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Determination of Acidic Constants of some Phenyl-hydroxyiminoethyl Quinolinium Compounds

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Mixed acidic constants (pK'_a) of quinolinium oximes [1-(2-phenyl-2-hydroxyiminoethyl)-1-quinolinium chloride (**F**-1), 1-(2-phenyl-2-hydroxyiminoethyl)-1-isoquinolinium chloride (**F**-2), 1-(2-phenyl-2-hydroxyiminoethyl)-1-(4′-methyl)-quinolinium chloride (**F**-3), and 1-(2-phenyl-2-hydroxyiminoethyl)-1-(6′-methyl)-quinolinium chloride (**F**-4)] have been determined via their UV absorption spectra recorded in the series of *Britton-Robinson*'s buffer solutions in the pH region 8.74–11.28 ($t = 25 \pm 0.5\,°C$, $\mu = 0.2$). The obtained pK'_a values are in good agreement with those achieved by applying graphical methods. The following pK'_a values have been obtained: 9.93 for **F**-1, 9.90 for **F**-2, and 10.02 for **F**-3 and **F**-4.

On the basis of potentiometric titrations thermodynamic acidic constants (pK_a) of compounds **F**-1, **F**-2, **F**-3, and **F**-4 have been determined and they were found to be 9.82, 9.71, 9.91, and 9.86, respectively. The values obtained by transferring pK_a into pK'_a are in good agreement with the values obtained spectrophotometrically.

(Keywords: Acidic constants; Potential antidotes; Quinolinium oximes)

Bestimmung der Aciditätskonstanten einiger Phenyl-hydroxyiminoethylchinolin-Verbindungen

Die Mischaciditätskonstanten (pK'_a) der Chinolin-Oxime 1-(2-Phenyl-2-hydroxyiminoethyl)-1-chinolinium chlorid (**F**-1), 1-(2-Phenyl-2-hydroxyiminoethyl)-1-isochinolium chlorid (**F**-2), 1-(2-Phenyl-2-hydroxyiminoethyl)-1-(4′-methyl)-chinolinium chlorid (**F**-3) und 1-(2-Phenyl-2-hydroxyiminoethyl)-1-(6′-methyl)-chinolinium chlorid (**F**-4) wurden durch ihre UV-Absorptionspektren

in einer Reihe von *Britton-Robinson*-Pufferlösungen im *pH*-Intervall 8.74–11.28 ($t = 25 \pm 0.5$ °C; $\mu = 0.2$) bestimmt. Die berechneten pK_a-Werte stimmen mit den über graphische Methoden erhaltenen Ergebnissen überein. Der pK_a'-Wert beträgt 9.93 für die Verbindung **F**-1 und 9.90 für **F**-2, sowie 10.02 für **F**-3 and **F**-4.

Auf Grund der potentiometrischen Titration wurden auch die thermodynamischen Aciditätskonstanten (pK_a) berechnet: 9.82 für **F**-1, 9.71 für **F**-2, 9.91 für **F**-3 und 9.86 für **F**-4. Wenn man diese Konstanten in Mischaciditätskonstanten überträgt, erhält man Werte, die mit den durch spektrophotometrischen Bestimmungen erhaltenen Werten gut übereinstimmen.

Introduction

Pyridinium oximes are of special interest as antidotes in organophosphorus (pesticides, nerve gases) poisonings because they are able to reactivate cholinesterases inhibited by these poisons and thus save lives of intoxicated[1].

According to some authors[2–4] the pK_a values of oximes are of prime importance for the reactivating efficiency, i.e. it should be such that sufficient amount of ionized form of oxime is present at physiological *pH*. The optimal pK_a value of pyridinium oximes is evaluated to be about 8 Refs.[2–4] though compound HI-6* ($pK_a = 7.2$) is an excellent reactivator[5].

Besides pyridinium oximes some other oximes were also tested as potential antidotes in organophosphorus poisonings and among them were phenyl-hydroxyiminoethyl quinolinium compounds[6–8]. It was found that they were efficient in treating poisoned animals, but were ineffective as reactivators of inhibited cholinesterases. Having in mind the above finding as well as the fact that we could not find any data on their acidic constants in the available literature, it seemed of interest to determine their acidic constants and thus contribute to better understanding of their antidotal efficiency.

