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Potentiometric Determination of Acidity Constants of Some Synthesized Organic Compounds in Organic-Water Media

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Abstract

The acidity constants of some synthesized protonated pyrazolo quinazoline compounds were determined potentiometrically at ionic strength of 0.1 M in DMF: water (60:40 v/v) system at different temperatures (298.15 K to 318.15 K). The pKa values have been found to increase with increasing electron-donating nature of substitutions. Some thermodynamics parameters such as enthalpy (ΔH°), Gibb's free energy (ΔG°) and entropy (ΔS°) of reactions have also been evaluated at different temperatures for these systems. The thermodynamic parameters indicate that dissociation process is not spontaneous and exothermic.

Keywords: Acidity constant; Pyrazolo[5,1-b]quinazolines; Enthalpy; Entropy; Gibb's energy.

Introduction

The acidity concept has been used in various areas of research as it is an important parameter in estimating various physical and biological properties. It plays an important role in various analytical processes such as chromatographic retention behavior and pharmaceutical properties of organic acids and bases [1], acid-base titrations [2], solvent extraction and complex formation [3], structure and solute-solvent interactions [4], etc. Further, it is used to determine stereo-chemical and conformational structures, active sites in enzymes, directions of nucleophilic and electrophilic attack, stability of intermediates etc. [5]. Further, acidity constant or dissociation constant are of vital importance in understanding transport behavior, solubility, binding to receptors, lipophilicity and mechanism of action of certain pharmaceutical samples. The relationship between the dissociation constants and structure in drug design studies is important in medicinal chemistry [6].

Literature survey shows that quinazoline derivatives exhibit wide spectrum of biological activities such as antimicrobial [7], anti-bacterial [8-10], anti fungal [11, 12], anti cancer [13-15], anti-inflammatory [16-19], etc. So, it would be interesting to study the acidity constant of some biologically active quinazoline derivatives. The data may be useful for further studies of these derivatives in pharmaceutical field.

Thus in the present work, some new quinazoline derivatives are synthesized and their dissociation constants are determined in DMF-water medium at different temperatures (298.15 K to 318.15 K). Using these experimental data, some thermodynamic parameters such as enthalpy ($\Delta H°$), Gibb's free energy ($\Delta G°$) and entropy ($\Delta S°$) of solutions were evaluated to understand dissociation process.

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Materials and Methods

Materials

α-tetralone and different substituted benzaldehydes used for the synthesis were supplied from Spectrochem Pvt. Ltd. (Mumbai, India) and were used without any treatment.

Sodium nitrate (CAS No.: 7631-99-4), Nitric acid (CAS No.: 7697-37-2) and Sodium hydroxide (CAS No.: 1310-73-2) were purchased from SD FINE CHEM. Ltd (Vadodara, India).

The DMF used to determine dissociation constant was of AR grade supplied by Spectrochem Pvt. Ltd. (Mumbai, India) and was purified according to the standard procedure [20]. The distilled DMF was stored over molecular sieves. The purity of DMF was confirmed by GC-MS (SHIMADZU-Model No.-QP-2010) equipped with column DB-5MS, (25 m in length, 0.20 mm internal diameter and 0.33μm film) and was found to be 99.99%. The Milli-Q water (Millipore Pvt. Ltd. Bangalore, India) was used for the study.

Synthesis

Synthesis of (different chalcones) Int.-I: Equimolar mixture of α-tetralone and different substituted benzaldehydes in methanol were refluxed for 1.5 h in presence of catalytic amount of potassium hydroxide. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (Performed on aluminum coated plates Gel $60F_{254}$ (E. Merck)) using (7:3-Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the reaction mass was cooled and the resulting solid was filtered, washed with water and dried under vacuum to give crude product. The obtained crude product was purified by adding suitable solvent (diethyl ether) to remove colored, non polar impurity by scratching/stirring. The product was then allowed to settle down and the above solution was decanted. The procedure was repeated 3-4 times to remove impurities. The purity of Int.-I was 99.5 % as determined by gas chromatography.

