

# Determination of Dissociation Constants of Some Novel Tetrahydropyrimidine Derivatives in Mixed Organic-Water System by Simple pH Measurement

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**Abstract.** Some tetrahydropyrimidine derivatives have been synthesized and their structures have been confirmed by IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectral data. The dissociation constants of these derivatives of tetrahydropyrimidine have been measured by Calvin Bjerrum pH titration method in DMF-water (60: 40 v/v) system at 303.15 K. It is observed that dissociation constant depends on substituent groups present in the compounds.

**Keywords:** Tetrahydropyrimidine derivatives, dissociation constant, DMF-water system, Calvin Bjerrum pH titration method

## 1 Introduction

Synthesis of tetrahydropyrimidine and its derivatives is of high interest in organic chemistry. The pyrimidine fragment is present in various biologically active compounds, many of which are used therapeutically [1-3]. Thus, much attention has been paid to derivatives of pyrimidines, including their hydrogenation products. This class of compounds possesses a wide range of biological and pharmacological properties such as antidepressant [4], calcium antagonist [5,6], antitumor [7], anti-tubercular [8] anti-inflammatory [9, 10], antibacterial and antifungal effects [11, 12], analgesic [13,14], antioxidant [15], etc.

Therefore, the synthesis of tetrahydropyrimidine derivatives continues to attract much interest in organic chemistry. These applications prompted us to study their dissociation constant which is an important parameter required in various fields such as pharmaceutical, chemical, biological and environmental research. Further, it helps to study the transport of drugs into cells and for optimizing drug delivery [16]. A literature survey shows that various workers have studied the dissociation constant of organic compounds [17, 18]. In the present work, the dissociation constant of synthesized tetrahydropyrimidine derivatives are studied in dimethyl formamide-water mixture at 303.15K by Calvin-Bjerrum *pH* titration technique.

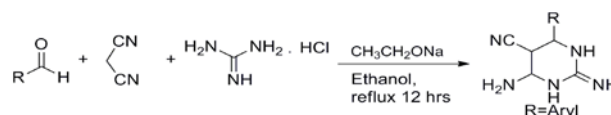
## 2 Experimental

### 2.1 Materials

Different aromatic aldehydes, malenonitrile, and guanidine hydrochloride used in the synthesis were of AR grade and were purchased from Spectrochem Pvt. Ltd. (Mumbai, India). Sodium ethoxide was prepared in our laboratory by dissolving sodium metal in ethanol (99.5% V/V) (Baroda Chemical Industries Ltd. Vadodara). Sodium nitrate ( $\text{NaNO}_3$ ) (CAS No.: 7631-99-4), Nitric acid ( $\text{HNO}_3$ ) (CAS No.: 7697-37-2) and Sodium hydroxide ( $\text{NaOH}$ ) (CAS No.: 1310-73-2) were purchased from SD FINE CHEM. Ltd (Vadodara-India). The solvent DMF used in the present work was AR grade supplied by Spectrochem Pvt. Ltd. (Mumbai, India) and was purified according to the standard procedure [19]. The purity of solvent was checked by GC-MS (SHIMADZU-Model No.-QP-2010) and was found to be greater than 99.8 %.

## 2.2 Synthesis

To an equimolar mixture of substituted aldehyde, malenonitrile, guanidine hydrochloride and freshly prepared ethanolic sodium ethoxide solution was added and the mixture was refluxed for 12 h. The progress of the reaction was monitored with the aid of analytical thin layer chromatography (Performed on aluminum coated TLC plates Gel 60 F254 (E. Merck)). After the completion of reaction, the reaction mixture was poured into crushed ice. The solution was neutralized with aqueous HCl solution and the product was extracted using chloroform. The solvent was removed under reduced pressure and the resulting compound was crystallized using chloroform. The synthesized compounds were purified. The reaction scheme is given in Fig. 1.



