Synthesis and Structure Elucidation of Chromogenic Calix[4]arene Indophenols Capped by Carboxamide Bridges[‡]

Barbara Balázs,[a] Gábor Tóth,*[a] Gyula Horváth,[b] Alajos Grün,[c] Viktor Csokai,[c]
László Töke,[c] and István Bitter*[c]

Keywords: Calixarenes / Macrocycles / Chromophores / Tautomerism / NMR spectroscopy

Calix[4]arenes capped by di- and triamide bridges on the lower rim were used to synthesize 2,3,4,5 chromogenic molecules supplied with indophenol indicator unit(s). The *endo*/*exo* quinoid tautomerism of the chromophore and the mechanism of the coloration process were studied by NMR spectroscopy.

Introduction

The molecular design of chromogenic calixarenes has attracted much attention in the past decade. If these ligands give rise to a specific colour change upon selective complexation with guest species then this phenomenon can sometimes be utilised in developing optical sensors. In molecular devices possessing recognition and optical sensing functions, the latter can facilitate the detection of the receptor−substrate interactions.

During our ongoing research program we hoped to synthesize novel calix[4]arene receptors (e.g. derivatives of **1** capped by diamide bridges of different lengths existing in cone[2] or 1,3-alternate[1] conformations, in addition to several doubly bridged calixarenes[3]) and calix[4]arene chromoionophores, containing 2,4-dinitrophenylazo[4] and various pyridinium[5−7] chromogenic functions, for the selective optical recognition of alkali and alkaline earth metal cations. All these ligands contain dissociable phenolic OH groups on the lower rim conjugated to the chromophore: metal-ion induced deprotonation upon complexation brings about significant bathochromic shifts in the visible spectra.

Since we were interested in discerning the mechanism of the coloration process with other proton-ionisable chromogenic calixarenes, we decided to prepare ligands containing sensitive chromophoric moieties which were different from the previous ones we have tested. Indophenol dyes are well-known indicators which have recently been reported to append to the calixcrown platform.[8−10] Since they have strong absorptions in the red region and exhibit remarkable (more than 100 nm) bathochromic shifts upon complexation, these chromogenic molecules are an attractive choice for the construction of optical sensing systems.[10] Actually, 1,1′-binaphtho-calixcrown ligands (e.g. **11**) are claimed to bind primary amines in EtOH by proton transfer and subsequent complexation of the ammonium ion thus formed. During this process a discernible coloration takes place.[8−10] However, the relationship between the colour change and the structure of the chromoionophore has not been investigated in detail.

Therefore, we synthesised two groups of molecules **2a**,**b**, **3** and **4**, **5a**,**b** (the *exo*-quinoid tautomers are represented below), differing only in the substitution pattern of the calix and the number of the indicator units, in order to study by comprehensive NMR methods the solvent-dependent tautomerism of the free ligands and the structural alterations taking place upon coloration.

Results and Discussion

The synthesis of ligands **2a**,**b** was accomplished by the oxidative treatment of the readily available **1a** and **1b**[2] with 4-amino-*m*-cresol under alkaline conditions and a large excess of aqueous ferricyanide and DBU in MeCN at room temperature, according to literature procedures,[8−10] and obtained **2a**,**b** in fair yields after column chromatography (Scheme 1). Later on this procedure was applied for the synthesis of all chromogenic ligands in similar yields.

For the preparation of ligands **3−5**, compounds **7**, **9** and **10** obtained from our amination studies with calixarene esters were utilised as starting materials.

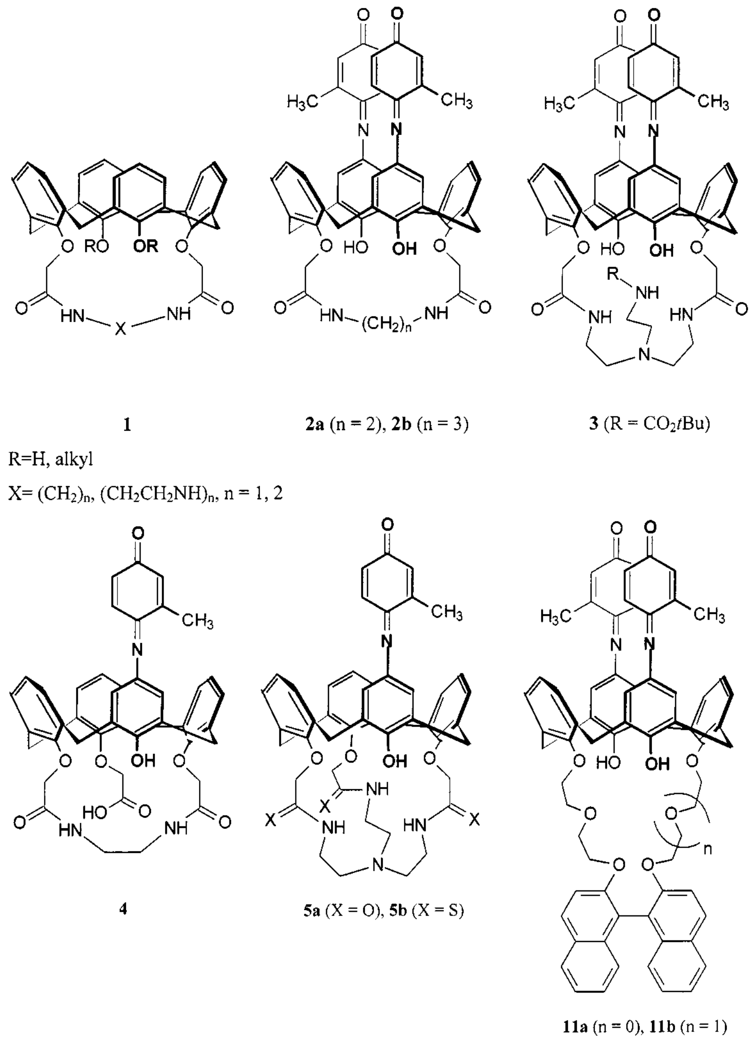
[‡] Studies on Calix(aza)crowns, IV. − Part III: Ref.[1]

[a] Technical Analytical Research Group of the Hungarian Academy of Sciences, Institute for General and Analytical Chemistry of the Technical University of Budapest,
1111 Budapest, St. Gellért tér 4, Hungary
Fax: (internat.) +36-1463-3408
E-mail: g-toth@chem.bme.hu

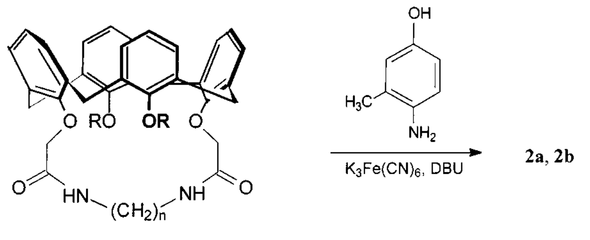
[b] Institute for Drug Research
1045 Budapest, Berlini u. 47−49, Hungary

[c] Department of Organic Chemical Technology, Technical University of Budapest,
1521 Budapest, Hungary
E-mail: bitter@oct.bme.hu

1434−193X/01/0101−0061 $ 17.50+.50/0



Structural formulas **1**-**5** and **11**

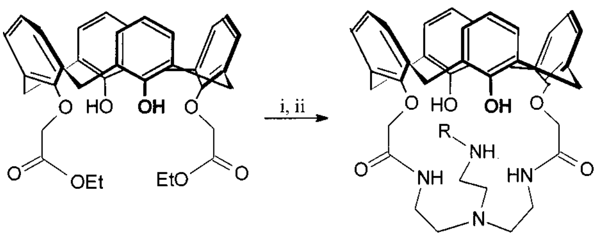


1a (n = 2), **1b** (n = 3)

Scheme 1. Synthesis of **2**

Our experience with the cycloamidation of 25,27-di(ethoxycarbonyl)methoxy-26,28-dihydroxycalix[4]arene (**6**) with various di- and polyamines revealed that only intramolecular reaction took place, even with a large excess of amine, affording exclusively **1** (R = H) cyclised products.[2] No intermolecular reaction resulting in the formation of calixarene dimers was observed even if tris(2-aminoethyl)amine was used for the ring closure, and **7a** was formed exclusively in good yield (Scheme 2). Prior to the reaction of **7a** with 4-amino-*m*-cresol a *tert*-butoxycarbonyl protecting group was introduced (**7b**) followed by the oxidative condensation to afford **3**.

A similar reaction pathway, but associated with regioselectivity, was found when 25,26,27-tri(ethoxycarbonyl)methoxy-28-hydroxycalix[4]arene (**8**) was subjected to cyclisation with ethylenediamine. The reaction was much slower even in boiling solvent (toluene/methanol, 1:1 mixture) but proved to be selective with respect to the formation of the distal 25,27-bridged derivative **10**, and the 26-(ethoxycarbonyl)methoxy group remained unaffected except for trans-

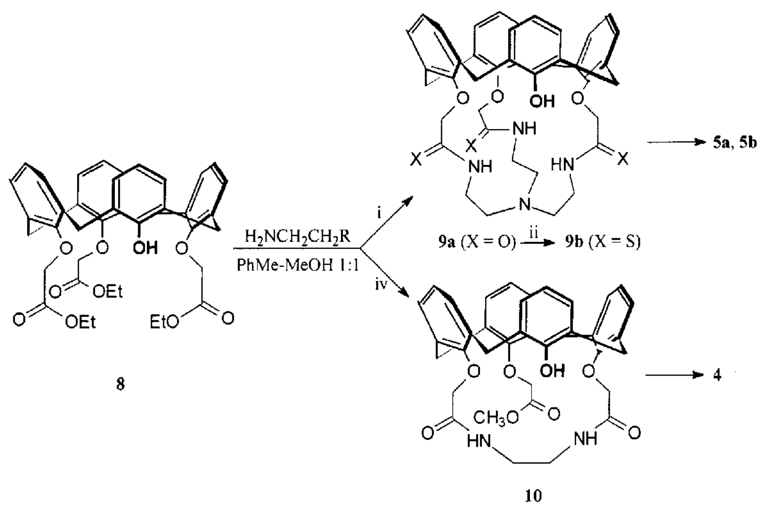


6

7a (R = H) $\xrightarrow{ii}$ **7b** (R = CO_2tBu) $\xrightarrow{iv}$ **3**

Reagents and conditions, i: $N(CH_2CH_2NH_2)_3$, PhMe-MeOH, Δ (**7a**),
ii: BOC-anhydride, rt (**7b**), iv: 4-amino-m-cresol, $K_3[Fe(CN)_6]$, DBU (**3**)

Scheme 2. Synthesis of **3** and **7**



Reagents and conditions, i: R= $N(CH_2CH_2NH_2)_2$, rt; ii: Lawesson reagent, iv: R= NH_2, Δ

Scheme 3. Synthesis of **4**, **5** and **9**, **10**

esterification due to the methanolic solvent (Scheme 3). The proximally cyclised product could not be detected.