Synthesis of ((5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile) Int.-II: A mixture of malanonitrile (0.01 mmol) and dry K_2CO_3 (0.012 mmol) were stirred in dry DMF at room temperature (RT) for 30 min. To this reaction mixture, 0.02 mole of carbon disulphide was added drop wise and the resulting solution was stirred for 2.5 hrs at room temperature. The solution was then cooled at 0 to 5^0C. To this cooled solution, 0.02 mole dimethyl sulphate was added and the solution was again stirred for 5-6 hrs at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, it was poured into crushed ice to give solid product. The resulting solid was filtered, washed with cold water and dried under vacuum to give crude product.

Equimolar solution of this crude product and hydrazine hydrate in isopropyl alcohol (IPA) was refluxed for 30 min. The reaction mixture was then poured into crushed ice. The resulting solid was filtered, washed with water and dried under vacuum to give product. The obtained product was purified and used in the next step without further purification.

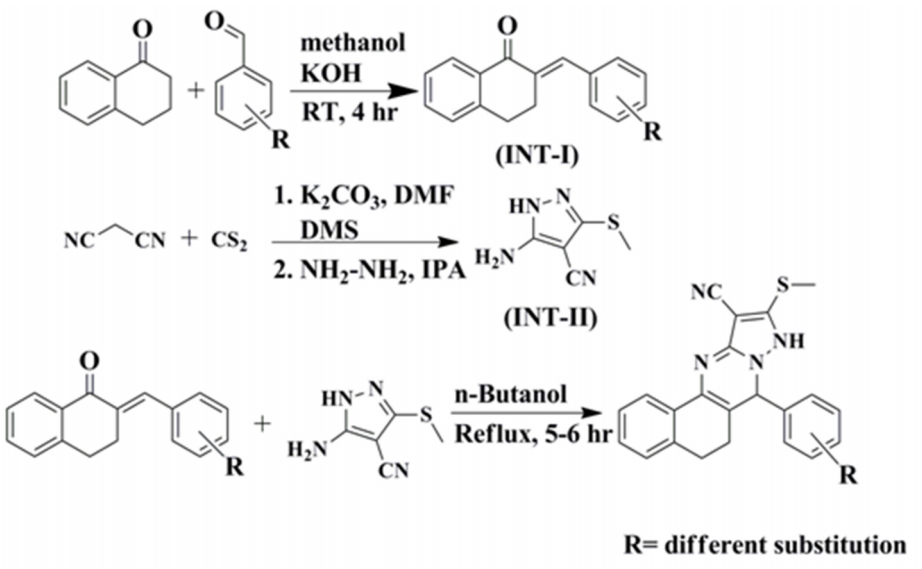

Figure 1. Synthesis scheme of pyrazoloquinazolines compounds

Table 1. Physical constants of synthesized pyrazoloquinazoline compounds.

Compound Code	Substitution R	M.F.	M.W.	Yield (%)
K-1	-4-CN	$C_{23}H_{17}N_5S$	395.12	75
K-2	-3-Cl	$C_{22}H_{17}ClN_4S$	404.09	72
K-3	-3-OCH_3	$C_{23}H_{20}N_4OS$	400.14	79
K-4	-3-Br	$C_{22}H_{17}BrN_4S$	448.04	71
K-5	-4-CH_3	$C_{23}H_{20}N_4S$	384.14	69

Synthesis of pyrazoloquinazoline derivatives

An equimolar mixture of Int-I (chalcones) and Int-II (5-amino-3-(methylthio)-1*H*-pyrazole-4-carbonitrile) were refluxed in n-butanol for 4-5 hrs. The completion of reaction was confirmed by Thin Layer Chromatography using (6:4- Hexane: Ethyl acetate) as a mobile phase. The reaction mixture was then allowed to cool and the resulting solid was filtered, washed with diethyl ether to remove impurities. The procedure was repeated 3-4 times to free the product from impurities. All the reaction schemes are given in Figure 1.

