SOLVENT EFFECT ON THE ^{1}H NMR SPECTRA OF A PYRIDINOCALIX(4)ARENE DERIVATIVE AND ITS PROTONATION CONSTANTS IN METHANOL

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Dedicated to Prof. Pedro J. Aymonino on the occasion of his 75th birthday

Abstract

*The solvent effect on the ^{1}H NMR spectra of 5, 11, 17, 23 tetra-tert-butyl-25, 26, 27, 28-tetra-[2-(4-pyridyl) methoxy]calix(4) arene, **1c** in a wide range of solvents with different dielectric constants was investigated and the results are discussed. It is shown that the ^{1}H NMR spectrum of this macrocycle is sensitive to the nature of the solvent. In all solvents the ligand shows a distorted 'cone' conformation..The aromatic protons show the most significant deshielding effect in acetonitrile, nitromethane and pyridine relative to chlroform, which may be attributed to the interaction of these solvents (acetonitrile,nitromethane) through their methyl groups with the hydrophobic cavity of the ligand. For pyridine, π-π interactions between the pyridyl groups and this solvent may occur.*

*The protonation constants of this ligand in methanol were derived from potentiometric titration data in this solvent. The results are compared with those for structural isomers of **1c** as well as with those previously reported for lower rim calix(4)arene derivatives containing aliphatic and alicyclic amines as pendant arms. Protonation constant data show that the affinity of the latter to interact with the proton is greater than that of the former macrocycle in methanol.*

Final conclusions are given.

Resumen

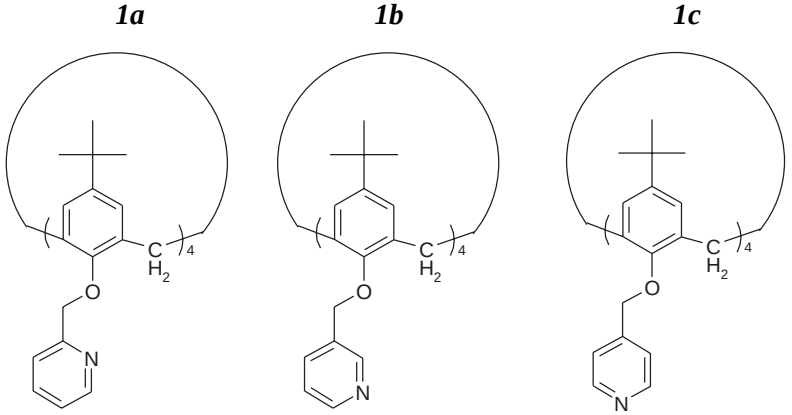
*El efecto del solvente en los espectros ^{1}H RMN de 5, 11, 17, 23 tetra-tert-butilo-25, 26, 27, 28-tetra-[2-(4-piridil)metoxi]cálix(4)areno, **1c**, en un amplio rango de solventes con distintas constantes dieléctricas fue investigado y los resultados son discutidos. Se muestra que el ^{1}H RMN espectro de este macrociclo es sensible a la naturaleza del solvente. En estos solventes la conformación del ligando corresponde a un cono distorsionado. Los desplazamientos químicos mas pronunciados de los protones aromáticos con respecto a cloroformo son observados en acetonitrilo, nitrometano y piridina. En los dos primeros*

solventes estos desplazamientos pueden ser atribuídos a una interacción entre los grupos metilos de estos solventes con la cavidad hidrofóbica del ligando. En piridina los resultados sugieren la posibilidad de interacciones del tipo π-π. Las constantes de protonación de este ligando en metanol fueron derivadas de datos obtenidos de titulaciones potenciométricas en este solvente. Los resultados son comparados con aquellos correspondiente al de un isómero estructural de ***1c*** *como también con aquellos reportados en la literatura para derivados de calix(4)arenos conteniendo aminas alifáticas y alicíclicas en el borde inferior del macrociclo. Los valores de las constantes de protonación muestran que la afinidad de estos últimos para interaccionar con el protón es mucho mayor que aquellos correspondiente a los piridino-calix(4)arenos in metanol. Conclusiones finales son dadas.*

Introduction

Calixarenes [1-5] are excellent platforms for the design of receptors for binding ions and molecules. Depending of the nature of the functional groups at the lower and upper rim, calixarene derivatives show different and interesting complexing abilities.