Experimental

UV spectra were recorded on a spectrophotometer Pye Unicam SP-6-500 with quartz cells of 10 mm. A PHM-62 standard *pH*-meter (Radiometer, Copenhagen) equipped with a glass electrode was used for all *pH* determinations (accuracy ± 0.01 *pH* units). For potentiometric titrations a TTT 60 titrator with autoburrete ABU 12 (Radiometer, Copenhagen) was used (accuracy 0.001 ml). Ultra-Thermostat Medigen (Dresden) was used for keeping a constant temperature (25 ± 0.2 °C) during the titrations. The pK_a values were calculated using a Texas Instruments TI 59.

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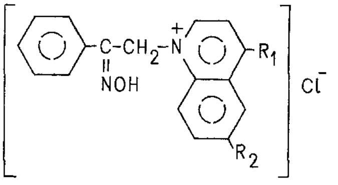
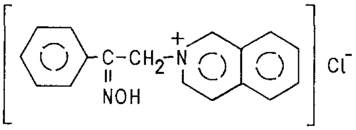
* 1-(2-Hydroxyiminomethyl-1-pyridinio)-3-(4-carbamoyl-1-pyridinio)-2-oxapropane dichloride.

The compounds **F**-1–4 were synthesized according to the procedures described previously[6,7] and were > 99.5% pure. All other chemicals used were of analytical grade purity (Merck) and the water was bidistilled. Boiled bidistilled water was used to prepare all the solutions for potentiometric pK_a determinations.



R_1=H, R_2=H, (F-1)
R_1=CH_3, R_2=H, (F-3)
R_1=H, R_2=CH_3, (F-4)



(F-2)

For spectrophotometric determination of pK'_a values freshly prepared standard water solutions of the oximes (10^{-3} *M*) were used. The *pH* was adjusted by using 2 *M* solutions of hydrochloric acid and sodium hydroxide. For determinations in the *pH* region 8.74–11.28 *Britton-Robinson* buffer solutions were used[9]. The mixtures of phosphoric, boric and acetic acid (0.04 *M*) were stirred together with the corresponding volumes of sodium hydroxide (0.2 *M*). The ionic strength of 0.1 *M* was kept constant by addition of potassium chloride (2 *M*). The ionic strength of solutions used for spectrophotometric determinations was 0.2 *M*; it was kept constant by the addition of 2 *M* potassium chloride solution. For potentiometric determinations of pK_a values freshly prepared 10^{-2} *M* standard water solutions of the compounds were used. The solutions were prepared by diluting accurately weighted solid substances in boiled and cooled bidistilled water. For potentiometric titrations a 0.1455 *M* standard sodium hydroxide solution was used; the concentration was determined by titrating standard potassium hydrogenphthalate solution using phenolphthalein as indicator.

Spectrophotometric Determination of pK'_a

To a 10 ml volumetric flask standard oxime solution (1.00 ml) was transferred 5.00 ml of *Britton-Robinson* buffer solution (*pH* 2.17–11.27); 0.50 ml of potassium chloride solution were added and the flask was filled up with bidistilled water to the mark.

By the same procedure the oxime solutions of the same concentration were prepared in 0.1 *M* solutions of hydrochloric acid and sodium hydroxide.

The measurements were performed immediately after the preparation of probes with referent solutions at 25 ± 0.5 °C and at constant ionic strength (0.2 *M*).

The pK'_a values were calculated using the following equation:

$$pK'_a = pH - \log \frac{\varepsilon_{HB} - \varepsilon}{\varepsilon - \varepsilon_B} \qquad (1)$$

where ε_{HB} and ε_B are the molar absorption coefficients of the acid and its conjugated base and ε is the molar absorption coefficient at given *pH* and wavelength[10].

Graphical Determinations of pK'_a

A graph $\log\frac{\varepsilon_{HB}-\varepsilon}{\varepsilon-\varepsilon_B}$ vs. *pH* gives a straight line, the intercept at the abscisa giving the pK'_a value.

The pK'_a values can also be determined by following the absorption changes in dependence of *pH* at wavelengths where these changes are most pronounced.

Potentiometric Determination of pK'_a

Into a special potentiometric titration vessel with a double bottom (which could be thermostated) 5.00–20.00 ml of standard oxime solution is transferred and bidistilled water added up to 20.00 ml.