Spectroscopic study

Mass, ^{1}H NMR, IR spectral data were done for all the synthesized compounds. The IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. The Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR was determined in DMSO solution on a Bruker Ac 400 MHz spectrometer.

The physical constants of all the five synthesized compounds (K-1 to K-5) are given in Table 1.

Dissociation constant measurement

The DMF used in the study was distilled and its purity was determined by GCMS. The purity was found to be 99.8%.

All the synthesized compounds were purified and were recrystallised before measurement. For each compound, 0.1 M solution was prepared in DMF.

The solutions of nitric acid (HNO_3) (1.0 M), sodium nitrate ($NaNO_3$) (1.0 M), sodium Hydroxide (NaOH) (0.25M) were prepared in Milli-Q water.

An electronic balance (Mettler Toledo AB204-S) with an accuracy of ± 0.1mg was used for solution preparation. The solutions of nitric acid and Sodium Hydroxide were standardized by titrating with 0.1 M NaOH and 0.05M Succinic acid solutions respectively.

The Calvin Bjerrum pH titration method [21, 22], was used to determine dissociation constant. For this, glass and saturated calomel electrodes was used for dissociation constant. The Systronic pH meter (Model No. EQ-664) was calibrated before use with buffer solution of known pH. The buffers used were potassium hydrogen phthalate and sodium borate decahydrate.

For the determination of dissociation constant, two sets of solution were prepared.

(i) ***Blank solution***: 2.0 ml HNO_3 (1.0 M) + 10.0 ml water + 24.0 ml DMF + 4.0 ml $NaNO_3$ (1.0 M)

(ii) ***Compound solution***: 2.0 ml HNO_3 (1.0 M) + 10.0 ml water + 22.0 ml DMF + 2.0 ml compound solution (0.1M)+ 4.0 ml $NaNO_3$ (1.0 M)

For each set, DMF: water ratio was 60:40 (v/v).

The above mentioned solutions were allowed to attain a definite temperature by circulating water through the outer jacket of the vessel using a thermostat ((NOVA NV-8550 E) maintained at desired constant temperature. The uncertainty in temperature is ± 0.05K. These solutions were titrated against 0.25 M NaOH at different temperatures and the corresponding pH was recorded by Systronic pH meter for ach compound. The accuracy of pH meter was ±0.01 pH unit.

The pH correlation was done using following relation [23]:

(1)

$$-\log[H^+] = pH + \log f + logU_H^0$$

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. U_H^0 is taken as unity in aqueous media.

Results and Discussion

All the five compounds are synthesized and their physical properties (K-1 to K-5) are given in Table 1. Figures 2, 3 and 4 show mass, IR and ^{1}H NMR spectrum for the compound K-1 respectively

Spectral Data

K-1

***IR (cm^{-1}, KBr)*:** 3475.85(-NH (sec.) str.), 3049.56 (Ar-H str.), 2924.18(-CH_2 sym. str.), 2227.86 (-CN str.), 1664.62(C=C str. α,β unsaturated 6-member ring),

