_2C(S)], 4.65 (t, J = 7.7 Hz, 4H;

$CHC_{11}H_{23}$), 4.49 and 3.27 (ABq, $J = 12.1$ Hz, 8H; $ArCH_2Ar$), 4.04 [d, $J = 6.8$ Hz, 4H; OCH_2O (inner)], 3.82 (t, $J = 7.6$ Hz, 8H; $ArOCH_2$), 2.1–1.95 (m, 8H; $CHCH_2$), 1.91 (2t, $J = 7.6$ Hz, 8H; OCH_2CH_2), 1.3–1.0 [m, 75H; $CHCH_2(CH_2)_9 + CH_3$ *trans* to carbonyl], 0.97 (t, $J = 7.5$ Hz, 12H; CH_3), 0.82 (t, $J = 6.1$ Hz, 12H; CH_3), −0.98 [bs, 3H; CH_3 *cis* to carbonyl], −2.08 (brs, 3H; $C(O)CH_3$); ^{13}C NMR: $\delta = 194.9$ (C=S), 154.4 (*p*-NHArC), 145.6 ($ArCOCH_2O$), 141.5 [$ArCOCH_2C(S)$], 139.7, 136.4, 132.1, 123.3, 114.1, 97.6, 77.2 (OCH_2CH_2), 36.9, 31.9 ($ArCH_2Ar$), 29.7, 29.4, 27.8, 23.3, 22.7, 14.1, 10.2; MS (FAB): $m/z = 2204.8$ ($[M+Na]^+$, calcd. for $C_{128}H_{173}N_5O_{17}S_4Na$ 2205.0).

NMP Thiacarceplex 28: M.p. > 275 °C (dec); ^1H NMR: $\delta = 9.15$ and 9.08 [2s, 4H; NH (major + minor conformer)], 7.23 (s, 8H; *o*-NHArH), 6.75 and 6.70 [2s, 4H; *m*-OArH (major + minor conformer)], 5.75–5.70 [m, 4H; OCH_2O (outer)], 5.15–5.10 [m, 8H; $CH_2C(S)$], 4.54 (t, $J = 6.9$ Hz, 4H; $CHC_{11}H_{23}$), 4.5–4.45 (m, 4H; $ArCH_2Ar$), 4.06 [d, $J = 6.7$ Hz, 4H; OCH_2O (inner)], 3.82 (t, $J = 7.6$ Hz, 8H; $ArOCH_2$), 3.27 (part of ABq, $J = 12.2$ Hz, 4H; $ArCH_2Ar$), 2.10–1.95 (m, 8H; $CHCH_2$), 1.95–1.9 (m, 8H; OCH_2CH_2), 1.45–1.0 [m, 72H; $CHCH_2(CH_2)_9$], 0.99 (t, $J = 7.4$ Hz, 12H; CH_3), 0.82 (t, $J = 6.5$ Hz, 12H; CH_3), −0.9 to −1.2 [m, 2H; CH_2 (guest)], −1.31 [s, 3H; NCH_3 (major conformer)], −1.4 to −1.6 [m, 2H; CH_2 (guest)], −1.69 [s, 3H; NCH_3 (minor conformer)]; ^{13}C NMR: $\delta = 153.7$, 145.8, 139.4, 135.9, 77.2 (OCH_2CH_2), 31.9 ($ArCH_2Ar$), 29.7, 23.3, 22.7, 14.1, 10.2; MS (FAB): $m/z = 2216.6$ ($[M+Na]^+$, calcd. for $C_{129}H_{173}N_5O_{17}S_4Na$ 2217.1).

