Direct Determination of pK_a Values of Cationic Acids Conjugated to Heterocyclic Amine *N*-Oxides in Polar Aprotic and Amphiprotic Solvents

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The applicability of the direct method of pK_a determination in the case of protonated heterocyclic amine *N*-oxides in a series of polar non-aqueous (aprotic and amphiprotic) solvents has been tested. The method is based on the *p*H determination of the non-aqueous solution of complex salt (the semiperchlorate in this case) formed by the *N*-oxides studied. The direct method not only provides for quick (one data point per each pK_a determined), but also relatively accurate estimates of acidic dissociation constants. It has been experimentally shown on the example of substituted pyridine *N*-oxides that this method is precise enough in all studied non-aqueous solvents when applied to compounds of not too low basicity (the pK_a being of the order of 5 or higher). To prove this, the pK_a values of protonated monocyclic *N*-oxides obtained by the direct method have been compared with those resulting from the potentiometric titration curve. The agreement between the results found by using both methods is very good in most cases, the differences being within standard deviations. Based upon this observation it can be inferred that the pK_a values of protonated bicyclic *N*-oxides in solvents studied determined by using the direct method can be also considered reliable, especially in the case of polar aprotic solvents.

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Introduction.

The potentiometric titration is the most reliable and widely used method, as far as the determination of acid-base equilibrium constants is concerned [1-4]. Many papers have been published [5-8] which refer to the determination of the acidity constants using the potentiometric titration technique. Some work, especially concerning the acidity constants of protonated *N*-oxides has been carried out in our laboratory [3,9-13]. However, to determine the pK_a value from a potentiometric titration curve it is necessary to take into account all the other equilibria present in the systems studied (first of all the homoconjugation equilibrium). Moreover, this way of pK_a determination requires at least one full potentiometric run to obtain one pK_a value.

It is well-known [14-15] that heterocyclic amine *N*-oxides form two types of solid salts with perchloric acid, namely simple perchlorates which contain simple cations of protonated *N*-oxides, BH^+, and semiperchlorates (the complex salts) which contain homoconjugated cations, BHB^+ (where B stands for the *N*-oxide molecule). Direct evidence of the existence of such species are the crystallographic data [16] of the solid semiperchlorates in which the homoconjugated cations with very short symmetrical hydrogen bonds are observed. The presence of the strong symmetrical bonds of this type is also well reflected in the ir [14,17] and nmr [18] spectra of semiperchlorates. The shape of the potentiometric titration curve [9,19], as well as uv-spectra of heterocyclic amine *N*-oxides [20,21], can also serve as confirmation of the presence of the homoconjugated *N*-oxide cations in solutions. The results of semiempirical calculations of homoconjugation energies [22], as well as the theoretical spectra of homoconjugated cations [21], can also be treated as proof of the existence of such chemical species.

Basing on the fact that heterocyclic amine *N*-oxides form semiperchlorates with perchloric acid, a direct method for the determination of the pK_a values of cationic acids conjugated to *N*-oxides was proposed [23]. The direct method is based on the single e.m.f. measurement of the non-aqueous solution of the *N*-oxide semiperchlorate, and assumes that the semiperchlorate solution has an identical composition to that obtained at the stoichiometric point of potentiometric titration in the *N*-oxide simple perchlorate-*N*-oxide system (if the conditions of the same concentrations of semiperchlorate and simple perchlorate solutions is fulfilled). In fact, dissolving a given amount of the complex salt gives, formally, the same effect as mixing the equivalent amounts of protonated and free *N*-oxide, a situation identical with the 1:1 point of the

Table 1

pK_a Values of Substituted Pyridine *N*-Oxides (Monocyclic *N*-Oxides) in Non-aqueous Solvents Studied, Obtained fom Direct Measurements (bold) and Titration Method (values in parentheses are standard deviations), 298.15 K

