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Research Article

POTENTIOMETRIC INVESTIGATION OF ACID-BASE EQUILIBRIA OF CHALCONES IN DMF–WATER MEDIA AT 303.15 K

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ABSTRACT

The dissociation constants of some synthesized chalcones 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 the substituent groups present in compounds.

Keywords: *Dissociation Constant, pK$_a$, Potentiometry, Chalcones, DMF*

INTRODUCTION

Because most drugs are weak acids or bases, information about their ionization at physiological pH values carry important information related to the behaviour of drugs in penetrating different parts of the body. The dissociation constant i.e., pK of a drug influences its lipophilicity, solubility and permeability that, in turn, directly affect pharmacokinetic characteristics such as absorption, distribution, metabolism and excretion. The value of pK is also an important parameter in choosing optimum conditions when developing analysis methods for the drug molecule (Manallack, 2007).

The dissociation constants of organic reagents play a fundamental role in many analytical procedures such as acid-base titration, solvent extraction, complex formation, and ion transport (Zhao *et al.*, 1996; Roshester, 1971; Hammet, 1940).

It has been shown that the acid-base properties affect the toxicity, chromatographic retention behaviour, and pharmaceutical properties of organic acids and bases. Much of the theoretical foundation of modern organic chemistry is based on the observation of the effects on acid-base equilibrium of changing molecular structure (Albert *et al.*, 1962; Zhou *et al.*, 2008; Minton, 2001).

Chalcones are an important class of biologically active compounds which are known to exhibit a wide spectrum of biological and pharmacological activities like antispasmodic, anti-helmintics (Das *et al.*, 2010), anti-inflammatory (Jeon *et al.*, 2012), antiviral (Mallikarjun, 2005), anti allergic (Oganesyan *et al.*, 1991), antifungal and antibacterial (Gafner *et al.*, 1996), anticancer (Syam *et al.*, 2012), anti-HIV (Meena Devi *et al.*, 2005), antiulcer (Suwa *et al.*, 1984) etc.

Owing to vast biological and pharmacological applications of chalcones, it would be interesting to study dissociation constants of such compounds. The obtained data may be useful to scientists for Quantitative Structure Activity Relationship (QSAR) study of these compounds.

Thus, in the present work, some new chalcones are synthesized and their structure characterization was done by IR, ^{1}H NMR and mass spectral data. The dissociation constant of these synthesized Chalcones has been studied in dimethyl formamide-water system at 303.15 K by Calvin Bjerrum pH titration technique (Bjerrum, 1941).

MATERIALS AND METHODS

Materials

α-tetralone, methanol, 4-fluoro benzaldehyde and 4-methyl benzaldehyde used in the synthesis were supplied from Spectrochem Pvt. Ltd. (Mumbai, India). The solvents, DMF and chloroform used in the present work were of AR grade supplied by LOBA Chemie Pvt. Ltd. (Mumbai, India) and were purified according to the standard reported method (Riddick *et al.*, 1986). The purified solvents were kept over molecular sieves. The final purities of the solvents were checked by GC-MS (SHIMADZU-Model No.-QP-2010).

Synthesis

Equimolar mixture of α-tetralone and substituted benzaldehydes in ethanol was refluxed for 4 hr in presence of catalytic amount of potassium hydroxide. The reaction progress was checked by analytical thin layer chromatography (TLC) using (4:1-Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the temperature of reaction mass was allowed to cool up to room temperature. The resulting solid was filtered, washed with water and was dried under vacuum to give crude product. The obtained crude product was purified by tituration with diethyl ether.

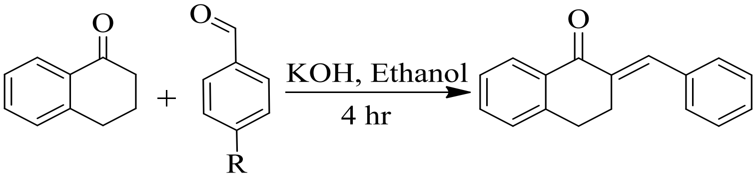


Figure 1: Reaction Scheme to Synthesis of Chalcones

The reaction scheme is given in Figure 1. Overall, two compounds were synthesized and the IUPAC names of these compounds are as follow.
SB-1:2-(4-fluorobenzylidine)-3,4-dihydro napthalene-1,(2*H*)-one
SB-2:2-(4-methylbenzylidine)-3,4-dihydro napthalene-1,(2*H*)-one

Spectroscopy Study

The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR and mass spectral analysis. The IR spectra of compounds were taken on FT-IR (SHIMADZU Model-IRaffinity-1S). ^{1}H NMR spectra were taken on a Bruker AVANCE III (400 MHz). In all the cases, ^{1}H NMR spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) using TMS as an internal standard. The NMR signals are reported in δ ppm. Mass spectra were determined using direct inlet probe on a GC-MS (SHIMADZU Model-QP2010) mass spectrometer.