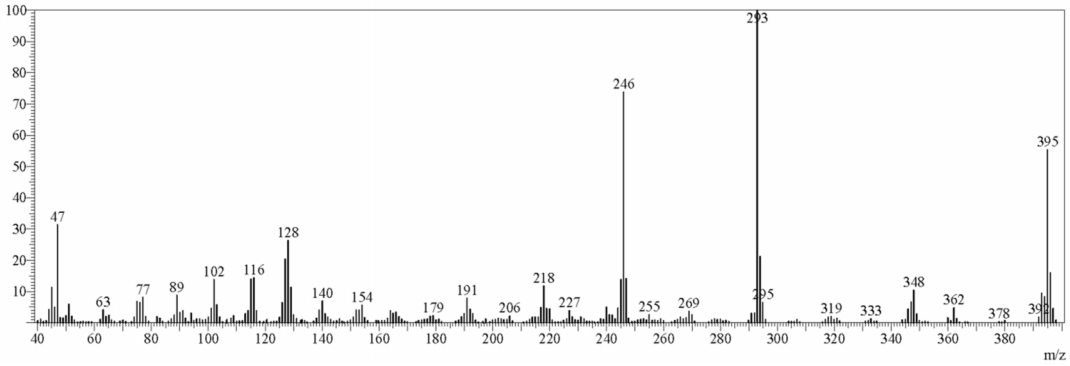

Figure 2. Mass spectrum of K-1

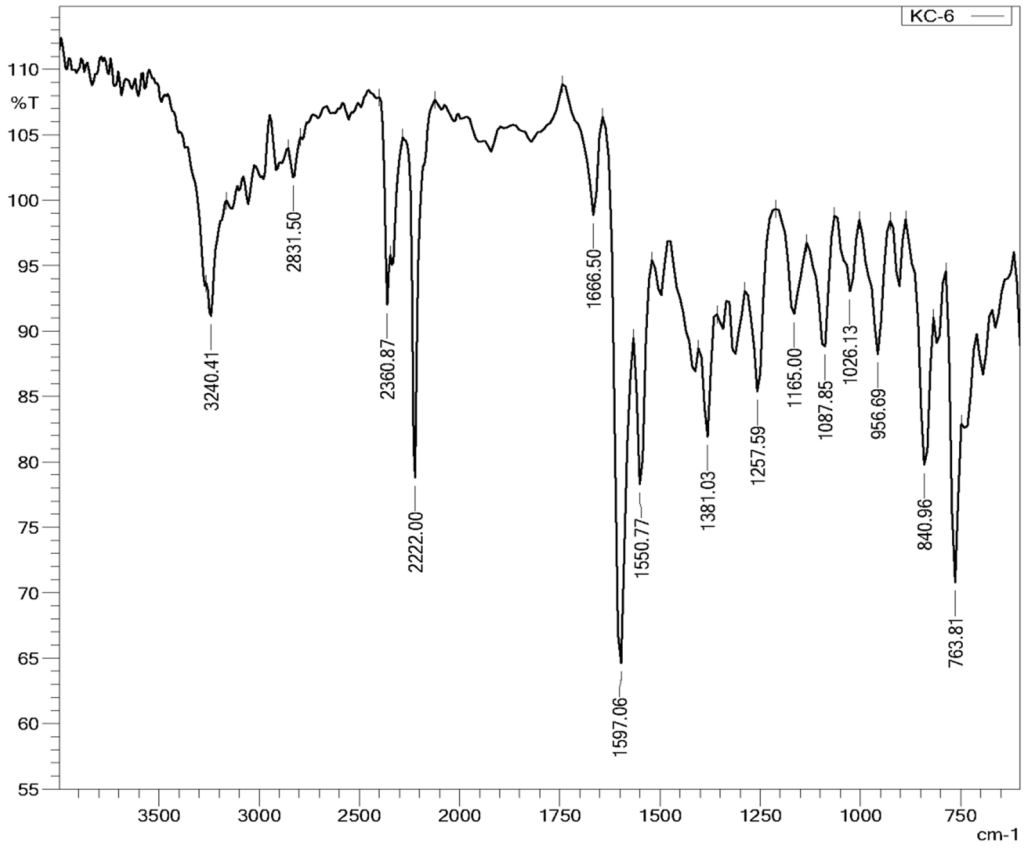

Figure 3. IR spectrum of K-1

1604.83(-NH bending vib. Secondary amine), 1381.08 (-CH bending.), 1315.50(C-N (sec) bending.), 1242-1010(C-H in plane bending, phenyl ring), 767.69 (C-H str. 5-adjecent c atoms), ***^{1}H NMR (DMSO-d_6) δ(ppm)*** **:** 2.389 (3H, singlet, -CH_3), 1.713-2.796 (4H, multiplet, C-H), 6.170 (1H, singlet, C-H), 7.196-7.936 (8H, multipletC-H), 10.201 (1H, singlet, -NH), ***MS*****: *(m/z)*** = 395