Ethyl Methyl Sulfoxide Thiacarceplex 29: M.p. 197–200 °C; ^1H NMR: $\delta = 9.26$ (s, 4H, NH), 7.12 (s, 8H; *o*-NHArH), 6.71 (s, 4H; *m*-OArH), 5.80 [d, $J = 7.1$ Hz, 4H; OCH_2O (outer)], 5.15 [s, 8H; $CH_2C(S)$], 4.65 (t, $J = 7.7$ Hz, 4H; $CHC_{11}H_{23}$), 4.50 and 3.27 (ABq, $J = 12.0$ Hz, 8H; $ArCH_2Ar$), 4.10 [d, $J = 6.8$ Hz, 4H; OCH_2O (inner)], 3.83 (t, $J = 7.3$ Hz, 8H; $ArOCH_2$), 2.1–1.95 (m, 8H; $CHCH_2$), 1.95–1.8 (m, 8H; OCH_2CH_2), 1.4–1.0 [m, 72H; $CHCH_2(CH_2)_9$], 1.00 (t, $J = 7.5$ Hz, 12H; CH_3), 0.82 (t, $J = 7.8$ Hz, 12H; CH_3), 0.34 [q, $J = 7.7$ Hz, 2H; CH_2 (guest)], −1.79 [s, 3H; $S(O)CH_3$], −2.62 [t, $J = 8.2$ Hz, 3H; CH_2CH_3 (guest)]; ^{13}C NMR: $\delta = 77.2$ (OCH_2), 31.9 ($ArCH_2Ar$), 29.7, 29.4, 23.3, 22.7, 14.1, 10.2; MS (FAB): $m/z = 2208.9$ ($[M - H + Na]^+$, calcd. for $C_{127}H_{171}N_4O_{17}S_5Na$ 2209.1).

2-Butanone Thiacarceplex 30: M.p. > 280 °C (decomp.); ^1H NMR: $\delta = 9.1$ (s, 4H; NH), 7.19 (s, 8H; *o*-NHArH), 6.77 (s, 4H; *m*-OArH), 5.89 [d, $J = 6.8$ Hz, 4H; OCH_2O (outer)], 5.20 [s, 8H; $CH_2C(S)$], 4.69 (t, $J = 7.7$ Hz, 4H; $CHC_{11}H_{23}$), 4.55 and 3.32 (ABq, $J = 12.4$ Hz, 8H; $ArCH_2Ar$), 4.04 [d, $J = 6.8$ Hz, 4H; OCH_2O (inner)], 3.87 (t, $J = 7.7$ Hz, 8H; $ArOCH_2$), 2.1–2.05 (m, 8H; $CHCH_2$), 2.0–1.95 (m, 8H; OCH_2CH_2), 1.3–1.0 [m, 72H; $CHCH_2(CH_2)_9$], 0.82 (t, $J = 6.1$ Hz, 12H; CH_3), 0.30 [q, $J = 7.3$ Hz, 4H; CH_2 (guest)], −2.01 [s, 3H; $C(O)CH_3$ (guest)], −2.81 [t, $J = 7.0$ Hz, 3H; CH_2CH_3 (guest)]; ^{13}C NMR: $\delta = 139.4$, 136.4, 112.7, 77.2 (OCH_2), 31.9 ($ArCH_2Ar$), 29.7, 27.1, 14.1; MS (FAB): $m/z = 2188.7$ ($[M - H + Na]^+$, calcd. for $C_{128}H_{171}N_4O_{17}S_4Na$ 2189.0).

Ethyl Methyl Sulfoxide (31) was obtained by a modified literature procedure for the corresponding sulfoxides. To a solution of ethylmethylsulfide (75 mL, 0.83 mol) in MeOH (0.5 L) was added dropwise H_2O_2 (143 mL, 35 wt%) with initial cooling. After stirring the reaction mixture for 2 h at room temperature brine was added (250 mL) and the crude mixture was extracted with $CHCl_3$ (4 × 100 mL). The combined organic layers were dried over $MgSO_4$ and after evaporation of the solvents the residue was distilled from BaO under reduced pressure. Yield 38.0 g (50%); b.p. 86–89 °C (38 mm Hg); ^1H NMR: $\delta = 2.73$ (dq, $J = 5.0$ Hz, 2H; CH_2), 2.49 [s, 3H; $S(O)CH_3$], 1.27 (t, $J = 7.5$ Hz, 3H; CH_2CH_3); ^{13}C NMR: $\delta = 47.8$ [$S(O)CH_3$], 37.7 [$S(O)CH_2$], 6.6 (CH_2CH_3).

