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Young Ju Lee[a]; Ki Deok Park[a]; Hyoung Min Yeo[b]; Seung Whan Ko[b]; Byung Ju Ryu[b]; Kye Chun Nam[b]
[a] Korea Basic Science Institute, Gwangju Center, Gwangju, South Korea [b] Department of Chemistry, Chonnam National University, Gwangju, South Korea

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The Molecular Recognition of Amines with Calix[6]arene: Conclusive X-ray and NMR Evidence for *Endo* and *Exo* Complex Formation between Calix[6]arene and Amines

YOUNG JU LEE[a], KI DEOK PARK[a], HYOUNG MIN YEO[b], SEUNG WHAN KO[b], BYUNG JU RYU[b] and KYE CHUN NAM[b,*]

[a]*Korea Basic Science Institute, Gwangju Center, Gwangju 500-757, South Korea;* [b]*Department of Chemistry, Chonnam National University, Gwangju 500-757, South Korea*

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Calix[6]arene formed an *endo*-complex with piperidine and its inclusion properties were investigated by NMR spectroscopy and X-ray crystallography. Especially, the DOSY spectrum showed that piperidine formed a unique complex with calix[6]arene.

Keywords: Calix[6]arene; Amine recognition; *Exo* complex; *Endo* complex; DOSY

INTRODUCTION

Ammonium ions play a fundamental role in a wide range of chemical and biological processes [1–4], and some are crucial in the medical field [5–7], which makes the recognition and sensing of amines a matter of great interest.

Since the first report of Gutsche's basic work on the interaction between calixarenes and amines [8], several papers have dealt with the thermodynamic and electrochemical aspects of these interactions [9–11]. Some X-ray crystallographic studies have been reported about the structure and the mode of complexation. Thuery *et al*. [12] reported the X-ray structure of the doubly deprotonated form of calix[6]arene with two protonated triethylamines as counter-ions in a distorted 1,2,3-alternate conformation. Recently, Nachtigall *et al*. [13] studied the interactions of *t*-butylcalix[6]arene with aliphatic amines by ^{1}H NMR and spectrophotometric titrations, and showed that calix[6]arene could be doubly deprotonated by aliphatic amines. Moreover, they reported that the extent of the second proton transfer was governed by the size of the substituent of the amine. The X-ray crystal structure of the dihexylammonium complex of the *p*-*t*-butylcalix[6]arene dianion confirmed its 1,2,3-alternate conformation and showed that one of the two ammonium moieties was encapsulated in the inner cavity of the calix[6]arene.

The interaction between calixarene and amines proceeds by the transfer of a proton from the calixarene to the amine, followed by the formation of an *endo*-calixarene complex as evidenced by the ^{1}H NMR spectroscopy. The apparent value of the chemical shift observed in such cases corresponds to the sum of the downfield shift induced by ion formation and the upfield shift caused by cation-π interaction. The stability of the conformations of unsubstituted calixarenes is determined by intramolecular hydrogen bond formation [14]. Only two phenolic groups have ionizable protons and these have p*K*a values of 4.76 and 3.44, respectively [15].

Herein, we report on the binding properties of calix[6]arene and various amines based on NMR spectroscopy and X-ray structure analysis. Piperidine formed a strong *endo*-complex with calix[6]arene due to the strong basicity and a compact shape.

RESULTS AND DISCUSSION

^{1}H NMR and T_1 Analysis

In order to investigate the interaction between calix[6]arene and amines, ^{1}H NMR analysis was carried out. Figure 1 shows the ^{1}H NMR spectra of

