

## SYNTHESIS AND DISSOCIATION CONSTANTS OF CALIX(6)ARENE HYDROXAMIC ACIDS\*

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**Abstract** – Calix(6)arene hydroxamic acids (III) are synthesised for the first time by reacting calix(6)arene acid chloride(II) with substituted hydroxylamines at low temperature in the presence of sodium bicarbonate. The *p*-carboxycalix(6)arene(I) is obtained by an acid catalysed condensation reaction of *p*-hydroxybenzoic acid and formaldehyde. These calixarenes are characterised by melting point, UV, IR, <sup>1</sup>H NMR and mass spectra. The thermodynamic ionization constants of calixarene hydroxamic acids have been determined by a pH titration technique in dioxane-water media.

**Keywords** – Calixarene, calixhydroxamic acid, synthesis, ionization constant

### 1. INTRODUCTION

There has been a growing interest in calixarenes in recent years [1]. Calixarenes are phenol-formaldehyde cyclic oligomers made of several phenolic units corrected by methylene bridges [2]. Functional groups may be present in the para position with respect to the hydroxyl group of the phenol ring, and the hydroxyl group may be substituted. The phenolic OH group and para positions of phenols are called the lower and upper rim, respectively. Since calixarenes contain both polar and apolar molecular regions, they are an interesting class of synthetic host systems.

Calixarenes with four phenolic subunits have received the most attention to date. Calixarene derivatives with amide, ketones and esters at the lower rim have been significant cation affinities [3-5].

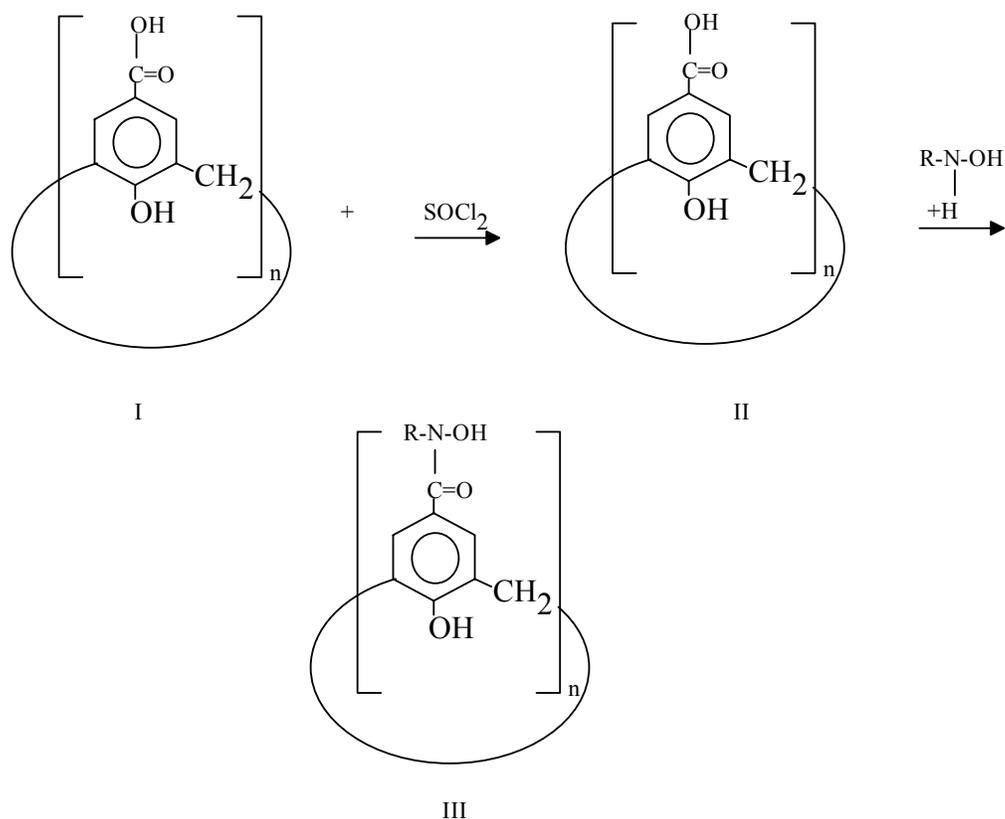
Generally these are synthesised by the acid or base catalytic reaction of *p*-tert-butylphenol and formaldehyde. Most of the calixarenes are of upper rim substitution, which were synthesized by debutylation[1, 6-8]. The synthesis is time consuming and involves several steps to get the desired substituted calixarenes. In the present investigation, a novel new one pot synthesis of calix(6)arene hydroxamic acid as a direct substitution in the upper ring of calixarene is reported (Fig. 1).