K-2

IR (cm^{-1}, KBr)**:** 3284.83(-NH (sec.) str.), 3064.99 (Ar-H str.), 2908.75(-CH_2 sym. str.), 2225.93 (-CN str.), 1666.55(C=C str. α,β unsaturated 6-member ring), 1604.83(-NH bending vib. Secondary amine), 1383.01 (-CH bending.), 1336.71(C-N (sec) bending.), 1242-1010(C-H in plane bending, phenyl ring), 767.69 (C-H str. 5-adjecent c atoms), 731.05(C-H in plane bending),

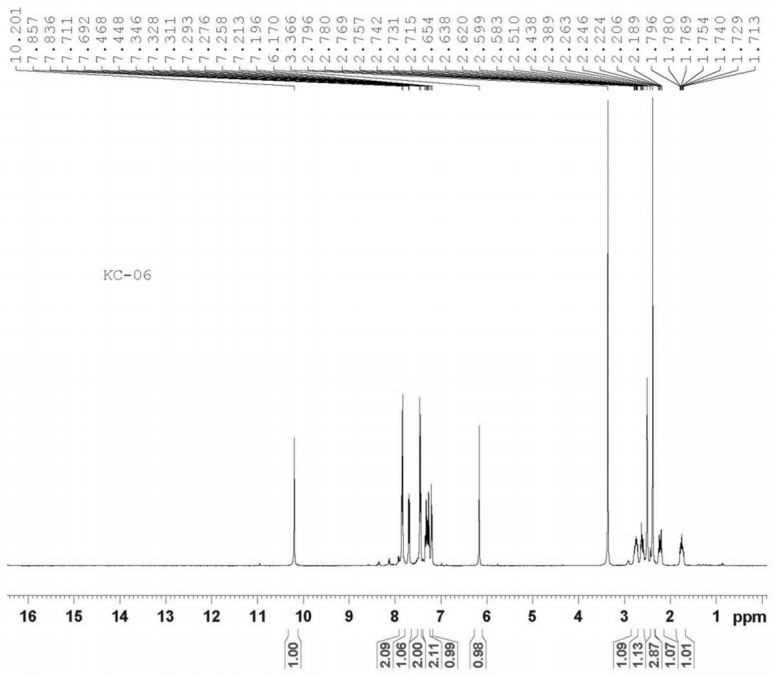

Figure 4. ^{1}H NMR spectrum of K-1

763.25 (C-Cl str.), ***^{1}H NMR (DMSO-d$_6$) δ(ppm)*** **:**2.400 (3H, singlet,-CH_3), 1.785-2.750 (4H, multiplet, C-H), 6.068 (1H, singlet, C-H), 7.216-7.704 (8H, multiplet C-H), 10.139 (1H, singlet, -NH), ***MS*****: *(m/z)*** = 404

K-3

IR (cm^{-1}, KBr)**:** 3479.70(-NH (sec.) str.), 3037.99 (Ar-H str.), 2918.40(-CH_2 sym. str.), 2227.86 (-CN str.), 1666.55 (C=C str. α,β unsaturated 6-member ring), 1599.04 (-NH bending vib. Secondary amine), 1381.08 (-CH bending.), 1319.08 (C-N (sec) bending.), 1242-1010(C-H in plane bending, phenyl ring), 1093.67 (C-F str.), 725.26 (C-H str. 5-adjecent c atoms),***^{1}H NMR (DMSO-d$_6$) δ(ppm)*** **:** 2.428 (3H, singlet, -CH_3), 3.687 (3H, singlet-OCH_3), 1.799-2.787 (4H, multiplet, C-H), 6.007 (1H, singlet, C-H), 7.198-7.697 (8H, multiplet C-H), 10.125 (1H, singlet, -NH), ***MS*****: *(m/z)*** = 400

