Nitrophenoxazines as Neutralization Indicators in Acetone and Pyridine
Determination of Derivatives of Malonic Acid

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Nitrophenoxazines were used as indicators for determinations of a number of weak acids in pyridine and acetone media. The obtained results were checked potentiometrically. Potentiometric measurements in acetone showed that for substituted derivatives of malonic acid, arylhydrazonocyanacetylurethanes, the Hammett equation is valid in the range of potentials between the half-neutralization potentials and the values of σ constants. It has been also shown that considerable attention should be paid to the purity of the solvents used in the determinations of these substances.

In our preceding papers [1, 2] we dealt with the basic study of nitrophenoxazines as perspective acid-base indicators suitable for the use in nonaqueous solutions. The colours of their acidic and basic forms are almost complementary, their absorption maxima are considerably different and, hence, the colour transition is very contrast. When solid or in the solution the indicators are very stable and their preparation is easy. These properties make nitrophenoxazines more advantageous than the indicators recommended for these purposes, such as *o*-nitroaniline [3] or nitrodiphenylamines [4]. From the measured values of dissociation constants and half-neutralization potentials [2] it follows that, similarly as the indicators cited, the nitrophenoxazines could be used in determinations of weak acids.

The aim of this work was to test the suitability of nitrophenoxazines in practical determinations. There were titrated several weak acids whose determinations in acetone and pyridine were already described [5] (pp. 143 and 152), a number of arylhydrazonocyanacetylurethanes, arylhydrazonodiurethanes of malonic acid and nitriles of 1-aryl-6-azauracil-5-carboxylic acid. The choice of indicator suitable for the given determination was made on the basis of the course of potentiometric titration curve of titrated compound and according to previously determined potential region of colour transition [2]. At the same time, in order to follow the influence of the structure of the titrated compounds on the acidity, we measured the values of half-neutralization potentials (HNP).

Experimental

The indicators were prepared as previously described [6]. The stock solutions of indicators in pyridine or acetone were 1×10^{-3} M.

Acetone, anal. grade, was purified by oxidation with $KMnO_4$, dried over anhydrous

$CaCl_2$, and distilled. After this procedure acetone still contained 0.34% of water (according to K. Fischer) and was not suitable in all cases. Therefore, it was further dried over molecular sieve Calsit 5 (activated at 300°C) and redistilled in the absence of atmospheric humidity and carbon dioxide. Acetone contained 0.024% of water.

Pyridine, anal. grade, was dried over solid KOH and anhydrous BaO. It was then fractionated by distillation and fraction boiling at 115—116°C was collected. The water content of the purified pyridine was 0.20%.

0.07 M solution of tetrabutylammonium hydroxide was prepared from ethyl acetate—crystallized tetrabutylammonium iodide (m.p. 144.5—145°C) and from freshly prepared silver oxide [5] (p. 82). Prepared solution of quaternary base was poured through the Amberlite IRA 400 in OH^- form [7]. The titrant was standardized weekly by potentiometric titration against benzoic acid (a standard for organic analysis — B. D. H.). The introduction of different factors for titrations of strong or weak acids (correction for the contents of tetrabutylammonium carbonate [8]) was not necessary when the titrant solution was prepared in the described way.

Methanol was purified by fractional distillation (middle fraction having constant b.p.) and benzene was dried with sodium and distilled.

The titrated compounds were either analytical grade chemicals or were prepared and purified in our laboratory.

Titrations were carried out in closed vessels protected against access of carbon dioxide. A stream of nitrogen purified over anhydrone and ascarite was passed through the titrated solution.

Potentiometric titrations were carried out with a PHK-1 pH-meter using Beckman No. 40308 glass electrode and No. 39970 calomel electrode. The bridge was filled with a saturated solution of KCl in methanol. For titrations in pyridine the pH-meter Radiometer PHM-4 equipped with the same electrode pair was used. Connecting cords to the electrodes were shielded. Reproducibility of measured potentials, namely the half-neutralization potentials, was checked by repeated titrations of benzoic acid which served as a reference standard.

Potentiometric titrations

Weight of the sample (0.2—0.5 mequiv.) was dissolved in 50 ml of acetone or pyridine free of carbon dioxide in a titration vessel. The electrodes, previously washed with solvent, were then introduced and after 2 minutes' passage of nitrogen the solution was titrated with 0.07 M tetrabutylammonium hydroxide.

Titrations with indicators

0.2—0.5 mequiv. of acid was dissolved in 25 ml of acetone or pyridine in the titration vessel, washed with nitrogen and titrated with the same titrant until the maximum colour transition of the indicator was achieved.