*Corresponding author. E-mail: kcnam@chonnam.ac.kr

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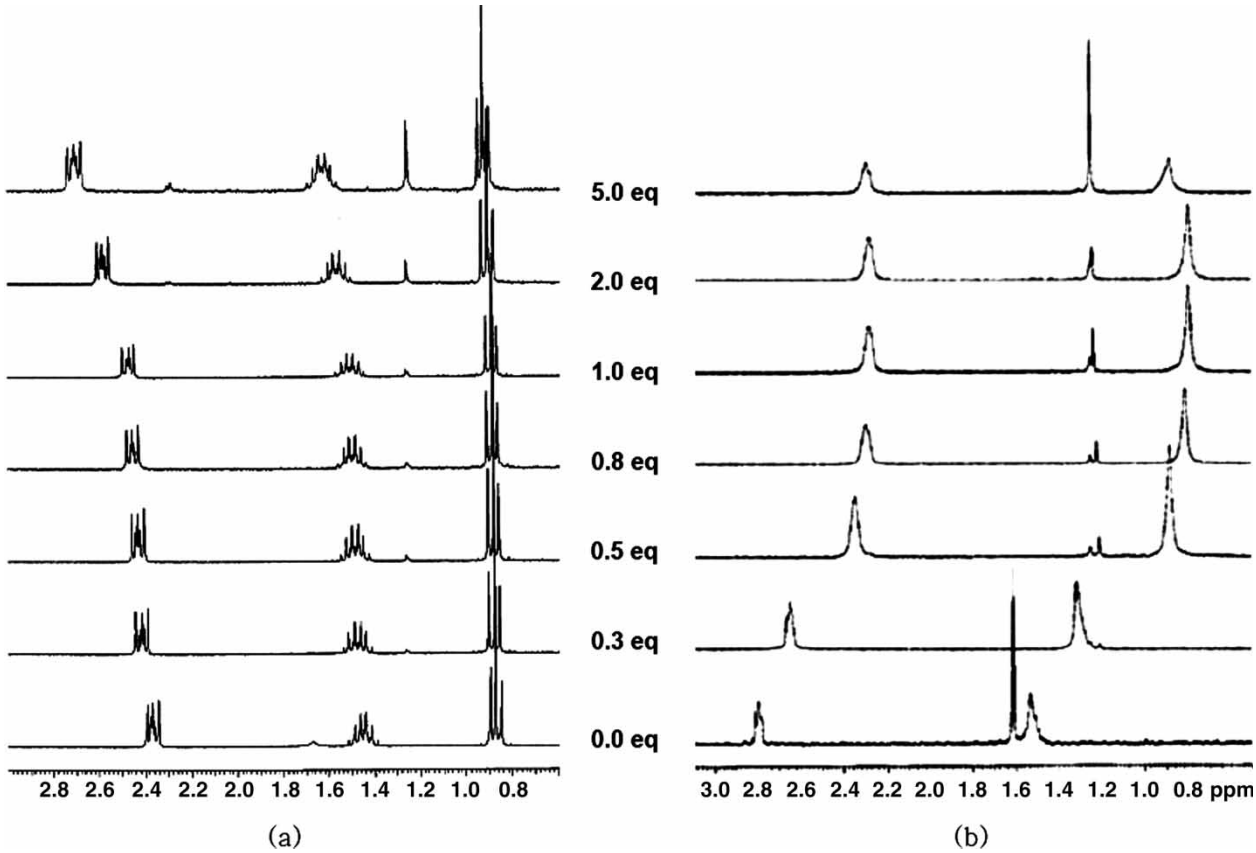

FIGURE 1 ^{1}H NMR spectra of tripropylamine (a) and piperidine (b) in the presence of calix[6]arene in $CDCl_3$. The numbers in the middle part indicate the number of molar equivalents of calixarene added.

tripropylamine and piperidine in the presence of calix[6]arene. The triplet at δ 2.37 ppm from methylene resonance of tripropylamine (Fig. 1a) was shifted downfield in the presence of calix[6]arene. On the other hand, the two broad singlets at δ 2.80 ppm and 1.52 ppm from piperidine (Fig. 1b) were shifted upfield considerably in the presence of calix[6]arene. Proton transfer from calix[6]arene to the amine forms an ammonium salt which makes the ^{1}H NMR resonance shift downfield as shown in Fig. 1a, suggesting that the tripropylamine salt forms an *exo*-complex with calix[6]arene. However, the large upfield shift of the proton resonance of piperidine in the presence of calix[6]arene indicates that the piperidine salt forms an *endo*-complex with calix[6]arene.

