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A Study of Acid-Base Equilibria in Acetonitrile Systems of 2-Halo(Cl,Br,I)-4-nitropicoline(3,5,6) N-oxides

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Abstract: An attempt has been made to determine potentiometrically (1) acid dissociation constants of cations obtained by protonation of nine trisubstituted pyridine N-oxides, namely 2-halo(Cl, Br and I)-4-nitropicoline N-oxides with the methyl group at positions *3*, *5*, and *6*, as well as (2) the cationic homoconjugation constants of these cationic acids with conjugated N-oxides in acetonitrile. On the basis of the substitution effect, variations of the acid dissociation constants of the trisubstituted pyridine N-oxide cations are discussed. The determined pK_a values of the protonated 2-halo-4-nitropicoline N-oxides are compared with the previously determined equilibrium constants of the cationic acids conjugated with the mono- and disubstituted pyridine N-oxides in acetonitrile. Further, based on the pK_a values of the protonated 2-halo-4-nitropicoline N-oxides in acetonitrile, supplemented with correlations between pK_a's of the protonated mono- and disubstituted pyridine N-oxides in acetonitrile and water, the pK_a's of the acids conjugated with the trisubstituted N-oxides studied in aqueous solutions have been estimated. Moreover, it has been concluded that the cationic homoconjugation constants cannot be determined by potentiometric titration in acetonitrile solutions of the 2-halo-4-nitropicoline N-oxide systems.

Keywords: acidic dissociation, cationic homoconjugation, 2-halogeno(Cl,Br,I)-4-nitro-(3,5,6)-picoline N-oxides, potentiometric titration, acetonitrile.

Introduction

The chemistry of heterocyclic amine N-oxides has aroused widespread interest owing to exceptionally high bioactivity of these compounds [1] encompassing, among others, antibiotics, antibiotic antagonists and compounds exhibiting cancerostatic, mutagenic, sedative, anticonvulsive and fungistatic efficacy [2]. However, the mechanism of these activities has been neither recognized nor explained. According to recent reports, the N-oxides of heterocyclic amines play an important role in reactions of the modification of enzymes and biological reductive systems, as well as factors substituting some functions of nucleic acids [3,4]. Referring to the 2-halo-4-nitropicoline N-oxides studied here, an important feature is [5] that the presence of the nitro group has been crucial for developing antifungal efficacy of these compounds. In this respect, all studies concerned directly or indirectly with the electronic structure of the N-oxides of heterocyclic amines substituted with the nitro group and with their protonated forms are of particular importance, as they may contribute to understanding the mechanism of antifungal activity of these compounds. Previously, spectral characteristics of 2-chloro- [6], 2-bromo- [7] and 2-iodo-4-nitropicoline N-oxides [8] have been reported both in the UV and IR spectral ranges [9]. Further, this being of particular importance owing to the presence in their molecules of substituents of different electronegativities in resonance positions to each other and to the N-oxide group, the ^{1}H-NMR [10] and ^{13}C-NMR [9,11] spectra were carried out. This allowed not only the effect of the position and nature of the substituents on chemical shifts to be determined, but also to assess their influence on the coupling constants. Furthermore, a satisfactory agreement has been found between the measured and calculated dipole moments of the N-oxides considered [12]. However, there are very few data in the chemical literature on acid-base properties of trisubstituted pyridine N-oxides, in particular of 2-halo-4-nitropicoline N-oxides, in both non-aqueous and aqueous solutions.

On the other hand, within the framework of a research project on equilibria in solution of heterocyclic amine N-oxides in the polar aprotic solvent, acetonitrile, dissociation equilibria of cationic acids conjugated with mono- [13-15] and disubstituted [16] derivatives of pyridine N-oxide, Eq. (1), were investigated [1-5]:

$$BH^{+} + SH \rightleftarrows B + SH_2^{+} \qquad K_a \qquad (1)$$

along with the equilibria of cationic homoconjugation of these acids with conjugated N-oxides resulting in the formation of symmetric hydrogen-bonded complex cations, BHB^{+} [18-24]:

$$BH^{+} + B \rightleftarrows BHB^{+} \qquad K_{HOMO} \qquad (2)$$

In these equations B stands for an N-oxide molecule and SH for an acetonitrile molecule, the latter being an aprotic polar solvent of weak amphiprotic properties.