The thermodynamic dissociation constant of calixarene (I) [Fig. 1] and calixarene hydroxamic acids (III) have been determined.

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\*Received by the editor May 6, 2003 and in final revised form December 21, 2004

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III R= (a) -p-Cl-C<sub>6</sub>H<sub>5</sub> (b) -m-Cl-C<sub>6</sub>H<sub>5</sub> (c) -p-CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> (d) -m-CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> (e)-C<sub>6</sub>H<sub>5</sub> (f)-H

Fig. 1. Synthesis scheme of calix(6)arene hydroxamic acid

## 2. EXPERIMENTAL METHOD

Melting points were taken in a sealed capillary tube using a melting point apparatus and are uncorrected. <sup>1</sup>H NMR spectra were obtained on a Perkin Elmer EM-360 MHz NMR spectrometer using CDCl<sub>3</sub> + DMSO-d<sub>6</sub> as a solvent. The FAB mass spectra were recorded on a JEOL 3 X 102/DA 6000 mass spectrometer using xenon (6 KV, 10 mA) as the FAB gas. The accelerating voltage was 10 KV and the spectra were recorded at room temperature. Thioglycol was used as the matrix.

Infrared spectra were obtained on a Shimadzu 402 spectrometer. The ultraviolet spectra were recorded on Hitachi 3210 UV-Visible spectrophotometer using matched 10 mm quartz cells.

A Chrompack HPLC equipped with an CPISOS/GRAS LC pump, Chrompack UV-VAR detector (190-800 nm) and Rheodyne  $\mu$ l syringe loaded sample valve Model 7125 with Shimadzu CR-6A integrator was used.

**a) Synthesis of 37, 38, 39, 40, 41, 42-hexa hydroxy 1, 8, 13, 19, 25, 31-hexa carboxy calix(6)arene(I)**

69 g (0.5M) of *p*-hydroxybenzoic acid, 276 ml (0.1M) of 37% formaldehyde and 172.5 ml of conc. hydrochloric acid were taken from a 1 litre round bottomed flask equipped with a Dean and Stark apparatus. The mixture was refluxed for 8 h in a water bath at 70°C. White solid, thus separated, was washed with hot distilled water to remove acidic impurities and recrystallized from acetone-petroleum ether (60-80), mp 110°C, yield-80%, UV  $\lambda_{\max}$  255( $\epsilon=4.3 \times 10^4$ ) and 227nm ( $\epsilon=3.6 \times 10^4$ ); IR(KBr), 3000cm<sup>-1</sup> ( $\nu_{\text{OH}}$  stretching), 1670cm<sup>-1</sup>, ( $\nu_{\text{C=O}}$ ); <sup>1</sup>H NMR (CDCl<sub>3</sub> + DMSO d<sub>6</sub>);  $\delta$  0.9[d, CH<sub>2</sub>, equatorial];  $\delta$  5.3[d, CH<sub>2</sub>, axial];  $\delta$  3.9 [s, OH, intramolecular]; mass spectrum [FAB (Xenon 6Kv/10mA), molecular ion peak 798, base peak 119; (m/z = 900, 798, 630 613, 579, 565, 548, 531, 399, 385, 357, 301, 284, 250, 196, 162, 105, 91); Anal. Calcd for C<sub>48</sub>H<sub>36</sub>O<sub>18</sub>, C: 64.00, H: 4.03%; Found, C: 63.82, H: 4.00%.