The chemical shifts of the various amines in the presence of calix[6]arene are summarized in Table I. A large upfield shift was observed in the case of piperidine (Δδ − 0.42 ppm and −0.60 ppm), cyclohexylamine (Δδ − 0.57 ppm), *n*-butylamine (Δδ −0.49 ppm, −0.27 ppm and −0.18 ppm), and DABCO (Δδ −0.21 ppm), indicating that when these amines were used as the guest, they were embedded inside the cavity. This proves that the *endo*-type complexes are formed by CH-π interactions. A slight upfield shift was observed in the case of *t*-butylamine (Δδ −0.12 ppm), morpholine (Δδ −0.06 ppm and −0.03 ppm), and diethylamine (Δδ −0.07 ppm and −0.15 ppm). In the case of diallylamine, and pyridine, the chemical shifts did not change at all. Downfield shifts were observed from triethylamine (Δδ +0.16 ppm and 0.15 ppm) and tripropylamine (Δδ +0.10 ppm, 0.06 ppm and 0.02 ppm). Obviously, it is necessary for the amines to have a certain basicity in order for them to withdraw protons from calix[6]arene. When the amine salts are formed, upfield or downfield shifts should be observed depending on whether *exo*- or *endo*-complexes are formed, respectively.

Figure 2 shows the relationship between amine basicity (p*K*a) and change in the chemical shift representing that amine basicity needs to be higher than p*K*a value of 10 for the formation of amine salts, except in the case of DABCO (p*K*a = 8.7). *Exo*-complexes were formed from triethylamine and tripropylamine, whereas *endo*-complexes were formed from piperidine, cyclohexylamine, *n*-butylamine and DABCO, indicating that the shape (or size) of the amine determines the type of complex that is produced. The relatively compact shape of piperidine and cyclohexylamine due to their cyclic form made them the best fit for the calix[6]arene cavity. On the other hand, the bulkiness of triethylamine and tripropylamine prevented them from forming an *endo*-complex with calix[6]arene. Even though DABCO has a low basicity

TABLE I Chemical shift and relaxation time values for the protons in various amines in the presence of an equimolar amount of calix[6]arene in $CDCl_3$

Amine			pKa	neat		Calix[6]arene		
				$\delta^{(a)}$	T_1	$\delta^{(b)}$	T_1	$\Delta\delta$ (c)
Primary amines	*n*-Butylamine	H-1		2.69	1.67	2.2	0.81	−0.49
		H-2	10.64	1.36	1.84	1.09	0.91	−0.27
		H-3		0.92	2.45	0.74	0.82	−0.18
	t-Butylamine	H-1	10.83	1.15	2.88	1.03	1.63	−0.12
	Cyclohexylamine	H-1	10.64	2.62	2.51	2.05	0.89	−0.57
Secondary amines	Piperidine	H-1	11.12	2.8	3.84	2.38	0.44	−0.42
		H-2		1.52	3.89	0.92	0.49	−0.60
	Morpholine	H-1	8.49	3.69	3.27	3.62	2.09	−0.06
		H-2		2.88	2.98	2.85	1.55	−0.03
	Diethylamine	H-1	10.8	2.69	2.76	2.62	0.74	−0.07
		H-2		1.13	3.04	0.98	1.06	−0.15
	Diallylamine	H-1		5.91	4.32	5.91	3.34	0
		H-2	9.29	5.18	3.94	5.18	3.91	0
		H-3		5.1	4.03	5.1	4.02	0
		H-4		3.26	2.7	3.26	2.03	0
Tertiary amines	Triethylamine	H-1	10.72	2.56	3.15	2.72	1.03	0.16
		H-2		1.04	3.36	1.19	1.2	0.15
	Tripropylamine	H-1		2.37	1.99	2.47	1.23	0.10
		H-2	10.66	1.45	2.42	1.51	1.51	0.06
		H-3		0.87	2.61	0.89	1.86	0.02
	DABCO	H-1	3.0/8.7	2.8	2.74	2.59	0.96	−0.21
	Pyridine	H-1	5.19	7.68	5.49	7.68	4.84	0

*Chemical shift (δ) and T_1 were measured with the concentration of 10 mM at 27°C using 300 MHz NMR spectrometer. (a) $\delta^{(a)}$ = Chemical shift of Amines in $CDCl_3$ (b) $\delta^{(b)}$ = Chemical shift of Amines in the presence of Calix[6]arene in $CDCl_3$ (c) $\Delta\delta = \delta^{(b)} - \delta^{(a)}$.