K-4

IR (cm^{-1}, KBr)**:** 3257.88(-NH (sec.) str.), 3047.63 (Ar-H str.), 2929.97 (-CH_2 sym. str.), 2227.86 (-CN str.), 1653.05 (C=C str. α,β unsaturated 6-member ring), 1604.83 (-NH bending vib. Secondary amine), 1383.01 (-CH bending.), 1315.50 (C-N (sec) bending.), 1242-1010(C-H in plane bending, phenyl ring), 723.33 (C-H str. 5-adjecent c atoms), 582.52 (C-Br str.), ***^{1}H NMR (DMSO-d$_6$) δ(ppm)*** **:** 2.397 (3H, singlet, -CH_3), 1.742-2.795 (4H, multiplet, C-H), 6.057 (1H, singlet, C-H), 7.202-7.740 (8H, multiplet C-H), 10.123 (1H, singlet, -NH), ***MS*****: *(m/z)*** = 448

K-5

IR (cm^{-1}, KBr)**:** 3236.66(-NH (sec.) str.), 3007.12 (Ar-H str.), 2929.97 (-CH_2 sym. str.), 2224.40 (-CN str.), 1666.55(C=C str. α, β unsaturated 6-member ring), 1604.83(-NH bending vib. Secondary amine), 1383.09 (-CH bending), 1334.78 (C-N (sec) bending.), 1242-1010(C-H in plane bending, phenyl ring), 702.11 (C-H str. 5-adjecent c atoms), 731.05(C-H in plane bending), ***^{1}H NMR (DMSO-d$_6$) δ(ppm)*** **:**2.442 (3H, singlet,-CH_3), 3.023 (3H, singlet –CH_3), 1.788-2.769(4H, multiplet, C-H), 6.005 (1H, singlet, C-H), 7.102-7.767 (8H, multiplet C-H), 10.189 (1H, singlet, -NH), **MS: (m/z)** = 384

Dissociation constant and thermodynamic study

Figure 5 shows the titration curves of blank and compound solutions for K-1 at 298.15 K. It is clear from the figure that for the same volume of NaOH, the titration curve for blank solution shows higher pH than that for compound solution. From these curves, the average number of protons associated with compound ($\bar{n}_H$ was evaluated using Irving and Rossotti equation [24]