**a) Synthesis of 5, 11, 17, 23, 29, 35-hexachloroformyl 37, 38, 39, 40, 41, 42-hexa hydroxycalix(6)arene(II)**

In a 100-ml round bottom flask, 20 g (0.02M) of calix(6)arene(I) was refluxed with the thionyl chloride in a water bath with occasional shaking for 6 h. The reaction mixture was allowed to cool and excess thionyl chloride was removed under vacuum and finally distilled under reduced pressure.

**c) Synthesis of 37, 38, 39, 40, 41, 42-hexa hydroxy 8, 13, 23, 31-tetracarboxy 1, 19(bis *N-p*-chlorophenylbenzo) calix(6)arene hydroxamic acid (III a)**

In a 500-ml conical flask fitted with a dropping funnel, 5 g (0.035 M) of freshly prepared and crystallized *N-p*-chlorophenyl hydroxylamine was dissolved in 50 ml of pure toluene. An aqueous suspension of 5 g (0.058 M) of sodium bicarbonate in 30 ml of water is added and stirred with a magnetic stirrer. After the mixture is cooled to 0-5 °C, 21.5 g (0.02M) of acid chloride of calix(6)arene in 20 ml of anhydrous ether was added through the dropping funnel over a period of 30 minutes and the stirring was continued for another 15 minutes. Almost the entire amount of hydroxamic acid formed is precipitated as a yellowish granular solid. The solid is filtered off, washed with water and the ether layer is distilled under vacuum and any solid thus obtained is combined with the bulk. It is recrystallised from a chloroform-heptane mixture twice to yield a pale yellow compound of mp 176°C, Yield 75%, UV  $\lambda_{\max}$  264 ( $\epsilon=4.3 \times 10^4$ ) and 225nm ( $\epsilon=5.1 \times 10^4$ ); IR(KBr), 3300 cm<sup>-1</sup> ( $\nu_{\text{OH}}$ ); 1675cm<sup>-1</sup> ( $\nu_{\text{C=O}}$ ); <sup>1</sup>H NMR(CDCl<sub>3</sub> + DMSO d<sub>6</sub>),  $\delta$  1.0 [d, CH<sub>2</sub>, equatorial],  $\delta$  5.3 [d, CH<sub>2</sub>, axial],  $\delta$  3.8 [s, OH, intramolecular]; <sup>13</sup>C NMR, 140,138,137, 129, 128, 120; mass spectrum [FAB (Xenon 6Kv/10mA) molecular ion peak 1146, base peak 119; (m/z = 1146, 1078, 1009,808,694); Anal. Calcd for C<sub>60</sub>H<sub>44</sub>O<sub>18</sub>N<sub>2</sub>Cl<sub>2</sub>; C: 62.56, H: 3.85, N: 2.43, Cl: 6.16%; Found, C: 62.76, H: 3.70, N: 2.28, Cl: 6.69%.

**d) Synthesis of 37, 38, 39, 40, 41, 42-hexa hydroxy 8, 13, 23, 31-tetracarboxy 1, 19(bis *N-m*-chlorophenylbenzo) calix(6)arene hydroxamic acid (III b)**

A similar procedure described for the preparation of IIIa has been followed for the synthesis of IIIb, using an *N-m*-chlorophenylhydroxylamine yield of 75%, mp-164°C; UV  $\lambda_{\max}$  261nm ( $\epsilon=5.3 \times 10^4$ ), and 225 nm ( $\epsilon=5.1 \times 10^4$ ); IR(KBr), 3300cm<sup>-1</sup> ( $\nu_{\text{OH}}$  stretching), 1675cm<sup>-1</sup> ( $\nu_{\text{C=O}}$ ); <sup>1</sup>H NMR(CDCl<sub>3</sub> + DMSO d<sub>6</sub>),  $\delta$  1.2[d, CH<sub>2</sub>, equatorial], & 5.3[d, CH<sub>2</sub>, axial];  $\delta$  3.8 [s, OH, intramolecular]; <sup>13</sup>C NMR, 140, 138, 135, 129, 128, 122, 120; mass spectrum [FAB (Xenon

6Kv/10mA] molecular ion peak 1146, base peak 119; ( $m/z = 1146, 1078, 1009, 808, 694$ ); Anal. Calcd for  $C_{60}H_{44}O_{18}N_2Cl_2$ ; Found C: 62.56, H: 3.85, N: 2.43, Cl: 6.16%; C: 62.60; H: 3.70, N: 2.30 Cl: 6.71%.

