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A potentiometric study of (acid + base) equilibria in substituted 4-nitropyridine *N*-oxide systems in methanol and dimethyl sulfoxide

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Abstract

The acid dissociation constants for cationic acids conjugated with 4-nitropyridine *N*-oxides have been determined using potentiometric titration method. The measurements in the systems of thirteen 4-nitropyridine *N*-oxide derivatives were carried out in the polar amphiprotic methanol (MeOH) and in the aprotic protophilic dimethyl sulfoxide (DMSO). Likewise as in the polar aprotic protophobic solvents (acetonitrile, acetone) it was found that in MeOH for all *N*-oxides studied the pK_a values were readily determinable, whereas in DMSO the pK_a values were hardly determinable or indeterminable by using the potentiometric method. In addition, just like in our previous investigations it was revealed that the sequence of the pK_a values of the cationic acids in methanol is the same as in the water and the values are lower than those determined in acetonitrile and acetone. Also, it was found that the phenomenon of cationic homoconjugation equilibria was not present in the systems involving 4-nitropyridine *N*-oxide derivatives in both solvents used. Furthermore, protonation energies, ΔE_{prot}, and Gibbs free enthalpies, ΔG_{prot}, *in vacuo* have been compared with acid dissociation constants (expressed as pK_a^{MeOH} values) of the protonated *N*-oxides determined by potentiometric titration in methanol to establish a correlation between these magnitudes.

Keywords: 4-Nitropyridine *N*-oxide derivatives; (Acid + base) equilibria; Potentiometric titration; Methanol; Dimethyl sulfoxide; Water

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1. Introduction

Fundamental equilibria taking place in substituted pyridine *N*-oxides and conjugate cationic acids systems in polar non-aqueous solvents [1] are those of acid dissociation (1), as well as of cationic homoconjugation (2) and heteroconjugation (3)

$$BH^+ \rightleftarrows B + H^+ \qquad K_a \tag{1}$$

$$BH^+ + B \rightleftarrows BHB^+ \qquad K_{BHB^+} \tag{2}$$

$$BH^+ + B_1 \rightleftarrows BHB_1^+ \qquad K_{BHB_1^+} \tag{3}$$

where B and B_1 are the base molecules (amine *N*-oxide) and BH^+ is a cation of protonated *N*-oxide. Equation (2) shows that the cationic homoconjugation reactions create symmetric complex ions, $[BHB]^+$, whereas as seen from equation (3) cationic heteroconjugation is a reaction in which a cationic acid BH^+ reacts with base B_1conjugated with an acid other than BH^+ to afford a hydrogen-bonded cations, $[BHB_1]^+$.

A number of studies of (acid + base) equilibria in non-aqueous solvents were carried out at our laboratory using polar aprotic solvents with diverse polarity and donor properties, such as acetone [1,2], acetonitrile [1,3], benzonitrile [1,4,5], propylene carbonate [1,6], nitromethane [1,7,8], *N′*,*N′*-dimethylformamide (DMF) [1,8], dimethyl sulfoxide (DMSO) [1,9,10], as well as in the selected amphiprotic solvent, methanol [1,2,11]. In these investigations we revealed that the acidity constants (pK_a) obtained in non-aqueous solvents are linearly correlated with the pK_a values in water [11]. Furthermore, we found that in

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above-mentioned solutions, there are good linear correlations between pK_a values and lg K_{BHB^+} [2,3,5].

The equilibria of acid dissociation and cationic homoconjugation in non-aqueous solvents, in system formed by pyridine *N*-oxides have been studied by using a variety of experimental techniques, including UV–Vis, IR, NMR spectroscopies [12–14], conductometry [15–17], solubility [18] and potentiometric [19–21] methods. Also in this work, the potentiometric method was used as a basic technique for the investigation of (acid + base) equilibria. The principal aim of this study was to determine the pK_a values and cationic homoconjugation constants in (acid + base) systems formed by a variety of substituted 4-nitropyridine *N*-oxides in polar non-aqueous solvents, the amphiprotic methanol of moderate basicity (donicity number, DN = 19.1 [22]), and the strongly basic aprotic protophilic dimethyl sulfoxide (DN = 29.0 [22]). Methanol (MeOH) as a solvent almost isoelectric in relation to acetonitrile (AN) and nitrobenzene (NM) and highly polar dimethyl sulfoxide (DMSO) has been chosen to avoid potential complications associated with establishing of intricate association equilibria as was the case with weak polar solvents.

