Synthesis and Functionalization of Calix[4]arene-based Carceplexes

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New calix[4]arene-based carceplexes are obtained *via* solvent or doped inclusion; chemical modification of calix[4]arene-based carcerands can be used to modify the rotational behaviour of the incarcerated guest.

Cram *et al.*[1] have shown that carcerands obtained by bridging of two identical resorcin[4]arene moieties (permanently) incarcerate guest molecules. The cavity created by the two resorcin[4]arene moieties is *symmetrical* and although different orientations of the guest molecules are possible this does not lead to different stereoisomers.† We have used combinations of functionalized calix[4]arenes and resorcin[4]arenes for the synthesis of preorganized receptor molecules.[2–5] Combination in a 1 : 1 ratio leads to calix[4]arene-based carcerands **2** in which amides are incarcerated.[5] Owing to the *non-symmetrical* cavity of **2**, different orientations of incarcerated guest molecules (*N*,*N*-dimethylacetamide and *N*-methylpyrrolidin-2-one) give two different diastereoisomers. This renders calix[4]arene-based carcerands of interest because of their potential use as molecular switches. However, this requires two different orientations which do not interconvert at room temperature. In the carcerands described previously rotation of incarcerated DMF, *N*,*N*-dimethylacetamide and *N*-methylpyrrolidin-2-one is fast on the ^{1}H NMR chemical shift time-scale at room temperature.[5] Currently we are investigating structural variations with the ultimate objective the synthesis of carcerands that have two diastereoisomeric forms that are stable at room temperature.

In this communication we describe the synthesis of new carceplexes in which mainly other than amide guests are included *via* both solvent and doped inclusion. Furthermore, modification of the carcerand after incarceration is described.

The synthesis of calix[4]arene-based carcerands **2** is based on the intramolecular cyclization of **1**, in which the calix[4]- and resorcin[4]-arene are connected *via* two bridges in a solvent that also serves as a guest (Method A). The incarceration of guest molecules takes place during the formation of the final bridges between the calix[4]- and resorcin[4]-arene moieties (Scheme 1).

One way to increase the activation energy for interconversion between the different diastereoisomers of incarcerated guests is the use of larger guests. In the case of 1,5-dimethyl-pyrrolidin-2-one as a solvent the carceplex was only isolated in ≤ 5% yield indicating that with this guest the steric limitations for incarceration by **2** are reached. The ^{1}H NMR spectrum of the carceplex shows characteristic resonances for incarcerated guests at high field ($\delta < 0$) which are 1.3–4.0 ppm upfield of resonances for 1,5-dimethyl-pyrrolidin-2-one in $CDCl_3$ solution. 2D NOESY and 2D ROESY NMR spectroscopy showed that the guest predominantly adopts one orientation inside the carcerand with the *N*-methyl group directed towards the calix[4]arene moiety.‡

Since the yield of the carceplexes decreases with increasing guest size we investigated methods for altering the rotational behaviour after incarceration of the guest molecules. The amide bridges of **2a–c** were converted into thioamides using Lawesson's reagent [2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide; 20 equiv.] in xylene at 140 °C in essentially quantitative yields. The ^{1}H NMR spectra of the resulting thiacarceplexes **3a–c** exhibit a downfield shift for the NH protons and the NHC(X)CH_2 protons of 1.41 ppm and 0.24 ppm, respectively. Only minor shifts (< 0.05 ppm) were observed for the guest protons. Furthermore, FAB MS shows for all thiacarceplexes an [M + guest] ion. This indicates that the incarcerated amide guests do not react under these conditions. The activation energy for interconversion between the different