**Figure 1.** Reaction scheme of tetrahydropyrimidine derivatives

Spectroscopic study of all the synthesized compounds was done by IR,  $^1\text{H}$  NMR and mass spectrometry. IR spectra were recorded on KBr discs, using FT-IR Model No.-8400 (Shimadzu) spectrophotometer.  $^1\text{H}$ -NMR spectra were taken on a Bruker Avance II-400. In all cases, NMR spectra were obtained in  $\text{DMSO}-d_6$  using TMS as an internal standard. The NMR signals are reported in  $\delta$  ppm. Mass spectra were obtained using direct inlet probe on a GCMS-QP-2010 mass spectrometer. The melting points of all the synthesized compounds were determined in open capillary tubes and were uncorrected.

## 2.3 Dissociation Constant Measurement

0.1 M solutions of all the compounds were prepared in DMF. These solutions were retained at the desired temperature. The stock solutions of desired concentration of  $\text{HNO}_3$ , NaOH and  $\text{NaNO}_3$  required for titrations were prepared in Milli-Q water (Millipore Pvt. Lt. Bangalore, India). An electrical balance (Mettler Toledo AB204-S) with an accuracy of  $\pm 0.1\text{mg}$  was used.

The Calvin Bjerrum pH titration method [20, 21] was used to determine dissociation constants of all the synthesized compounds. For this, two sets of solution were prepared.

- (i) 2.0 ml  $\text{HNO}_3$  (0.1M) + 4.0 ml water + 30.0 ml (DMF) + 4.0 ml  $\text{NaNO}_3$  (1.0 M).
- (ii) 2.0 ml  $\text{HNO}_3$  (0.1M) + 4.0 ml water + 28.0 ml (DMF) + 2.0 ml compound solution (0.1M) + 4.0 ml  $\text{NaNO}_3$  (1.0 M).

At temperature 303.15 K, both sets of solutions were titrated against 0.5 M NaOH and corresponding pH was noted by Systronic pH meter (Model No. EQ-664). The Systronic glass electrode and a saturated calomel electrode were used as indicator and reference electrodes respectively. Before measurement, the pH meter was calibrated with buffer solution of known pH (pH 4.0 and 9.18).

However, in the present study, DMF-water (60:40 v/v) solvent systems are used, so the following [22] relation was used for pH correction.

$$-\log [H^+] = pH + \log f + \log U_H^0 \quad (1)$$

where  $f$  is the activity coefficient of the hydrogen ions in the solvent mixtures under consideration at the same temperature and ionic strength and  $U_H^0$  is a correction factor at zero ionic strength, which depends only on the solvent composition and temperature.

The constant temperature was adjusted to 0.05 K by circulating the thermo stated water through the outer jacket of the vessel.

## 3 Results and Discussion

Ten compounds (PAB-100 to PAB-110) are synthesized and their physical properties are given in Table 1. IR,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectrum for compound PAB-107 are given in Figures 2, 3 and 4 respectively.

Table 1. Physical properties of synthesized tetrahydropyrimidine derivatives.

Comp. Code	R	Molecular formula	Molecular weight	Yield (%)	R <sub>f</sub> *
<i>PAB-101</i>	C <sub>6</sub> H <sub>5</sub> -	C <sub>11</sub> H <sub>13</sub> N <sub>5</sub>	215.25	78	0.68
<i>PAB-102</i>	C <sub>6</sub> H <sub>4</sub> -CH=CH-	C <sub>13</sub> H <sub>15</sub> N <sub>5</sub>	241.29	60	0.73
<i>PAB-103</i>	3-Cl,C <sub>6</sub> H <sub>4</sub> -	C <sub>11</sub> H <sub>12</sub> ClN <sub>5</sub>	249.70	68	0.44
<i>PAB-104</i>	4-Cl,C <sub>6</sub> H <sub>4</sub> -	C <sub>11</sub> H <sub>12</sub> ClN <sub>5</sub>	249.70	66	0.46
<i>PAB-105</i>	4-F,C <sub>6</sub> H <sub>4</sub> -	C <sub>12</sub> H <sub>15</sub> FN <sub>5</sub>	233.24	62	0.52
<i>PAB-106</i>	4-OCH <sub>3</sub> ,C <sub>6</sub> H <sub>4</sub> -	C <sub>12</sub> H <sub>15</sub> N <sub>5</sub> O	245.28	84	0.42
<i>PAB-107</i>	3-NO <sub>2</sub> ,C <sub>6</sub> H <sub>4</sub> -	C <sub>11</sub> H <sub>12</sub> N <sub>5</sub> O <sub>2</sub>	260.25	60	0.62
<i>PAB-108</i>	3-OCH <sub>3</sub> ,4-OH C <sub>6</sub> H <sub>4</sub> -	C <sub>12</sub> H <sub>15</sub> N <sub>5</sub> O <sub>2</sub>	261.28	74	0.34
<i>PAB-109</i>	4(α-C <sub>4</sub> H <sub>3</sub> O)-	C <sub>9</sub> H <sub>11</sub> N <sub>5</sub> O	205.22	82	0.36
<i>PAB-110</i>	4-OH-C <sub>6</sub> H <sub>4</sub> -	C <sub>11</sub> H <sub>13</sub> N <sub>5</sub> O	231.25	56	0.30