N-Oxide	Acetonitrile [a]		Nitromethane [b]		Acetone [c]		Methanol	
	DM [d]	KL [e]	DM [d]	KL [e]	DM [d]	KL [e]	DM [d]	KL [e,f]
4-(*N*,*N*-Dimethylamino)pyridine *N*-oxide	**15.62**	15.63 (0.01)	**12.81**	---	**10.20**	---	**6.53**	---
4-Methoxypyridine *N*-oxide	**12.37**	12.28 (0.01)	**10.58**	11.33 (0.02)	---	---	**4.49**	4.69 (0.02)
4-Methylpyridine *N*-oxide	**11.00**	11.00 (0.01)	**9.42**	9.61 (0.12)	**6.20**	6.39 (0.01)	**3.63**	3.50 (0.01)
3-Methylpyridine *N*-oxide	**10.30**	10.31 (0.01)	**8.89**	8.90 (0.16)	**5.47**	5.73 (0.01)	**3.38**	2.91 (0.02)
2-Methylpyridine *N*-oxide	**10.25**	10.23 (0.01)	**8.67**	8.84 (0.26)	**5.12**	5.40 (0.04)	**3.24**	2.80 (0.01)
4-Phenylpyridine *N*-oxide	---	---	**8.66**	8.72 (0.12)	---	---	**3.33**	2.95 (0.01)
Pyridine *N*-oxide	**9.97**	10.04 (0.01)	**8.45**	8.66 (0.07)	**4.95**	5.11 (0.02)	**3.28**	2.69 (0.03)
4-Chloropyridine *N*-oxide	**9.06**	9.05 (0.01)	**7.68**	7.56 (0.07)	---	---	**3.12**	2.05 (0.06)
3-Chloropyridine *N*-oxide	**8.10**	8.17 (0.01)	**7.07**	---	---	---	**3.03**	---
4-Cyanopyridine *N*-oxide	**6.10**	6.28 (0.03)	**5.05**	4.93 (0.15)	**1.35**	2.78 (0.02)	**2.99**	---
4-Nitropyridine *N*-oxide	**5.35**	5.64 (0.03)	**4.02**	4.15 (0.05)	**0.89**	2.05 (0.04)	---	---

[a] pK_a values from ref 23. [b] pK_a values from ref 10. [c] pK_a values from ref 11. [d] pK_a values determinated by using direct method (DM). [e] Data processing by the general algorithm according to Kostrowicki and Liwo (KL). [f] pK_a values from ref 12.

potentiometric titration of simple perchlorate by free base solution. In consequence, the e.m.f. value of the *N*-oxide semiperchlorate solution should have the same value (assuming that titrated *N*-oxide simple perchlorate has the same analytical concentration as the semiperchlorate solution) as at the stoichiometric point of potentiometric titration in the protonated - free *N*-oxide system which corresponds with definite pK_a value:

$$pK_a = \frac{\mathbf{E}^\circ - \mathbf{E}}{\mathbf{S}} \qquad (1)$$

where $\mathbf{E}^\circ$ denotes the value of the standard e.m.f., **E** is the e.m.f. value of *N*-oxide semiperchlorate solution and **s** denotes the slope of the glass electrode characteristic. (Values of $\mathbf{E}^\circ$ and **s** parameters are calculated from the standardization titration curve).

It was proved [23] that the homoconjugation equilibrium does not influence the *p*H value (equal to the pK_a) at the 1:1 point of the potentiometric titration of cationic acid by conjugated base. However, it should be noted that the homoconjugation constant must not be so large as to lead to extremely small equilibrium concentrations of free and protonated base *(i.e.* comparable with the concentration of proton). Moreover, the following conditions have to be fulfilled [23]:

i) The degree of autodissociation of the solvent is negligible. This condition is presumably satisfied for aprotic solvents for which the autodissociation constants are of the order of 10^{-20} and even smaller.

ii) The *N*-oxide semiperchlorate is almost completely dissociated in non-aqueous solvent into homoconjugated cations and anions. It is fully satisfied for moderately polar solvents (all the solvents studied belong to this category) in the concentration range applied [9,19].

iii) The *N*-oxide is a strong enough base in the solvent under study to ensure that the degree of dissociation of its protonated form is very small. The fulfillment of this condition depends on the particular pK_a value. It is well satisfied for the relatively strong bases. It is worth noting that this condition was applied in the derivation of the equations of the Kolthoff method [24], widely used to the determination of acid-base constants.

The main aim of this work is to test the applicability of the direct method of pK_a determination in non-aqueous (polar aprotic and amphiprotic solvents) solutions of heterocyclic amine *N*-oxide semiperchlorates. To do this, the pK_a values of a number of *N*-oxides have been determined in polar aprotic solvents: acetonitrile, nitromethane and acetone, as well as in the polar amphiprotic solvent methanol. Two series of heterocyclic *N*-oxides have been studied, substituted pyridine *N*-oxides (monocyclic *N*-oxides) and substituted quinoline *N*-oxide (bicyclic *N*-oxides).