During the formation of the chromophore the ester group in **10** suffered hydrolysis due to the strongly basic medium (aqueous MeCN, DBU) resulting in the formation of carboxylic acid **4**.

The preference of the intramolecular reactions of calixarene esters with various polyamines forecast the success of threefold cyclisation on the lower rim. Actually, when triester **8** and tris(2-aminoethyl)amine, which is capable of triamidation, were allowed to stand at room temperature for a week, the product separated from the solution in high yield and was characterised as pure **9a** (Scheme 3.). No other condensation compounds were found in the filtrate. The related thioamide **9b** was also prepared by oxygen/sulfur exchange of **9a** (Lawesson reagent, toluene, 18 h, 110°C) and the same procedure as described above was applied to form the indophenol unit in both compounds giving rise to the formation of **5a**,**b**.

Structure Determination of Chromogenic Capped Calix[4]arenes. *endo*/*exo* Quinoid Tautomerism

It is known that substituted indophenols can exist in two tautomeric forms.[11] The ^1H NMR spectra of indophenol and its symmetrical methyl-substituted derivatives, determined in [D$_6$]DMSO, indicated rapid tautomerisation between the two equivalent structures. In the case of asymmetric substitution of the semiquinone and benzene rings, different tautomer ratios and two sets of NMR signals with a slow exchange on the NMR timescale were observed.[12]

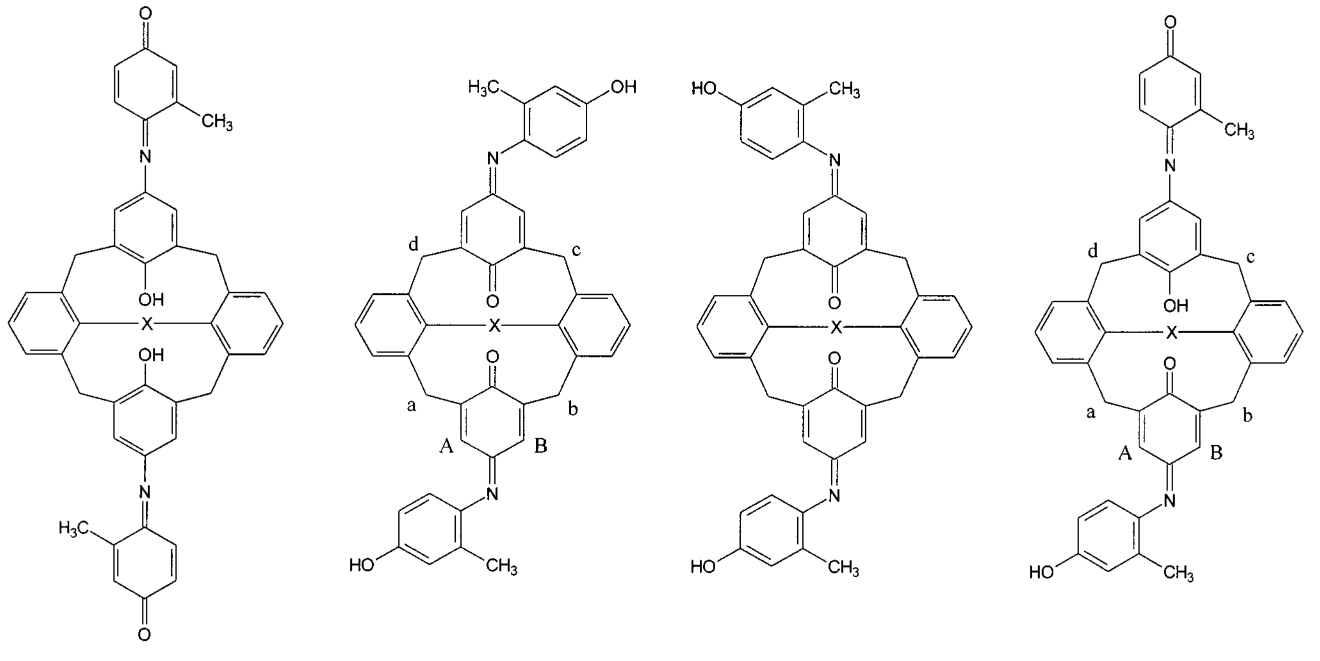
In the calixarene chemistry only a few calix[4]arene-1,1′-binaphtho-crown-5 and -6 derivatives (e.g. **11**) supplied with two indophenol chromogenic moieties were reported and stated to exhibit an *exo*-quinoid tautomer structure in $CDCl_3$ [8−10] in which the quinoneimine moieties are not part of the calixarene core. This observation seems to be reasonable, since the two distal phenolic OH in the *endo*-calix position can be stabilised by intramolecular H-bonding with the neighbouring ether oxygen atoms. Unfortunately, the structure of the free ligands in protic solvents (e.g. [D$_4$]MeOH) was not investigated even though the complexation measurements were carried out in EtOH and not in $CHCl_3$. Therefore the existence of tautomer species in the coloured complexes cannot be excluded.

Taking into consideration the tautomerism of indophenols published in earlier studies, and the lack of relevant data on calixarene indophenols, we decided to investigate thoroughly the structure of our ligands **2**−**5** by NMR spectroscopy.

Theoretically, compounds **2** and **3**, in which two indophenol units are available, may exist in three tautomeric forms: *exo*-, *endo*- and *endo*/*exo*-quinoid structure referring to the position of the quinoneimine subunit. In the *endo* tautomer, however, the two opposite arylimino groups can occupy *anti* (inherently chiral) and *syn* (achiral) arrangements which can be distinguished if the *Z*/*E* isomerisation is slow (Scheme 4). In the first case all the four $ArCH_2Ar$ methylene groups are diastereotopic, whereas in the achiral arrangement by pairs two are equivalent. In the chiral *endo*/*exo*-quinoid tautomer, all the four methylenes are diastereotopic again, but both of the *endo*- and *exo*-quinoid moieties should exhibit different chemical shifts, resulting in an increased number of signals.

The ^1H and ^{13}C chemical shifts and HMBC responses proving the two- and three-bond $^1H/^{13}C$ connectivities are summarised in Table 1. To achieve complete ^1H and ^{13}C signal assignments ^1H, ^{13}C, DEPT, HMQC,[13] ^1H,^1H-COSY, TOCSY,[14] HSQC-TOCSY,[13] HMBC[13] and ROESY[15] measurements were performed. The route of structure elucidation will be demonstrated with compound **2b** as an example.

The section of the HMBC spectrum of **2b** (Figure 1), measured in [D$_6$]DMSO at 350 K, showing the ^1H and ^{13}C spectra as projections proves the inherently chiral *endo*-qui-



exo-quinoid tautomer *(achiral)*

endo-quinoid tautomer *(chiral)*

endo-quinoid tautomer *(achiral)*

endo/exo-quinoid tautomer *(chiral)*

Scheme 4. Tautomerism and *Z*/*E* isomers of chromophoric calix[4]arene indophenols **2**

noid tautomer structure due to the three-bond correlations between the $ArCH_2Ar$ protons and the quinone carbonyls.

The splitting pattern of the $ArCH_2Ar$ signals appearing as four pairs of doublets (H_{cis} $\delta = 3.96-3.85$; H_{trans} $\delta = 3.44-3.31$, $J_{gem} = 12.6$ Hz) in the ^1H NMR spectrum indicates either the presence of a flattened cone conformation, or a rapidly interconverting equilibrium of cone and partial cone conformers. Similar conformational equilibria were observed for calixdiquinones by Beer[16] et al. and by Ungaro[17] and co-workers. On the basis of variable temperature ^1H NMR studies, they were able to observe at low temperature the signals of both conformers in a ratio of ca. 1:1. These results were explained by the rotation of the quinone oxygen through the annulus. Similar conformational motion with compounds **2** is also possible but, due to the strong steric interactions between the bridge and the indophenol moiety, the partial cone conformation seems to be energetically unfavourable. Since low temperature NMR measurements could not be performed in DMSO, we relied on the methylene $ArCH_2Ar$ ^{13}C chemical shifts ($\delta = 31.3-31.9$) which are consistent with a flattened cone conformation.[18−20]

The assignment of the =CH signals in the quinoid ring is straightforward from the ^3J(C,H) correlations with $ArCH_2Ar$ protons. Due to the restricted imine inversion the =CH units, marked as A and B, are different. The diamagnetic shift of the C-6 and C-18 signals, due to the γ_{steric} effect, allows a differentiation between the C-6/18 and C-4/16 carbon atoms. Moreover, the HMBC cross-peaks C-6/H_t-8 and C-6/H_c-8 revealed the methylene group in position 8, whereas the C-4/H_t-2 and C-4/H_c-2 correlations marked out the 2-CH_2 group.