\*Mobile phase: (9.5:0.5-Dichloromethane : methanol)

### 3.1 Spectral Data

**2,4-diamino-6-phenyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-101).** mp. 141-143°C; IR (KBr) : 3151(N-H str), 3093 (Ar, C-H str.), 2943 (C-H str.), 2245 (C≡N str.), 1610 (Ar, C=C str.), 1519 (Ar, C=C str.), 1512(Ar, C=C str.), 1490 (C-H bend.), 1427(C-H bend.), 1377 (C-H bend.), 1265 (C-C str.) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.59 (s, 1H, -CH) 3.22-3.36 (t, 1H, -CH), 4.09-4.12 (d, J = 9.81 Hz 1H, -CH), 6.29 (s, 2H, NH<sub>2</sub>), 6.66 (s, 2H, NH<sub>2</sub>), 8.38- 8.42 (m, 5H, Ar- H), 8.64 (s, 1H, -NH). MS: m/z= 215 [M]<sup>+</sup>.

**2,4-diamino-6-(styryl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile(PAB-102).** mp. 112-114°C; IR (KBr) : 3161(N-H str), 3021 (CH=CH str.), 3091 (Ar, C-H str.), 2952 (C-H str.), 2267 (C≡N str.), 1609 (Ar, C=C str.), 1515 (Ar, C=C str.), 1508 (Ar, C=C str.), 1481(C-H bend.), 1425 (C-H bend.), 1379 (C-H bend.), 1252 (C-C str.) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.55 (s, 1H, -CH) 3.29-3.37 (t, 1H, -CH), 4.05-4.18 ( d, J = 9.79 Hz 1H, -CH), 5.04-5.07 (dd, J=9.79 Hz 1H, -CH), 5.04-5.07 (dd, J=8.24 Hz), 6.32 (s, 2H, NH<sub>2</sub>), 6.6 (s, 2H, NH<sub>2</sub>), 8.34-8.39 (m, 5H, Ar-H), 8.74 (s, 1H, -NH), MS: m/z= 241 [M]<sup>+</sup>.

**2,4-diamino-6-(3-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-103).** mp. 153-155°C; IR (KBr) : 3163 (N-H str), 3097 (Ar, C-H str.), 2933 (C-H str.), 2265 (C≡N str.), 1608 (Ar, C=C str.), 1514 (Ar, C=C str.), 1502(Ar, C=C str.), 1489 (C-H bend.), 1421 (C-H bend.), 1371 (C-H bend.), 1255 (C-C str.), 744 (C-Cl) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.61 (s, 1H, -CH) 3.30-3.34 (t, 1H, -CH), 4.07-4.09 ( d, J = 9.78 Hz 1H, -CH), 6.21 (s, 2H, NH<sub>2</sub>), 6.68 (s, 2H, NH<sub>2</sub>), 7.82-7.87 (t, 1H, Ar- H), 8.39-8.42 (d, 1H, Ar-H), 8.44-8.49 (m, 1H, Ar-H), 8.64 (s, 1H, -NH), 8.81 (s, 1H, Ar-H). MS: m/z= 249 [M]<sup>+</sup>.