(p*Ka* = 8.7), its compact shape allowed it to form an *endo*-complex with calix[6]arene.

Decreases in the ^1H spin lattice relaxation time (T_1) values were observed upon the complexation of calix[6]arene with the ammonium ions. This is consistent with a decrease in the mobility of the complexed calixarene in comparison with the free ligand. A significant decrease in the value of T_1 was observed for piperidine (0.44 *sec* and 0.49 *sec* from 3.84 *sec* and 3.89 *sec*) when it was complexed with calix[6]arene, indicating that the *endo*-complex was formed. A decrease in the value of T_1 observed for *n*-butylamine was less than that of piperidine (0.81, 0.91 and 0.82 *sec* from 1.67, 1.84 and 2.45 *sec*). On the other hand, a relatively small decrease of T_1 was observed for tripropylamine (1.23, 1.51 and 1.86 *sec* from 1.99, 2.42 and 2.61 *sec*), suggesting that the ^1H spin lattice relaxation was relatively slow due to the formation of the *exo*-complex of tripropylamine.

NOESY Analysis

The formation of the *endo*-complex can be confirmed by the 2D-NOESY spectrum of the calix[6]arene-piperidine complex. The correlation peaks between piperidine and the aromatic protons of calix[6]arene are shown in Fig. 3. The two peaks for piperidine (2.39 ppm and 0.92 ppm) were correlated with H_a, H_b and H_c of calix[6]arene, clearly indicating that the *endo*-complex was formed with piperidine. However, in the case of triethylamine, no correlation peaks were observed between calix[6]arene and triethylamine in the NOESY anaysis.

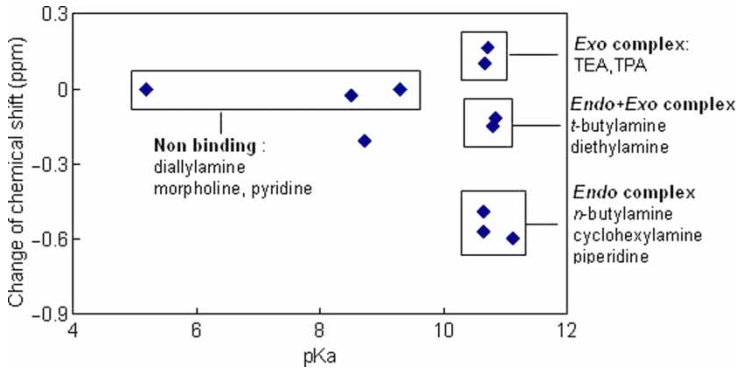

FIGURE 2 Relationship between amine basicity and change in the chemical shift.