The H-6 and H-18 protons are situated above the plane of the phenol ring experiencing their anisotropic shielding effect ($\delta_{H-4} - \delta_{H-6} = 0.24$ ppm). This assignment was further supported with NOE data proving the close proximity of the H-6 and H-6′′ protons. The arrows in Scheme 5 indicate proton-proton proximities obtained from the ROESY spectrum of **2b** (Figure 2). Further evidence for the *endo*-quinoid tautomer structure are provided by the OH-4′′/H-3′′ and OH-4′′/H-5′′ NOE correlations. The cross-peaks NH/H_c-8 and NH/H_c-20 indicate that the NH bonds are oriented towards the calixarene cavity. We have recently reported the distortion of the cone conformation depending on the character of the bridging unit.[2] The H_c-8 and H_c-2 protons give NOE cross-peaks only with the =CH protons H-4 and H-6 of the quinoid ring, and no correlations to the aryl rings of the calix[4]arene frame. This fact can be explained with a distorted *cone* conformation where the planes of the quinoid rings are becoming flattened and at the same time the aryl groups of the calix[4]arene skeleton are getting nearer to each other and finally become parallel.

The conformational mobility of the bridge connecting the C-25 and C-27 atoms is rather limited. At 300 K the OCH_2 groups appear as a broad signal with 4 H intensity in the ^1H NMR spectrum. Upon raising the temperature to 350 K, this signal turned into two AB signals [centre of the signals are $\delta = 4.21$ (2 H) and 4.26 (2 H)]. Coalescence of the three NH signals [$\delta_{NH} = 8.90$ (t), 8.85 (t) and 8.80 (t), all 2 H] observed at room temperature, was also achieved

Table 1. ^{1}H and ^{13}C chemical shifts of **2b** and **5a**

	2b^{+}			**2b**$^{\neq}$			**2b**			**5a**		
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	HMBC
	CDCl$_3$ 300 K			CDCl$_3$ 300 K			DMSO-d_6 350 K			acetone-d$_6$ 300 K		
1		132.5			131.1			131.6			131.7	
2c	4.19	31.3	1,3,4,24,25,26	4.25	29.9	1,3,4,24,25,26	3.96	31.3	25,26	4.31	30.3	1,3,4,24,25,26
2t	3.57		1,3,4,24,25,26	3.26		1,3,4,24,25,26	3.44		1,3,4,24,25,26	3.30		1,3,4,25,26
3		128.0			142.9			142.1			144.5	
4	6.74	122.2	2,6,3,1,5,26	7.32	139.1	2,6	7.44	137.4	6,26	7.38	139.7	2,26
5		143.0			155.9			155.4			156.8	
6	6.74	122.2	8,4,7,9,5,26	7.12	125.3	4,8	7.20	123.8	8,26	7.26	126.1	8,26
7		128.0			144.0			143.3			145.6	
8c	4.19	31.3		4.23	30.3	6,7,10,26,27	3.88	31.9	26,27	4.28	30.3	6,7,9,10,26,27
8t	3.57			3.07		6,7,9,10,26,27	3.32		6,7,9,10,26,27	3.19		6,7,9,26,27
9		132.5			130.9			131.6			131.4	
10	7.08	129.8	8,9,12,27	6.88	129.2	27	6.95	129.6	8,12	6.80	130.2	8,12,27
11	6.95	127.1	27	6.88	125.8	9,13	6.87	124.4		6.64	125.3	9,13
12	7.08	129.8	9,10,14,27	7.02	130.2	10,14	7.12	129.6	12,14	7.01	130.4	14
13		132.5			133.1			131.6			135.8	
14c	4.19	31.3		4.19	31.5	28	3.93	31.3	27,28	4.53	30.3	15,16,27,28
14t	3.57			3.46		12,13,15,16,27	3.41		12,13,15,16,27,28	3.46		15,16,27,28
15		128.0			128.5			142.1			136.0	
16	6.74	122.2		6.72	122.1	18	7.44	137.4	18,28	7.33	130.1	14,18,28
17		143.0			142.5			155.4		6.94	125.3	
18	6.74	122.2		6.72	122.1	16	7.20	123.8	16,20,28	7.34	130.1	16,20,28
19		128.0			128.3			143.3			136.0	
20c	4.19	31.3		4.19	31.5	28	3.85	31.9	25,28	4.56	30.3	18,19,25,28
20t	3.57			3.50		18,19,21,22,25	3.31		18,19,21,22,25,28	3.47		18,19,25,28
21		132.5			133.0			131.6			135.8	
22	7.08	129.8		7.02	130.1		6.96	129.6	24,25	7.05	130.4	20
23	6.95	127.1		6.94	126.0	1,24	6.87	124.4	1,21	6.72	125.3	1,21
24	7.08	129.8		7.09	129.6	2,25	7.10	129.6	22,25	6.99	130.3	2,22
25		149.5			151.3			153.4			155.1	
26		150.6			186.2			185.8			187.9	
27		149.5			151.5			153.4			155.1	
28		150.6			151.4			185.8			156.8	
2’a	4.62	74.6	3’,27	4.38	73.6	3’	4.20	70.5	3’	3.90	75.3	3’,27
2’b	4.62			4.58		3’	4.26			4.70		27
3’		167.8			169.0			167.7			169.7	
4’	8.75		5’,2’	9.28						9.05		
5’a	3.58	36.2		3.65	36.9	3’,6’,7’	3.36	37.6	6’,7’,3’	3.32	40.1	
5’b							3.42			3.61		
6’	2.36	23.4		2.37	23.4		1.81	27.0		a	a	
7’a	3.58	36.2	5’,6’	3.65	36.8	5’,9’	3.36	37.6	5’,9’	3.32	40.2	
7’b							3.42			3.61		
8’	8.75		7’,9’	9.37						9.16		
9’		167.8			168.8			167.9			169.7	
10’a	4.62	74.6		4.42	73.8	9’	4.20	70.5	9’	3.96	75.3	9’,25
10’b	4.62			4.66		9’	4.26			4.74		9’
1”					141.6			140.4			142.2	
2”					134.1			132.7			134.6	
3”				6.87	118.0	1”,5”,Me	6.78	117.3	1”,4”,5”,Me	6.84	118.4	2”
4”					156.2			156.4			157.9	
5”				6.77[c]	112.9	1”,3”	6.71[e]	112.9	1”,3”	6.73[f]	113.7	
6”				6.47[c]	121.5	2”,4”	6.50[e]	121.3	2”,4”	6.58[f]	122.7	
2”-Me				2.20	18.3	1”,2”,3”	2.18	17.6	1”,2”,3”	2.17	18.5	1”,2”,3”
1*		157.5			157.2							
2*		149.7			149.8							
3*	6.57	130.6	1*,5*,Me	6.57	130.5							
4*		188.0			188.1							
5*	6.45[b]	132.3	1*	6.44[d]	132.0	3*						
6*	7.04[b]	128.7	1*,2*,4*	7.03[d]	128.9	1*,2*,Me						
2*-Me	2.29	18.1	1*,2*,3*	2.30	18.1	1*,2*,3*						
OH	8.60		3,7,26	8.05		15,28	9.44					

[a] 6′: $N(CH_2)_2CH_2CH_2NHCOCH_2O$ δ = 2.75/3.03 (57.9), 2.72 (56.7), 3.37 (39.5), 8.01 (170.0), 4.43 (75.6). – [b] ^{3}J(H-5*,H-6*) = 10.2 Hz. – [c] ^{3}J(H-5′′,H-6′′) = 8.2 Hz. – [d] ^{3}J(H-5*,H-6*) = 10.3 Hz. – [e] ^{3}J(H-5′′,H-6′′) = 8.2 Hz. – [f] ^{3}J(H-5′′,H-6′′) = 8.5 Hz. – $^{+}$ *exo*-quinoid tautomer; $^{\neq}$ *endo*/*exo*-quinoid tautomer.

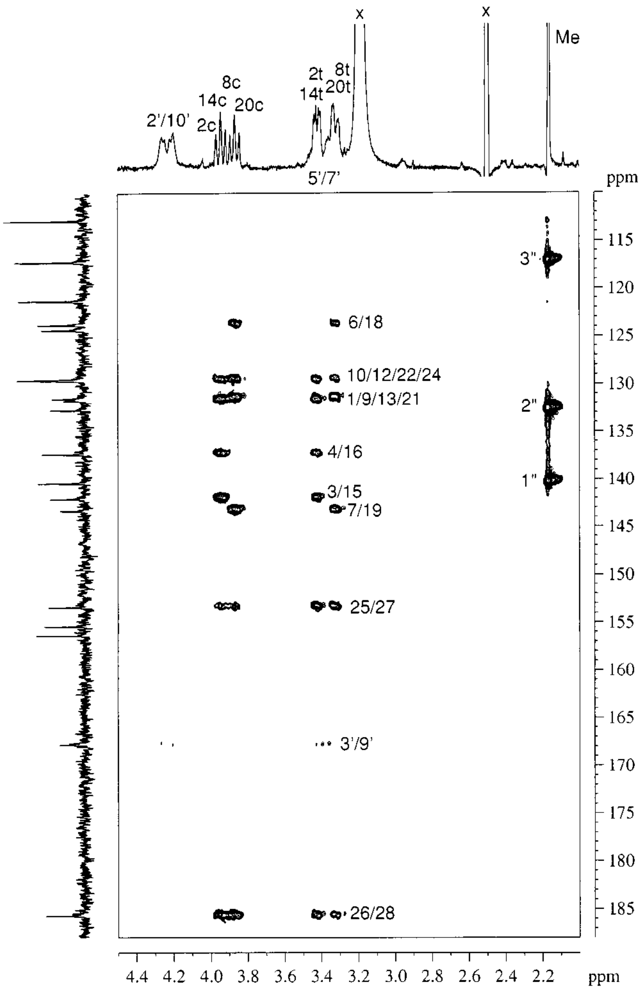
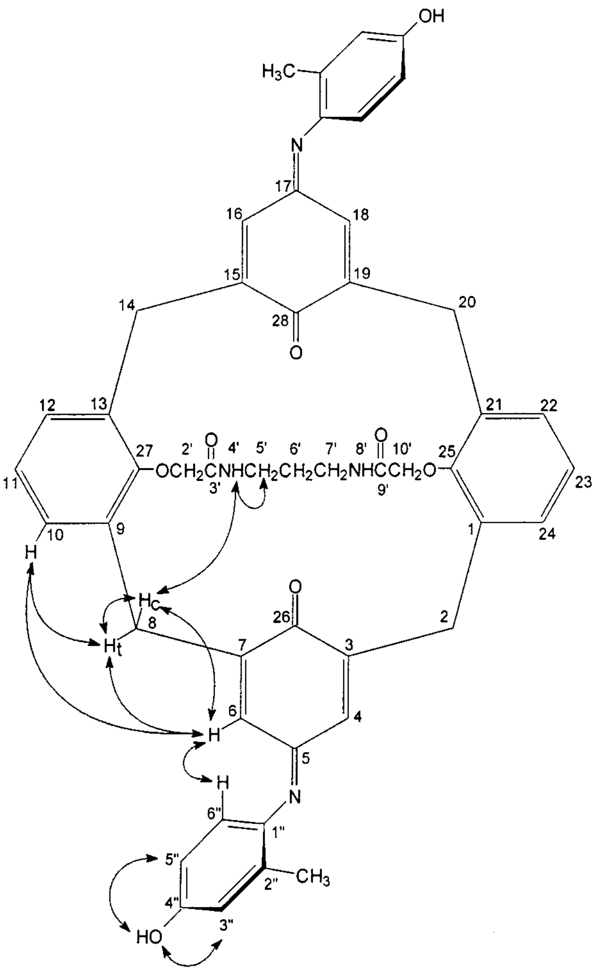


Figure 1. Section of HMBC spectum of **2b** in [D$_6$]DMSO



Scheme 5. Proton-proton proximities obtained from a ROESY experiment

at 380 K. All these support the restricted conformational motion of the bridge which is getting free at elevated temperature.