**2,4-diamino-6-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile(PAB-104).** mp. 162-164°C; IR (KBr) : 3167 (N-H str), 3092 (Ar, C-H str.), 2942 (C-H str.), 2260 (C≡N str.), 1609 (Ar, C=C str.), 1508 (Ar, C=C str.), 1518 (Ar, C=C str.), 1481 (C-H bend.), 1422 (C-H bend.), 1376 (C-H bend.), 1250 (C-C str.), 742 (C-Cl) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.63 (s, 1H, -CH) 3.24-3.29 (t, 1H, -CH), 4.12-4.15 ( d, J = 9.78 Hz 1H, -CH), 6.21 (s, 2H, NH<sub>2</sub>), 6.63 (s, 2H, NH<sub>2</sub>), 7.82-7.87 (dd, 2H, Ar- H), 8.39-8.42 (dd, 2H, Ar-H), 8.64 (s, 1H, -NH). MS: m/z= 249 [M]<sup>+</sup>.

**2,4-diamino-6-(4-fluorophenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-105).** mp. 128-130°C; IR (KBr) : 3170 (N-H str), 3094 (Ar, C-H str.), 2949 (C-H str.), 2250 (C≡N str.), 1622 (Ar, C=C str.), 1510 (Ar, C=C str.), 1520 (Ar, C=C str.), 1486 (C-H bend.), 1422 (C-H bend.), 1371 (C-H bend.), 1259 (C-C str.), 1065 (C-F) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.60 (s, 1H, -CH), 3.25-3.28 (t, 1H, -CH), 4.15-4.19 ( d, J = 9.78 Hz 1H, -CH), 6.21 (s, 2H, NH<sub>2</sub>), 6.69 (s, 2H, NH<sub>2</sub>), 7.96-7.99 (dd, 2H, Ar- H), 8.46-8.49 (dd, 2H, Ar-H), 8.66 (s, 1H, -NH), MS: m/z= 233 [M]<sup>+</sup>.

**2,4-diamino-6-(4-methoxyphenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-106).** mp. 116-118°C; IR (KBr) : 3170 (N-H str), 3094 (Ar, C-H str.), 2949 (C-H str.), 2250 (C≡N str.), 1619 (Ar, C=C str.), 1508 (Ar, C=C str.), 1478 (C-H bend.), 1426 (C-H bend.), 1368 (C-H bend.), 1254 (C-C str.), 1157 (C-O-C) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.67 (s, 1H, -CH), 3.71 (s, 3H, -OCH<sub>3</sub>),

3.24-3.29 (t, 1H, -CH), 4.10-4.13 (d,  $J = 9.75$  Hz 1H, -CH), 6.23 (s, 2H, NH<sub>2</sub>), 6.67 (s, 2H, NH<sub>2</sub>), 7.83-7.87 (dd, 2H, Ar- H), 8.39-8.43 (dd, 2H, Ar-H), 8.54 (s, 1H, Ar-H). *MS*:  $m/z = 245$  [M]<sup>+</sup>.

**2,4-diamino-6-(3-nitrophenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-107)**. mp. 141-143°C; *IR (KBr)* : 3107 (N-H str), 3086 (Ar, C-H str.), 3047 (C-H str.), 2250 (C≡N str.), 1597 (Ar, C=C str.), 1527 (Ar, C=C str.), 1512 (Ar, C=C str.), 1479 (C-H bend.), 1427 (C-H bend.), 1315 (C-H bend.), 1217 (C-C str.) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.56 (s, 1H, -CH) 3.20-3.34 (t, 1H, -CH), 4.06-4.08 (d,  $J = 9.80$  Hz 1H, -CH), 6.24 (s, 2H, NH<sub>2</sub>), 6.60 (s, 2H, NH<sub>2</sub>), 7.84-7.88 (t, 1H, Ar- H), 8.35-8.37 (d, 1H, Ar-H), 8.44-8.47 (m, 1H, Ar-H), 8.63 (s, 1H, -NH), 8.83 (s, 1H, Ar-H). <sup>13</sup>C NMR (100 MHz, DMSO): δ ppm 38.96, 39.17, 58.50, 119.68, 123.40, 128.37, 133.56, 138.54, 164.05; <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>) δ(ppm): 164.05, 148.99, 138.54, 133.56, 129.06, 128.37, 123.40, 78.94, 78.74, 78.41, 58.80, *MS*:  $m/z = 260$  [M]<sup>+</sup>.