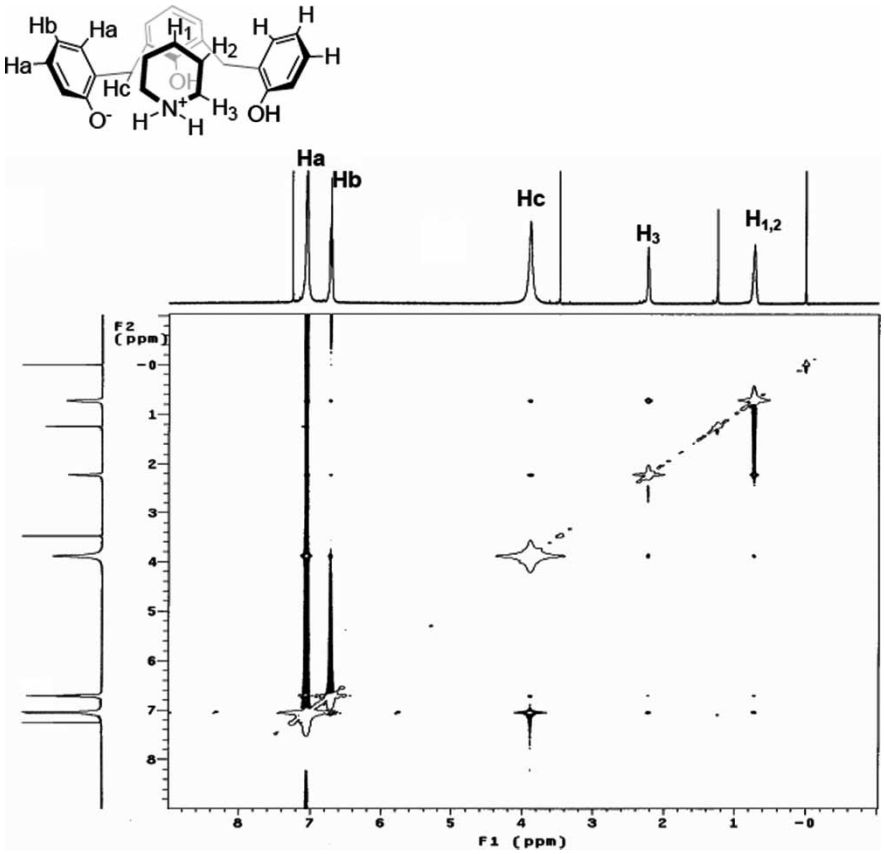

FIGURE 3 NOESY spectrum of the calix[6]arene-piperidine complex in $CDCl_3$.

X-ray Structure Analysis

The crystal structure confirms that the calix[6]arene dianion exists as the 1,2,3-alternate conformation and the salt with the piperidinium ion. The molecular structure and perspective drawing of the complex are depicted in Fig. 4.

The calix[6]arene dianions form a complex with two piperidium cations for each calix[6]arene unit. One piperidium ion (N2) is placed in the cavity formed by three aromatic units of the 1,2,3-alternate conformation and binds the oxygens (O2, O6) of two other phenolic units by hydrogen bonds. On the other hand, the other piperidium ion (N1) sits outside the cavity and interacts only with one phenolate (O4) through a strong hydrogen bond. The detailed hydrogen bonding data for the X-ray structure are shown in Table II. A strong hydrogen bond was formed between the piperidium situated outside of the cavity and the phenolic hydroxyl group, so that a short distance of 2.598 Å was observed for N1—O4. On the other hand, two hydrogen bonds were formed between the *endo*-piperidinium and calix[6]arene, corresponding to the N2—O2 and N2—O6 linkages with bond distances of 2.841 Å for 2.753 Å, respectively.

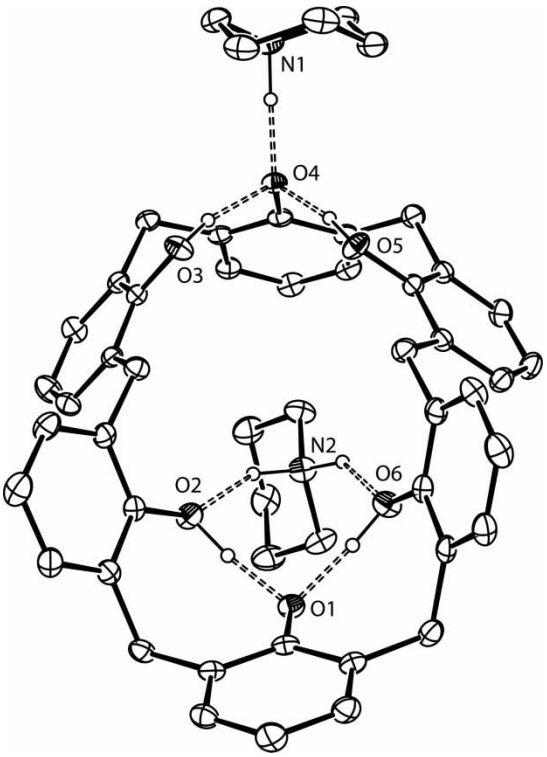

FIGURE 4 ORTEP projection of calix[6]arene dianion and piperidinium cations at the *endo*-calix (N2) and *exo*-calix (N1) positions. Hydrogen atoms involved in hydrogen bonds are only represented.