The *Z*/*E* isomerism of the imino group needs much higher energy of activation as shown by the lack of coalescence of the H-4 and H-6 signals even at 400 K. This means that the free enthalpy of activation $\Delta G^{\ddagger} > 21.5$ kcal/mol.[21] It should be mentioned that the proton signals of the aromatic rings of the skeleton are becoming broad at this elevated temperature.

The exchange rate of the *Z*/*E* isomerisation can be calculated from the ROESY exchange cross-peak intensities of H-4 and H-6 signals, measured with the application of different t_m mixing times, according to Equation (1):[22]

$$\ln\left(\frac{r+1}{r-1}\right) = kt_m$$

where $r = 4X_ZX_E(I_{Z\text{-}Z} + I_{E\text{-}E})/(I_{Z\text{-}E} + I_{E\text{-}Z}) - (X_Z - X_E)^2$, and X_Z and X_E are the respective mol fractions (this equation is simplified since the mol fractions of the two isomers are equal), $I_{Z\text{-}Z}$ and $I_{E\text{-}E}$ are the intensities of the diagonal peaks, $I_{Z\text{-}E}$ and $I_{E\text{-}Z}$ are the intensities of the cross peaks, k is the exchange rate constant (s^{-1}), which is the sum of the *Z* to *E* and the *E* to *Z* reaction rates, and t_m is the mixing time of the ROESY experiments. From linear regression, $k = 0.106$ s^{-1} was obtained for the exchange rate at 350 K in [D$_6$]DMSO (Figure 3).[21]

In the ^{1}H NMR spectrum of **2b** a characteristic temperature dependence of OH and NH signals was observed. The high chemical shifts of these signals (300 K, $\delta_{OH} = 9.62$, $\delta_{NH} = 8.90-8.80$) indicate strong hydrogen bonding. Raising the temperature from 300 K to 400 K the observed $\Delta\delta$ upfield shifts were 0.45 and 0.2 ppm, respectively. These data suggest that the OH groups form intermolecular hydrogen bonding with the DMSO solvent molecules, whereas the amide NH protons take part in intramolecular hydrogen bonds, probably with the oxygen atoms of the neighbouring OCH$_2$ groups.

Changing the solvent from [D$_6$]DMSO to CDCl$_3$ caused dramatic alterations in the ^{1}H and ^{13}C NMR spectra of **2b** as well. The most characteristic feature of the ^{13}C spectrum is the appearance of two sets of signals with an intensity ratio of 2:1. The number of ^{13}C signals of the component with the higher intensity is about the half that of the other component. A similar feature can also be observed in the ^{1}H NMR spectrum. The intensive quinoid carbonyl signal at $\delta = 188.0$ shows an HMBC correlation (Figure 4) with

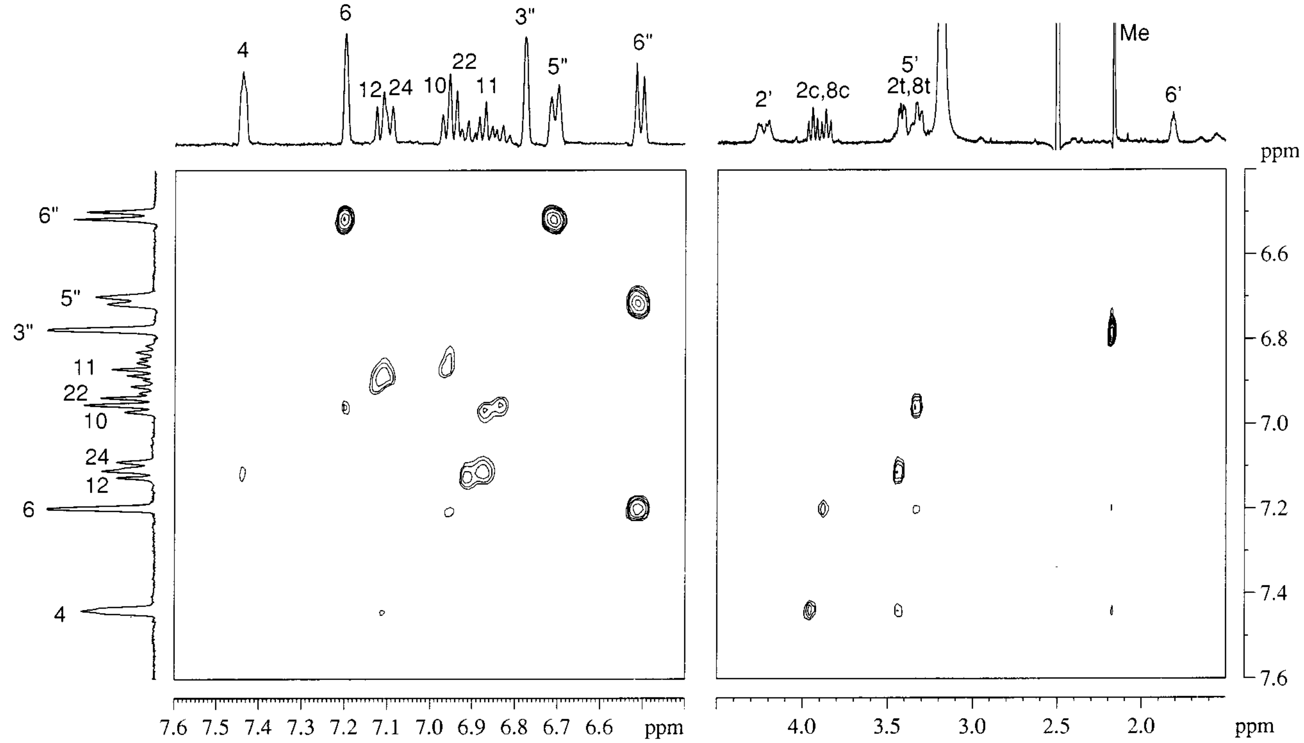


Figure 2. Section of the ROESY spectrum of **2b** in [D$_6$]DMSO

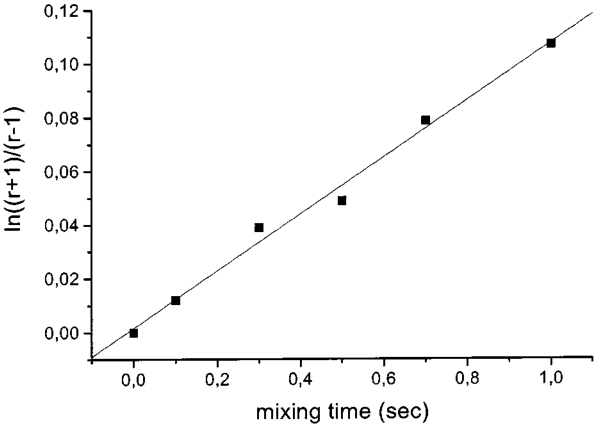


Figure 3. Calculation of the *Z*/*E* imine isomerisation rate based on the ROESY exchange peak intensities of the H-4 and H-6 signals

the doublet of H-6* (δ = 7.04, $J_{\text{H-6*,H-5*}}$ = 10.2 Hz) supporting the *exo*-quinoid structure. The 0.5 ppm downfield shift ($\delta_{\text{H-6}''}$ = 6.50 → $\delta_{\text{H-6*}}$ = 7.04) and the change of the coupling constant (J_{ortho} = 8.2 → 10.2 Hz), and a comparison of these parameters with those observed in [D$_6$]DMSO, are now in agreement with an *exo*-quinone-imine tautomer. The structure of this component is achiral and so the H-4/H-6 signal appears as a singlet (δ = 6.74), whereas the four ArCH$_2$Ar methylenes give rise to one AB pair of doublets (δ = 3.57 and 4.19, J_{AB} = 13.4 Hz). Both the methylenes and H-4/H-6 protons show HMBC cross-peaks with the carbon signal at δ = 150.6 proving the existence of OH groups in the positions C-26 and C-28 (Figure 4). The methylene protons of the bridge C-25 ↔ C-27 show time-averaged chemical shifts confirming the rapid conformational motion of this flexible chain.