**e) Synthesis of 37, 38, 39, 40, 41, 42-Hexa hydroxy 8, 13, 23, 31-tetracarboxy 1, 19(bis *N-p*-tolylbenzo) calix(6)arene hydroxamic acid (III c)**

It was synthesised from *N-p*-tolylhydroxylamine and yield in 75% yield as a white yellow solid, m.p.-144°C; UV  $\lambda_{max}$  260nm ( $\epsilon=3.1 \times 10^4$ ) and 227nm ( $\epsilon=5.0 \times 10^4$ ); IR(KBr), 3300 $cm^{-1}$  ( $\nu_{OH}$  stretching), 1675 $cm^{-1}$  ( $\nu_{C=O}$ );  $^1H$  NMR( $CDCl_3 + DMSO d_6$ )  $\delta$  0.96[d,  $CH_2$ , equatorial],  $\delta$  4.8[d,  $CH_2$ , axial],  $\delta$  3.8 [s, OH, intramolecular];  $^{13}C$  NMR, 140, 138, 135, 129, 128, 122, 120; mass spectrum [FAB (Xenon 6Kv/10mA)], molecular ion peak 1110, base peak 119; ( $m/z = 1110, 1042, 994, 875, 808$ ); Anal. Calcd for  $C_{62}H_{50}O_{18}N_2$ ; C: 67.02, H: 4.54, N: 2.52%; Found C: 67.89, H: 4.37, N: 2.38%.

**f) Synthesis of 37, 38, 39, 40, 41, 42-hexa hydroxy 8, 13, 23, 31-tetracarboxy 1, 19(bis *N-m*-tolylbenzo) calix(6)arene hydroxamic acid (III d)**

Prepared from *N-m*-tolyl hydroxylamine in 75% yield as a white solid, m.p.-142°C; UV  $\lambda_{max}$  262nm ( $\epsilon = 5.0 \times 10^4$ ) and 225nm ( $\epsilon = 7.3 \times 10^4$ ); IR(KBr) 3300 $cm^{-1}$  ( $\nu_{OH}$  stretching), 1675 $cm^{-1}$  ( $\nu_{C=O}$ );  $^1H$  NMR( $CDCl_3 + DMSO d_6$ )  $\delta$  0.96[d,  $CH_2$ , equatorial],  $\delta$  4.8[d,  $CH_2$ , axial],  $\delta$  3.8 [s, OH, intramolecular];  $^{13}C$  NMR, 140, 138, 135, 129, 128, 125, 120; mass spectrum [FAB (Xenon 6Kv/10mA)], molecular ion peak 1110, base peak 119; ( $m/z = 1110, 1042, 994, 875, 808$ ); Anal. Calcd for  $C_{62}H_{50}O_{18}N_2$  C: 67.62, H: 4.54, N: 2.52%; Found C: 67.51, H: 4.18, N: 2.75%.

**g) Synthesis of 37, 38, 3, 40, 41, 42-hexa hydroxy 8, 13, 23, 31-tetracarboxy 1, 19(bis *N-phenyl benzo-*) calix(6)arene hydroxamic acid (III e)**