Pyridinocalix(4)arenes (**1a, 1b, 1c)** have received considerable attention in recent years. Three structural isomers of pyridinocalix(4)arenes are known.



The ability of these ligands to interact with hard and soft metal cations is largely dependent on the position of the nitrogen atoms of the pyridyl rings with respect to the ethereal oxygens. Thus in previous papers we have reported the solution properties of 2-pyridinocalix(4)arene (**1a**) and its structural isomer (**1b**) [7-9]. It was shown that while the former interacts with alkali-metal cations to form 1:1 (metal cation-ligand) complexes, the latter is unable to enter complexation with these cations. This was attributed to an increase in the distance between the pyridyl nitrogen and the ethereal oxygen in moving from **1a** to **1b**. X-ray crystallographic evidence of alkali-metal complexes of **1a** have been reported [8]. As a continuation of this research the work goals of this paper are:

(i) To assess the effect of the solvent on the proton chemical shifts of **1c** by carrying out ^{1}H NMR measurements in various solvents at 298 K given that the presence of a hydrophobic cavity in calix(4)arene derivatives may permit interaction with the solvent molecules. It is therefore of considerable interest to investigate the extent in which the different donor-

acceptor abilities of various solvents as well as other properties such as dielectric constant, dipole moments and other factors lead to shift changes in the ^1H NMR signals of 4 pyridinocalix(4)arene that are proportional to the extent of the interaction.

(ii) Interaction of **1c** with the proton by ^1H NMR studies in CD_3OD followed by the determination of the protonation constants in the same solvent at 298.15 K.

Experimental Part

The compound 5,11,17,23 – tetra-*tert*-butyl-25,26,27,28-tetra-[2-(4-pyridyl) methoxy]calix(4)arene, **1c**, was synthesised and characterised as described elsewhere [10].

^1H NMR measurements

This technique was used to investigate the interaction of a variety of solvents with **1c** and to study the conformational changes that this ligand undergoes in these media. ^1H NMR measurements were conducted at 300 MHz in the following deuterated solvents, chloroform ($CDCl_3$), acetone (CD_3COCD_3), nitromethane (CD_3NO_2), benzene (C_6D_6), pyridine (C_5D_5N), methanol (CD_3OD), nitromethane (CD_3NO_2) and dimethylsulfoxide (d_6-DMSO) (all purchased from Aldrich), at 298 K. Solutions of the sample of interest were prepared in 1 cm^3 in the appropriate deuterated solvent and placed in the 5 mm NMR tube using TMS as internal reference. ^1H NMR data were processed using the NUTS program [11]. Chemical shifts (δ ppm) and difference in the chemical shifts ($\Delta\delta = \delta - \delta_{CDCl3}$ ppm) with respect to $CDCl_3$ (as a reference solvent) were recorded.

Determination of the protonation constants of 1c in methanol at 298.15 K.
These were determined by potentiometry as discussed elsewhere [12].

Results and Discussion

(i) Interaction of 1c with the solvent: ^1H NMR studies.

The interaction that occurs between a solvent molecule and the hydrophobic cavity of calyx(4)arene derivatives was described as 'Allosteric effect'.[6] It is this kind of pre-organization of the hydrophilic cavity that contribute to the ability of the ligand to recognise selectively between its guests. This solvent-ligand interaction is best reflected by the difference in the chemical shifts of the hydrophobic cavity protons and those of the methylene bridging carbon in one solvent relative to another (reference solvent). Chemical shifts data for **1c** in the different solvents investigated are given in Table 1 at 298 K According to these data, the difference in the chemical shifts between the axial (H-5) and equatorial (H-6) protons of the methylene bridging carbon ($\Delta\delta_{ax\text{-}eq} = \delta_{ax.} - \delta_{eq.}$ ppm), suggest that in all cases **1c** exhibits a distorted 'cone' conformation ($\Delta\delta_{ax\text{-}eq}$ = 1.21, 1.17, 1.18, 1.24, 1.24, 1.12, 1.14 and 1.13 ppm in C_6D_6, $CDCl_3$, C_5D_5N, CD_3COCD_3, CD_3OD, CD_3CN, CD_3NO_2 and d6-DMSO, respectively).