In both cases the consumption of the titrant necessary for reaching the equivalence potential or maximum colour transition was referred to the equal amounts of the solvent. Separate blank titrations for acids of different strength were necessary since the difference in the consumption of the reagent in titrations of strong and very weak acids in 50 ml of the solvent reached up to 0.06 ml. In all determinations corrections were made for the change of titrant factor with varying laboratory temperature. In nearly all cases three parallel determinations of each titrated compound were carried out.

Table 1. Titrations in acetone

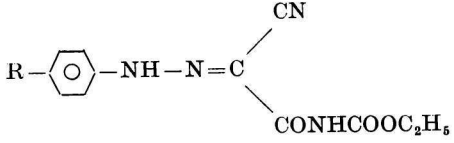
Compound	R	HNP [mV]	Found [%] potentiom.	Found [%] visually	Indicator	Colour change
benzoic acid	—	−114	standard	100.1 ± 0.3	3-NO_2	yellow—blue
benzoic acid	—	−114	standard	100.9 ± 0.5	1-NO_2	orange—blue
sulfuric acid *I*[a]	—	+399	99.25 ± 0.4	99.4 ± 0.5	1,3,7,9-NO_2	orange—greenish-blue
sulfuric acid *I*	—	+399	99.25 ± 0.4	99.6 ± 0.6	1,3,7-NO_2	yellow—blue
sulfuric acid *I*	—	+399	99.25 ± 0.4	101.1 ± 0.8	1,3-NO_2	yellow—violet
sulfuric acid *II*[a]	—	—	99.3 ± 0.2	98.4 ± 0.7	3-NO_2	yellow—blue
sulfuric acid *II*	—	—	99.3 ± 0.2	99.5 ± 0.4	1-NO_2	orange—blue
phenol	—	−382	99.9 ± 0.8	—	—	—
p-acetaminophenol	—	−367	102.5 ± 1.3	—	—	—
o-acetaminophenol	—	−289	101.6 ± 1.1	—		—
p-chlorophenol	—	−319	99.7 ± 0.5	—	—	—
p-carbethoxyphenol	—	−246	100.7 ± 0.8	100.2 ± 0.7	1-NO_2	orange—greenish-blue
p-nitrophenol	—	−103	100.8 ± 0.6	100.2 ± 0.4	1-CH_3-3-NO_2	yellow—green
2,4-dinitrophenol	—	+229	99.65 ± 0.4	—	—	—
2-phenylbenzimidazole	—	−248	100.3[b]	99.9 ± 1.5	1-NO_2	orange—violet
2-(*o*-chlorophenyl)-benzimidazole	—	−236	99.0[b]	—	—	—
phenylhydrazono-malondinitrile		+172	98.3 ± 0.5			—
phenylhydrazono-maloncyanamide	—	+ 16	100.1 ± 0.6	—		—
phenylhydrazono-malondiamide	—	−370	99.9[b]	—	—	—
I	4-H	+124	99.8 ± 0.9	99.3 ± 0.7	3-NO_2	orange—green
I	4-H	+124	99.8 ± 0.9	99.9 ± 0.6	1-NO_2	orange—green
I	4-OC_2H_5	+109	100.6[c]	100.4 ± 1.2	3-NO_2	orange—green
I	4-OC_2H_5	+109	100.6	100.5 ± 1.4	1-NO_2	orange—green
I	4-OCH_3	+108	98 8 ± 0.8	98.7 ± 0.9	3-NO_2	orange—greyish-green
I	4-OCH_3	+108	98.8 ± 0.8	98.9 ± 0.6	1-NO_2	orange—greyish-green
I	4-CH_3	+132	99.2 ± 0.6	99.3 ± 0.7	3-NO_2	orange—green
I	4-CH_3	+132	99.2 ± 0.6	99.5 ± 1.0	1-NO_2	orange—greyish-green
I	3,4-benzo-	+134	100.0 ± 0.5	—	—	—
I	4-Br	+148	99.8 ± 0.6	99.4 ± 0.5	3-NO_2	yellowish-orange—green
I	4-Br	+148	99.8 ± 0.6	99.6 ± 0.8	1-NO_2	yellowish-orange—green
I	4-I	+151	99.9 ± 0.8	—	—	—
I	4-$COCH_3$	+161	100.2 ± 0.8	—	—	—

Table 1 (Continued)