TABLE II Selected hydrogen bonds (Å) and angles (°) in the crystal structure of dipiperidium calix[6]arene diphenolate

D—H...A	d(D—H)	d(H...A)	d(D...A)	Angle(D—H...A)
N(2)—H(22N)...O(6)	1.03(3)	1.86(3)	2.753(3)	143(2)
N(2)—H(21N)...O(2)	1.02(3)	1.91(3)	2.841(3)	150(3)
N(1)—H(11N)...O(4)	1.05(3)	1.56(3)	2.598(2)	171(2)
O(6)—H(6O)...O(1)	0.96(3)	1.54(3)	2.496(2)	175(3)
O(5)—H(5O)...O(4)	0.99(3)	1.59(3)	2.562(2)	169(3)
O(3)—H(3O)...O(4)	0.89(3)	1.71(3)	2.583(2)	168(3)
O(2)—H(2O)...O(1)	1.03(3)	1.49(3)	2.518(2)	173(3)

Symmetry transformations used to generate equivalent atoms.

DOSY

Diffusion-ordered NMR spectroscopy (DOSY), which utilizes stimulated spin echo (SPE) and its variants, separate the NMR signals of the different components in a mixture on the basis of their diffusion characteristics [16–19]. In this method, a series of spin-echo spectra are measured with different pulsed field gradient strengths, and the signal decays are analyzed in order to extract a set of diffusion coefficients. The 2D DOSY spectrum displays the conventional chemical shifts in one dimension and the diffusion coefficients in the other dimension. The diffusion dimension reveals the distribution of molecular sizes and allows different molecular species to be identified.

Therefore, we performed a DOSY experiment for a mixture of calix[6]arene, piperidine and tripropylamine in chloroform-*d* in order to examine the mobility of the host-guest complex. Figure 5a represents a DOSY spectrum of an equimolar mixture of piperidine and tripropylamine (each of 10 mM) and Fig. 5b shows a DOSY spectrum of the same mixture of amines with calix[6]arene (10 mM). When observing the mobility of a host and two guest molecules (Fig. 5b), it was found that the self diffusion coefficients of calix[6]arene and piperidine are almost the same, whereas tripropylamine shows significantly different diffusion coefficients suggesting supramolecular motion by a host-guest complex formed only from calix[6]arene and piperidine. A striking decrease in self diffusion coefficient of piperidine as the host-guest complex forms after addition of calix[6]arene can be seen by comparing two DOSY spectra. DOSY analysis is regarded as a powerful tool for molecular recognition in this case, because of showing its high selectivity for piperidine resulted from the shape of amine.

The chemical shift of piperidine (c) in the complex of calix[6]arene, piperidine and tripropylamine was upfield shifted as compared to the chemical shift of piperidine (b) in the 1:2 complex of calix[6]arene and piperidine as shown in Fig. 6. This is assumed to be due to the fact that the occupancy of the outer space by tripropylamine made it more likely for piperidine to exist in the cavity. The X-ray results showed that two piperidine molecules existed in the outer or inner cavity of the host. Meanwhile the NMR chemical shift of piperidine corresponded to the average value of the *exo* and *endo* forms, resulting from their interchange in the solution state.

EXPERIMENTAL

Calix[6]arene was prepared according to the known procedure.[20] The $CDCl_3$ used for the NMR experiments was purchased from Aldrich and used without further purification. For the relaxation measurement, NMR samples were prepared in 5 mm o.d. tubes, which were sealed under vacuum after degassing by several freeze-pump-thaw cycles. The ^1H NMR spectra were recorded at 300 MHz on a Varian *Unity* 300 spectrometer and the chemical shifts of the ^1H NMR spectra were referenced to TMS. The spin-lattice relaxation times (T_1) for protons were measured in $CDCl_3$ by means of the conventional inversion recovery method, using at least 16 different delays between π and $\pi/2$ pulses, on a Varian *Unity* 300 spectrometer. Each T_1 value was estimated with the aid of an exponential fitting program. The 2D experiments such as NOESY and DOSY, were performed on a Varian INOVA Unity-500 spectrometer equipped with a Performa II PFG system (up to 60 G/cm in the z-direction). The 2D-NOESY spectra were measured in the phase-sensitive mode with mixing time and relaxation delay of 200 ms and 2.0 sec, respectively, at 27°C. The DOSY spectra were acquired with a single gradient (Z) at 25°C using a 5 mm triple resonance indirect detection PFG probe, and measured by incrementing the amplitude of the field gradient pulses in 16 steps ($0 \sim 46\,Gcm^{-1}$) using gcsteSL pulse sequence. The diffusion delay (Δ) and the gradient pulse length (δ) used were 50 ms and 2 ms, respectively.