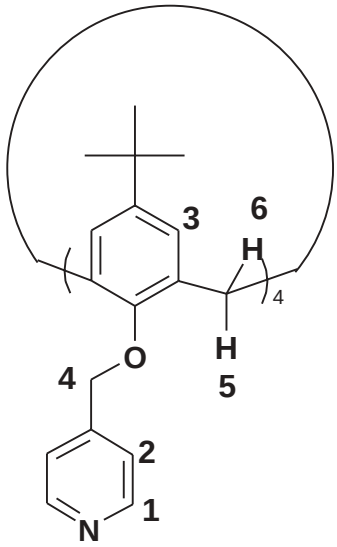


Table 1. *Chemical shifts in ppm for the proton signals of* ***1c*** *in different solvents at 298 K*

Solvent[a]	Dielectric constant	H-1	H-2	H-3	H-4	H-5[b]	H-6[c]	*t*-But
C_6D_6	-2.27	8.52	6.98	6.95	4.63	4.17	2.96	1.21
CD_3Cl	4.81[d]	8.47	7.22	6.78	4.85	4.12	2.95	1.08
C_5D_5N	13.2	8.68	7.44	7.15	5.02	4.47	3.29	1.27
CD_3COCD_3	20.7	8.43	7.37	6.92	4.98	4.30	3.06	1.12
CD_3OD	32.6	8.34	7.42	6.91	4.94	4.30	3.06	1.11
CD_3CN	36.7	8.43	7.20	7.18	4.81	4.14	3.02	1.18
CD_3NO_2	38.6	8.45	7.30	7.19	4.93	4.28	3.11	1.16
d_6-DMSO	46.7	7.26	6.29	5.81	3.79	3.16	2.03	1.45

a Abbreviations used; benzene C_6D_6; chloroform; $CDCl_3$ pyridine, C_5D_5N; acetone; CD_3COCD_3; methanol CD_3OD, acetonitrile; CD_3CN, nitromethane, CD_3NO_2; dimethylsueforide; d_6-DMSO

[b]H-5 = H axial [b]H-6 = H equatorial [d] determined at 293.15 K

On the other hand, a quick inspection of the chemical shifts for H-1 and 2, as well as those of the hydrophilic cavity, indicate that the nature of the solvent (protic or aprotic) [14, 15] is affecting both cavities.

Taking chloroform as the reference solvent, chemical shift changes ($\Delta\delta$ ppm) are calculated and these are shown in Table 2.

Table 2: *Chemical shifts changes in ppm for the proton signals of 1c in different solvents taking chloroform as the reference solvent at 298 K.*

Solvent[a]	H-1	H-2	H-3	H-4	H-5[b]	H-6[c]	$H_{t\text{-}But}$
C6D6	0.05	-0.24	0.17	-0.22	0.05	0.01	0.13
C_5D_5N	0.21	0.22	0.37	0.17	0.30	0.34	0.19
CD_3COCD_3	-0.04	0.15	0.14	0.13	0.13	0.11	0.04
CD_3OD	-0.13	0.20	0.13	0.09	0.13	0.11	0.03
CD_3CN	-0.04	-0.02	0.40	-0.04	-0.03	0.07	0.10
CD_3NO_2	-0.02	0.08	0.41	0.08	0.11	0.06	0.08
$d_{6\text{-}}$DMSO	-1.21	-0.93	-0.97	-1.06	-1.01	-0.92	0.37

A pronounced deshielding effect is observed for the H-3 proton (except in d6-DMSO), which suggest that these solvents interact with the hydrophobic cavity of 1c. Furthermore, the *tert*-butyl group protons show a deshielding effect in C_6D_6, CD_3CN and d6-DMSO ($\Delta\delta$ H-3= 0.13, 0.19, 0.10 and 0.37 ppm), while this effect is less pronounced in the other solvents ($\Delta\delta$ H-3 $\approx$ 0.05 ppm). Therefore, this indicates that d6-DMSO might be forming an *exo*-complex with 1c ($\Delta\delta$ H-3 = -0.97 ppm while $\Delta\delta$ $H\text{-}_{t\text{-}Bu}$ = 0.37 ppm).