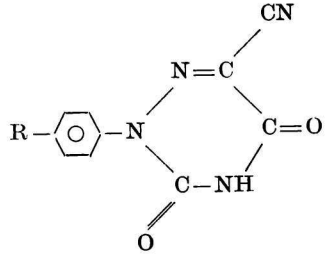
Compound	R	HNP [mV]	Found [%] potentiom.	Found [%] visually	Indicator	Colour change
I	4-$COOC_2H_5$	+164	99.3 ± 0.6	—		—
I	4-NO_2	+194	98.9 ± 0.3	—	—	—
II	4-H	+106	98.7 ± 0.6	—	—	—
II	4-OC_2H_5	+ 96	98.9 ± 0.8	—	—	—
II	4-Br	+134	99.8 ± 0.7	—	—	—
II	4-$COCH_3$	+155	99.85 ± 0.7	—	—	—
II	4-NO_2	+168	98.7[d]	—	—	—
III	4-OCH_3	−134	100.0 ± 1.1	—	—	—
III	4-NO_2	− 51	99.1 ± 0.4	—	—	—

a) Standardized by alkalimetric titration in water; *b*) two parallel determinations; *c*) five parallel determinations; *d*) one determination.

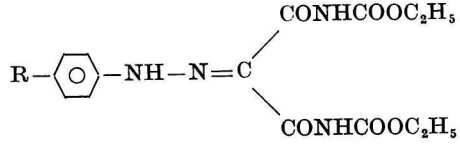
Compounds *I* — arylhydrazonocyanacetylurethanes; *II* — nitriles of 1-aryl-6-azauracil-5-carboxylic acid; *III* — ethyl arylhydrazonomalonyl-bis-carbamines of the following general formulas:



I



II



III

Indicators are marked according to the substitution of the phenoxazine skeleton. *E.g.*, 1-CH_3-3-NO_2 means 1-methyl-3-nitrophenoxazine. The results are given in the form $\bar{x} \pm K_n R$ according to Dean and Dixon.

Table 2

Titrations in pyridine

Compound	R	HNP [mV]	Found [%] potentiom.	Found [%] visually	Indicator	Colour change
benzoic acid	—	−320	standard	99.7[a]	3-NO_2	orange—blue
benzoic acid	—	−320	standard	100.1[a]	1-NO_2	light pink—blue
p-chlorophenol	—	−550	100.3 ± 0.6	—	—	—
p-carbethoxyphenol	—	−432	100.5 ± 0.5	99.1 ± 0.8	1-NO_2	light pink—blue
2,4-dinitrophenol	—	− 74	99.9 ± 0.3	—		—
phenylhydrazono-malondinitrile	—	− 54	100.0 ± 0.5	—	—	—
phenylhydrazono-maloncyanamide	—	−215	100.8 ± 1.0	99.7 ± 0.7	3-NO_2	yellow—green
phenylhydrazonomalondiamide	—	−540	99.9 ± 0.4	—	—	—
I	4-H	−112	99.8 ± 0.6	100.8 ± 1.0	3-NO_2	yellowish-orange—green
I	4-H	−112	99.8 ± 0.6	100.0 ± 0.5	3,7-NO_2	orange—yellowish-green
I	4-OC_2H_5	−147	100.8 ± 0.5	101.3 ± 0.7	3-NO_2	yellowish-orange—green
I	4-OC_2H_5	−147	100.8 ± 0.5	100.6 ± 0.4	3,7-NO_2	orange—yellowish-green
I	4-OCH_3	−141	99.4[b]	—	—	—
I	4-CH_3	−118	99.8 ± 0.8	99.9 ± 1.5	3-NO_2	yellowish-orange—green
I	4-Br	−101	100.4 ± 0.5	101.1 ± 0.8	3-NO_2	yellow—green
I	4-Br	−101	100.4 ± 0.5	100.5 ± 0.0	3,7-NO_2	orange—yellowish-green
I	4-Br	−101	100.4 ± 0.5	100.0 ± 0.9	1,3-NO_2	yellow—greyish-green
I	4-$COCH_3$	−108	100.9[c]	—	—	—
I	4-$COOC_2H_5$	− 78	99.8 ± 0.2	100.2 ± 0.8	3,7-NO_2	orange—greyish-green
II	4-Br	− 70	99.6 ± 0.2	101.3 ± 1.2	3-NO_2	yellow—bluish-green
II	4-Br	− 70	99.6 ± 0.2	100.3 ± 0.5	3,7-NO_2	yellow—green
II	4-$COCH_3$	− 54	100.4 ± 0.7	—	—	—

a) five parallel determinations; *b*) two determinations; *c*) one determination.

The ratio of the weight of samples was 1 : 2 : 2.5 in order to exclude eventual constant errors. The variation range in parallel potentiometric determinations did not exceed 1.2 and 1.8% in the determinations with the indicators.

