



Potentiometric determination of dissociation constant and thermodynamic parameters of dissociation process of some newly synthesized pyrimidine derivatives in MeOH/DMF–water medium at different temperatures



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ABSTRACT

Some new pyrimidine derivatives have been synthesized and their structures have been confirmed by IR, ¹H NMR and mass spectral data. The thermodynamic dissociation constants of pyrimidine derivatives were studied in methanol/DMF–water (60:40 v/v) solvent systems at different temperatures ranging from 25 °C to 45 °C at 10 °C interval using Calvin–Bjerrum pH titration method. Further, some thermodynamic parameters such as enthalpy (ΔH°), Gibb's free energy (ΔG°) and entropy (ΔS°) of solutions have also been evaluated at different temperatures for these systems.

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1. Introduction

The pyrimidine ring is an important structure in numerous natural products and bioactive compounds [1]. Literature survey reveals that substituted pyrimidine scaffolds are pharmacologically active compounds and show important activities like antimicrobial [2,3], antimalarial [4], anticancer [5], antimycotic activities [1] etc. These reports 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 [6]. Dissociation constant of many organic compounds is reported [7–9]. In the present paper, dissociation constants of some newly synthesized pyrimidine derivatives have been determined in methanol/DMF–water systems by Calvin–Bjerrum pH titration method at different temperatures (298.15 to 318.15 K).

2. Experimental

2.1. Materials

2,4-Dichloropyrimidine (DCP) (CAS No.:3934-20-1) and 4-((1H-1,2,4-triazol-1-yl)methyl)aniline (TMA) (CAS No.: 119192-10-8) used in the synthesis were purchased from Sigma-Aldrich. N, N-diisopropylethyl amine (DIPEA) (CAS No.: 7087-68-5), 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 solvents methanol and dimethylformamide (DMF) used in the present work were of AR grade supplied by Spectrochem Pvt. Ltd. (Mumbai, India) and were purified according to the standard procedure [10]. The purity of solvents was checked by GC–MS (SHIMADZU-Model No.-QP-2010) and found to be greater than 99.0%.

2.2. Synthesis

A mixture of 2,4-dichloropyrimidine (DCP) (1.0 equ.), 4-((1H-1,2,4-triazol-1-yl)methyl)aniline (TMA) and N,N-diisopropylethyl amine (DIPEA) (1.2 equ.) in n-Butanol was refluxed for 3 h. The completion of reaction was confirmed by analytical thin layer chromatography (TLC). After completion of reaction, reaction mass was cooled and the

Abbreviations: DCP, 2, 4-dichloropyrimidine; TMA, 4-((1H-1, 2, 4-triazol-1-yl)methyl)aniline; DIPEA, N, N-diisopropylethyl amine; DMF, N, N-dimethylformamide; A R, Analytical reagent.

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resulting solid was filtered, washed with cold water and dried under vacuo to give crude product.

This resulting product was refluxed for 3 h with ethanolic solution of different aromatic amines (1.1 equ.) in presence of glacial acetic acid (2–3 drops). After completion of reaction, the reaction mass was cooled and the resulting solid was filtered, washed with cold ethanol and dried under vacuo to give crude product. The obtained crude product was purified by trituration with diethyl ether and purity of all these synthesized compounds was checked by TLC (performed on aluminum coated TLC plates Gel 60F254 (E. Merck)). The reaction scheme is given in Fig. 1.

2.2.1. Spectroscopy study

Spectroscopic study of all the synthesized compounds was done by IR, ^1H NMR and mass spectroscopy. IR spectra were recorded on KBr discs, using FT-IR, (Shimadzu spectrophotometer Model no.-8400). ^1H NMR spectra were taken on a Bruker AVANCE II 400. In all the cases, NMR spectra were obtained in 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 GCMS-QP-2010 mass spectrometer. Melting points of compounds were measured by Differential Scanning Calorimeter (Shimadzu-DSC-60).

2.3. Dissociation constant measurement

0.1 M solutions of all the compounds were prepared in methanol and DMF. These solutions were retained at the desired temperature. The stock solutions of desired concentrations of nitric acid (HNO_3), sodium hydroxide (NaOH) and sodium nitrate (NaNO_3) required for titrations were prepared in Milli-Q water (Millipore Pvt. Ltd. Bangalore, India). An electrical balance (Mettler Toledo AB204-S) with an accuracy of ± 0.1 mg was used for solution preparation.

The Calvin Bjerrum pH titration method [11,12] was used to determine dissociation constants of all the synthesized compounds. For this, two sets of solutions were prepared.

- (i) 2.0 ml HNO_3 (0.1 M) + 4.0 ml water + 30.0 ml (methanol/DMF) + 4.0 ml NaNO_3 (1.0 M).
- (ii) 2.0 ml HNO_3 (0.1 M) + 4.0 ml water + 28.0 ml (methanol/DMF) + 2.0 ml compound solution (0.1 M) + 4.0 ml NaNO_3 (1.0 M).