**2,4-diamino-6-(4-hydroxy-3-methoxyphenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-108)**. mp. 132-134°C; *IR (KBr)* : 3480 (OH str.), 3164 (N-H str), 3023 (Ar, C-H str.), 2947 (C-H str.), 2241 (C≡N str.), 1606 (Ar, C=C str.), 1523 (Ar, C=C str.), 1538 (Ar, C=C str.), 1482 (C-H bend.), 1357 (C-H bend.), 1230 (C-C str.), 1078 (C-O-C str.) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.50 (s, 1H, -CH) 3.29-3.33 (t, 1H, -CH), 3.74 (s, 3H, OCH<sub>3</sub>), 4.07-4.09 (d,  $J = 9.86$  Hz 1H, -CH), 4.89 (s, 1H, -OH), 6.26 (s, 2H, NH<sub>2</sub>), 6.65 (s, 2H, NH<sub>2</sub>), 7.84-7.88 (t, 1H, Ar- H), 8.35-8.37 (d, 1H, Ar-H), 8.45-8.49 (m, 1H, Ar-H), 8.69 (s, 1H, -NH). *MS*:  $m/z = 261$  [M]<sup>+</sup>.

**2,4-diamino-6-(furan-2-yl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-109)**. mp. 72-74°C; *IR (KBr)* : 3124 (N-H str), 3043 (Ar, C-H str.), 2922 (C-H str.), 2245 (C≡N str.), 1606 (Ar, C=C str.), 1552 (Ar, C=C str.), 1529 (Ar, C=C str.), 1456 (C-H bend.), 1394 (C-H bend.), 1330 (C-H bend.), 1230 (C-C str.), 1070 (C-O-C), 1022 (C-O-C str.) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.57 (s, 1H, -CH) 3.32-3.35 (t, 1H, -CH), 4.07-4.09 (d,  $J = 9.80$  Hz 1H, -CH), 6.18 (s, 2H, NH<sub>2</sub>), 6.64 (s, 2H, NH<sub>2</sub>), 7.84-7.88 (t, 1H, Ar- H), 8.35-8.37 (s, 1H, Ar-H), 8.45-8.49 (s, 1H, Ar-H), 8.71 (s, 1H, -NH). *MS*:  $m/z = 205$  [M]<sup>+</sup>.

**2,4-diamino-6-(4-hydroxyphenyl)-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (PAB-110)**. mp. 176-178°C; *IR (KBr)* : 3635 (OH str.), 3165 (N-H str), 3088 (Ar, C-H str.), 2942 (C-H str.), 2250 (C≡N str.), 1619 (Ar, C=C str.), 1528 (Ar, C=C str.), 1510 (Ar, C=C str.), 1482 (C-H bend.), 1426 (C-H bend.), 1371 (C-H bend.), 1259 (C-C str.), 1210 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) : δ ppm 2.69 (s, 1H, -CH), 3.29-3.32 (t, 1H, -CH), 4.15-4.18 (d,  $J = 9.78$  Hz 1H, -CH), 4.64 (s, 1H, OH), 6.28 (s, 2H, NH<sub>2</sub>), 6.69 (s, 2H, NH<sub>2</sub>), 7.85-7.89 (dd, 2H, Ar- H), 8.46-8.50 (dd, 2H, Ar-H), 8.59 (s, 1H, -NH). *MS*:  $m/z = 231$  [M]<sup>+</sup>.