On the other hand, more bulky solvents (C_6D_6 and C_5D_5N) than d6-DMSO, have produced a deshielding effect for both protons H-3 and $H\text{-}_{t\text{-}Bu}$, suggesting that the interaction between the solvent and the hydrophobic cavity is of the π–π type which can be the result of *exo*- or *endo*-complex formation with 1c.

The deshielding effect observed for the H-5 and 6 in the solvents investigated (except d6-DMSO) relative to $CDCl_3$ and the $\Delta\delta_{ax\text{-}eq}$ (discussed above), indicate that the hydrophobic cavity of **1c** does not undergo a pronounced conformational change in these solvents with respect to $CDCl_3$ at 298 K. This might be due to the rigidity of the hydrophobic cavity caused by the bulky pendant arms (pyridine group) in the hydrophilic cavity, being incapable of getting closer to each other due to the electrostatic effect.

An interesting observation is that on increasing the dielectric constant of the solvent, the signal of the H-1 proton of the pyridine ring (see Table 1) shifts upfield to a smaller extent that the signal of the H-2 proton.

The shielding effect observed for H-1 (except C_6D_6 and C_5D_5N) suggest that not all solvents interact with the pyridyl groups in the hydrophilic cavity. On the other hand, a pronounced deshielding effect (H-1,2 and 4) is recorded in C_5D_5N suggesting a π-π interaction between the pyridyl groups and this solvent. For C_6D_6 slight deshielding effect is observed for H-1 and a pronounced shielding effect for H-2 and H-4 indicating that no interaction is taking place between this solvent and the hydrophilic cavity of **1c**.[16].

The chemical shift changes of **1c** in CD_3OD and CD_3COCD_3 relative to $CDCl_3$ show a deshielding effect for the H-2 and the H- 4 signals. This suggests an interaction between these

solvents and the pendant arms at the lower rim of **1c**. In acetone which is a dipolar aprotric solvent with a moderate dielectric constant, broadening of the signals for H-1 and H-2 occurs. The H-1 signal shifts upfield but the H-2 signal shifts downfield compared to C_6D_6 and $CDCl_3$. This may indicate specific interactions at sites away from the nitrogen of the pyridine ring. In d6-DMSO which is a solvent with moderate dielectric constant and a high donor number [13,14], shielding effects are observed for all the protons of the hydrophilic cavity suggesting that no interaction is taking place with the pendant arms of **1c** relative to $CDCl_3$ at 298 K.

In summary the conclusions are as follows,

i) In all solvents the ligand shows a distorted 'cone' conformation.

ii) The aromatic protons (H-3) show the most significant deshielding effect in CD_3CN, CD_3NO_2 and C_5D_5N relative to $CDCl_3$, which may be attributed to the interaction of these solvents (CD_3CN, CD_3NO_2) through their methyl groups with the hydrophobic cavity of the ligand. This interaction has been observed for various calixarene derivatives and acetonitrile [18,19.]. In C_5D_5N a π-π interaction between the pyridyl groups and this solvent is likely to occur..

(ii) Protonation constants of 1c in methanol at 298.15 K

The potentiometric titration curve of **1c** with a methanolic solution of tetramethylammonium hydroxide is shown in Fig 1 as a plot of E/volts against the base/ligand ([OH-]/[**lc**]) ratio. Also included in this figure is its first derivative.

