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Determination of dissociation constants and thermodynamic parameters of pyrimidine derivatives in organic-water mixed solvents at different temperatures

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ABSTRACT

Two novel pyrimidine derivatives have been synthesized and their structures have been confirmed by IR, ^{1}H NMR and mass spectral data. The dissociation constants of these two compounds; 4-(naphthalen-1-yloxy)-N-(p-tolyl) pyrimidin-2-amine (TP-1) and N-(4-fluoro phenyl)-4-(naphthalen-1-yloxy) pyrimidin-2-amine (FP-1) were studied in methanol/DMF - water (60:40 v/v) solvent systems at different temperatures ranging from 25 °C to 45 °C at a 10 °C interval using the Calvin–Bjerrum pH titration method. The results are interpreted in terms of substituent present in the compounds. Furthermore, some thermodynamic parameters such as enthalpy ($\Delta H°$), Gibb's free energy ($\Delta G°$) and entropy ($\Delta S°$) of these dissociations have also been evaluated at different temperatures from dissociation constant data.

1. Introduction

Dissociation constant is the core physicochemical parameter of any electrolyte, which helps in understanding various processes of industrial applications. In biological terms, the dissociation constant i.e., p*K* value gives an idea about the presence of a compound in the polar or non-polar phase (partition). From a computational chemistry point of view, p*K* calculations are a benchmark for quantum mechanical and free solvation energy calculations. Further, the accurate determination of p*K* value is important for the analysis of drugs to understand their distribution, transport behavior, binding to receptors and mechanism of action in various chemical and biochemical processes [1,2].

Heterocyclic compounds play an important role in industry as well as in our life. Various heterocyclic compounds are known to act as therapeutic agents. Among these compounds, pyrimidines are one of the most important heterocycles exhibiting remarkable pharmacological activities. It is an essential constituent of all cells of living matter as a pyrimidine ring is a building unit of DNA and RNA [3]. These pyrimidine compounds exhibit a range of biological activities such as anti-microbial [4], analgesic [5,6], anti-inflammatory [7,8], anti-tubercular [9], anti-tumor [10], anti-cancer [11], etc.

The applications of these compounds attracted us to determine their dissociation constants and thermodynamic parameters in different solvents.

A literature survey shows that very little work has been done for the determination of the dissociation constant of synthetic organic compounds [12,13]. In continuation of our research work [14,15], the present work deals with the synthesis, characterization and determination of the dissociation constant of synthesized pyrimidine derivatives in a methanol/DMF–water system by the 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 1-naphthol (NTL) (CAS No.: 90-15-3) used in the synthesis were purchased from Sigma-Aldrich. Potassium carbonate (K_2CO_3) (CAS No.: 584-08-7) was purchased from Sisco Chem. Pvt. Ltd. (Mumbai, India). 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 [16] and were kept over molecular sieves. The

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purity of solvents was checked by GC–MS (SHIMADZU Model No. QP-2010) and found to be greater than 99.7%.

2.2. Spectroscopy study

Spectroscopic study of both the synthesized compounds was done by IR, ^{1}H NMR and mass spectroscopy. IR spectra were recorded on KBr discs, using FT-IR (Shimadzu spectrophotometer Model no. 8400). ^{1}H-NMR spectra were taken on a Bruker Avance II 400. In all the cases, NMR spectra were obtained in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. The NMR signals are reported in δppm. Mass spectra were determined using a direct inlet probe on a GCMS-QP-2010 mass spectrometer. Melting points of compounds were determined by a differential scanning calorimeter (Shimadzu-DSC-60).

2.3. Synthesis of 4-(naphthalen-1-yloxy)-N-(p-tolyl) pyrimidin-2-amine (TP-1) and N-(4-fluorophenyl)-4-(naphthalen-1-yloxy) pyrimidin-2-amine (FP-1)

A mixture of 2,4-dichloropyrimidine (DCP) (0.1 mmol), 1-naphthol (NTL) (0.1 mmol) and potassium carbonate (K_2CO_3) (0.15 mmol) in DMF was refluxed for 4 h. The completion of the reaction was confirmed by analytical thin layer chromatography (TLC) using hexane: ethyl acetate (7:3) as mobile phase. After the completion of the reaction, the reaction mass was cooled and the resulting solid was filtered, washed with cold water and dried under vacuum to get a crude product.