NMR Measurements

Structure Determination: All dynamic NMR measurements were performed on a Varian Unity 400WB spectrometer (^1H: 400 MHz). NOESY,[13] ROESY,[14] TOCSY (MLEV17),[15] and HMQC[16] measurements were carried out with standard Varian pulse programs. The mixing time for TOCSY experiments was 15–35 ms. All NOESY experiments were performed with mixing times between 40 and 150 ms. For the ROESY experiments the mixing time consisted of a spin lock pulse of 2 kHz field strength with a duration of 300 ms or a train of $\pi/6$ pulses resulting in an effective field strength of 2 kHz. Data were Fourier transformed in the States-Haberkorn phase-sensitive mode after weighting with square sine-bells or shifted Gaussian functions.

Determination of Distances: For the DMF (**15**), DMA (**16**), NMP (**17**), and thiolane-1-oxide (**21**) carceplexes the intermolecular distances between hydrogen atoms of the guest and the carcerand were determined by measuring NOE build-up rates with three different mixing times in $CDCl_3$. To increase the accuracy both off-diagonal signals were used to calculate the distances. As a reference the distance between the two methylene hydrogen atoms of the calix[4]arene moiety was used ($R_{ref} = 1.79$ Å).

Determination of Energy Barriers for Interconversion between Different Orientations of Incarcerated Guests: The energy barrier for interconversion between the different diastereoisomers of DMA carceplex **16** was determined by lineshape analysis; for NMP carceplex **17** exchange rates were determined at five different temperatures. The energy barriers at 273 K were calculated by linear regression methods. For the corresponding thiacarceplexes **27** (DMA) and **28** (NMP) the energy barriers at 273 K were determined by measuring the exchange rates, k_{ex}, with different mixing times (30–100 ms). For ethyl methyl sulfoxide thiacarceplex **29** the exchange rate between the different diastereoisomers was determined at −55 °C with mixing times of 150, 200, and 225 ms. The $\Delta G^{\ddagger}$-values (J mol^{-1}) were calculated with Equation (1), where k_{ex} = exchange rate).[56]

$$\Delta G^{\ddagger} = 19.14\, T\left\{10.32 + \log\left(\frac{T}{k_{ex}}\right)\right\} \quad (1)$$

Determination of Rotational Barriers Around the Amide Bond of Incarcerated DMF and DMA: The energy barriers around the amide bonds of incarcerated DMF and DMA were determined by measuring exchange rates at three (DMF) or four (DMA) different temperatures from 50 to 120 °C in $C_2D_2Cl_4$ by a procedure from Ernst et al.[56, 57] The activation energies at 298 K were calculated from linear regression methods.

Molecular Modeling

General: For all calculations CHARMM versions 22.2r and 22.3 were used (no differences were observed between the different versions). The partial charges were calculated with charge templates provided by QUANTA.[58] Small residual charges were smoothed into nonpolar hydrogens and carbons. Calculations were carried out with a distant dependent dielectric constant ($\varepsilon = 1/r$) as a rough model for a solvent.[59, 60] No cut-offs for the nonbonded interactions were used. Since no parameters were available for the improper torsion of the CT-S(O)-CT fragment the value for a tetrahedral carbon, $\omega_0 = 35.4°$, was used to keep the sulfur in a tetrahedral geometry. All other parameters were used as supplied by QUANTA/CHARMM.

Determination of Local and Global Minima: Systematic Search: A systematic search of all possible orientations of guests inside the calix[4]arene-based (thia)carcerands was carried out by rotating the guests around the three symmetry axis (x 0–60°, y 0–60°, z 0–330°) in steps of 30°. Starting structures were generated by manually placing the guest inside the carcerand with C_{4v} symmetry followed by a quick minimization. After rotation of the guest the structure was minimized by Steepest Descent (SD) (maximum 100 steps) followed by Adopted Basis Set Newton Raphson (ABNR) until the root mean square (rms) of the gradient was < 0.01 kcal mol^{-1} Å^{-1}. The structures were analysed visually resulting in a set of structures representing the (local) minima.