The other component of the tautomer equilibrium in CDCl$_3$ should be the chiral *endo*/*exo*-quinoid tautomer, and this is supported by the following facts: in the ^{13}C NMR spectrum there are two quinoid carbonyl signals at δ = 186.2 and 188.1. The former one correlates in the HMBC spectrum with the H-4 and H-6 protons of the quinoid ring [δ = 7.32 (d), 7.12 (d), $J_{\text{H-4,H-6}}$ = 2.6 Hz] and also with the methylene protons in the positions C-2 and C-8. Consequently, this carbonyl should belong to an *endo*-quinoid indophenol moiety. Considering the cross-peaks of the C-14 and C-20 methylene protons with the signal at δ = 151.4, we can conclude that there is an OH function in the position C-28. The OH proton [δ_{OH} = 8.05 (s)] correlates with the C-28, C-15 and C-19 atoms. The other quinoid carbonyl signal at δ = 188.1 correlates with H-6* [δ = 7.03 (d), J = 11.3 Hz] supporting the appearance of the other indophenol moiety in the *exo*-quinoid form. As a consequence of two different *exo*- and *endo*-quinoid indophenols in one molecule, we observed two different CH$_3$ signals. On the basis of the $J_{\text{C,H}}$ couplings of the methyl protons with the carbon atoms in two and three bond distances, the signal at δ = 2.20 (3 H) should be assigned to CH$_3$-2$''$, and that at δ = 2.30 (3 H) to CH$_3$-2*. The ratio of the *exo*-quinoid:-*endo*/*exo*-quinoid tautomers is 1:1.

It should be mentioned that tautomer exchange was not observed either in the TOCSY (τ_{mixing} = 150 msec) or in the ROESY (τ_{mixing} = 1 sec) spectra. By adding one drop of trifluoroacetic acid the signals of the ^{1}H NMR spectrum

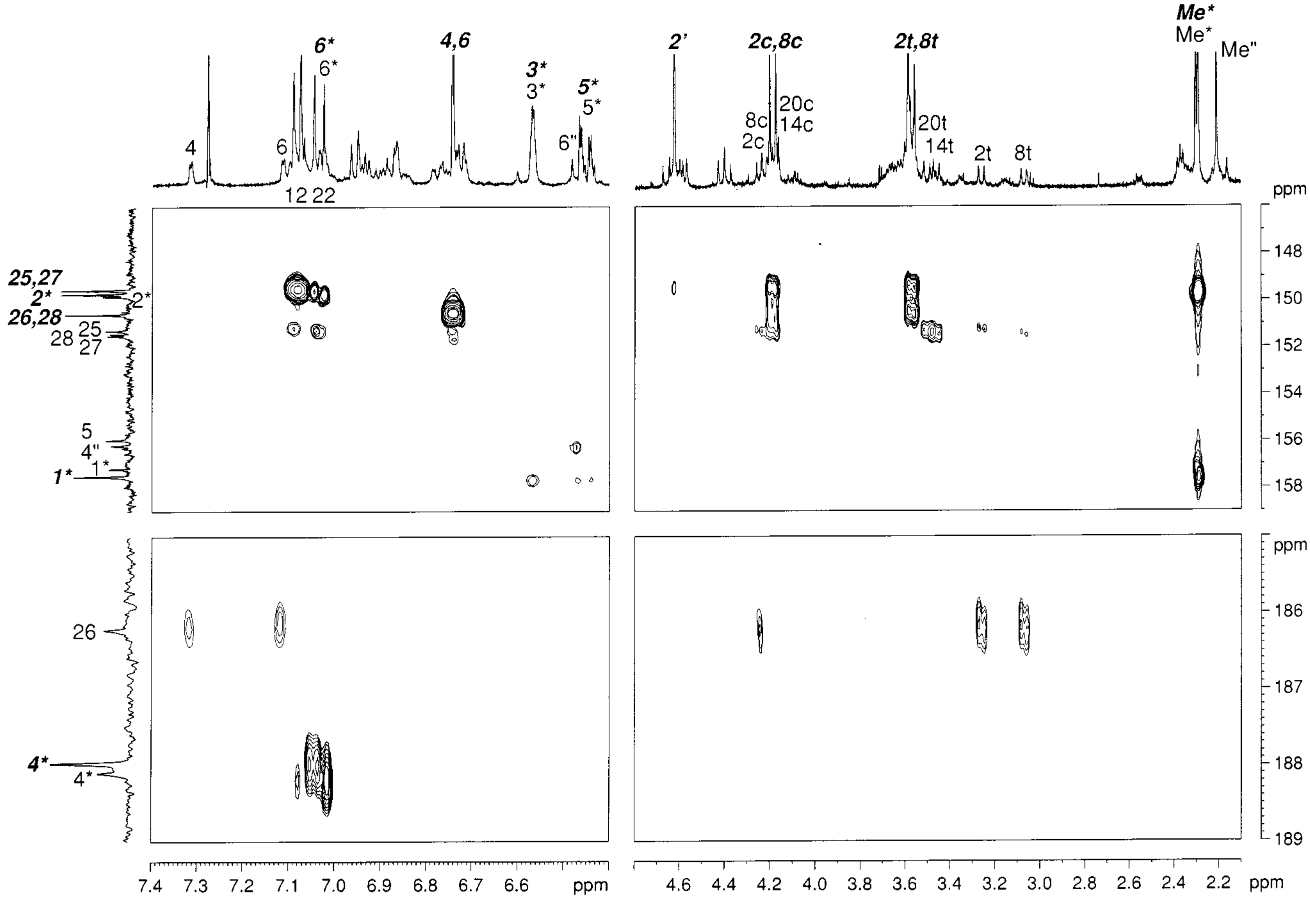


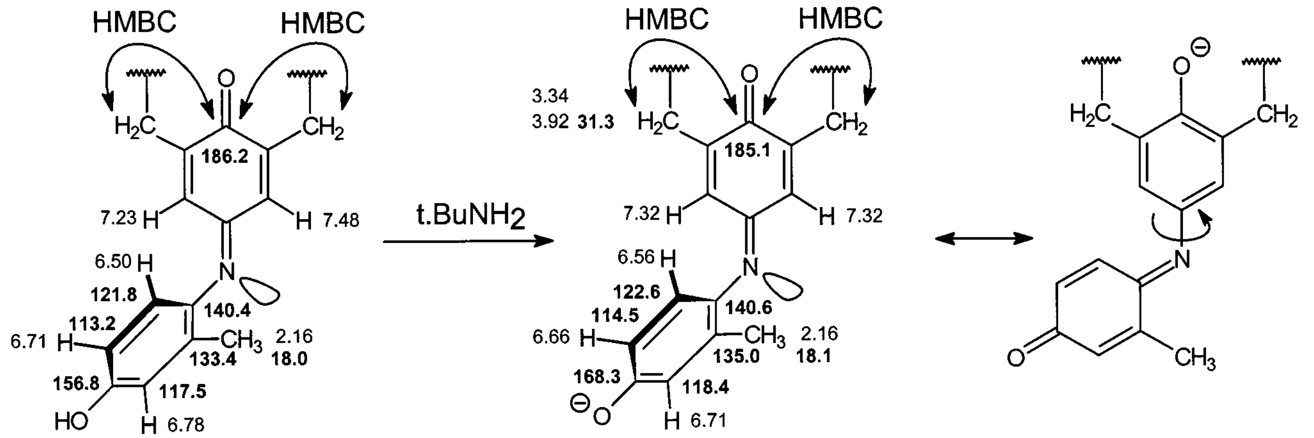
Figure 4. Section of the HMBC spectrum of **2b** in $CDCl_3$; for discrimination of the cross-peaks of the *exo*- and *endo*/*exo*-quinoid tautomers we applied bold/italic numbering for the latter case

became broad indicating exchange, but at the same time the beginning of precipitation was observed.

The NMR investigation of compound **2a** led to similar results (see the NMR spectroscopic data in the Experimental Section), with the only exception that the ratio of the *exo*-quinoid:*endo*/*exo*-quinoid tautomers is now 5:2. Investigating the ^1H NMR spectrum measured in $CDCl_3$ between +27 °C and −80 °C neither appearance of a new set of signals nor coalescence was observed.

After this comprehensive NMR study the elucidation of the tautomerism of the calixhemicryptand-like compound **5** containing only one indophenol seemed to be much easier since only the *exo*-quinoid and *endo*-quinoid tautomer forms had to be considered. We investigated the tautomerism in [D_6]DMSO, $CDCl_3$, [D_4]methanol and [D_6]acetone solutions. In all cases the ^1H and ^{13}C NMR spectra of **5a** exhibited one set of signals indicating one preferred tautomer, which turned to be the *endo*-quinoid form. The ^1H and ^{13}C NMR spectroscopic data of **5a** measured in [D_6]acetone are summarized in Table 1. The structure is chiral and so in the ^1H NMR spectrum we observed four pairs of AB doublets for the $ArCH_2Ar$ methylenes. In the HMBC spectrum the 2- and 8-methylene protons correlate with the C-26 carbonyl signal at $\delta = 187.9$, whereas the 14- and 20-methylenes correlate with the oxygen-substituted C-28 carbon atom at $\delta = 156.8$. According to the ^{13}C chemical shift of the four methylenes ($\delta = 30.3$) the *cone* structure of the calix frame is straightforward. Due to the hindered imine inversion the =CH groups in positions 4 and 6 display characteristically different ^1H and ^{13}C chemical shifts (vide infra). The strong cross-peak between the H-6 and H-6′′ protons in the ROESY spectra gave further support for the steric arrangement along the imine group. In contrast to the single capped compounds **2**, the H-4 and H-6 protons show steric proximities only to H_t-2 and H_t-8, respectively, and no responses to the corresponding *cis* protons. These observations support a cone conformation without pronounced distortion, which is a result of the threefold bridging on the lower rim. The NH signals at $\delta = 9.16$ (t) and 9.05 (t) gave ROESY responses to H_c-2 and H_c-8, respectively, and the third NH signal at $\delta = 8.01$ (t) to H_c-14 and H_c-20. It emerges that all three NH bonds are oriented towards the cavity. In the EXSY spectrum, the H-4′/H-8′ and H-4/H-6 cross-peaks are in accordance with a slow *Z*/*E* isomerisation as is also observed for compounds **2**.

The tautomer structures of the other chromogenic molecules **3**, **5b** and **4** were also determined in $CDCl_3$ and [D_4]methanol, and characterised in each case as the *endo*-quinoid tautomer, too. The existence of the *exo* form in other solvents cannot be excluded, although this was not studied.