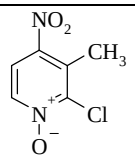
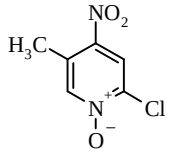
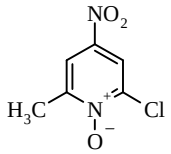
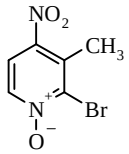
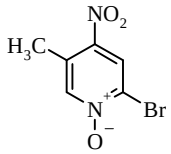
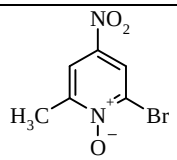
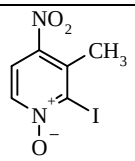
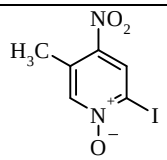
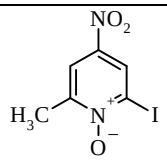
The purpose of this work was to determine the acid dissociation constants of protonated 2-halo-4-

nitropicoline N-oxides and, in the case of attaining an equilibrium, of the equilibrium constant of cationic homoconjugation of these acids with conjugated nonprotonated N-oxides in acetonitrile (AN). The determined pK_a values were subsequently utilized to discuss the influence of the substitution, including position of the substituent, on the basicity of the pyridine N-oxide. Moreover, on the basis of the pK_a values of the trisubstituted pyridine N-oxides determined in acetonitrile, and by utilizing the previously established correlation between the pK_a's in acetonitrile and water for the mono- and disubstituted pyridine N-oxides, the pK_a values of the 2-halo-4-nitropicoline N-oxides in aqueous solutions were estimated. The main series of N-oxides studied were trisubstituted pyridine N-oxide derivatives {2-halo(Cl,Br,I)-4-nitropicoline(3,5,6-CH_3 substituted) N-oxides}: 2-chloro-4-nitro-3-methylpyridine N-oxide (2Cl4$NO_2$3PicO, **1**), 2-chloro-4-nitro-5-methylpyridine N-oxide (2Cl4$NO_2$5PicO, **2**), 2-chloro-4-nitro-6-methylpyridine N-oxide (2Cl4$NO_2$6PicO, **3**), 2-bromo-4-nitro-3-methylpyridine N-oxide (2Br4$NO_2$3PicO, **4**), 2-bromo-4-nitro-5-methylpyridine N-oxide (2Br4$NO_2$5PicO, **5**), 2-bromo-4-nitro-6-methylpyridine N-oxide (2Br4$NO_2$6PicO, **6**), 2-iodo-4-nitro-3-methylpyridine N-oxide (2I4$NO_2$3PicO, **7**), 2-iodo-4-nitro-5-methylpyridine N-oxide (2I4$NO_2$5PicO, **8**), and 2-iodo-4-nitro-6-methylpyridine N-oxide (2I4$NO_2$6PicO, **9**).

Results and Discussion

The acid dissociation constants of the protonated 2-halo-4-nitropicoline N-oxides in acetonitrile are summarized in Table 1. They are characterized by relatively small standard deviations, thus indicating that they are well determinable from the potentiometric measurements. The pK_a values are relatively low, of the order of 5 (the highest value 5.56 being for the 2I4$NO_2$5PicO system) and less. This may be explained in terms of the presence of two strong electron-accepting substituents (the nitro group and a halogen) which significantly suppress the basicity of the N-oxide relative to the unsubstituted pyridine N-oxide (pK_a^{AN} = 10.04 [14]). It is worth noting that the values characteristic for the cations of the 2-halo-4-nitropicoline N-oxides are by ten or so, and in extreme case by more than twenty orders of magnitude lower than those of carboxylic acids (pK_a^{AN} values falling in the range 17-21 [26]) and phenols (pK_a^{AN} values are of the order of 16-27 [27], with the exception of picric acid with pK_a^{AN} = 11.0 [28]). In order to visualize the difference in acidities of the cationic acids under investigation and the aforementioned classes of molecular acids it should be borne in mind that the autoionization constant of acetonitrile, pK_s, is 32.2 [29]. Moreover, the pK_a values of the cationic acids conjugated with the 2-halo-4-nitropicoline N-oxides are by several orders of magnitude higher than those typical for mineral acids [30] including sulfuric acid (pK_a^{AN} = 7.9), nitric and hydrochloric acid (pK_a^{AN} = 8.9 for both). This facts allow a conclusion to be drawn that acids conjugated with the trisubstituted pyridine N-oxides are strong ones in the acetonitrile medium, and conversely, the conjugate 2-halo-4-nitropicoline N-oxides are very weak bases comparable with a mono-substituted derivative of pyridine N-oxide, 4-nitropyridine N-oxide, and a disubstituted derivative, 3-bromo-4-nitropyridine N-oxide, with pK_a values of 5.64 [15,17] and 5.19 [16,17], respectively.