Before beginning the titration a stream on nitrogen is passed through for 5–10 min and the inert atmosphere should be kept constant during the titration. At the beginning of the titrations 0.005 ml portions of standard sodium-hydroxide solution were added from autoburrete, until a constant *pH* value is obtained. In the neutralization region $\tau(0.2\text{–}0.8)$* 0.01 ml portions of sodium-hydroxide solution were added. Each *pH* value is read several times and the stirrer is stopped only during readings. The temperature during titration is kept constant (25 ± 0.2 °C) using a thermostat.

Before each titration the *pH*-meter was calibrated by using standard buffers (4.01 ± 0.01 and 9.18 ± 0.01).

Determination of pK_a *Values*

The reactions of compounds **F**-1–4 during titration with sodium hydroxide can be presented by the following equation:

$$HB^+ + NaOH \rightarrow H_2O + Na^+ + B \tag{2}$$

For potentiometric titrations with standard sodium-hydroxide solution according to which the pK_a values were determined the following relationship is valid:

$$c_{tot,corr} = \frac{c_{tot}\cdot V_{H_2O}}{V_{H_2O}+V_{NaOH}} \tag{3}$$

where $c_{tot,corr}$ is the momentary total concentration of acid base pair, c_{tot} is the corresponding initial concentration of acid-base pair, V_{H_2O} is the initial volume of the solution and V_{NaOH} the volume of the titrant added.

The concentration of the titrant in the solution (c_{NaOH}) is:

$$c_{NaOH} = \frac{M_{NaOH}\cdot V_{NaOH}}{V_{H_2O}+V_{NaOH}} \tag{4}$$

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* τ is the degree of titration which represents the ratio of the amount of added base and that amount of base required for total neutralization.

from which follows:

$$[B] = c_{\mathrm{NaOH}} - [\mathrm{OH}^-] \tag{5}$$

$$[\mathrm{H}B^+] = c_{\mathrm{tot,corr}} - [B] \tag{6}$$

For the determination of pK_a of compounds tested ($\mathrm{H}B^+$) the following equation is applied:

$$K_a = \frac{a_{\mathrm{H_3O^+}} \cdot [B]}{[\mathrm{H}B^+] \cdot f_{+/-}} \tag{7}$$

By inserting the expressions from equations (5) and (6) into equation (7) we obtain:

$$K_a = \frac{a_{\mathrm{H_3O^+}} \cdot (c_{\mathrm{NaOH}} - [\mathrm{O\bar{H}}])}{(c_{\mathrm{tot,corr}} - [B]) \cdot f_{+/-}} \tag{8}$$

where $f_{+/-}$ is calculated according to *Davies* equation[10].

The pK_a values were transferred into pK_a' values using the equation:

$$K_a \cdot f_{+/-} = K_a' \tag{9}$$

Results and Discussion

The spectrophotometric determination of pK_a' values of compounds **F**-1, **F**-2 and **F**-3 at 265 nm, and of **F**-4 at 260 nm and some nearby wavelengths was made on the basis of their absorption spectra recorded between 240 and 370 nm in solutions of hydrochloric acid and sodiumhydroxide (0.1 *M*). (Fig. 1 and 2) because at these wavelengths the changes of absorbance were most pronounced.

On the basis of absorption spectra recorded in *Britton-Robinson* buffer solutions in the *pH* region 2.17–11.28 it was observed that there were no changes in absorbance of the examined compounds in the *pH* region between 2.18 and 8.00. Since it was observed that the absorbance changes with the *pH* value in the region 8.74–11.28, this interval was used for spectrophotometric determination of pK_a' values.

The measurements of compound **F**-4 were performed at wavelengths 255 nm, 260 nm and 265 nm, and of other compounds at 260 nm, 265 nm and 270 nm, in a series of seven buffer solutions. The results obtained are presented in Table 1.

The dependence of $\log \frac{\varepsilon_{\mathrm{H}B} - \varepsilon}{\varepsilon - \varepsilon_B}$ on *pH* at $\lambda = 265$ nm for compounds **F**-2 and **F**-3 are presented in Fig. 3, the pK_a' values for compounds **F**-1–4 at three different wavelengths are given in Table 2.

The pK_a' values obtained from intercept points of bilogarithmic curves (Fig. 4) are 9.95, 9.92, 10.02, and 10.03 for compounds **F**-1–4, respectively.