Scheme 6. Base-catalyzed *Z*/*E* isomerization of the *endo*-quinoid tautomer **2b** at 300 K

Having completed the structure determinations of our ligands and unambiguously assigning every proton and carbon signal in their NMR spectra we supposed that complexation experiments carried out in the NMR tube would provide exact information on the nature of binding and give a deeper insight into the chemistry of the coloration process.

In analogy to Kubo's experiments[8] with calixcrown **11**, we added *t*BuNH$_2$ to the [D$_6$]DMSO solution of **2b** and also experienced a significant colour change (red → blue). At the same time characteristic alterations in the ^{1}H and ^{13}C NMR spectra were observed (Scheme 6).

These changes can be explained as follows: the phenolic OH group was deprotonated by the amine, forming a phenolate anion, as can be seen from the 12 ppm downfield shift of C-4′′.[23] Due to the strong electron-releasing effect of the phenolate, electron transfer occurs towards the *endo*-quinoid ring, which is associated with the decrease of the free energy of activation of the *Z*/*E* isomerisation. As a consequence of this the H-4 and H-6 chemical shifts are becoming equal. Moreover, the rapid interconversion of the *Z*/*E* isomers results in the loss of the chiral character of **2b**, and thus in the ^{1}H NMR spectrum only one AB pair of doublets (δ = 3.92 and 3.34, J_{AB} = 13.5 Hz) appear for the ArCH$_2$Ar protons and one signal appears at δ = 31.1 in the ^{13}C NMR spectrum for the corresponding methylene carbons. It is important to underline that, due to the addition of *t*BuNH$_2$, no tautomerisation takes place. The indophenol moiety retains the *endo*-quinoid form, as seen by the HMBC correlation between C-26 (185.1) and the ArCH$_2$Ar protons. The signal of the OCH$_2$ protons upon treatment with *t*BuNH$_2$ remained broad, and became a sharp singlet at δ = 4.28 at elevated temperature (400 K). By addition of TFA to the [D$_6$]DMSO solution of **2b** and *t*BuNH$_2$ the original ^{1}H chemical shifts of **2b**, and the chiral character of the ligand was recovered. In CDCl$_3$ no change of the NMR chemical shifts of **2b** was observed by adding *t*BuNH$_2$ and the red colour of the solution remained unchanged.

We also investigated the coloration of **5a** in [D$_4$]methanol with *t*BuNH$_2$ and the effect was similar to that of **2b**. The salt formation reduced the energy of the imine inversion and, due to the rapid *Z*/*E* interconversion, the structure became achiral. The signals of the methylene protons of the bridges connecting the central nitrogen atom to C-25 and C-27 remained diastereotopic, whereas those in the bridge from C-28 to the nitrogen atom became enantiotopic. However, no significant change in the chemical shifts of the bridging protons appeared and so any interaction between the amine and the capped lower rim of the calix was not detected.

Conclusion

In conclusion, monitoring the coloration process in the NMR tube revealed that an acid-base equilibrium is responsible for the colour change of **2a**, **2b** and **5a** in the presence of *t*BuNH$_2$ (the other molecules have not been tested yet), and the original tautomer structure of the free ligands remained. Complexation under these conditions could not be observed by NMR spectroscopy.

However, UV/Vis measurements carried out in the low concentration region with a series of aliphatic amines clearly indicated that the optical spectra of ligands **2a**, **2b** and **5a** were strongly affected by primary amines and much less so with secondary or tertiary amines of similar p*K* values.[26] Although a quantitative evaluation of the complex formation is underway it has already been seen that the binding is not strong (the apparent K_{ass} = 20−150 dm^3·mol^{-1} calculated for a 1:1 stoichiometry in EtOH) and the linearity of the Benesi−Hildebrand plot is restricted to an amine concentration of 10^{-4}−10^{-3} mol·dm^{-3}.

We did not succeed in monitoring the complexation of ligand **11b** by ^{1}H NMR spectroscopy, either, although it has been reported to form a much stronger complex with *t*BuNH$_2$ (K_{ass} = 1090±135 dm^3·mol^{-1}).[8] We have also found, in accordance with these authors, that **11b** exists in the *exo*-quinoid tautomer form in CDCl$_3$, but in [D$_4$]MeOH or in [D$_6$]DMSO the signals became very broad, possibly due to rapid tautomerisation, and no signal sharpening was observed after the addition of *t*BuNH$_2$ either.

Experimental Section

Melting points are uncorrected. − NMR spectra were recorded in $CDCl_3$, [D$_6$]dimethylsulfoxide, [D$_4$]methanol or [D$_6$]acetone at 500/125 MHz on Bruker Avance DRX-500 spectrometer. Chemical shifts are given on the δ scale. Experiments were taken from the Bruker software library. HMBC measurements were optimized for 7 Hz long-range couplings. − Fast atom bombardement (FAB) mass spectra were recorded on a Finnigan MAT 8430 instrument with *m*-nitrobenzyl alcohol as the matrix and Xe as the FAB gas at 9 kV, ion source temperature: 25 °C. The $[M + 2 H + H]^+$ ions resulted presumably from the reduction of the calix[4]arene indophenols by the matrix. − Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC. All chemicals were reagent grade and used without further purifications. Compounds **1a,b**[2] and **6,**[24] **8**[25] were prepared as described in the literature.

General Procedure for the Synthesis of 2a,b, 3, 4 and 5a,b: Aqueous $K_3Fe(CN)_6$ solution (2.64 g, 8 mmol in 8 mL water) was added to the solution of the appropriate starting material (1 mmol **1a**, **1b**, **7b**, **9a**, **9b 10**), 4-amino-*m*-cresol (0.5 g, 4 mmol) and DBU (3 mL, 20 mmol) in MeCN (80 mL). The mixture was stirred at room temperature for 24 h. Then the solvent was removed at reduced pressure. The remaining oil was dissolved in $CHCl_3$ (200 mL) and washed with water. The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by column chromatography on silica to give red crystals.

2a: Yield 57%, M.p. >390 °C (eluent: EtOAc/MeOH, 95:5). − ^{1}H NMR ($CDCl_3$): δ = 8.56 (s, 2 H, OH), 8.45 (t, 2 H, NH), 7.10 (d, 4 H, ArH), 7.03 (d, 2 H, quinoid-H), 6.97 (t, 2 H, ArH), 6.73 (s, 4 H, ArH), 6.56 (d, 2 H, quinoid-H), 6.45 (dd, 2 H, quinoid-H), 4.61 (s, 4 H, OCH_2), 4.21 and 3.56 (d, *J* = 13.3 Hz, 4+4 H, $ArCH_2Ar$), 3.74 (m, 4 H, NCH_2), 2.29 (s, 6 H, CH_3). − ^{13}C NMR ($CDCl_3$): δ = 188.0 (C=O), 167.2 (CONH), 150.7, 149.1, 142.9, 132.7, 129.8, 128.1, 127.2, 122.3 (Ar), 157.5, 149.7, 132.3, 130.6, 128.7 (quinoid), 74.8 (OCH_2), 39.3 (NCH_2), 31.3 ($ArCH_2Ar$), 18.1 (CH_3). − ^{1}H NMR ([D$_6$]DMSO): δ = 9.62 (s, 2 H, OH), 8.96, 8.81, 8.68 (br, 2 H, NH), 7.46 (s, 2 H, quinoid-H), 7.25 (s, 2 H, quinoid-H), 7.14 (d, 1 H, ArH), 7.12 (d, 1 H, ArH), 6.98 (d, 1 H, ArH), 6.96 (d, 1 H, ArH), 6.92 (t, 1 H, ArH), 6.88 (t, 1 H, ArH), 6.77 (s, 2 H, ArH), 6.71 (d, 2 H, ArH), 6.51 (d, 2 H, ArH), 4.23 (s, 4 H, OCH_2), 3.98 and 3.90 (d, *J* = 16.0 Hz, 2+2 H, $ArCH_2Ar$), 3.95 and 3.86 (d, *J* = 14.5 Hz, 2+2 H, $ArCH_2Ar$), 3.39 (m, 4 H, NCH_2), 2.17 (s, 6 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO): δ = 186.5 (C=O), 168.2 (CONH), 157.3, 153.2, 140.9, 134.1, 132.8, 130.3, 124.5, 122.4, 117.9, 113.6 (Ar), 155.9, 144.2, 142.7 138.5, 125.4 (quinoid), 70.7 (OCH_2), 38.2 (NCH_2), 29.5 ($ArCH_2Ar$), 18.6 (CH_3). − MS; *m/z* (%): 803 (98) $[M + H]^+$. − $C_{48}H_{42}N_4O_8$ (802.88): calcd. C 71.81, H 5.27, N 6.98; found C 71.02, H 5.20, N 6.89.

2b: Yield 25%, M.p. >380 °C (eluent: EtOAc). − ^{1}H and ^{13}C NMR data see Table 1. − MS; *m/z* (%): 817 (47) $[M + H]^+$, 819 (100) $[M + 2 H + H]^+$ (this ion results from the reduction of the calix by the matrix). − $C_{49}H_{44}N_4O_8$ (816.91): calcd. C 72.04, H 5.43, N 6.86; found C 71.75, H 5.48, N 6.93.