Prepared from *N-phenyl* droxylamine and was obtained in 75% yield as a white solid, mp-140°C; UV  $\lambda_{max}$  264nm ( $\epsilon=2.9 \times 10^4$ ) and 225nm ( $\epsilon=4.5 \times 10^4$ ); IR(KBr), 3300 $cm^{-1}$  ( $\nu_{OH}$ ), 1675 $cm^{-1}$  ( $\nu_{C=O}$ );  $^1H$  NMR( $CDCl_3 + DMSO d_6$ )  $\delta$  0.9[d,  $CH_2$ , equatorial],  $\delta$  4.8[d,  $CH_2$ , axial],  $\delta$  3.9 [s, OH, intramolecular];  $^{13}C$  NMR, 140, 138, 135, 129, 128, 120; Mass Spectrum [FAB (Xenon 6Kv/10mA)], molecular ion peak 1089, base peak 119; ( $m/z = 1082, 1000, 983, 966, 784, 728, 694$ ); Anal. Calcd for  $C_{60}H_{46}O_{18}N_2$ , C: 66.54, H: 4.28, N: 2.59%; Found C: 66.13, H: 4.23, N: 2.60%.

**h) Synthesis of 37, 38, 39, 40, 41, 42-hexa hydroxy 8,13,23,31 - tetracarboxy 1,19(bis benzo-) calix(6)arene hydroxamic acid (III f)**

Prepared from hydroxylamine and was obtained in 75% yield as a white solid. mp- 125°C; UV  $\lambda_{max}$  227nm ( $\epsilon=3.5 \times 10^4$ ) and 218 ( $\epsilon=3.8 \times 10^4$ ) IR(KBr) 3300 $cm^{-1}$  ( $\nu_{OH}$  stretching), 1675 $cm^{-1}$  ( $\nu_{C=O}$ );  $^1HNMR(CDCl_3 + DMSO d_6)$   $\delta$  0.9[d,  $CH_2$ , equatorial],  $\delta$  4.8[d,  $CH_2$ , axial],  $\delta$  3.9 [s, OH, intramolecular];  $^{13}C$  NMR, 138, 129, 128, 120; Mass Spectrum [FAB (Xenon 6Kv/10mA)], molecular ion peak 798, base peak 119; ( $m/z = 930, 798, 784, 756, 711, 683, 666, 649$ ); Anal. Calcd for  $C_{48}H_{38}O_{18}N_2$ , C: 61.94, H: 4.11, N: 3.01%; Found C: 61.28, H: 4.02, N: 2.98%.

### 3. RESULTS AND DISCUSSION

#### a) Synthesis of calix(6)arene hydroxamic acids(III)

The one pot synthesis for *p*-carboxycalix(6)arene gives high yield and its acid chloride can be easily prepared, which is an attractive starting material for the synthesis of various *N*-substituted calix(6)arene hydroxamic acids.

It may be noted that for the synthesis of substituted calixarene hydroxamic acids, the use of a stoichiometric proportion of *N*-arylhydroxylamines and the acid chloride of carboxycalix(6)arene was most satisfactory. Excess of acid chloride or hydroxylamine leads to an impure product, probably due to decomposition of the hydroxylamine or due to the well-known acid catalysed rearrangement of *N*-arylhydroxylamine and its decomposition to the complex product [9, 10]. The present procedure employed freshly prepared and crystallized *N*-arylhydroxylamine dissolved in diethyl ether and mixed with an aqueous suspension of sodium bicarbonate at 0-5°C.

All the calixarene hydroxamic acids are stable white crystalline compounds except the chloro-substituted, which are light pale yellow in colour. The purity of these acids is determined by HPLC and have been found to be 99% pure. The UV spectra in dioxane show two distinct bands, one around 220-227 nm and another around 225-264 nm. These are the characteristics of benzene bands I and II, respectively [9, 11]. The II bands show a bathochromic shift. The infrared spectra of the acids as KBr pellets show the frequencies of the hydroxyl, carbonyl and N-O absorptions, which are characteristic of the hydroxamic group similar to those reported earlier [9-12].