Table 1 summarizes the results obtained in the titrations in acetone and Table 2 the results of titrations in pyridine. The results are given as mean values from three determinations in per cent of the theoretical consumption of the titrant related to the weight of samples.

Discussion

By comparing the values given in Tables 1 and 2, one can see that the best indicator for the titration of weak acids in acetone is that having the HNP values by about 220—260 mV more negative than the HNP of the titrated compound. This difference is even greater in pyridine. With stronger acids the choice of the indicator does not have any importance (similarly as in titrations in water). For example, the titrations of sulfuric acid in acetone give, due to the high and steep potential jumps, identical results using either tetranitro- or trinitrophenoxazine as indicator. The titration with 1,3-dinitrophenoxazine bears a positive error. It is necessary to titrate sulfuric acid in the second stage of ionization with 1-nitrophenoxazine as indicator. The titration in both stages of ionization can be also accomplished in one sample when 0.1 ml of 1×10^{-3} M solution of tetranitrophenoxazine is added and the sample is titrated from orange to greenish-blue colour transition. Then 0.3 ml of 1×10^{-3} M solution of 1-nitrophenoxazine is added and the titration is continued until composed pinky-violet colour turns to an intensively blue.

Very weak acids (phenol, phenylhydrazone malondiamide) cannot be titrated with indicators in either medium since the least acidic indicator of the series used, 1-nitrophenoxazine, is for this purpose too acidic and also since the potential jumps are too low. Compounds having HNP lower than −400 mV in acetone and lower than −600 mV in pyridine cannot be titrated even potentiometrically. Phenol and phenylhydrazone malondiamide can be yet determined. In the titrations of these compounds the potential jumps are already low and exact results (obtained within low variation range) are only occasional. About twofold rise of the potential jump in the region of the end point was achieved using a combination of smooth platinum and glass electrodes for the titration of phenol and *p*-chlorophenol in acetone. The course of the titration curve was, however, not smooth.

If the content of water in acetone is less than 2% the potential jumps are only slightly lowered and, in visual determinations, the colour transitions at the end point are sharper. As it will be further shown, the potentiometric determinations in wet acetone cannot be recommended generally. The higher results obtained in titrations of acetaminophenols and carbethoxyphenol could be due to their partial hydrolysis during titration.

It is surprising, with regard to the potentiometric titrations, that in acetone benzoic acid can be titrated with 3-nitrophenoxazine as indicator and the compounds of structure *I* (see Table 1) can be titrated both with 3-nitro- and with 1-nitrophenoxazine as indicators. The difference in the results obtained with the two indicators does not seem to be statistically significant.

The choice of the indicator for the titrations in pyridine should be done more carefully since in this case, due to the lower polarity of the solvent, the differences between individual acids become more expressed. Benzoic acid is undertitrated when using 3-nitrophenoxazine as indicator; the titration with 1-nitrophenoxazine used as indicator

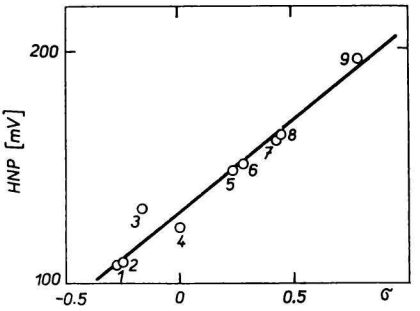


Fig. 1. Dependence of the values of σ constants on HNP with the model *I* in acetone at 25°C.

The values of σ constants were taken from [9]. The line was drawn using the least-square method; $\varrho = 79.5 \pm 4.8$ mV/σ ($\varrho = 1.35 \pm 0.08$ assuming that the unit in the pK_a scale corresponds to 59 mV at 25°C); $HNP_0 = 130.7 \pm 1.8$ mV; $r_{x,y} = 0.987$ and $s_0 = 4.9$ mV at 95% probability level.

1. R = $-OCH_3$; *2.* R = $-OC_2H_5$; *3.* R = $-CH_3$; *4.* R = $-H$; *5.* R = $-Br$; *6.* R = $-I$; *7.* R = $-COCH_3$; *8.* R = $-COOC_2H_5$; *9.* R = $-NO_2$.

gives best results. On the other hand the titration of compounds of the type *I* and *II* with 1-nitro- and 3-nitrophenoxazine bears a positive error. Here, the dinitro derivatives are most suitable indicators. From these 1,3-dinitro derivative has a disadvantage of having less distinct colour transition. The weakest acid that can be determined with 1-nitrophenoxazine as indicator in acetone is ethyl *p*-hydroxybenzoate. Its determination in pyridine bears a negative error, too.