$$\bar{n}_H = Y - \{(v'' - v')\,(N^0 + E^0)\}/\{(v^0 + v')T_L^0\} \quad (2)$$

where Y is number of replaceable proton per

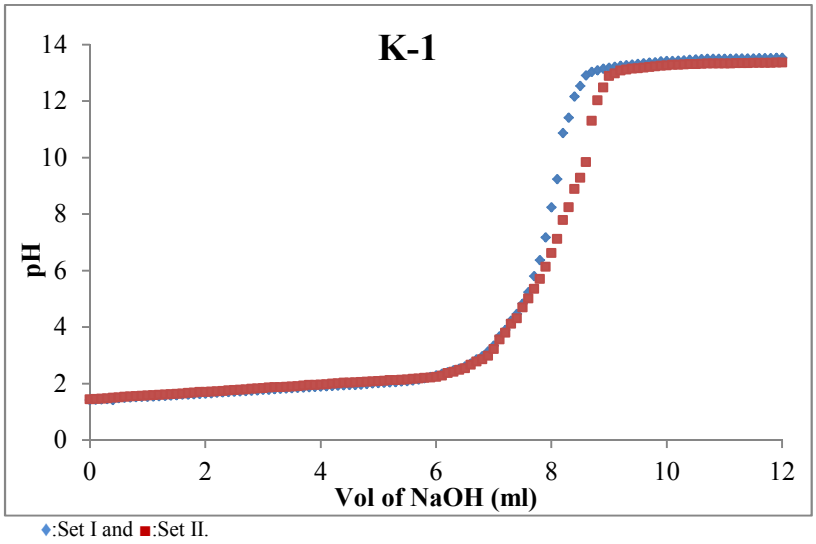

Figure 5. Variation of pH against volume of NaOH for K-1 at 298.15 K

molecule. For all the studied compounds, value of Y is one. $V^{/}$ and $V^{//}$ are volume of NaOH required for blank and compound titration curves at the same pH.N^0, E^0 and T^0_L are the initial concentration of the alkali, acid and compound respectively. The values of $\bar{n}_H$ is found to be between 0 to 1 for all the compounds indicating thereby that there is only one dissociation step.

For the evaluation of dissociation constants, two methods have been used:

(1) ***Half-integral method***: In this method, the dissociation constants were evaluated at $\bar{n}_H$ =0.5 from the plot of $\bar{n}_H$ verses pH.

(2) ***Average method***: Using the following equation,

$$pK = pH + log\left[\frac{\bar{n}_H}{\bar{n}_H - 1}\right]$$

The dissociation constants were calculated at various pH values. The average of these pK_a values was calculated.

The evaluated values by both methods are given in Table 3 at different temperatures. It is clear from Table 3 that the dissociation constants evaluated by both methods are in good agreement. Further, dissociation of compounds increases with increase in the temperature [25]. This is due to the fact that as temperature increases, dissociation of compounds also increases due to increase in interactions or disturbances in solution. It is observed that order of pK_a values for the studied compounds are: K-5 > K-3 > K-4 > K-2 >K-1.

All the compounds have the same central moiety but different substitutions (Table 1). Table 2 shows the electro negativity of different substitutions of studied compounds. Thus, the presence of different substituent influences the dissociation of compounds due to their different effects [26]. The electro negativity of different substitutions present in studied compounds are: 4-CN > 3-Cl > 3-Br > 3-OCH_3> 4-CH_3. The electronegativity of 4-CN is highest which causes an increase in acidic character of K-1.This is followed by K-2 and K-4 containing 3-Cl and 3-Br groups respectively. The electro negativities of these two groups are also in the same order. The methyl substitution is in K-5 which is found to be most basic. The methyl group has lone pair of electrons which causes hyper conjugation effect due to three hydrogen atoms. Thus, it is more basic than other four studied substitutions.

Using these dissociation constant data, some thermodynamic parameters such as enthalpy change ($\Delta H°$), Gibb's energy change ($\Delta G°$) and entropy change ($\Delta S°$) have been evaluated.

Table 2. The electro negativity of different substitutions of studied compounds.

Compound code	K-1	K-2	K-3	K-4	K-5
Substitution	4-CN	3-Cl	3-OCH_3	3-Br	4-CH_3
Electro negativity	3.84	3.0	2.68	2.8	2.27

Table 3. Dissociation constants of compounds at 298.15 K, 308.15 K and 318.15 K in DMF-water system

Compound code	T/K	Average method	Half-integral method
		pKa	
	298.15	9.32 ± 0.01	9.32 ± 0.04
K-1	308.15	9.12 ± 0.03	9.11 ± 0.05
	318.15	8.96 ± 0.06	8.96 ± 0.03
	298.15	9.51 ± 0.06	9.51 ± 0.07
K-2	308.15	9.27 ± 0.03	9.27 ± 0.06
	318.15	9.03 ± 0.02	9.02 ± 0.01
	298.15	9.67 ± 0.03	9.67 ± 0.09
K-3	308.15	9.35 ± 0.04	9.34 ± 0.06
	318.15	9.00 ± 0.05	9.00 ± 0.04
	298.15	9.58 ± 0.02	9.58 ± 0.07
K-4	308.15	9.30 ± 0.01	9.30 ± 0.02
	318.15	9.07 ± 0.03	9.07 ± 0.03
	298.15	9.91 ± 0.04	9.91 ± 0.06
K-5	308.15	9.80 ± 0.01	9.81 ± 0.03
	318.15	9.69 ± 0.02	9.69 ± 0.04