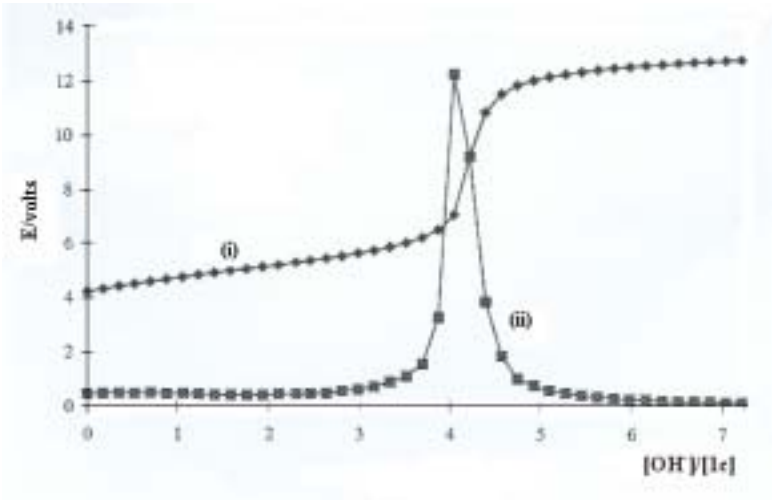


***Figure 1**. Potentiometric titration of 1c with tetramethyl ammonium hydroxide in methanol at 298.15 K*

The experimental data indicate that the inflection point in (i) or the maximum in (ii) corresponds to the following stoichiometry.

$$\mathbf{1c}\ (MeOH) + 4\ H^+\ (MeOH) \rightarrow H_4\mathbf{1c}^{4+}\ (MeOH) \qquad (\mathbf{1})$$

Potentiometric data were analysed by the use of the MINIQUAD program [20,21]. The calculated protonation constants of **1c** in methanol are shown in Table 3 and these are referred to the processes described by eqs 2-5.

$$\underline{\mathbf{1c}}\ (MeOH) + H^+\ (MeOH) \xrightarrow{K_{P1}} [H\mathbf{1c}]^+\ (MeOH) \qquad (\mathbf{2})$$

$$[H_1\mathbf{c}]^+\ (MeOH) + H^+\ (MeOH) \xrightarrow{K_{P2}} [H_2\mathbf{1c}]^{2+}\ (MeOH) \qquad (\mathbf{3})$$

$$[H_2\mathbf{1c}]^{2+}\ (MeOH) + H^+\ (MeOH) \xrightarrow{K_{P3}} [H_3\mathbf{1c}]^{3+}\ (MeOH) \qquad (\mathbf{4})$$

$$[H_3\mathbf{1c}]^{3+}\ (MeOH) + H^+\ (MeOH) \xrightarrow{K_{P4}} [H_4\mathbf{1c}]^{4+}\ (MeOH) \qquad (\mathbf{5})$$

Table 3.*Protonation constants of 1c in methanol at 298.15 K (expressed as log Kp) and overall protonation constants (expressed as log β) in the same solvent.*

$\log K_{P_1}$	5.91	$\text{Log } \beta_1$	5.91
$\log K_{P_2}$	5.35	$\text{Log } \beta_2$	11.26
$\log K_{P_3}$	5.03	$\text{Log } \beta_3$	16.29
$\log K_{P_4}$	4.70	$\text{Log } \beta_4$	20.99

The overall protonation constants, log β corresponds to the following processes.

$$\mathbf{1c}\ (MeOH) + H^+\ (MeOH) \xrightarrow{\beta_1} [H\mathbf{1c}]^+\ (MeOH) \qquad (\mathbf{6})$$