Single crystals of the complex of *bis*-piperidinium calix[6]arene diphenolate were obtained by slow evaporation from chloroform. X-ray structure analysis was determined from data collection on a Bruker SMART CCD diffractometer equipped with graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å). The frame data were processed to give structure factors using the SAINT [21], and the structure was solved

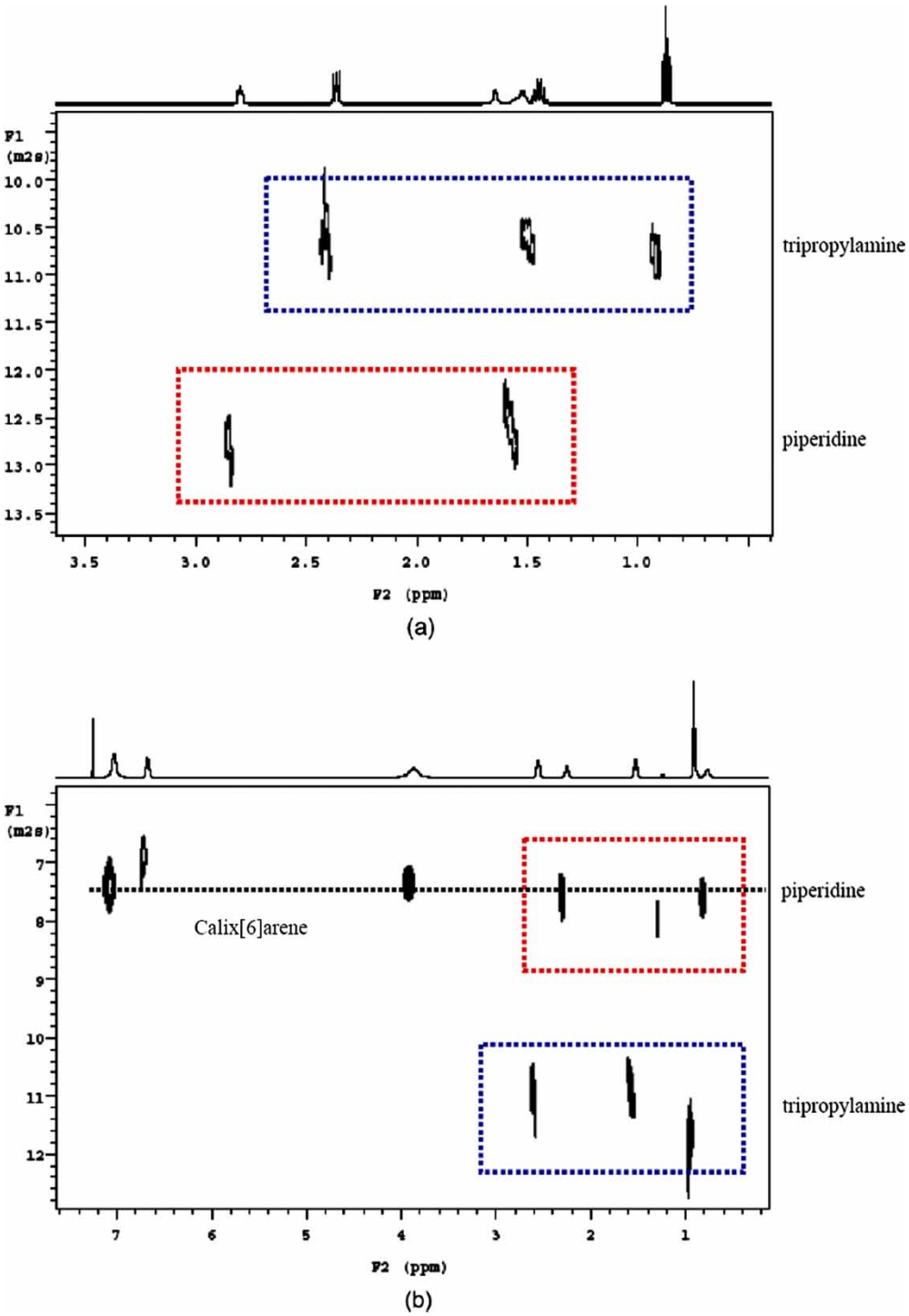

FIGURE 5 DOSY spectra in $CDCl_3$. (a) piperidine: tripropyl amine = 1:1, (b) piperidine: tripropylamine: calix[6]arene = 1:1:1.

by direct methods and refined by full-matrix least-squares on F^2 using SHELXTL software [22].

The positions of all hydrogen atoms including the hydrogen atoms on the ammonium(N1, N2) and phenolate (O2, O3, O5, O6) were found on the difference Fourier map and were refined with isotropic thermal displacement parameters.