Table 4. Some thermodynamic parameters of compounds

Compound code	T/K	Average Method			Half-Integral method		
		ΔG kJ/mol	-ΔH kJ/mol	-ΔS J/mol K	ΔG kJ/mol	-ΔH kJ/mol	-ΔS J/mol K
	298.15	23.1026 ± 0.02		125.12 ± 0.02	23.1026 ± 0.04		125.14 ± 0.07
K-1	308.15	23.3651 ± 0.04	14.2003 ±	121.91 ± 0.04	23.3395 ± 0.06	14.2086	121.85 ± 0.02
	318.15	23.7001 ± 0.03	0.07	119.13 ± 0.01	23.7001 ± 0.01	± 0.08	119.15 ± 0.03
	298.15	23.5736 ± 0.00		142.51 ± 0.02	23.5736 ± 0.06		143.82 ± 0.09
K-2	308.15	23.7494 ± 0.06	18.9144 ±	138.45 ± 0.03	23.7494 ± 0.04	19.3051	139.72 ± 0.04
	318.15	23.8853 ± 0.05	0.05	134.53 ± 0.08	23.8588 ± 0.01	± 0.07	135.67 ± 0.03
	298.15	23.9702 ± 0.06		168.93 ± 0.03	23.9702 ± 0.03		168.96 ± 0.07
K-3	308.15	23.9543 ± 0.01	26.3970 ±	163.40 ± 0.01	23.9287 ± 0.05	26.4053	163.34 ± 0.04
	318.15	23.8059 ± 0.06	0.04	157.80 ± 0.02	23.8059 ±0.02	± 0.02	157.82 ± 0.01
	298.15	23.7471 ± 0.03		147.13 ± 0.02	23.7470 ± 0.04		147.13 ±0.05
K-4	308.15	23.8262 ± 0.03	20.1199 ±	142.61 ± 0.07	23.8262 ± 0.03	20.1198	142.61 ± 0.06
	318.15	23.9911 ± 0.04	0.09	138.65 ± 0.06	23.9910 ± 0.08	± 0.02	138.64 ± 0.01
	298.15	24.5651 ± 0.08		111.48 ± 0.07	24.5651 ± 0.09		111.45 ± 0.02
K-5	308.15	25.1072 ± 0.03	8.6715 ±	109.62 ± 0.01	25.1328 ± 0.04	8.6631	109.68 ± 0.07
	318.15	25.6310 ± 0.08	0.07	107.82 ± 0.04	25.6310 ± 0.07	± 0.08	107.80 ± 0.01

Van't Hoff relation [27] is used for the evaluation of enthalpy change and Gibb's free energy is calculated by equation:

$$\Delta G^0 = RTpK \quad (4)$$

By using ΔH° and ΔG° values, entropy change (ΔS°) is calculated by the equation (5) [28]:

$$\Delta S^0 = \frac{(\Delta H^0 - \Delta G^0)}{T} \quad (5)$$

All the calculated thermodynamic parameters evaluated by dissociation constants (for both average and half integral methods) are given in Table 4. It is evident from Table 4that enthalpy and entropy values are negative whereas Gibb's free energy values are positive for all the compounds. The negative enthalpy suggests exothermic dissociation process whereas the positive Gibb's free energy indicates non-spontaneous dissociation. The negative entropy change proves greater solvation [29] which causes more ordered structure [30].

Conclusion

The dissociation of studied compounds increases with increase in temperature. The dissociation is affected by the nature of substitution. The highly electronegative group causes an increase in dissociation constant as observed for K-1. The thermodynamic parameters suggest that for all the studied compounds, dissociation process is exothermic and non spontaneous resulting in more ordered structure in solutions which decreases with increase in temperature as expected.

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