Table 2

pK_a Values of Quinoline *N*-Oxide and its Substituted Derivatives (bicyclic amine *N*-oxides) in Some Non-aqueous Solvents Studied, Determined by the Direct Method, 298.15 K

N-Oxide	Acetonitrile	Nitromethane	Methanol
4-Methylquinoline *N*-oxide	11.80	9.16	3.56
Isoquinoline *N*-oxide	11.49	8.74	3.47
Quinoline *N*-oxide	10.82	8.17	3.28
4-Chloroquinoline *N*-oxide	9.91	7.62	3.14

EXPERIMENTAL

The semiperchlorates of the heterocyclic amine *N*-oxides under study were synthesized similar to that of pyridine *N*-oxide [25]. In the case of 4-nitro- and 4-cyanopyridine *N*-oxide semiperchlorates appropriate amounts of ethyl acetate were used. Tetra-*n*-butylammonium picrate and perchlorate, as well as picric acid and tetra-*n*-butylammonium chloride were obtained and/or purified by using the standard procedures described elsewhere [19]. Acetonitrile was purified by the modified [9,19] Coetzee method [26]; nitromethane [10], acetone [11] and methanol [12] by using methods described previously.

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

indicator glass electrode	0.001 mole dm^{-3} non-aqueous solution of the *N*-oxide semiperchlorate	modified calomel electrode

were run by an OP-208 digital potentiometer (Radelkis) with the accuracy of ±0.1 mV. The reference calomel electrode, modified by replacing the aqueous potassium chloride solution by a 0.1 mole dm^{-3} solution of tetra-*n*-butylammonium chloride in non-aqueous solvent, was placed in a shortened salt bridge filled with 0.01 mole dm^{-3} tetra-*n*-butylammonium perchlorate solution in the solvent under study.

Each e.m.f. measurement in the solution 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 aprotic solvents was checked by means of the standardizing system: tetra-*n*-butylammonium picrate - picric acid (pK_a^{AN} = 11.0) [24], (pK_a^{NM} = 10.55) [27], (pK_a^{AC} = 6.3) [28] at constant ionic strength. 0.001 mole dm^{-3} tetra-*n*-butylammonium picrate solution was titrated by the solution containing picric acid and tetra-*n*-butylammonium picrate at a concentration of 0.01 mole dm^{-3} and 0.001 mole dm^{-3}, respectively in order to keep the formal ionic strength constant. In the case of methanol solutions, the tetra-*n*-butylammonium 2,6-dinitrophenolate-2,6-dinitrophenol standardizing system (pK_a in methanol [29] is 7.8) was used. (It was found [12] that for the picric acid standardizing system the response of indicator glass electrode is no longer linear in methanol solutions).

Solutions for potentiometric measurements were prepared on the volume basis. All potentiometric measurements were run at 298.15 ±0.10 K.

Results and Discussion.

Using the direct method described above, the pK_a values of two series of heterocyclic *N*-oxides were determined in polar non-aqueous solvents under study. In the case of substituted pyridine *N*-oxides the results of direct measurements have been compared with those resulting from the potentiometric titration method, whereas for bicyclic *N*-oxides the pK_a values were determined using the direct method only. The values obtained for monocyclic *N*-oxides together with those resulting from the potentiometric titration curve are collected in Table 1. As shown, in the case of acetonitrile, conformity between these values is very good in most cases, the differences being within the standard deviations. For the least basic *N*-oxides (4-nitropyridine and 4-cyanopyridine *N*-oxide) however, the discrepancy is significant due to the considerable degree of dissociation of the protonated species. Based on the values obtained, it can be concluded that the direct method gives correct values if pK_a is higher than 9, though reliable estimates can be obtained in all the cases considered, even for values as low as 5.

Table 1 shows also the nitromethane pK_a values of substituted pyridine *N*-oxides obtained using the direct method, as well as those calculated from the complete titration curve. The agreement between the values of constants found by the two above-mentioned methods is quite good (the discrepancy being almost within the standard deviation) for most *N*-oxides under study. According to expectations, the discrepancy is significant for the least basic *N*-oxides (*e.g.*, 4-nitropyridine, 4-cyanopyridine) due to the degree of dissociation of their protonated forms. On this basis it can be inferred that the lower limit of reliable estimates of the pK_a values in nitromethane solutions can be evaluated as being 5 (as in acetonitrile). However, one can notice that for 4-methoxypyridine system the observed discrepancy is also significant. Nevertheless, in this case the above-mentioned phenomenon has a different reason, and can be explained in terms of the presence of the additional equilibria of hydration of the *N*-oxide and its protonated form. The presence of every user-defined additional equilibria (hydration in this case) can be taken into account when to the calculations of the acid-base equilibrium constants the "general" method of Kostrowicki and Liwo [30-32] is applied. On the contrary, in the case of direct method all the additional equilibria are neglected (owing to the simplifications of method). On this basis it can be concluded that the direct method of pK_a determination is limited to the equilibria systems which consist of only the fundamental acid-base equilibria (*i.e.* the acid dissociation and cationic homoconjugation), as well as the ionic association of the *N*-oxide semiperchlorate. Therefore, when hydration equilibria occur in the acid-base system considered (or/and any other additional ones), the pK_a values obtained by the direct method and calculated from the complete titration curve cannot be compared.