Table 1. Structures, full names, abbreviations and numbers used in text for 2-halo-4-nitropicoline N-oxides.

	2-chloro-4-nitro-3-methylpyridine N-oxide	2Cl4NO$_2$3PicO	**1**
	2-chloro-4-nitro-5-methylpyridine N-oxide	2Cl4NO$_2$5PicO	**2**
	2-chloro-4 nitro-6-methylpyridyne N-oxide	2Cl4NO$_2$6PicO	**3**
	2-bromo-4-nitro-3-methylpyridine N- oxide	2Br4NO$_2$3PicO	**4**
	2-bromo-4-nitro-5-methylpyridine N-oxide	2Br4NO$_2$5PicO	**5**
	2-bromo-4-nitro-6-methylpyridine N-oxide	2Br4NO$_2$6PicO	**6**
	2-iodo-4-nitro-3-methylpyridine N-oxide	2I4NO$_2$3PicO	**7**
	2-iodo-4-nitro-5-methylpyridine N-oxide	2I4NO$_2$5PicO	**8**
	2-iodo-4-nitro-6-methylpyridine N-oxide	2I4NO$_2$6PicO	**9**

A comparison of the latter pK_a with those of the 2-bromo-4-nitropicoline N-oxides which vary from 3.27 to 3.74 shows that the substitution of the electronegative halogen in position *2* of the pyridine ring suppresses more dramatically the basicity of the pyridine N-oxide than substitution of the halogen in position *3* (the difference being ca 2 pK_a units; it should, however, be remembered that substitution of the methyl group in the pyridine N-oxide ring increases its pK_a, hence for 2-bromo-4-nitropyridine N-oxide a still lower pK_a value should be expected than for the N-oxides of 2-bromo-4-nitropicolines).

When analyzing the pK_a values of the 2-halo-4-nitropicoline N-oxides, it can be stated that they tend towards a direction foreseeable on the basis of inspection of the influence of substitution effect on the basicity of a pyridine N-oxide derivative. Thus, at a fixed position of one of the electron-acceptor groups (say, the 4-nitro group) and exchange of the halogen at position *2*, the pK_a values markedly decrease when replacing iodine by bromine, the exchange of bromine for chlorine results in a slightly smaller yet distinct decrease (from 3.67 - 5.56 for 2-iodo-4-nitropicoline N-oxides through 3.27 - 3.74 for 2-bromo-4-nitropicoline N-oxides to 3.14 - 3.38 for 2-chloro-4-nitropicoline N-oxides). The most distinct variations are exemplified by 2-halo-4-nitro-5-picoline N-oxides, where the pK_a values sink from 5.56 through 3.74 to 3.38 for the 2-iodo-, 2-bromo-, and 2-chloro- N-oxides, respectively. On the contrary, the smallest changes can be observed for 2-halo-4-nitro-6-picoline N-oxides, for which the pK_a values vary from 3.67 through 3.27 to 3.14 for the 2-iodo-, 2-bromo-, and 2-chloro- *ortho* substituted derivatives, respectively.

Again, at a fixed halogen (Cl, Br or I) at position *2*, the pK_a values change in a regular way depending on the position of the methyl group. The lowest values are observed with 6-methyl substituted derivatives, i.e. *ortho*-substituted relative to the N-oxide group (pK_a varying from 3.67 to 3.14) and the highest with 5-methyl substituted derivatives (pK_a values in the range 5.56 - 3.38). The 3-methyl compounds have intermediate pK_a values (4.29 - 3.19). This order is understandable bearing in mind on the one hand, that positions *3* and *5* are *meta* positions relative to the N-oxide group, and on the other hand that the previously established [13] sequence of pK_a variations for the mono methyl substituted pyridine N-oxides (increase in pK_a of picoline N-oxides substituted at positions *ortho*, through *meta* to *para*). With 2-chloro-4-nitropicoline N-oxides the observed changes are smallest, the pK_a values being in the range 3.14 - 3.38, for 2-bromo-4-nitropicoline N-oxides the pK_a values increase from 3.27 through 3.42 to 3.74 for the 6-methyl derivative, 3-methyl derivative and 2-methyl derivative, respectively, and the distinct changes can be observed in the case of 2-iodo-4-nitropicoline N-oxides (the pK_a values varying from 3.67 to 5.56).