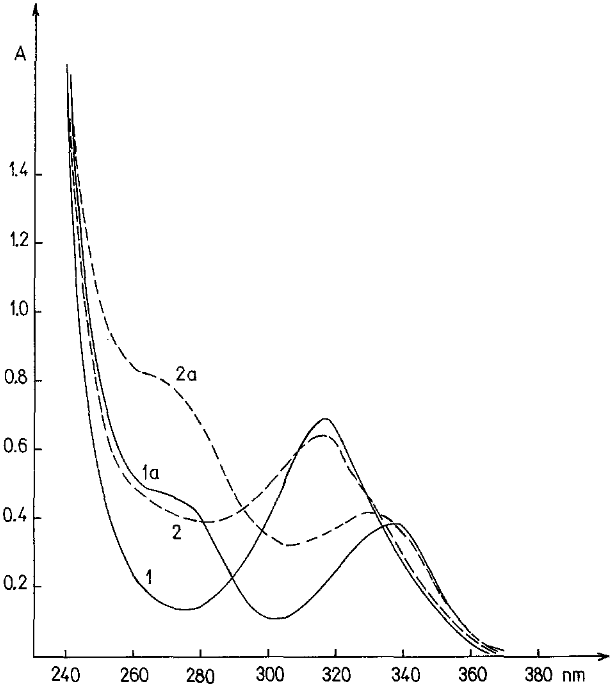

Fig. 1. Absorption spectra of compound **F**-1 (*1* and *2*) and **F**-2 (*1a* and *2a*), conc. $1 \cdot 10^{-4}$ *M*; *1* and *1a* were obtained in HCl (0.1 *M*) and *2* and *2a* in NaOH (0.1 *M*)

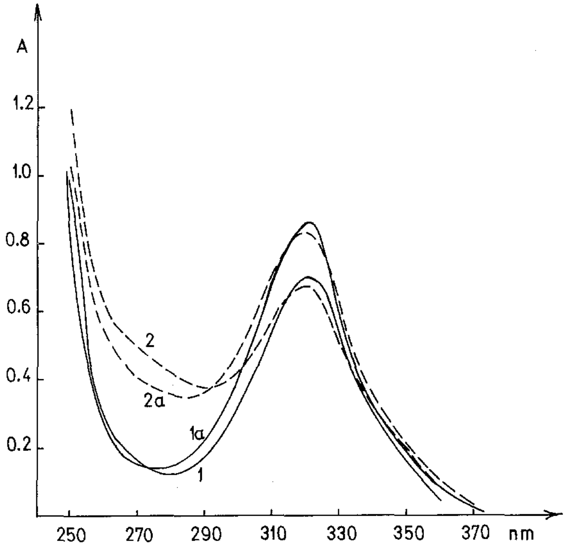

Fig. 2. Absorption spectra of compound **F**-3 (*1* and *2*) and **F**-4 (*1a* and *2a*), conc. $1 \cdot 10^{-4}$ *M*; *1* and *1a* were obtained in HCl (0.1 *M*) and *2* and *2a* in NaOH (0.1 *M*)

Table 1. *Statistical data on spectrophotometric determinations of* pK'_a
[$\mu = 0.2$ *(KCl);* $t = 25 \pm 0.5\,°C$*]*

	F-1	F-2	F-3	F-4
$\bar{x}$	9.93	9.90	10.02	10.02
SD	0.1230	0.1246	0.1225	0.0694
S$\bar{x}$	0.0268	0.0294	0.0267	0.0157
CV (%)	1.24	1.25	1.22	0.69

($n = 21$); $\bar{x}$ — mean value; SD — standard deviation; S$\bar{x}$ — standard deviation of mean value; CV (%) — coefficient of variation; n — the number of determinations.

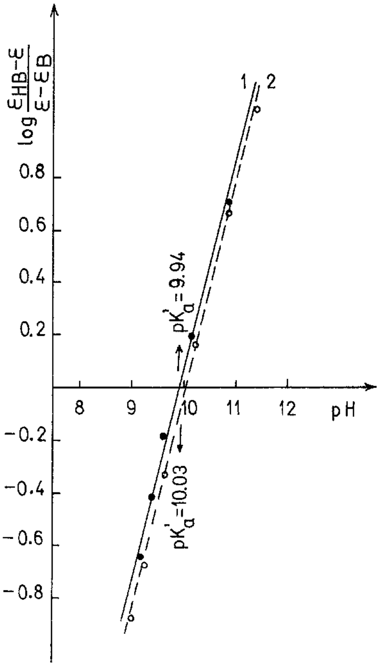

Fig. 3. Spectrophotometric determination of pK'_a of compound F-2 (*1*) and F-3 (*2*) at $\lambda = 265$ nm; $\mu = 0.2$ (KCl); $t = 25 \pm 0.5$ °C

The pK_a values were determined on the basis of potentiometric titrations of oximes with standard sodium-hydroxide solution, using equation (8). Each compound was titrated twice with two different initial oxime concentrations. The pK_a calculations were performed in the neutralization region, the values are given in Table 3.