#### b) Dissociation constants of calix(6)arene hydroxamic acids

The ionisation constants of the synthesized hydroxamic acids were determined in 70 volume percent dioxane-water by pH titration technique at 25° and 35 ° ± 0.1°C using a glass and saturated calomel electrode. Since calixarene hydroxamic acids are insoluble in water and in most of the organic solvents, but soluble in chloroform, dioxane, ethyl acetate etc, the choice of a dioxane-water mixture for the present study has been considered for several reasons. Dioxane is completely miscible with water and has a neutral character. The boiling range of both solvents is approximately the same. Many of the physical properties of dioxane-water mixtures needed for the proton-ligand equilibria are accurately known and easily available [13-15]. The activity coefficient needed in this work have been interpolated from the data of Harned and Owen [13] and Agrawal *et al.* [14-17] The empirical corrections,

$$-\log [H^+] = B + \log U_H^0 + \log \gamma_{\pm} \quad (1)$$

for medium effect have been applied (B = pH meter reading and  $\log U_H^0$  is the conversion factor for the glass electrode, which is determined experimentally [15]).

The ionization of calixarene hydroxamic acid in aqueous solution gives the hydrogen ion and hydroxamate ion, and the equilibrium constant will be

$$K_{a(aq)} = ([H^+] [A^-]) / ([HA]) (\gamma_{H^+} \cdot \gamma_{A^-} / \gamma_{HA})$$

or

$$pK_a = -\log [H^+] + \log [HA] / [A^-] - 2 \log \gamma_{\pm} \quad (2)$$

Assuming  $\gamma_{\text{HA}}$ , the activity coefficient of unionized acid is unity. The  $\text{pK}_a$  can be obtained from equations (1) and (2),

$$\text{pK}_a = B + \log U_{\text{H}}^0 + \log ([\text{HA}] / [\text{A}^-]) - \log \gamma_{\pm} \quad (3)$$

The calixarene and calixarene hydroxamic acids are insoluble in water, hence their ionisation constants in aqueous media could not be determined. Thus they were determined in dioxane water media. The values of thermodynamic ionization constants of calixarene and substituted calixarene hydroxamic acids in 70 volume percent dioxane water at  $25^\circ \pm 0.1^\circ \text{C}$  and  $35^\circ \pm 0.1^\circ \text{C}$  are given in Table 1. It is believed that the  $\text{pK}_a$  are accurate to  $\pm 0.02$  unit, but not beyond  $\pm 0.03$  in any case. The data for  $\Delta G^\circ$ ,  $\Delta H^\circ$  and  $\Delta S^\circ$ , are given in Table 2. The ionization constant of a weak acid is a function of temperature, and generally, it has a maximum value,  $K_a(\text{max})$  or  $\text{pK}_a(\text{min})$ , near room temperature. An examination of the data given in Table 1 reveals that  $\text{pK}_a$  of all calixarene hydroxamic acids decreases as the temperature increases. Their heats of ionisation are positive. Their  $T_{\text{max}}$  can be known if  $\text{pK}_a$  are determined at several temperatures.

Table 1. Ionization constants ( $\text{pK}_a$ ) of calixarene hydroxamic acid at  $25^\circ$  and  $35^\circ \pm 0.1^\circ \text{C}$

Compd. No.	Calixarene hydroxamic acid	25 °C				35 °C			
		$\text{pK}_{a1}$	$\text{pK}_{a2}$	$\text{pK}_{a3}$	$\text{pK}_{a4}$	$\text{pK}_{a1}$	$\text{pK}_{a2}$	$\text{pK}_{a3}$	$\text{pK}_{a4}$
I	<i>p</i> -carboxy calixarene	7.84	8.99	9.93	12.99	7.78	8.5	9.34	12.12
III a	NPCCHA	12.56	13.05	13.85	>14	12.15	12.65	13.45	>14
III b	NMCCHA	12.06	12.56	13.35	>14	11.66	12.15	12.96	>14
III c	NPTCHA	12.75	13.25	14.05	>14	12.35	12.85	13.85	>14
III d	NMTCHA	12.60	13.10	13.90	>14	12.20	12.20	13.50	>14
III e	NPCHA	12.48	12.89	13.99	>14	12.08	12.48	13.58	>14
III f	CHA	8.37				8.23			

The  $\text{pK}_a$  values given in Table 1 describes that the first deprotonation of calix(6)arene takes place at low pH compared to calix(6)arene hydroxamic acids. It has also been observed that  $\text{pK}_{a2}$  and  $\text{pK}_{a3}$  are very close, however,  $\text{pK}_{a4}$  is more than 14 in all cases.