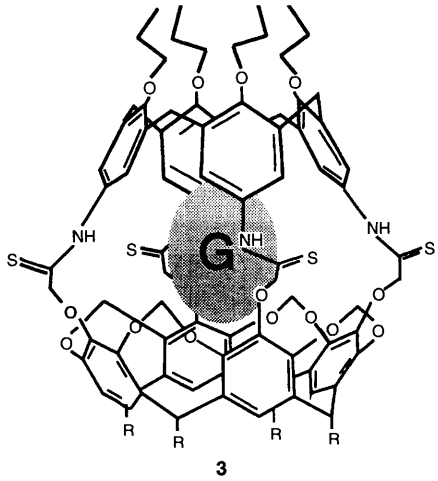

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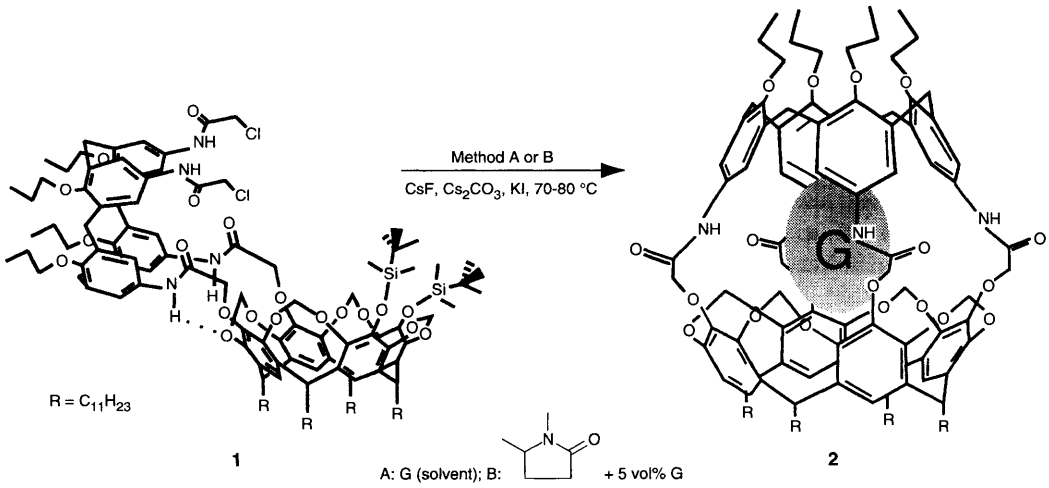
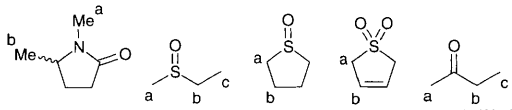
Fig. 1 For **3** R = $C_{11}H_{23}$; **a** G = DMF; **b** G = *N*,*N*-dimethylacetamide; **c** G = *N*-methylpyrrolidin-2-one



Scheme 1 For **2** R = $C_{11}H_{23}$; **a** G = DMF; **b** G = *N*,*N*-dimethylacetamide; **c** G = *N*-methylpyrrolidin-2-one

Table 2 Yields and selected 1D ^{1}H NMR data of calix[4]arene-based carceplexes **2**



Guest	Method[a]	Yield (%)	Proton	δ ($CDCl_3$)	δ (carceplex)[b]	Δδ (ppm)
1,5-Dimethylpyrrolidin-2-one	A	≤5	a	2.70	−1.45 (s)	4.15
			b	1.01	−0.25 (d)	1.26
Ethyl methyl sulfoxide	A	100	a	2.48	−1.81 (s)	4.29
			b	2.67	1.05 (q)	3.72
			b′		0.41 (q)	3.08
			c	1.27	−2.48 (t)	3.75
Thiolane 1-oxide	A	16	a	1.85–2.1	0.0–0.1 (m)	1.9[c]
			a′	2.3–2.5	−0.25 to −0.4 (m)	2.7[c]
			b	2.6–2.9	−0.55 to −0.7 (m)	3.2[c]
3-Sulfolene	B	26	a	3.69	0.18 (s)	3.51
			b	6.00	3.23 (s)	2.77
Butan-2-one	B	16	a	2.10	−2.01 (s)	4.11
			b	2.45	0.39 (q)	2.06
			c	1.05	−2.85 (t)	3.85

[a] A: direct, B: doped. [b] Multiplicity in parentheses. [c] Average.