Similar conclusions can be drawn regarding acetone pK_a val-

ues obtained by using the two potentiometric methods discussed. However, better conformity [12] can be observed when the pK_a values obtained by the direct method are compared with those calculated from a potentiometric titration curve with the use of Kolthoff's method [24]. This observation can serve to confirm that the direct method offers the same simplifications as Kolthoff's treatment, therefore these two methods give very similar results of calculations. The Kolthoff's algorithm neglects the solvated proton concentration in mass-balance equations which certainly holds for sufficiently strong bases, but causes a gradual increase in error with increasing acidity of the conjugated acids. The small discrepancy between the results of both treatments mentioned, even for the least basic *N*-oxides, confirms with the conclusions based on the acetonitrile and nitromethane pK_a values that the simplifications introduced do not cause a significant error if pK_a value is higher than 5.

Results of the direct and potentiometric titration methods in methanol indicate worse conformity of the pK_a values with respect to those obtained in aprotic solvents. Quite good agreement has been observed in the case of the most basic *N*-oxides (*e.g.*, 4-methoxypyridine, 4-picoline *N*-oxide) only. The existence of this conformity in the case of 4-methoxypyridine *N*-oxide, despite the fact that this *N*-oxide is hydrated, can be explained in terms of similar values of the autoprotolysis constants of water and methanol [33] (their p*K* values equal to 14 and 16.7, respectively). This similarity means that the pK_a values determined by using two potentiometric methods are not dependent on the degree of hydration. In the case of less basic *N*-oxides practically complete dissociation of their protonated forms makes the precise determination of pK_a impossible. It can be concluded from this that in methanol solutions the direct method is limited to the most basic *N*-oxides only (not being precise in the case of medium and feebly acidic ones), whereas in the case of aprotic solvents this limitation applies to the least basic *N*-oxides only. The above-mentioned limitation results from the relatively high value of the methanol autoprotolysis constant (16.7 in the p*K* scale) which results in the degree of autodissociation being significant.

Using the direct method, the pK_a values of protonated bicyclic *N*-oxides: 4-methylquinoline, isoquinoline, quinoline and 4-chloroquinoline in some non-aqueous solvents studied have been determined. Results of measurements have been shown in Table 2. On the basis of collected pK_a values it can be concluded that the basicity of quinoline *N*-oxide and its derivatives increases (likewise the basicity of substituted pyridine *N*-oxides) in the following order of non-aqueous solvents: methanol, nitromethane, acetonitrile. They also confirm the observation from the potentiometric titration method [10,12,13], that the basicity of quinoline *N*-oxide in all solvents under study is similar to the basicity of pyridine *N*-oxide (within the range of 0.5 pK_a) Moreover, the basicity of substituted quinoline *N*-oxides changes according to the substituent effect, the influence of substitution being, however, less pronounced than in the case of monocyclic *N*-oxides. This phenomenon can be explained in terms of the π-electron conjugation effect of aromatic rings.

To sum up, it can be concluded that the direct method not only provides for quick (one e.m.f. measurement per each pK_a value determined), but also accurate estimates of pK_a values for most systems studied, and comparatively accurate estimates for the other ones. This method can be recommended for the determination of the acid dissociation constants of weak cationic acids, especially in the cases when the simple salts are not formed, or the solubility of compounds studied (*N*-oxides or conjugated cationic acids) in solvent used is low.

It is worth noting that using semiperchlorates as reagents is particularly recommended for *N*-oxides, as, in contrast to hydroscopic and unstable simple perchlorates they are stable [34] and almost non-hygroscopic. They can be obtained easily and highly purified. For this reason heterocyclic amine *N*-oxides are very often purified, studied and characterized as the salts with strong inorganic acids. Some *N*-oxides are stable in the form of salts [35] only.

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