This resulting product (0.1 mmol) was refluxed for 4–5 h with ethanolic solution of appropriate aromatic amines (0.12 mmol) using hydrochloric acid as catalyst. The completion of the reaction was confirmed by TLC using hexane:ethyl acetate (7.5:2.5) mobile phase. After the completion of the reaction, the reaction mass was cooled and the resulting solid was filtered, washed with cold ethanol and dried under vacuum. The obtained crude product was purified by adding a suitable solvent (diethyl ether) to remove colored, nonpolar impurity by scratching/stirring. The product was then allowed to stabilize and the above solution was decanted. The procedure was repeated 3–4 times to free the product from impurities (trituration) and the purity of all these synthesized compounds was ascertained by TLC (performed on aluminum coated plates Gel 60 F_{254} (E. Merck)). The reaction scheme is given in Fig. 1.

The physical parameters of these compounds are summarized below:

TP-1: yield-71%; m.p. 294.6 °C; molecular formula—$C_{21}H_{17}N_3O$.
IR (cm^{-1}, KBr): 3267.52 (–NH (sec.) str.), 3188.44 (aryl ether C–H str.), 3057.27 (Ar–H str.), 2872 (Ar–CH_3 str.) 1585.54-1454.38 (C═C str. phenyl nucleus), 1421–1327 (C–H in plane bending), 1255–1217 (diarylethers str.), 1153.47-1076 (C–O–C sym. str.), 981 (pyrimidine ring breathing), 808 (C–H in plane bending), 628.81-723.33 (C–C out of plane bending).
^{1}H NMR (*DMSO-d_6*) δ(ppm): 2.107 (s, 3H), 6.628-6.744 (d, 1H, J = 5.6), 6.941-6.960 (d, 2H, J = 7.6), 7.284 (s, 2H), 7.475-7.493 (d, 1H, J = 7.2), 7.527-7.642 (m, 3H),7.808-7.829 (m, 1H) 7.968-7.988 (d, 1H, J = 8), 8.062-8.082 (d, 1H, J = 8), 8.429-8.443 (d, 1H, J = 5.6), 9.71 (s, 1H); MS: (m/z) = 327.38.
FP-1: yield-75%; m.p. 292.18 °C; molecular formula—$C_{20}H_{14}FN_3O$.
IR (cm^{-1}, KBr): 3262 (–NH (sec.) str.), 3084.28, 3061.13 (Ar-H str.), 1656.91-1664.02 (C═C str. phenyl nucleus), 1398.44 (C–H in plane bending), 1244.13-1103.32 (diarylethers str.), 1035 (C–F str.), 831 (C–H in plane bending), 794.7-619.17 (C–C out of plane bending).
^{1}H NMR (*DMSO-d_6*) δ(ppm): 6.610-6.624 (d, 1H, J = 5.6), 6.762 (s, 2H), 7.616-7.643 (m, 5H), 7.946-7.967 (d, 1H, J = 8.4), 8.069-8.089 (d, 1H, J = 8), 8.168-8.183 (d, 1H, J = 6), 8.400-8.414 (d, 1H, J = 5.6), 9.651 (s, 1H); MS: (m/z) = 331.11.

2.4. Dissociation constant measurement

0.1 M solutions of studied 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 [17,18] was used to find out dissociation constants of both 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 a Systronic pH meter (Model No. EQ-664). The accuracy of the pH meter was ±0.01 pH unit. The Systronic glass electrode and saturated calomel electrode were used as indicator and reference electrodes respectively. Before measurement, the pH meter was calibrated with a buffer solution of the 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–water (60:40 v/v) and DMF–water (60:40 v/v) solvent systems are used, so the following Van Uitert and Haas relation [19] was used for pH correction.

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

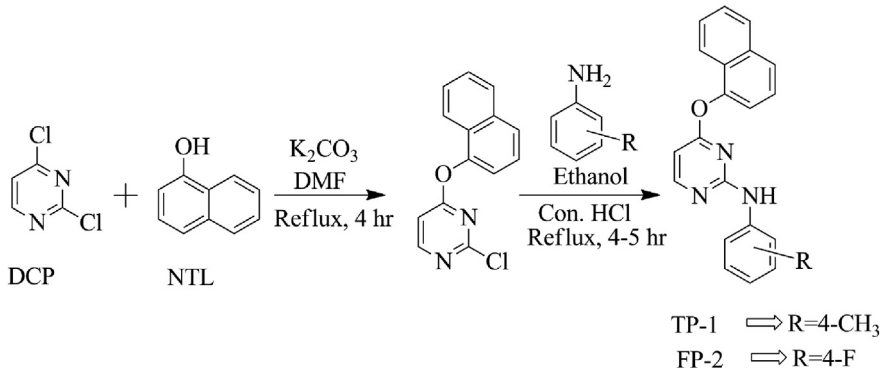

Fig. 1. Synthesis scheme of pyrimidine derivatives.

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