Crystal data: $C_{53}H_{59}Cl_3N_2O_6$, M = 926.37 gmol^{-1}, 0.30 × 0.25 × 0.07 mm, monoclinic, $P2_1/c$, Z = 4, Absorption coefficient = 0.245 mm^{-1}, a = 8.5458(4)Å, b = 28.0454(12) Å, c = 19.9517(9) Å, α = 90°, β = 96.3470(10)°, γ = 90°, V = 4752.5(4) Å^3, 30410 reflections measured, R(int) = 0.0680, $R1$ = 0.0480, w$R2$ = 0.1013.

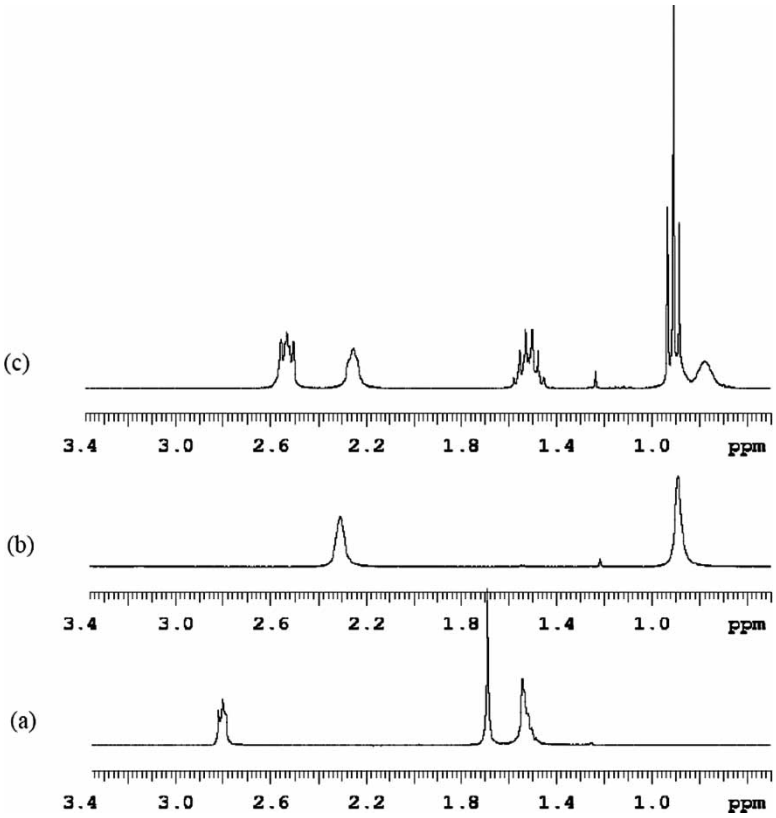

FIGURE 6 Comparison the chemical shift of piperidine in the ^{1}H NMR spectra (a) piperidine (b) 1:2 calix[6]arene: piperidine (c) 1:1:1 mixture of calix[6]arene, piperidine and tripropylamine.

Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 608666.

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