On the basis of a linear relationship between the pK_a values of cationic acids conjugated with these N-oxides in the acetonitrile and aqueous solutions established for the mono- and disubstituted pyridine N-oxides:

$$pK_a^{AN} = 1.83\ pK_a^{W} + 8.56 \qquad (3)$$

and the pK_a values in acetonitrile determined for the protonated 2-halo-4-nitropicoline N-oxides, the

pK_a values of these cationic acids in aqueous solutions, pK_a^W (Table 2) were estimated. As seen, they are very small, most of them falling within the pK_a range of -2 to -3.

Further, the potentiometric titrations have shown that the cationic homoconjugation constants could not be determined from potentiometric measurements for all cases, with the exception of 2I4NO$_2$5PicO system (cf. Table 2). Again, even in this system, where the pK_a is determinable and amounts to 1.54 with standard deviation of 0.85, it is so small and charged with such a large standard deviation, that it can only be considered as a qualitative indication of the presence of cationic homoconjugation equilibrium in this system. In summary, in the 2-halo-4-nitropicoline N-oxide systems studied, cationic homoconjugation equilibria either do not occur or their constants are so small that cannot be determined by the potentiometric method.

Table 2. Acid dissociation constants, pK_a^{AN}, and cationic homoconjugation constants, $logK_{BHB+}$ for 2-halo-4-nitropicoline N-oxides determined in acetonitrile at 298 K, and those estimated from correlation (3) of the pK_a^W values in water.

N-oxide	pK_a^{AN}	log K_{BHB+}	pK_a^W
2Cl4NO$_2$3PicO	3.19 (0.14)	a	-2.93
2Cl4NO$_2$5PicO	3.38 (0.04)	a	-2.83
2Cl4NO$_2$6PicO	3.14 (0.02)	a	-2.96
2Br4NO$_2$3PicO	3.42 (0.08)	a	-2.81
2Br4NO$_2$5PicO	3.74 (0.07)	a	-2.63
2Br4NO$_2$6PicO	3.27 (0.09)	a	-2.89
2I4NO$_2$3PicO	4.29 (0.08)	a	-2.33
2I4NO$_2$5PicO	5.56 (0.02)	1.54 (0.85)	-1.64
2I4NO$_2$6PicO	3.67 (0.01)	a	-2.67

a - the value of cationic homoconiugation constant could not be determined from potentiometric measurements

Experimental

General

Compounds

The N-oxides of 2-halo-(chloro-, bromo- and iodo-)-4-nitropicolines (with the methyl group at positions *3*, *5* and *6* in the pyridine ring) were obtained by the method of Talik and Puszko [31] as follows: to a solution of 10 g of the corresponding 2-halopicoline in 50 cm^3 of glacial acetic acid, 50 cm^3 of a 30% hydrogen peroxide solution was added gradually. The mixture was left for 24 hrs and then maintained at 333 K for 30 hrs. The excess of acetic acid was distilled off under reduced pressure and to the residue 30 cm^3 of concentrated sulfuric acid was added in small portions. This solution was poured on to a nitrating mixture prepared by mixing together 50 cm^3 of nitric acid (d=1.52 g/cm^3) and 30 cm^3 of concentrated sulfuric acid. The nitration was continued for 1.5 hrs at 373 K. The reaction mixture was then poured onto ice and neutralized initially with solid ammonium carbonate and then with ammonia to a distinctly basic reaction. The crude 2-halo-4-nitropicoline N-oxide was filtered off and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, the solvent was expelled and the residue was combined with the filtered product. The 2-halo-4-nitropicoline N-oxides are yellow, crystalline solids with melting points corresponding to those reported in the literature [31], namely 418, 425, 387, 402, 431, 404, 405, 438, and 438 K for the N-oxides of 2Cl4$NO_2$3PicO, 2Cl4$NO_2$5PicO, 2Cl4$NO_2$6PicO, 2Br4$NO_2$3PicO, 2Br4$NO_2$5PicO, 2Br4$NO_2$6PicO, 2I4$NO_2$3PicO, 2I4$NO_2$5PicO and 2I4$NO_2$6PicO.

Simple perchlorates of N-oxides under study were prepared by mixing together equivalent quantities of a 72% aqueous perchloric acid (Merck Co.) with N-oxide in methanol. The mixture was vacuum concentrated. The residue was filtered off, washed twice with chloroform and dried in vacuum over P_2O_5. Pyridine perchlorate was obtained in the same way.