Table 2. *pK'_a determined on the basis of* $\log\frac{\varepsilon_{HB}-\varepsilon}{\varepsilon-\varepsilon_B}$ *dependence on pH of the solutions* $\mu = 0.2$ *(KCl)*; $t = 25 \pm 0.5\,°C$

Compound	nm	pK'_a	mean value
F-1	260 265 270	9.95 9.95 9.93	9.94
F-2	260 265 270	9.94 9.94 9.93	9.94
F-3	260 265 270	10.05 10.03 9.98	10.02
F-4	255 260 265	9.97 10.02 10.08	10.02

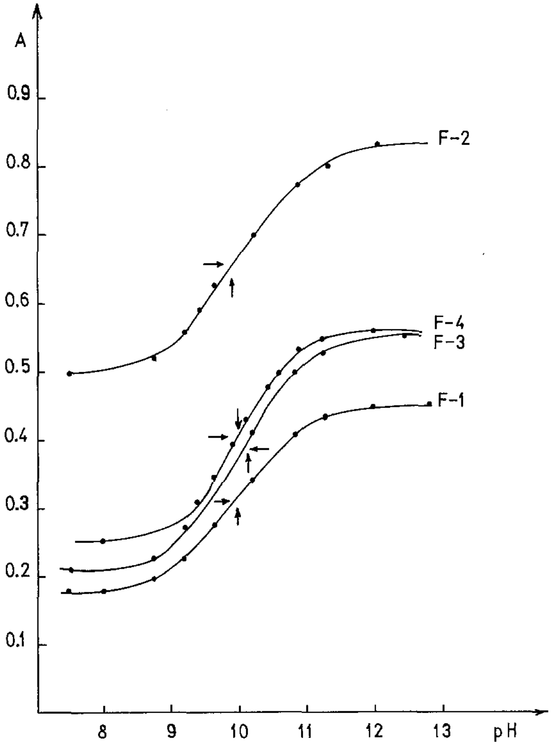

Fig. 4. Changes in absorbance of oxime solutions in dependence of *pH*; $1 \cdot 10^{-4} M$; $\mu = 0.2$ (KCl); $t = 25 \pm 0.5\,°C$

Table 3. *Potentiometric determinations of* pK_a *($t = 25 \pm 0.2\,°C$)*

Compound	c_{tot}	pK_a	n	SD	$S\bar{x}$	CV(%)	pK'_a*
F-1	$5 \cdot 10^{-3}$	9.82	15	0.0125	0.0032	0.13	9.96
	$2.5 \cdot 10^{-3}$	9.82	17	0.0141	0.0034	0.14	9.96
F-2	$1 \cdot 10^{-2}$	9.72	29	0.0162	0.0030	0.16	9.86
	$5 \cdot 10^{-3}$	9.71	15	0.0071	0.0018	0.07	9.85
F-3	$3.375 \cdot 10^{-3}$	9.90	20	0.0176	0.0039	0.17	10.04
	$2.50 \cdot 10^{-3}$	9.91	17	0.0196	0.0047	0.19	10.05
F-4	$3.25 \cdot 10^{-3}$	9.86	20	0.0056	0.0012	0.05	10.00
	$2.50 \cdot 10^{-3}$	9.87	18	0.0124	0.0029	0.13	10.01

* pK'_a calculated for $\mu = 0.2$ following equ. (9).

There is a perfect agreement between the pK_a values obtained from two titrations with various concentrations of oximes, and this proves potentiometry as a precise and reliable method for pK_a determination. Since the results are reproducible, which is important for estimating the rectivating efficiency of oxime[11], this method can be successfully applied for the determination of pK_a values of oximes.

The pK'_a values calculated from pK_a values following equation (9) ($\mu = 0.2$) are in good agreement with those obtained spectrophotometrically.

The somewhat higher pK'_a value of methylated derivatives should probably be ascribed to a positive inductive effect of the methyl group. The lower pK'_a value of compound **F**-2 in comparison to **F**-1 is probably due to the higher influence of isoquinoline compared to the quinoline ring on the dissociation of the hydroxyimino group.

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