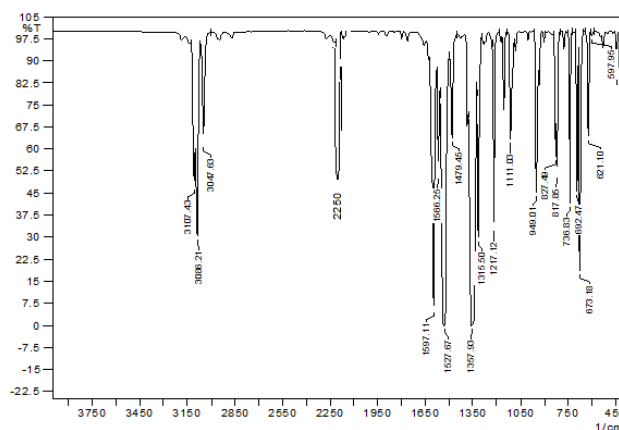


Figure 2. IR spectrum of PAB-107

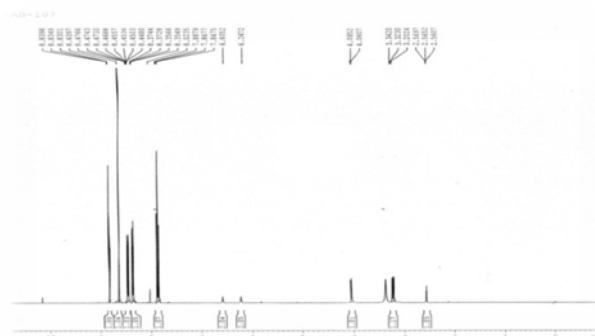


Figure 3.  $^1\text{H}$  NMR spectrum of PAB-107

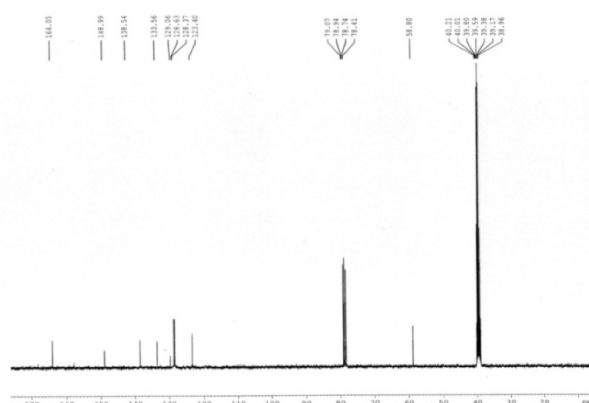


Figure 4.  $^{13}\text{C}$  NMR spectrum of PAB-107

### 3.2 Dissociation Constant Study

Fig. 5 shows typical titration curves of the acid in the absence and presence of compound for PAB-101. It can be seen that for the same volume of NaOH added, the compound titration curves showed a lower pH value than the titration curve of free acid.

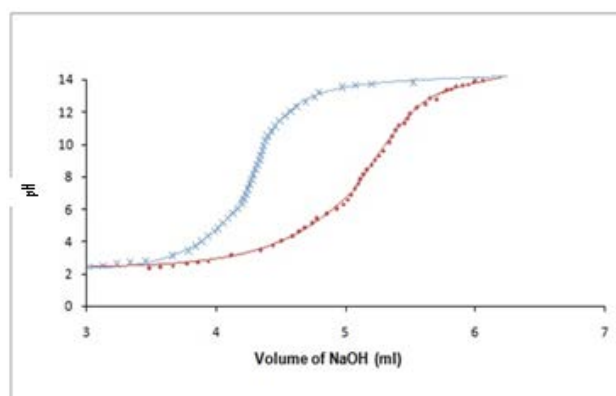


Figure 5. Plot of pH of acid (X) and acid + compound (■) against volume of NaOH ( $V$ ) for PAB-1 at 303.15 K

From these titration curves, the average number of protons associated with the compound ( $\overline{n_H}$ ) can be calculated by using Irving and Rossotti equation [23].

$$\overline{n_H} = Y - \left\{ (V'' - V') (N^0 + E^0) \right\} / \left\{ (V^0 + V') T_L^0 \right\} \quad (2)$$

$V'$  and  $V''$  are the volume of alkali required at the same pH for both acid and compound titration curves respectively.  $V^0$  is the initial volume of the test solution.  $N^0$ ,  $E^0$  and  $T_L^0$  are the initial concentration of the alkali, acid and compound respectively.  $Y$  is number of replaceable protons. For all the compounds (except PAB-108 and PAB-110), value of  $\overline{n_H}$  is less than one; for PAB-108 and PAB-110, value of  $\overline{n_H}$  is less than 2, suggesting thereby presence of two replaceable protons in these two compounds.