The melting points of compounds were measured by Different Scanning Calorimeter (SHIMADZU DSC-60) under nitrogen atmosphere.

Determination of Dissociation Constant

All the solutions (except synthesized compounds) used for the titration were prepared using Milli-Q distilled water. The solutions of synthesized compounds were made in N, N-Dimethyl formamide (DMF). Following are the concentrations of the solutions used for the titration.

Solutions	**Concentration (M)**
Nitric acid	1.00
Sodium hydroxide	0.25
Sodium nitrate	1.00
Synthesized Chalcones	0.10

Nitric acid and sodium hydroxide were standardized by titrating with 0.1 N NaOH and 0.25 M succinic acid solution respectively.

The buffer solutions used for the calibration of pH meter were 0.05 M potassium hydrogen phthalate and 0.01 M Borax buffer.

A Systronic pH meter (Model No. EQ 664) was used for the pH determination. The glass electrode and a saturated calomel electrode were used as indicator and reference electrodes respectively. Before operation, the glass electrode was immersed in 0.1 M HCl for twenty minutes. Then, it was washed thoroughly with distilled water. The pH meter was calibrated with buffer solution of known pH.

Calvin Bjerrum pH titration method (Bjerrum, 1941) was used for the determination of dissociation constant. For this, the following sets of mixtures were prepared for titration:
(i) 2 ml HNO_3 (1.0M) + 4 ml water + 30 ml DMF + 4.0 ml $NaNO_3$ (1.0 M).
(ii) 2 ml HNO_3 (1.0M) + 4 ml water + 28 ml DMF + 2.0 ml chalcone solution (0.1M) + 4.0 ml $NaNO_3$ (1.0 M).

Thus, total volume (V^0) in each set = 40.0 ml and DMF: Water ratio 60:40 (v/v).

RESULTS AND DISCUSSION

Table 1 shows the substitutions and other physical properties of synthesized compounds.

Table 1: Physical Constants of the Synthesized Compounds

Compound	Mol. Formula	Mol. Wt.	% Yield	R_f^*value	Melting Point (K)
SB-1	$C_{17}H_{13}FO$	252.12	78	0.49	386.15
SB-2	$C_{18}H_{16}O$	248.31	74	0.36	395.81

*4:1-Hexane: Ethyl acetate

Spectral Data

SB-1:

IR (cm^{-1}, KBr): 3059.20 (Ar-H asym. stretching), 2964.69-2839.31 (-CH_2 stretching of cyclohexanone ring), 1659.80 (C=O stretching), 1295.24-1227.73 (-CH_2 bending), 952.87 (ring stretching in cyclohexanone), 845 (C-H out of plane bending), 1139 (C-F stretching).

^{1}H NMR ($CDCl_3$) δ(ppm) **:** 2.955-2.987 (2H, triplet,J=6.4), 3.107-3.139 (2H, triplet, J=6.4), 7.111-7.154 (2H, triplet, J=8.6),7.266-7.285 (1H, doublet, J= 7.6),7.370-7.389 (1H,triplet, J=3.8), 7.408-7.466, (2H, quartet), 7.497-7.537 (1H, triplet, J=8.0), 7.851 (1H, Singlet), 8.141-8.162 (1H, doublet, J=8.4).

Mass: (m/z) = 252.12

SB-2:

IR (cm^{-1}, KBr): 3050.52 (Ar-H asym. str.), 2846.06 (-CH_2 stretching of cyclohexanone ring), 1663.80(C=O stretching), 1295.24-1224.73 (-CH_2 bending), 952.87 (ring stretching in cyclohexanone), 845 (C-H out of plane bending), 2951.19 (-CH_3 stretching).

^{1}H NMR ($CDCl_3$) δ(ppm) : 2.361 (3H, singlet) 2.855-2.932 (2H, triplet, J=6.4), 2.993-3.024 (2H, triplet, J=6.4), 6.996-7.152 (2H, triplet, J=8.6), 7.170-7.255 (1H, doublet, J= 7.6), 7.274-7.316 (1H, triplet, J=3.8), 7.329-7.351 (2H, quartet), 7.382-7.385 (1H, triplet, J=8.0), 7.401-7.404 (1H, Singlet), 7.419-7.422 (1H, doublet, J=8.4).