The  $\text{pK}_a$  of the *p*-methyl- substituted acids are higher compared to the chloro substitution. The introduction of the methyl group in the *p*-position of the phenyl ring (Compd. IIIc) causes an acid weakening effect due to the positive inductive effect, while the chloro, Compd. IIIa, has the acid strengthening effect due to the negative inductive and tautomeric effect. The compounds follow the order of  $\text{pK}_a$  as

$$\text{order of } \text{pK}_a \text{ CH}_3 > \text{Cl} > \text{H} \\ \text{compd. No. III c} > \text{III a} > \text{III f}$$

Similarly, the introduction of the methyl or chlorine atom in the *m*-position have the acid strengthening effect compared to the *p*-position, however, the same order of the substitutions is observed (Table 1) i.e.,  $\text{pK}_a$  of  $\text{CH}_3 > \text{Cl}$ ; Compd. III d > III b.

The  $\text{pK}_a$  have been determined with a precision of  $\pm 0.02$  to  $\pm 0.03$ , hence the error in  $\Delta G^\circ$  is estimated  $\pm 0.126$  and  $-0.167$  JK cal. The temperature coefficient method used here for the computation of  $\Delta H^\circ$  (Table 2) is subject to large error because (i) the enthalpy of the ionization of acid is low and (ii) the  $\text{pK}_a$  values have not been determined at several temperatures, which otherwise

would have enabled the adoption of a more precise graphical method for the evaluation. It is apparent that an error of 0.01 in  $pK_a$  causes an error of 1.76 J K cal in  $\Delta H^\circ$ , while the magnitude of error in  $pK_a$  depends on the cancellation or addition of errors of an individual set of  $pK_a$  determined at two temperatures. Despite the large errors in the values of  $\Delta H^\circ$  computed by the temperature coefficient method, the data are still of great significance for drawing certain valuable conclusions. In any case the positive value of  $\Delta H^\circ$  (Table 2) has real significance; it implied that the ionization process at temperatures up to 25 °C is endothermic and will be exothermic only above  $T_{max}$ .

Table 2. Thermodynamic parameters of calixarene hydroxamic acid at 25° and 35° ± 0.1°C

Compd No.	Calixarene hydroxamic acid	$\Delta G^\circ$ (KJ mol <sup>-1</sup> )		$\Delta H^\circ$ (KJ mol <sup>-1</sup> )	$\Delta S^\circ$ (10 <sup>-3</sup> ) (J mol <sup>-1</sup> )		
		25° C	35° C		25° C	35° C	
I	<i>p</i> -carboxy calixarene	pKa <sub>1</sub>	44.77	45.90	10.56	-479.9	477.8
		pKa <sub>2</sub>	51.33	50.15	86.30	489.7	-486.6
		pKa <sub>3</sub>	56.70	71.58	103.85	-661.5	-792.4
		pKa <sub>4</sub>	74.17	71.68	153.13	-1107.8	-1101.0
III a	NPCCHA	pKa <sub>1</sub>	71.72	71.68	72.17	-6.32	-5.5
		pKa <sub>2</sub>	74.52	74.64	79.48	-38.58	-64.7
		pKa <sub>3</sub>	79.08	79.36	70.41	120.9	-121.8
III b	NMCCHA	pKa <sub>1</sub>	68.86	68.79	70.40	-22.4	-20.9
		pKa <sub>2</sub>	71.72	71.68	72.20	-7.01	-5.5
		pKa <sub>3</sub>	76.23	76.46	68.64	110.6	7.9
III c	NPTCHA	pKa <sub>1</sub>	72.80	72.86	70.40	32.8	34.1
		pKa <sub>2</sub>	75.66	75.81	70.40	73.0	73.9
		pKa <sub>3</sub>	80.23	81.71	35.20	631.3	628.9
III d	NMTCHA	pKa <sub>1</sub>	71.95	71.98	70.40	-70.15	5.5
		pKa <sub>2</sub>	74.80	74.93	70.40	57	58.0
		pKa <sub>3</sub>	79.65	79.65	70.40	120.9	121.8
III e	NPCHA	pKa <sub>1</sub>	71.26	71.27	70.40	11.22	12.54
		pKa <sub>2</sub>	73.60	73.63	72.22	20.11	19.74
		pKa <sub>3</sub>	73.89	80.12	72.22	108.23	107.29
III f	CHA	pKa <sub>1</sub>	47.79	48.57	24.64	324.5	323.5