Our interest in the chemistry of heterocyclic amine *N*-oxide was triggered by their significant bioactivity [23–26] and interesting physicochemical properties [27–33]. For instance, it was found that a number of heterocyclic *N*-oxides exhibit anti-HIV efficacy, mutagenic, cancerostatic, sedative and herbicidal activity. To our investigations we selected a series of thirteen 4-nitropyridine *N*-oxide derivatives of differentiated basicity. This feature was achieved by substitution electron-donating and electron-accepting substituents to the pyridine ring. A scheme showing the general formula of the 4-nitropyridine *N*-oxide is shown in figure 1.

The following 4-nitropyridine *N*-oxides were investigated: 2-methyl (2Me), 3-methyl (3Me), 2,3-dimethyl ($2,3Me_2$), 2,5-dimethyl ($2,5Me_2$), 2,6-dimethyl ($2,6Me_2$), 3,5-dimethyl ($3,5Me_2$), 2,3,6-trimethyl ($2,3,6Me_3$), 2-methylamino-3-methyl (2MeNH3Me), 2-methylamino-5-methyl (2MeNH5Me), 2-methylamino-6-methyl (2MeNH6Me), 2-ethylamino-3-methyl (2EtNH3Me), 2-ethylamino-5-methyl (2EtNH5Me), and 2-ethylamino-6-methyl (2EtNH6Me). To expand the area for drawing conclusions about the influence of the medium on (acid + base) equilibria establishing in systems with the 4-nitropyridine *N*-oxides we performed a correlational analysis of the pK_a values of the protonated pyridine *N*-oxides in methanol and acetone and in methanol and acetonitrile, besides that in methanol and water. Because of lack in the literature acidity constants of the *N*-oxides studied in water, pK_a values in this solution [34] were obtained from a linear relationship between pK_a values of the protonated pyridine *N*-oxides in acetonitrile and water.

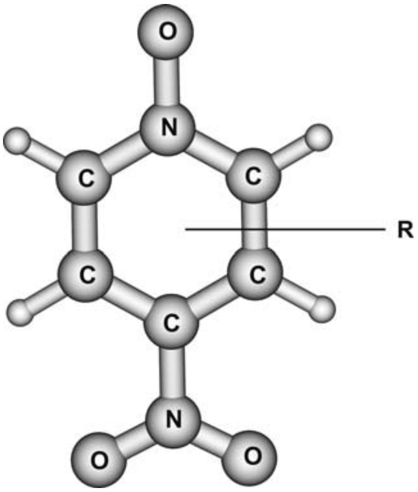

FIGURE 1. Structure of substituted 4-nitropyridine *N*-oxide. R denotes at least one substituent.

2. Experimental

The syntheses of derivatives of 4-nitropyridine *N*-oxide were described previously in paper [34] and references cited therein.

Perchlorates of *N*-oxides under study were prepared by mixing together equivalent quantities of a 72% aqueous perchloric acid with *N*-oxide in methanol. The mixture was vacuum concentrated. The residue was filtered off, washed twice with chloroform and dried in a vacuum dessicator over P_2O_5 at room temperature.

Picric acid was purified by triple crystallization from ethanol. Tetra-*n*-butylammonium picrate and perchlorate were obtained by mixing together equimolar amounts of the purified picric acid or 72% aqueous HClO4 solution with 25% tetra-butylammonium hydroxide in ethanol. The salts were crystallized twice from ethanol. Tetra-*n*-butylammonium picrate was obtained by mixing together equimolar amounts of the purified picric acid with 25% tetra-*n*-butylammonium hydroxide in methanol. Tetra-*n*-butylammonium perchlorate was obtained by mixing together equimolar amounts of 72% aqueous HClO4 solution with 25% tetra-*n*-butylammonium hydroxide in methanol. Both salts were crystallized twice from ethanol. Tetra-*n*- butylammonium chloride was purified by triple crystallization from a 1:1 mixture acetonitrile and ethyl acetate. Purity of the simple perchlorates of *N*-oxides was checked by the elemental analysis. The results about the purity of studied species are shown in table 1.

Methanol (MeOH) was dried over a freshly calcined sodium sulfate for several days. After decantation, *ca.* 100 cm^3 of the solvent was refluxed over 10 g of magnesium metal and 2 g of iodine until discoloration. After addition of 900 cm^3 of MeOH, the refluxing was continued for 30 min. The solvent was then distilled over a Vigreaux column. A fraction boiling at $T = 337.7$ K was collected and further distilled over tartaric acid ($0.4\ g \cdot dm^{-3}$ in methanol).

Dimethyl sulfoxide (DMSO) was kept over dried $4 \cdot 10^{-8}$ cm (4A) molecular sieves for 24 h. It was then dried