Picric acid (Fluka AG) was purified by triple crystallization from ethanol. Tetra-n-butylammonium picrate and perchlorate were obtained by mixing together equimolar quantities of the purified picric acid or 72% aqueous $HClO_4$ solution with 25% tetra-n-butylammonium hydroxide (Fluka AG) in ethanol. The salts were crystallized twice from ethanol.

Tetra-n-butylammonium picrate was obtained by mixing together equimolar quantities of the purified picric acid with 25% tetra-n-butylammonium hydroxide in methanol. Tetra-n-butylammonium perchlorate was obtained by mixing together equimolar quantities of 72% aqueous $HClO_4$ solution with 25% tetra-n-butylammonium hydroxide in methanol. Both salts were crystallized twice from ethanol. Tetra-n-butylammonium chloride (Serva Co.) was purified by triple crystallization from a 1:1 mixture acetonitrile and ethyl acetate.

2,6-Dinitrophenol (Fluka AG) was purified by triple crystallization from methanol. Tetra-n-butylammonium 2,6-dinitrophenolate was obtained in the same way as tetra-n-butylammonium picrate.

The salt was crystallized twice from ethyl acetate.

Solvents

Acetonitrile (Serva Co.) was purified by the modified Coetzee method [22]. At first the solvent was dried with CaH_2 (10 g/dm^3) for 48 h. After decantation AN was distilled over P_2O_5 (3 g/dm^3). The distillate was dried again with CaH_2 and distilled after 48 h. The purified solvent had a specific conductivity of 4-10 $\cdot 10^{-8}$ S $\cdot$ cm^{-1}.

Experimental procedures

The e.m.f. measurements of the cell:

indicator glass electrode | system studied || modified calomel electrode

were run by an OP-208 digital potentiometer (Radelkis) with an accuracy of ±0.1 mV. An OP-7183 (Radelkis) indicator glass electrode and an OP-08303 (Radelkis) reference calomel electrode were used. The reference calomel electrode, modified by replacing the aqueous KCl solution by a 0.1 mol/dm^3 solution of tetra-n-butylammonium chloride in non-aqueous solvent, was placed in a shortened salt bridge filled with 0.01 mol/dm^3 tetra-n-butylammonium perchlorate solution in the solvent under study. The e.m.f. measurements of the N-oxide perchlorate - N-oxide systems were run at a constant ionic strength. The solution containing N-oxide perchlorate ($BHClO_4$) at a concentration of about 10^{-3} mol/dm^3 was titrated with the solution containing the N-oxide B at a concentration of about 10^{-2} mol/dm^3 and $BHClO_4$ at the same concentration as that of the titrand (to keep the formal ionic strength constant for all titration points). The electromotive force (e.m.f.) was recorded for each titration point, after electrode relaxation (i.e. when the measured potential was stable).

Each e.m.f. measurement in the system studied was preceded by the determination of the characteristic of the glass electrode. The linearity of the response of the glass electrode vs. the modified calomel electrode in acetonitrile was checked by means of the standardizing system: tetra-n-butylammonium picrate - picric acid (pK_a^{AN}=11.0) [28] at a constant ionic strength. 0.001 mol/dm^3 tetra-n-butylammonium picrate solution was titrated with a solution containing picric acid and tetra-n-butylammonium picrate at a concentration of 0.01 mol/dm^3 and 0.001 mol/dm^3, respectively, in order to keep the formal ionic strength constant.

Solutions for potentiometric measurements were prepared on a volume basis. All potentiometric measurements were run at 298.1 ± 0.1 K.

Calculations

The acidic dissociation and cationic homoconjugation constants were calculated from the results of

e.m.f. measurements by the general method of Kostrowicki and Liwo [32-34]. As a basis for the determination of the constants in acetonitrile solutions served parameters **s** (slope of the response of the glass electrode) and $\mathbf{E^o}$ (standard e.m.f.), obtained from potentiometric titrations in standardizing systems together with the results of the potentiometric titrations performed in the systems BH^+/B. The general algorithm designed by Kostrowicki and Liwo is based on a general description of chemical equilibria in ideal solutions and uses non-linear confluence analysis to determine equilibrium parameters from physico-chemical data. It can also take into account the errors in electrode-calibration parameters and composition of the stock solutions and reagents. The aqueous pK_a values from the linear correlation between water and acetonitrile pK_a's were determined by linear regression method.

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