**Acknowledgements-** The financial assistance given by DST, New Delhi and The Royal Society of Chemistry, London is gratefully acknowledged.

## REFERENCES

- Gutsche, C. D. (1983). Calixarenes. *Acc Chem, Res.*, 16,161.
- Gutsche, C. D. (1998) *Calixarenes Revisited in Monograph in Supramolecular Chemistry*. Ed. Stoddart, J. F., Cambridge, The Royal Society of Chemistry.
- Agrawal, Y. K., Kunji, S. & Menon, S. K. (1998). Analytical Applications of Calixarene. *Rev, Anal. Chem.* 17, 69.
- Vicens, J. & Bohmer, V. (1990). *Calixarene a Versatile class of Macrocyclic Compounds*. Dordrecht, Kulwer Academic Publishers.

5. Van Loon, J. D., Verboom, W. & Reinhoudt, D. N. (1992). Selective Functionalization and Conformational Properties of Calix(4)arenes, A Review. *Org. Prep. Proced. Int.* 24, 437.
6. Madolini, L. & Ungaro, R. (Eds). (2000). *Calixarene in Action*. London, Imperial College Press.
7. Rha, S. G. & Chang, S. K. (1998). De-tert-butylation of p-tert-Butylcalix(4)arene with Nfion; A new route to the synthesis of completely and partially Debutylated p-tert-Butylcalix(4)arenes. *J. Org. Chem.*, 63, 2357.
8. Shinkai, S., Araki, T., Tasubaki, T., Arimura, T. & Manabe, O. (1987) New Synthesis of Calixarene-p-Sulphonates and p-Nitrocalixarenes. *J. Chem. Soc. Perkin Trans.*, 1, 2297.
9. Agrawal, Y. K. & Tandon, S. G. (1971). Preparation and Properties of N-Arylhydroxamic acid. *J. Chem. Eng. Data*, 16, 371.
10. Patel, K. R., Menon, S. K. & Agrawal, Y. K. (1995). Synthesis Properties and Thermodynamic Ionization Constants of  $\alpha$ -Phenyl Styrolhydroxamic acid. *J. Chem. Eng. Data*, 40, 423.
11. Agrawal, Y. K. & Tandon, S. G. (1973). Ultraviolet Absorption Spectra of Hydroxamic Acid. *Spectro. Sc Lett.*, 6, 547.
12. Agrawal, Y. K. & Tandon, S. G. (1972). Studies on hydroxamic acid Part XI: The Infrared spectra of N-hydroxamic acids. *J. Indian Chem. Soc.*, 49, 911.
13. Harned, H. S., Owen, B. B. (1958). *The Physical Chemistry of Electrolytic Solutions*. New York, Reinhold.
14. Agrawal, Y. K. & Tandon, S. G. (1972). Dissociation constants of N-Phenyl benzohydroxamic acid and Benzohydroxamic acid. *Talanta*, 19, 700.
15. Agrawal, Y. K. (1973). Correction factor for Glass Electrode for aqueous dioxane. *Talanta*, 20, 1354.
16. Agrawal, Y. K. (1979). Studies on Hydroxamic acids and their Metal Complexes. *Russ. Chem. Rev.*, 48, 1773.
17. Menon, S. K. & Agrawal, Y. K. (1996). Proton Ligand and Metal Ligand Stability Constants of Hydroxamic acid. *Rev. Inorg. Chem.*, 16, 1.