Mass: *(m/z)* = 248.32

Figure 2 shows that typical titrations curve of the acid in the absence and presence of compounds at 303.15 K. It can be seen that for the same volume of NaOH added, the titration curves of compound showed a lower pH value than the titration curve of free acid.

From these titration curves, the average number of protons associated with the chalcones ($\overline{n_H}$) can be calculated by the following equation (Irving and Rossoti, 1954).

$$\overline{n_H} = Y - \left\{ \left(V'' - V' \right) \left(N^0 + E^0 \right) \right\} / \left\{ \left(V^0 + V' \right) T_L^0 \right\} \qquad \text{...(1)}$$

Where, Y is the number of displaceable protons per compound molecule. For the synthesized compounds, Y is taken as one. $V^/$ 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^0_L are the initial concentration of the alkali, acid and compound respectively.

The value of $\overline{n_H}$ are found to be between 0 to 1, suggesting thereby that synthesized chalcones have only one replaceable proton.

The dissociation constants of chalcones were evaluated by two methods: (i) Average method and (ii) Half-integral method.

(i) *Average Method:* In this method, for all the points below $\overline{n_H}$ =1, the following equation was used to determine pK.

$$\log pK = pH + \log\left(\bar{n}_H / (\bar{n}_H - 1)\right) \qquad \text{...(2)}$$

From these evaluated various values of *log* pK, average value of pK was calculated.

(ii) *Half-Integral Method:* In this method, pK value was evaluated at $\overline{n}_H$ =0.5 from the plot of $\overline{n}_H$ versus pH which is shown in Figure 3.

Table 2 shows the pK values of chalcones by both average and half-integral methods. It is observed from this Table that pK values evaluated by two methods are in good agreement. Further, there is difference in pK values of the two compounds which is due to their different substitutions. SB-1 contains fluoro substitution whereas in SB-2, methyl group is present. Both substitutions are at para positions. Thus, difference in pK value is due to substitution only. p*K* is minimum in SB-1 and maximum in SB-2 suggesting thereby maximum dissociation in SB-1 which contains flouro group. SB-2 contains methyl group which decreases dissociation. SB-1 is found to be more acidic than SB-2 as expected as it contains fluoro group. Thus, SB-2 is more basic and SB-1 is most acidic. This suggests that presence of different substituent influences the dissociation of the compound due to inductive effect.

Table 2: Dissociation Constants (pK) of Synthesized Chalcones by Average and Half Integral Methods at 303.15 K

Compound Code	Average Method	Half Integral Method
SB-1	4.676	4.705
SB-2	5.275	5.215