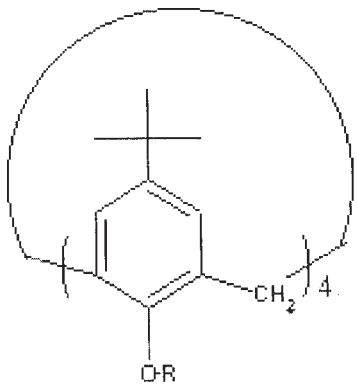
$$\mathbf{1c}\ (MeOH) + 2H^+\ (MeOH) \xrightarrow{\beta_2} [H_2\mathbf{1c}]^{2+}\ (MeOH) \qquad (\mathbf{7})$$

$$\mathbf{1c}\ (MeOH) + 3H^+\ (MeOH) \xrightarrow{\beta_3} [H_3\mathbf{1c}]^{3+}\ (MeOH) \qquad (\mathbf{8})$$

$$\mathbf{1c}\ (MeOH) + 4H^+\ (MeOH) \xrightarrow{\beta_4} [H_4\mathbf{1c}]^{4+}\ (MeOH) \qquad (\mathbf{9})$$

As the difference between the first and fourth protonation constants is only 1.21 units, it is reasonable to assume that the pyridine groups behave independently from each other with respect to protonation, otherwise protonation of one pyridine residue would markedly affect the basicity of another and give rise to significant pK differences [12].

If the protonation constants of **1c** are compared with those of **1b** (Table 4), it is noted that the oxygen of the ether group plays a key role in the acid-base properties of these derivatives. Thus the latter derivative is less basic than the former due to the close proximity of the pyridine nitrogen to the electron withdrawing ethereal oxygen. When the protonation constants of **1c** are compared to the corresponding values of alkylamino calix(4)arenes (**1d-1g**) (Table 4) dramatic changes in basic properties are observed.



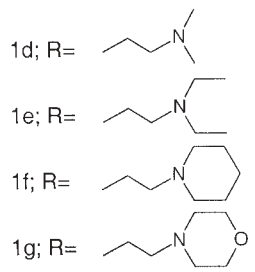


Table 4: *Protonation Constants of lower rim pyridinocalix(4)arenes (1b,1c), aliphatic (1d, 1e) and alicyclic (1f, 1g,) amino calix(4)arene derivatives in methanol at 298.15 K*

Derivative	log K_{P1}	log K_{P2}	log K_{P3}	log K_{P4}
1b	5.15	4.52	4.11	3.59
1c	5.91	5.35	5.03	4.70
1d	9.40	8.44	8.24	7.67
1e	9.48	8.96	8.69	8.10
1f	9.35	9.01	8.72	8.33
1g	7.49	6.93	6.93	5.98

Thus while dimethylaminocalix(4)arene, **1d**, has a value of 7.67 for log K_{p4}, that for **1c** is 4.70. The increased basicity of the alkylamines relative to pyridino calixarenes (**1c**, **1b**) parallels that observed for similar non-calixarene derivatives (eg alykylamines vs pyridines) and may be attributed to interaction of the pyridine nitrogen lone pair with the aromatic sextet [10]. In the case of the morpholine calix(4)arene, **1h**, the influence of the ring oxygen decreases the basic properties as expected. Species distribution curves as a function of pH were obtained for **1c** using a MINIQUAD computer program. As the pH changes from 3.5 to 7, the composition of the solution changes from one containing protonated forms of the ligand to one containing the unprotonated form. At a pH ≅ 4.7, the major species in solution is $[H_3\mathbf{1c}]^{3+}$ while at pH 5.2 is $[H_2\mathbf{1c}]^{2+}$ and at pH 5.6 it is $[H_1\mathbf{c}]^{+}$.

The complexation ability of **1c** for metal cations in non-aqueous media (acetonitrile and methanol) investigated by ^{1}H NMR, conductimetry, potentiometry and calorimetry is under investigation.[22]

Conclusions

From the above results it is concluded that:

(i) the variation in the chemical shifts of **1c** with the solvent will have implications on the thermodynamics of complexation of this ligand with metal cations particularly if the solvent

is hosted in the hydrophobic cavity of the ligand and as a result it may exert an allosteric effect on the hydropholic cavity which may lead to a re-organisation of the hydrophilic and thus unexpected recognition ability.

(ii) The position of the ethereal oxygen relative to the pyridyl nitrogen affects the basicity of the ligand. As expected calix(4)arene amino derivatives containing alicyclic and aliphatic amino groups **(1d –1g)** show a much higher basicity than pyridino calix(4)arenes.

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