For different temperatures, both sets of solutions were titrated against 0.25 M NaOH and the corresponding pH was recorded by Systronic pH meter (Model No. EQ-664). The accuracy of the pH meter was ± 0.01 pH unit. 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 4.0 (0.05 M potassium hydrogen phthalate buffer) and 9.18 (0.01 M Sodium borate decahydrate

buffer) for aqueous media. However, in the present study, methanol/DMF–water (60:40 v/v) solvent systems are used, so the following Van Uitert and Haas relation [13] was used for pH correction.

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

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 experiment was repeated at different temperatures. The constant temperature was adjusted to ± 0.05 K by circulating the thermostated water through the outer jacket of the vessel (NOVA NV-8550 E).

3. Results and discussion

The physical properties of all the synthesized compounds are given in Table 1. For compound BKD-5, IR and ^1H NMR spectra are shown in Figs. 2 and 3 respectively.

3.1. Spectral data

BKD-1: IR (cm^{-1} , KBr): 3375, 3225 (–NH (sec.) str.), 3095, 3036 (Ar–H str.), 2883 (– CH_2 asym. str.), 2833 (– CH_2 sym. str.), 1654–1489 (C=C str. phenyl nucleus), 1456 (– CH_2 bending vib.), 1371 (triazole ring str.), 1273 (C–N str.), 1242–1010 (C–H in plane bending, phenyl ring), 827 (C–H oop phenyl ring), 759 (C–Cl str.), 705–675 (C–H oop triazole ring), 626 (in plane pyrimidine ring bending), 422 (out of plane pyrimidine ring bending). **^1H NMR (DMSO- d_6) δ (ppm):** 5.458 (s, 2H), 6.559–6.575 (d, 1H, $J = 6.4$), 7.308–7.329 (d, 2H, $J = 8.4$), 7.396–7.418 (d, 2H, $J = 8.8$), 7.518–7.538 (d, 2H, $J = 8$), 7.583–7.601 (d, 2H, $J = 7.2$), 8.019–8.037 (d, 1H, $J = 7.2$), 8.095 (s, 1H), 8.820 (s, 1H), 10.984 (s, 1H), 11.282 (s, 1H). **MS: (m/z) = 377.**

BKD-2: IR (cm^{-1} , KBr): 3394, 3217 (–NH (sec.) str.), 3088 (Ar–H str.), 3041 (– CH_2 asym. str.), 2897 (– CH_3 sym. str.), 2837 (– CH_2 sym. str.), 1647–1516 (C=C str. phenyl nucleus), 1460 (– CH_2 bending vib.), 1352 (– CH_3 asym bending) 1274 (C–N str.), 1240–972 (C–H in plane bending, phenyl ring), 868–813 (C–H oop phenyl ring), 813 (C–Cl str.), 758 (C–H oop triazole ring). **^1H NMR (DMSO- d_6) δ (ppm):** 2.331 (s, 3H), 5.425 (s, 2H), 6.432–6.449 (d, 1H, $J = 6.8$), 7.161–7.181 (d, 2H, $J = 8$), 7.249–7.270 (d, 2H, $J = 8.4$), 7.342–7.363 (d, 2H, $J = 8.4$), 7.592–7.612 (d, 2H, $J = 8$), 7.930–7.947 (d, 1H, $J = 6.8$), 8.016 (s, 1H), 8.693 (s, 1H), 10.418 (s, 1H), 10.873 (s, 1H). **MS: (m/z) = 357.**

BKD-3: IR (cm^{-1} , KBr): 3391, 3213 (–NH (sec.) str.), 3059 (Ar–H str.), 2893 (– CH_2 asym. str.), 1654–1506 (C=C str. phenyl nucleus), 1462 (– CH_2 bending vib.), 1388 (triazole ring str.), 1273 (C–N str.), 1219–1136 (C–H in plane bending, phenyl ring), 1018 (C–F str.), 835–768 (C–H oop phenyl ring), 767 (C–H oop triazole ring).

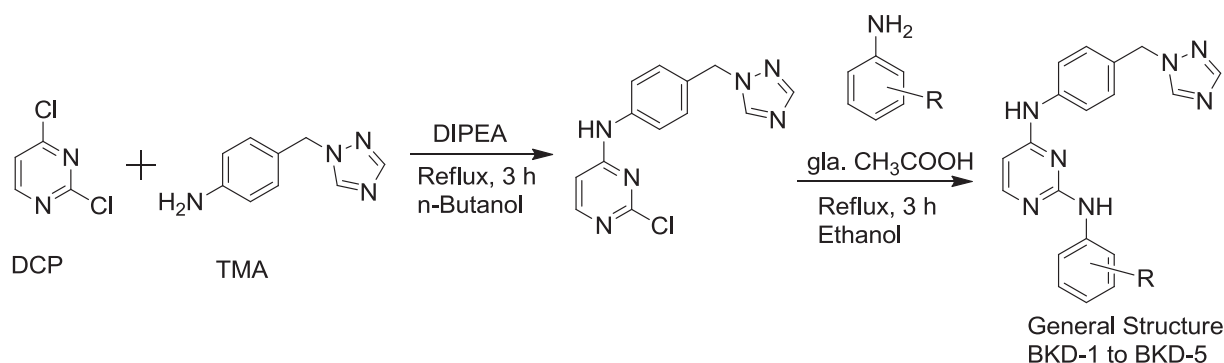


Fig. 1. Synthesis scheme of pyrimidine derivatives.

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