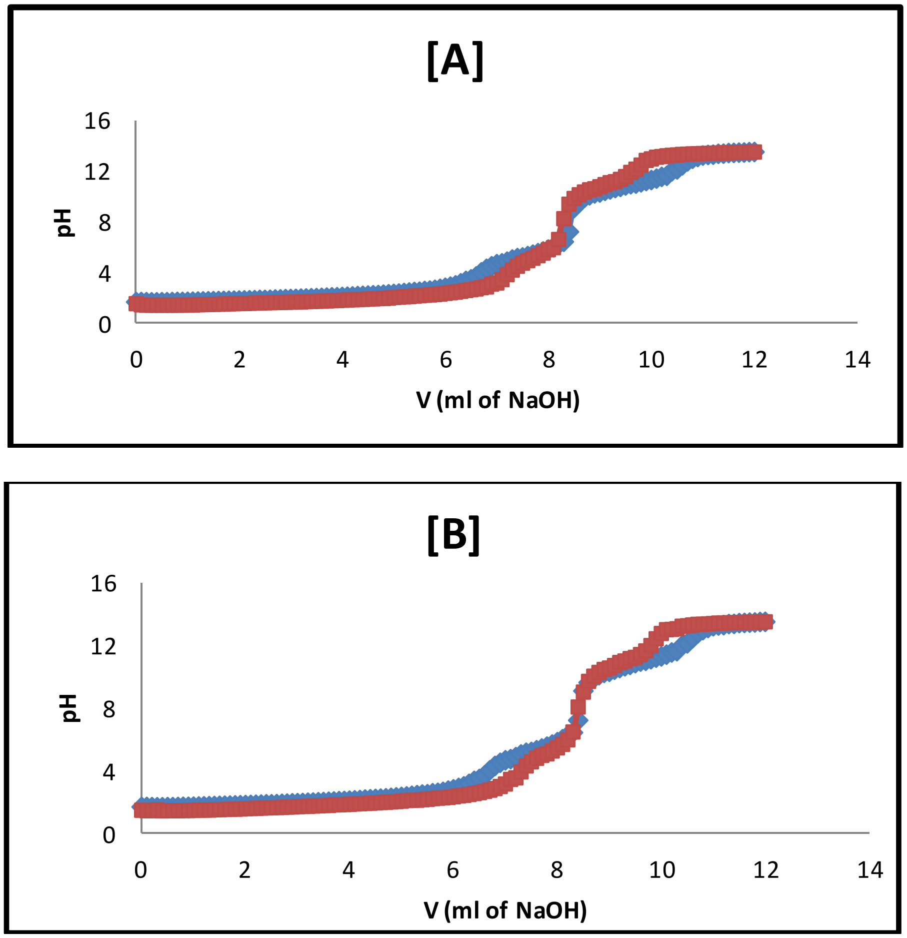
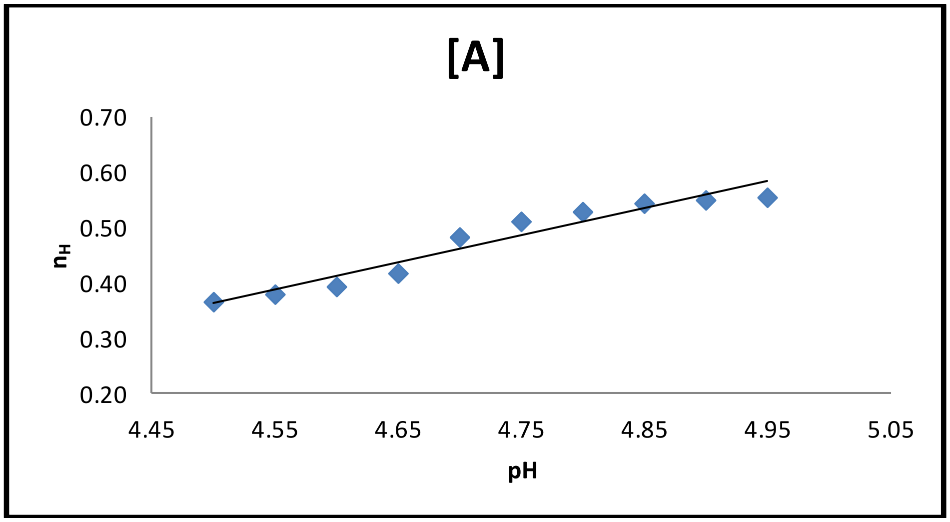


Figure 2: The Plot of pH against Volume of NaOH for [A] SB-1 and [B] SB-2 in DMF-Water System at 303.15 K
🟥 : Compound ; 🟦 : Blank



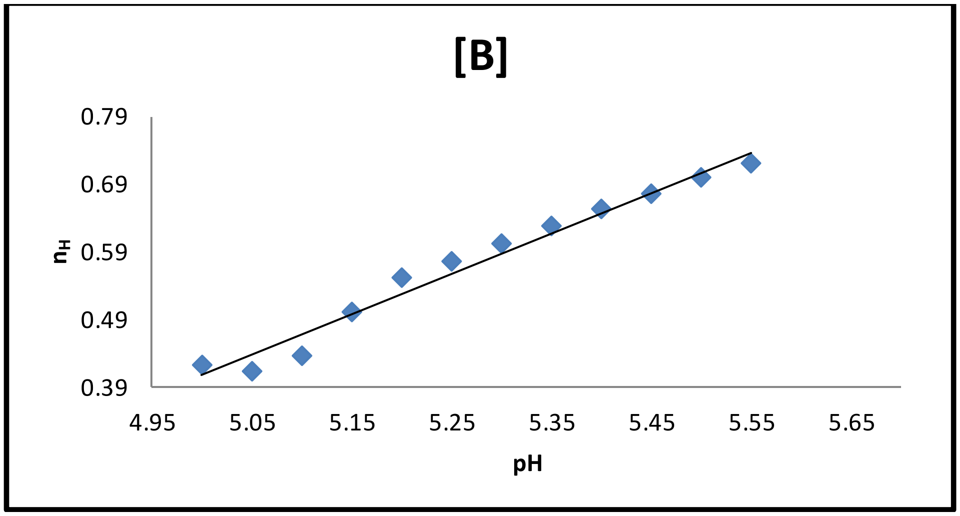


Figure 3: The Plot of n_H against pH for [A] SB-1 and [B] SB-2 in DMF-Water System at 303.15 K

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