Calculation of Energy Barriers for Interconversion between Different Diastereoisomers: The structures obtained after the systematic search were used as starting structures for the determination of the barrier for interconversion between different stereoisomers. For that purpose, structures were further minimized by the ABNR minimization method until the rms of the gradient was < 0.001 kcal mol^{-1} Å^{-1}. The TRAVEL module implemented in CHARMM by the CPR algorithm was used to calculate the saddle points for the interconversion between different stereoisomers.[61] In a first approach the calculations were carried out with the two structures with the lowest energy. If this did not give a (realistic) saddle point the structure with the third lowest energy was added as an intermediate and the reaction path calculated from the two lowest structures to this structure. This procedure was continued until a reaction pathway was found for the interconversion. The methodology prevents the calculation of *all* possible interconversions including unrealistic reaction paths with higher energy intermediates.

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[12] Cram et al. use the name (hemi)carcerand for the compounds obtained by combination of two resorcin[4]arenes. Since our compounds, obtained by combination of a calix[4]- and resorcin[4]arene, are closely related, throughout the paper we use the name calix[4]arene-based (hemi)carcerands. We are aware that according to the definition of Cram et al. (ref. [7]) carcerands are synthetic organic compounds with enforced cavities large enough to complex complementary organic compounds or ions. Our *hemi*carcerands should be considered as *potential* hemicarcerands since unfortunately no complexation could be observed.

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[19] Beside the 1:1 coupled product two fractions of different 2:1 coupled products were isolated after preparative TLC in $<10\%$ total yield. These products not only differ in the orientation of the calix[4]arene moiety with respect to the resorcin[4]arene moiety, that is, *endo* or *exo*, but also in the position of the phthalimido group on the calix[4]arene moieties, that is, *cis* or *trans*. Since these products were only formed in minor yields no further attempts were carried out to elucidate the exact nature of the products.

[20] The measurements were carried out at room temperature. Therefore, the observed structural properties correspond to those at room temperature and not at lower temperature.

[21] Since it is not possible to accurately determine distances with ROESY spectroscopy, the ratios of ROE build-up signals were determined. In a perfect cone conformation the ratios between the different distances will be 1, whereas in a pinched cone the ratios will be 1.1–1.2. For hemicarcerand **11** the ratios were 1.06 and 1.12.

[22] Several methods were applied in an attempt to obtain a hemicarcerand with an incarcerated guest. Addition of excess DMA or NMP (>50 equiv.) to a solution of hemicarcerand **11** in $C_2D_2Cl_4$, a solvent that is too large to fit into the cavity, and heating at 100 °C for 4 h did not result in the incarceration of the guests, as was deduced from the absence of signals in the ^{1}H NMR spectra below $\delta = 0$ that are characteristic for incarcerated guests. Furthermore, no indications were found for the inclusion of methane after bubbling a solution of hemicarcerand with methane gas. Refluxing in toluene or THF and heating in DMA or *N*-ethyl-2-pyrrolidinone did not result in any carceplex. Hemicarcerand **12**, bearing an extra *O*-propyl group, did not show the formation of a hemicarceplex after being heated in diphenyl ether/*N*-methyl-piperidone for 17 h. Inspection of CPK molecular models as well as molecular modeling calculations indicate that all potential guests fit into the cavity of the hemicarcerand.

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[42] Destruction of the carcerand would also lead to an increase in total ion current, which was not observed.

[43] No butadiene or SO_2 could be detected in the FD mass spectrometry experiment; this is most likely due to the technique used.

[44] Attempts to detect the extrusion of SO_2 and butadiene from carceplex **23** with differential scanning calorimetry failed.

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0947-6539/97/0304-0654 $ 17.50+.50/0