3: Yield 64%, M.p. >380 °C (eluent: CH_2Cl_2/MeOH, 9:1). − ^{1}H NMR ($CDCl_3$): δ = 7.30 (s, 2 H, quinoid-H), 7.16 (s, 2 H, quinoid-H), 7.08 (d, 1 H, ArH), 6.97 (d, 1 H, ArH), 6.93 (d, 1 H, ArH), 6.87 (s, 2 H, ArH), 6.86 (t, 2 H, ArH), 6.79 (d, 1 H, ArH), 6.75 (d, 2 H, ArH), 6.55 (d, 2 H, ArH), 4.68 (d, 2 H, OCH_2), 4.32 (d, 2 H, OCH_2), 4.25 and 3.51 (d, *J* = 13.8 Hz, 2+2 H, $ArCH_2Ar$), 4.25 and 3.40 (d, *J* = 14.0 Hz, 2+2 H, $ArCH_2Ar$), 3.58 (m, 2 H, $HNCH_2$), 3.47 (m, 2 H, $HNCH_2$), 3.22 (m, 2 H, $HNCH_2$), 2.86 (m, 4 H, NCH_2), 2.66 (m, 2 H, NCH_2), 2.31 (s, 6 H, CH_3), 1.40 (s, 9 H, *t*Bu). − ^{13}C NMR ($CDCl_3$): δ = 188.1 (C=O), 168.7 (CONH), 157.5, 152.2, 151.1, 149.7, 132.5, 132.0, 130.6, 129.9, 129.4, 128.4, 126.6, 121.6, 117.9, 112.8 (Ar), 156.1, 144.2, 142.9 138.3, 128.7 (quinoid), 79.1 (*t*Bu−C), 75.0, 73.9 (OCH_2), 56.0, 55.1, 54.7 (NCH_2), 39.6, 39.0, 38.9 ($HNCH_2$), 31.4 ($ArCH_2Ar$), 28.5 (*t*Bu − CH_3), 18.1 (CH_3). − $C_{57}H_{60}N_6O_{10}$ (989.14): calcd. C 69.21, H 6.11, N 8.50; found C 69.54, H 6.14, N 8.43.

4: Yield 75%, M.p. >380 °C (eluent: CH_2Cl_2/MeOH, 9:1). − ^{1}H NMR (CD_3OD): δ = 7.29 (s, 2 H, quinoid-H), 7.24 (d, 1 H, ArH), 7.23 (d, 1 H, ArH), 7.16 (d, 1 H, ArH), 7.11 (s, 2 H, quinoid-H), 6.90 (t, 1 H, ArH), 6.78 (t, 1 H, ArH), 6.77 (s, 2 H, ArH), 6.67 (d, 2 H, ArH), 6.40 (d, 2 H, ArH), 4.82 and 4.16 (d, *J* = 9.3 Hz, 2+2 H, OCH_2), 4.47 (s, 2 H, OCH_2), 4.26 and 3.29 (d, *J* = 12.6 Hz, 2+2 H, $ArCH_2Ar$), 4.20 and 3.12 (d, *J* = 12.5 Hz, 2+2 H, $ArCH_2Ar$), 3.85 and 3.65 (m, 2+2 H, NCH_2), 2.12 (s, 3 H, CH_3). − ^{13}C NMR (CD_3OD): δ = 187.6 (C=O), 176.8 (COOH), 172.6 (CONH), 158.5, 146.0, 145.2, 139.9, 127.2 (quinoid), 158.0, 157.7, 153.9, 142.4, 137.5, 136.2, 134.9, 133.2, 133.0, 131.0, 130.4, 130.2, 126.7, 125.4, 123.5, 118.7, 114.0 (Ar), 75.3, 74.3 (OCH_2), 39.5 (NCH_2), 31.7, 30.4, 30.2 ($ArCH_2Ar$), 18.6 (CH_3). − MS; *m/z* (%): 744 $[M + 2 H + H]^+$ (this ion results from the reduction of the calix by the matrix), 740 $[M - H]^-$, 742 $[M + 2 - H]^-$. − $C_{43}H_{39}N_3O_9$ (741.80): calcd. C 69.62, H 5.30, N 5.66; found C 69.35, H 5.36, N 5.62.

5a: Yield 47%, M.p. 262−66 °C (eluent: EtOAc/MeOH, 9:1). − ^{1}H and ^{13}C NMR data see Table 1. − MS; *m/z* (%): 810 (67) $[M + H]^+$, 690 (97) $[M + H - C_7H_6NO]^+$. − $C_{47}H_{47}N_5O_8$ (809.92): calcd. C 69.70, H 5.85, N 8.65; found C 70.02, H 5.87, N 8.62.

5b: Yield 25%, m.p. >370 °C (eluent: toluene/MeOH, 95:5). − ^{1}H NMR ($CDCl_3$): δ = 10.73 (t, 1 H, NH), 10.60 (t, 1 H, NH), 9.44 (t, 1 H, NH), 7.26 (s, 1 H, quinoid-H), 7.19 (d, 2 H, ArH), 7.02 (s, 1 H, quinoid-H), 6.98 (t, 1 H, ArH), 6.84 (d, 1 H, ArH), 6.81 (d, 2 H, ArH), 6.73 (d, 1 H, ArH), 6.71 (t, 1 H, ArH), 6.64 (t, 1 H, ArH), 6.58 (d, 1 H, ArH), 6.53 (d, 1 H, ArH), 5.12 and 4.41 (d, *J* = 17.5 Hz, 1+1 H, OCH_2), 5.09 and 4.36 (d, *J* = 17.5 Hz, 1+1 H, OCH_2), 4.91 and 4.88 (d, *J* = 17.0 Hz, 1+1 H, OCH_2), 4.34 and 3.36 (d, *J* = 12.0 Hz, 2+2 H, $ArCH_2Ar$), 4.18 (m, 2 H, $HNCH_2$), 4.02 and 3.13 (d, *J* = 13.0 Hz, 1+1 H, $ArCH_2Ar$), 4.00 and 2.94 (d, *J* = 13.0 Hz, 1+1 H, $ArCH_2Ar$), 3.86 (m, 2 H, $HNCH_2$), 3.72 (m, 2 H, $HNCH_2$), 3.34 (m, 2 H, NCH_2), 3.04 (m, 2 H, NCH_2), 2.88 (m, 2 H, NCH_2), 2.26 (3 H, CH_3). − ^{13}C NMR ($CDCl_3$): δ = 198.7, 196.9 (C=S), 187.9 (C=O), 155.8, 155.4, 152.8, 152.7, 141.8, 134.4, 134.3, 129.8, 129.7, 129.4, 129.1, 129.0, 128.7, 124.6 (Ar), 155.5, 144.2, 143.2, 138.6, 125.1 (quinoid), 80.8, 80.6, 80.5 (OCH_2), 56.5, 53.8 (NCH_2), 44.7, 44.6 ($HNCH_2$), 30.3 ($ArCH_2Ar$), 18.3 (CH_3). − $C_{47}H_{47}N_5O_5S_3$ (858.12): calcd. C 65.79, H 5.52, N 8.16; found C 65.41, H 5.59, N 8.21.

Synthesis of Precursors 7, 9 and 10

Compounds 7a,b: A solution of diethyl ester **6** (3.58 g, 6 mmol) and tris(2-aminoethyl)amine (2.8 mL, 19 mmol) in a mixture of methanol (90 mL) and toluene (90 mL) was allowed to stand at room temperature for 48 h. Then the solution was concentrated at reduced pressure. The residue was suspended in methanol and filtered to give **7a** as a white solid. Yield 93%, m.p. 250−252 °C. − ^{1}H NMR ($CDCl_3$): δ = 8.24 (t, 2 H, NH), 7.14 (d, 4 H, ArH), 6.81 (d, 4 H, ArH), 6.80 (t, 2 H, ArH), 6.68 (t, 2 H, ArH), 4.56 (s, 4 H, OCH_2), 4.22d and 3.47 (d, *J* = 13.5 Hz, 4+4 H, $ArCH_2Ar$), 3.55 (m, 4 H, $HNCH_2$), 2.81 (m, 4 H, NCH_2), 2.74 (t, 2 H, $HNCH_2$), 2.53 (t, 2 H, NCH_2). − ^{13}C NMR ($CDCl_3$): δ = 168.5 (C=O), 152.5, 151.2, 132.3, 129.7, 129.2, 128.1, 126.4, 120.6 (Ar), 75.0

(OCH$_2$), 58.1, 55.3 (NCH$_2$), 39.9, 39.1 (NHCH$_2$), 31.4 (ArCH$_2$Ar). − $C_{38}H_{42}N_4O_6$ (650.77): calcd. C 70.13, H 6.50, N 8.61; found C 70.33, H 6.35, N 8.53.

Compound **7a** (2.16 g, 3.33 mmol) was treated with BOC-anhydride (0.88 g, 4 mmol) in CH_2Cl_2 at room temperature for 4 h and **7b** was obtained in a yield of 75%, m.p. 248−249 °C (BuOH). − ^{1}H NMR (CDCl$_3$): δ = 8.61 (t, 2 H, NH), 7.58 (s, 2 H, OH), 7.13 (d, 4 H, ArH), 6.85 (d, 4 H, ArH), 6.79 (t, 2 H, ArH), 6.70 (t, 2 H, ArH), 4.60 (s, 4 H, OCH$_2$CO), 4.20 and 3.84 (d, *J* = 13.4 Hz, 4+4 H, ArCH$_2$Ar), 3.55 (br, 4 H, HNCH$_2$), 3.23 (br; 2 H, HNCH$_2$), 2.85 (br, 4 H, NCH$_2$), 2.66 (br, 2 H, NCH$_2$), 1.43 (s, 9 H, *t*Bu). − ^{13}C NMR (CDCl$_3$): δ = 168.6 (C=O), 152.2, 151.1, 132.4, 129.7, 129.2, 127.8, 126.6, 120.7 (Ar), 78.7 (*t*Bu−C), 75.0 (OCH$_2$), 55.0, 53.3 (NCH$_2$), 39.8, 38.9 (NHCH$_2$) 31.5 (ArCH$_2$Ar), 28.6 (*t*Bu−CH$_3$). − $C_{43}H_{50}N_4O_8$ (750.89): calcd. C 68.78, H 6.71, N 7.46; found C 68.46, H 6.78, N 7.52.