Table 1 Coalescence temperatures (T_c) and activation energies ($\Delta G^{\ddagger}$) for interconversion between different diastereoisomers of incarcerated guests in carceplexes **2** and thiacarceplexes **3** determined by 2D EXSY NMR spectroscopy (400 MHz) at 273 K

Carceplex	Guest	T_c/K	$\Delta G^{\ddagger}_{273}$/kJ mol^{-1}
2[a]	*N,N*-Dimethylacetamide	273	53.1 ± 2.0
2[a]	*N*-Methylpyrrolidin-2-one	>323	65.6 ± 2.0
3b	*N,N*-Dimethylacetamide	303	63.5 ± 2.0
3c	*N*-Methylpyrrolidin-2-one	>323	73.2 ± 2.0

[a] See ref. 5.

diastereoisomers of the incarcerated guests in thiacarceplexes **3** was determined with 2D EXSY NMR spectroscopy.§ The conversion into the thioamide bridges results in an increase in the activation energy for *N,N*-dimethylacetamide and *N*-methylpyrrolidin-2-one of about 10.0 kJ mol^{-1} (see Table 1). For DMF, rotation was still fast at temperatures ≥ −40 °C.

The increase in the activation energy may be a result of the stronger hydrogen bond donating character of the thioamides.[6,7]

Beside amides we also investigated the inclusion of other, non-amide guests. Using solvent inclusion new carceplexes **2** were obtained with ethyl methyl sulfoxide and thiolane 1-oxide as incarcerated guests; no carceplex was obtained when the reaction was carried out in acetonitrile or cyclopentanone. The yield of the reaction tends to decrease with increasing size of the guest molecule (Table 2). All incarcerated guests show characteristic ^{1}H NMR resonances at high field (δ < 0) due to the shielding effect of the calix[4]- and resorcin[4]-arene cavities. In general protons of incarcerated guests show an upfield shift of 2–4 ppm with respect to the original position in $CDCl_3$ solution (see Table 2).

Since only a limited number of solvents can be used for the closure of the carcerand the number of potential guests is restricted. Therefore we investigated the synthesis of new carceplexes **2** *via* so-called doped inclusion (Method B).¶ Reaction of **1** in 1,5-dimethyl pyrrolidin-2-one as a solvent (a poor template/guest for this reaction, *vide supra*), in the presence of *ca.* 5 vol% of potential guests, resulted in the selective formation of carceplexes **2** with *N,N*-dimethylacetamide, butan-2-one, and 3-sulfolene as incarcerated guests in 27, 16 and 26% yield, respectively. Doped inclusion experiments were unsuccessful with cyclopentanone and *N*-ethyl-*N*-methylacetamide.

Preliminary results show that at room temperature the guests predominantly adopt only one orientation inside the calix[4]-arene-based carcerand. Ethyl methyl sulfoxide and butan-2-one are oriented with the S(O)Me and C(O)Me groups, respectively, inside the calix[4]arene cavity. The ^{1}H NMR spectrum of the 3-sulfolene carceplex shows two resonances for the guest molecule indicating that the symmetry of the guest is preserved upon incarceration and that the guest is oriented parallel to the long axis of the carcerand. Unfortunately it was not possible to determine the precise orientation owing to the weakness of NOE contacts. The orientation of thiolane 1-oxide could not be established. A summary of the synthesized carceplexes **2** as well as selected NMR data are given in Table 2.

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Footnotes

† Very recently also an asymmetric resorcin[4]arene-based carcerand was reported: J. R. Fraser, B. Borecka, J. Trotter and J. C. Sherman, *J. Org. Chem.*, 1995, **60**, 1207.

‡ ROESY experiments were carried out at room temperature. If ROE contacts were not observed, NOESY experiments were carried out at lower temperatures. Since the new carceplexes showed no spectral changes upon lowering the temperature it is feasible that the orientation at lower temperatures is a good probe for the orientation at room temperature.

§ In the regime of slow exchange on the chemical shift time-scale 2D EXSY NMR spectroscopy provides a straightforward tool for determining exchange rate constants. These can be used to calculate Gibbs free energies. See: R. R. Ernst, G. Bodenhausen and A. Wokaun, *Principles of Nuclear Magnetic Presonance in One and Two Dimensions*, Clarendon, Oxford, 1987, ch. 9.

¶ Doped inclusion has been reported for resorcin[4]arene-based carcerands: R. G. Chapman, N. Copra, E. D. Cochien and J. C. Sherman, *J. Am. Chem. Soc.*, 1994, **116**, 369.

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