The dissociation constants of all the compounds were evaluated by two methods; average and half integral methods. For average method,  $pK_1^H$  values at  $\overline{n_H} = 0.5$  were evaluated for each compound (except PAB-108 and PAB-110) by using following equation:

$$\log pK^H = pH + \log \left( \overline{n_H} / (\overline{n_H} - 1) \right) \quad (3)$$

Whereas for compounds, PAB-108 and PAB-110, the dissociation constants were calculated by solving equations (4) and (5) for all the points below and above  $\overline{n_H} = 1$  respectively.

$$\log pK_1^H = pH + \log \left( \overline{n_H} / (\overline{n_H} - 1) \right) \quad (4)$$

$$\log pK_2^H = pH + \log \left[ (\overline{n_H} - 1) / (2 - \overline{n_H}) \right] \quad (5)$$

For half-integral method, at  $\overline{n_H} = 0.5$  value and  $\overline{n_H} = 1.5$ ,  $pK_1^H$  and  $pK_2^H$  value were evaluated from the plot of  $\overline{n_H}$  versus  $pH$ .

The evaluated dissociation constants by both average and half-integral methods are given in Table 2.

**Table 2.** The  $pK_1^H$  and  $pK_2^H$  values for compounds by different methods

Comp. Code	$pK_1^H$		$pK_1^H / pK_2^H$	
	Half-integral method	Average method	Half-integral method	Average method
<i>PAB-101</i>	9.88	9.54	<i>PAB-107</i>	10.90
<i>PAB-102</i>	12.78	12.33	<i>PAB-108</i>	3.86*
<i>PAB-103</i>	9.40	9.41		10.2 <sup>§</sup>
<i>PAB-104</i>	9.50	9.50	<i>PAB-109</i>	10.96
<i>PAB-105</i>	9.94	9.93	<i>PAB-110</i>	4.00*
<i>PAB-106</i>	9.84	9.86		9.8 <sup>§</sup>

\*at  $\overline{n_H} = 1.5$ ; §at  $\overline{n_H} = 0.5$

Comparison of  $pK_1^H$  and  $pK_2^H$  values evaluated by two methods shows good agreement. Comparison of  $pK_1^H$  values of studied compounds (except PAB-108 and PAB-110 which are having two replaceable hydrogens) shows that PAB-102 was most basic followed by PAB-109 while PAB-103 was most acidic.

All the compounds have the same central moiety but different side chains which affect the dissociation constant. PAB-102 contains cinnamaldehyde side chain which is found to increase the basic character of this compound whereas in PAB-109, due to furfulaldehyde side chain, basic character is greater than other studied compounds but less than that of PAB-102. PAB-103 contains chloro group at meta position and its acidic character is higher. However, PAB-104 also contains chloro group but at para position and acidic character of this compound is slightly decreased. This suggests that the position of groups also affects the dissociation. In case of PAB-105, fluoro group is at para position which further decreases the acidic character in comparison to p-chloro group (as in PAB-104). Other compounds show intermediate acidic character. PAB-108 and PAB-110 contain hydroxyl groups at para positions and are having two replaceable hydrogens. There is very small difference in  $pK^H$  values of these two compounds. However, considering the  $pK_2^H$  values of these two (PAB-108 and PAB-110) compounds indicates the higher acidity of PAB-108 which may be due to the presence of methoxy group. Similar characteristic behavior was also reported earlier [24]. Alteration of hydroxy group with any other functional group

changes the dissociation of compounds [25].

## 4 Conclusion

Out of ten studied compounds, two compounds; PAB-108 and PAB-110 have two displacable hydrogens and PAB-108 containing 3-methoxy and 4-hydroxy groups is more acidic than PAB-110 containing only 4-hydroxy group. Among remaining eight compounds, dissociation constant is maximum ( more acidic) for PAB-103 which is followed by PAB-104. PAB-102 exhibited minimum dissociation. The chloro group causes more dissociation as observed by PAB-103 and PAB-104 and its meta position increases dissociation slightly more than that in para position. The presence of cinnamaldehyde as in PAB-102 decreases dissociation. Thus, it can be concluded that type of substitution and their position in aromatic ring affects dissociation constant due to their inductive or mesomeric effects [26, 27].

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