Compounds 9a,b: A solution of triethyl ester **8** (8 mmol, 5.46 g) and tris(2-aminoethyl)amine (24 mmol, 3.51 g, 3.6 mL) in a mixture of methanol (100 mL) and toluene (100 mL) was allowed to stand at room temperature for 6 days. The solution was then concentrated at reduced pressure, the residue suspended in methanol and filtered to give **9a** as a white solid. Yield 64%, M.p. 360−362 °C. − ^{1}H NMR (CDCl$_3$): δ = 8.17 (t, 2 H, NH), 8.01 (t, 1 H, NH), 7.21 (d, 2 H, ArH), 7.11 (d, 2 H, ArH), 6.98 (d, 2 H, ArH), 6.93 (t, 1 H, ArH), 6.83 (d, 2 H, ArH), 6.80 (t, 1 H, ArH), 6.74 (t, 2 H, ArH), 6.35 (s, 1 H, OH), 4.62 and 4.23 (d, *J* = 15.7 Hz, 2+2 H, OCH$_2$), 4.43 (s, 2 H, OCH$_2$), 4.41 and 3.45 (d, *J* = 13.4 Hz, 2+2 H, ArCH$_2$Ar), 4.14 and 3.43 (d, *J* = 13.4 Hz, 2+2 H, ArCH$_2$Ar), 3.47 (br, 4 H, HNCH$_2$), 3.38 (br, 2 H, HNCH$_2$), 3.01 and 2.66 (m, 2+2 H, NCH$_2$), 2.77 (br, 2 H, NCH$_2$). − ^{13}C NMR (CDCl$_3$): δ = 169.2, 168.5 (C=O), 155.0, 152.2, 152.0, 134.6, 133.8, 131.5, 130.1, 129.3, 129.0, 128.2, 125.7, 125.2, 121.1 (Ar), 75.8, 75.2 (OCH$_2$), 55.8, 52.8 (NCH$_2$), 39.1, 38.8 (HNCH$_2$), 31.4, 29.7 (ArCH$_2$Ar). − $C_{40}H_{42}N_4O_7$ (690.79): calcd. C 69.55, H 6.13, N 8.11; found C 69.14, H 6.19, N 8.04.

The toluene solution (80 mL) of **9a** (1.45 g, 2.1 mmol) and Lawesson's reagent (1.58 g) was refluxed for 5 h. When the reaction was complete (monitored by TLC) the solvent was evaporated to dryness, the residue triturated with methanol and filtered to give **9b** as a pale yellow solid. Yield 97%, m.p. 259−260 °C. − ^{1}H NMR (CDCl$_3$): δ = 9.77 (t, 2 H, NH), 9.45 (t, 1 H, NH), 7.24 (d, 2 H, ArH), 7.11 (d, 2 H, ArH), 6.96 (t, 1 H, ArH), 6.95 (d, 2 H, ArH), 6.82 (t, 1 H, ArH), 6.79 (d, 2 H, ArH), 6.71 (t, 2 H, ArH), 5.94 (s, 1 H, OH), 4.99 and 4.63 (d, *J* = 17.0 Hz, 2+2 H, OCH$_2$), 4.81 (s, 2 H, OCH$_2$), 4.34 and 3.45 (d, *J* = 12.7 Hz, 2+2 H, ArCH$_2$Ar), 3.98 and 3.44 (d, *J* = 13.7 Hz, 2+2 H, ArCH$_2$Ar), 3.94 and 3.89 (br, 2+2 H, HNCH$_2$), 3.80 (br, 2 H, HNCH$_2$), 3.32 and 2.79 (m, 2+2 H, NCH$_2$), 3.07 (br, 2 H, NCH$_2$). − ^{13}C NMR (CDCl$_3$): δ = 197.7, 196.5 (C=S), 154.4, 151.6, 151.5, 134.6, 133.6, 131.3, 130.1, 129.4, 129.2, 129.1, 128.4, 125.8, 125.4, 121.5 (Ar), 81.9, 81.3 (OCH$_2$), 55.4, 51.7 (NCH$_2$), 44.6, 44.4 (HN CH$_2$), 31.4, 29.9 (ArCH$_2$Ar). − $C_{40}H_{42}N_4O_4S_3$ (738.99): calcd. C 65.01, H 5.73, N 7.58; found C 65.42, H 5.69, N 7.61.

Compound 10: A solution of triethyl ester **8** (6 mmol) and ethylenediamine (30 mmol) in a mixture of methanol (90 mL) and toluene (90 mL) was allowed to stand at room temperature for 3 days. After completion of the reaction the solution was concentrated at reduced pressure. The residue was suspended in methanol and filtered to give a white solid. Yield 54%, m.p. 294−295 °C. − ^{1}H NMR (CDCl$_3$): δ = 8.47 (t, 2 H, NH), 8.22 (s, 1 H, OH), 7.16 (d, 2 H, ArH), 7.15 (d, 2 H, ArH), 7.08 (d, 2 H, ArH), 7.04 (d, 2 H, ArH), 6.89 (t, 2 H, ArH), 6.85 (t, 1 H, ArH), 6.72 (t, 1 H, ArH), 4.73 and 3.49 (d, *J* = 12.7 Hz, 2+2 H, ArCH$_2$Ar), 4.68 and 4.32 (d, *J* = 13.7 Hz, 2+2 H, OCH$_2$), 4.66 (s, 2 H, OCH$_2$), 4.11 and 3.48 (d, 2+2 H, *J* = 13.4 Hz; ArCH$_2$Ar), 3.78 (s, 3 H, OCH$_3$), 3.70 (m, 4 H, NCH$_2$). − ^{13}C NMR (CDCl$_3$): δ = 170.2, 168.4 (C=O), 155.4, 152.2, 150.1, 135.4, 134.5, 133.0, 130.0, 129.7, 129.2, 129.0, 127.9, 126.4, 125.4, 120.9 (Ar), 74.9, 73.3 (OCH$_2$), 52.4 (OCH$_3$), 39.0 (NCH$_2$), 31.7, 30.5 (ArCH$_2$Ar). − $C_{37}H_{36}N_2O_8$ (636.70): calcd. C 69.80, H 5.70, N 4.40; found C 70.18, H 5.60, N 4.46.

Acknowledgments

We are indebted to the Ministy of Education (FKFP, Project No. 348/1997) and the Hungarian National Science Foundation (OTKA Project No. T 032180) for financial support for this research. B.B. thanks Pannonplast Ltd. for a grant.

---

[1] I. Bitter, A. Grün, B. Balázs, G. Tóth, Gy. Horváth, L. Töke, *Synth. Comm.* **1999**, *29*, 3905−3912.

[2] I. Bitter, A. Grün, G Tóth, B. Balázs, L. Töke, *Tetrahedron* **1997,** *53*, 9799−9812.

[3] I. Bitter, A. Grün, G. Tóth, B. Balázs, Gy. Horváth, L. Töke, *Tetrahedron* **1998,** *54*, 3857−3870.

[4] K. Tóth, B. T. T. Lan, J. Jeney, M. Horváth, I. Bitter, A. Grün, B. Ágai, L. Töke, *Talanta* **1994**, *41*, 1041−1049.

[5] I. Bitter, A. Grün, G. Tóth, Á. Szöllösy, Gy. Horváth, B. Ágai, L. Töke, *Tetrahedron* **1996**, *52*, 639−646.

[6] M. Kubinyi, I. Mohammed-Ziegler, A. Grofcsik, I. Bitter, W. J. Jones, *J. Mol. Structure* **1997**, *408/409,* 543−546.

[7] I. Bitter, A. Grün, L. Töke, G. Tóth, B. Balázs, I. Mohammed-Ziegler, A. Grofcsik, M. Kubinyi, *Tetrahedron* **1997,** *53*, 16867−16876.

[8] Y. Kubo, S. Maruyama, N. Ohhara, M. Nakamura, S. Tokita, *J. Chem. Soc., Chem. Commun.* **1995**, 1727−1728.

[9] Y. Kubo, S. Maeda, S. Tokita, M. Kubo, *Nature* **1996**, *382*, 522−524.

[10] Y. Kubo, *Synlett* **1999**, 161−174.

[11] J. F. Corbett, *J. Chem. Soc. (B)* **1970**, 1502−1509.

[12] I. Pallagi, A. Toró, Ö. Farkas, *J. Org. Chem.* **1994**, *59*, 6543−6557.

[13] W. Willker, D. Leibfritz, R. Kerssebaum, W. Bermel, *Magn. Reson. Chem.* **1993**, *31*, 287−292.

[14] R. E. Hurd, *J. Magn. Reson.* **1990**, *87*, 422−426.

[15] A. Bax, D. G. Davis, *J. Magn. Reson.* **1985**, *63*, 207−213.

[16] P. D. Beer, P. A. Gale, Z. Chen, M. G. B. Drew, J. A. Heath, M. I. Ogden, H. R. Powell, *Inorg. Chem.* **1997**, *36*, 5880−5893.

[17] A. Casnati, E. Comelli, M. Fabbi, V. Bocchi, G. Mori, F. Ugozzoli, A. M. M. Lanfredi, A. Pochini, R. Ungaro, Recl. Trav. Chim. Pays-*Bas* **1993**, *112*, 384.

[18] C. D. Gutsche, *Calixarenes, monographs in supramolecular chemistry*, the Royal Society of Chemistry, Cambridge, **1989**, Vol. 1.

[19] C. Jaime, J. Mendoza, P. Prados, P. M. Nieto, C. Sanchez, *J. Org. Chem.* **1991**, *56*, 3372−3376.

[20] W. Verboom, S. Datta, Z. Asfari, S. Harkema, D. N. Reinhoudt, *J. Org. Chem.* **1992**, *57*, 5394−5398.

[21] H. Günther, *NMR Spectroscopy*, 3nd Ed., Georg Thieme Verlag Stuttgart·New York, **1992**.

[22] Ch. L. Perrin, T. J. Dwyer, *Chem. Rev.* **1990**, *90*, 935−967.

[23] E. Pretsch, T. Clerc, J. Seibl, W. Simon, *Tabellen zur Structuraufklärung organischer Verbindungen*, Springer-Verlag, Berlin·Heidelberg·New York, **1981**.

[24] E. M. Collins, M. A. McKervey, S. J. Harris, *J. Chem. Soc., Perkin Trans. 1* **1989**, 372−374.

[25] H. Shimizu, K. Iwamoto, K. Fujimoto, S. Shinkai, *Chem. Lett.* **1991**, 2147−2150.

[26] I. Mohammed-Ziegler, B. Poór, M. Kubinyi, A. Grofcsik, A. Grün, I. Bitter, *J. Incl. Phenom. Mol. Recogn.* **1999**, *35*, 349−352.

Received April 21, 2000
[O00204]