The tables indicate also some correlations between the HNP values and the structures of titrated compounds. In the group of substituted phenols the HNP values obtained in acetone were in expected order. *o*-Acetaminophenol behaves, obviously due to the formation of hydrogen bond, as distinctly stronger acid than phenol or *p*-acetaminophenol.

In the group of compounds of structure *I* there appears the expected correlation, too. The acidity increases with increasing electronegativity of the substituents on the

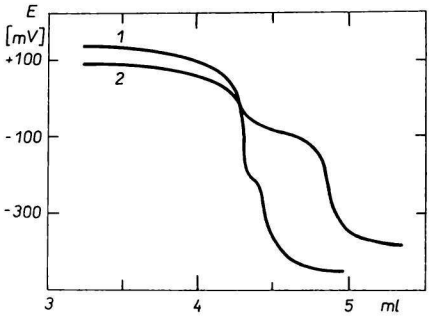
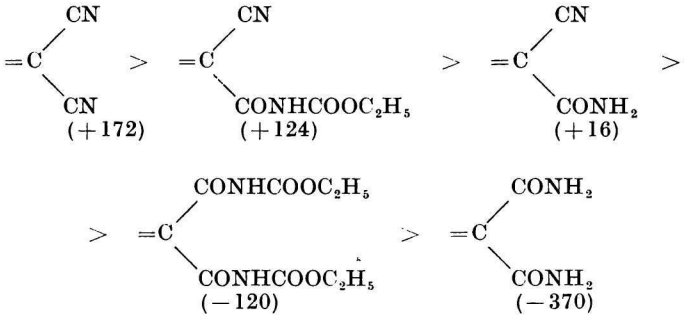


Fig. 2. Titration curves of the compounds of the type *I* in wet acetone.
1. R = $-COOC_2H_5$; *2.* R = $-OC_2H_5$.

phenyl ring. In spite of the fact that the group does not include *m*-substituted derivatives necessary for the confirmation of the Hammett equation, the dependence of HNP values on the σ constants of the substituents is, without doubt, linear (Fig. 1).

Effect of the substituent on the middle carbon atom in the malonic acid residue on the HNP value can be compared with the effects taking place in enols and imides [5] (p. 162). Nitrile group has the strongest effect on the enhancement of the acidity, the effect of other substituents is weaker, as demonstrated by the HNP values of derivatives of phenylhydrazonomalonic acid:



Similar analysis could be done also in pyridine medium, however, the HNP values are here less reproducible and less reliable. Methanol leaking from the bridge of calomel electrode causes a decrease in the range of potential scale and the potassium ions strongly influence the function of glass electrode [10]. The measurements in pyridine require a special calomel electrode [11] which was not used in our titrations.

The difficulties occurring during the titrations of the compounds of structures *I* and *III* in acetone containing 0.34% of water should be also mentioned. Two-step titration curves were recorded; an example is shown in Fig. 2.

The greatest difference occurred with *p*-ethoxy derivative which was contaminated by the product of cyclization. With the other compounds of structures *I* and *III* the difference of subsequent potential jumps was considerably smaller (2—6% of the total consumption of the titrant) and was roughly proportional to the weight of sample.

With other acids of comparable strength (nitrophenols) the one-step smooth potentiometric titration curves were recorded. With the compounds of structure *I* there occurs the increase of the potential in the region of the first potential jump during stabilization while in other regions of the titration curve the potential decreases after addition of the titrant.

As an explanation, the existence of hydrazo-azotautomers [13], stereoisomers [14], cyclization of structure *I* to structure *II* during titration (proceeds under influence of alkali) [12, 15] and hydrolysis of acylurethane or nitrile groups were considered. The detailed analysis of the described phenomenon revealed that the latter reaction, namely the hydrolysis catalyzed by impurities in the solvent, takes place. Similar irregularities did not occur in pyridine. If purified acetone containing 0.024% of water was used as a solvent, the two-step character of the titration curve was suppressed and the consumptions of the titrant were almost stoichiometric (see Table 1). Thus, the purity of the solvent in titrations of the compounds of structures *I* and *III* may be critical.

Slightly lower slopes of titration curves in the region of an end point (when compared with 2,4-dinitrophenol) persist even in highly purified dry acetone or pyridine. This fact can be ascribed to the influence of small amounts of azotautomers in the titrated

compounds. Azotautomers necessitated also the choice of a slightly less acidic indicator than it would correspond to HNP values of the given compounds.

It can be concluded that nitrophenoxazines are indicators that can be recommended for titrimetric determinations of acids of different strength in acetone and pyridine media.

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