DETERMINATION OF ACIDS AND THEIR STRENGTH IN ISOBUTYL METHYL KETONE

Vladimír DOSTÁL, Zdeněk STRÁNSKÝ and Jan SLOUKA

Department of Analytical and Organic Chemistry, Palacký University, 771 46 Olomouc

Received September 11th, 1980

The dissociation constants of nitrophenoxazines in isobutyl methyl ketone (MIBK) were determined and correlated with the HNP values in acetone. Of the derivatives studied, the strongest acid is 1,3,7-trinitrophenoxazine ($pK = 19{\cdot}8$), the weakest, 1-nitrophenoxazine ($pK > 26$). The compounds have no tendency to homo- or heteroconjugation, and were used as indicators in determination of weak acids in MIBK. Some derivatives of malonic acid and of 1,2,4-triazine as well as the intermediates used in their synthesis were determined; their HNP and pK values were established. The shape of the potentiometric titration curves can be of assistance in solving some structure problems.

Isobutyl methyl ketone (4-methyl-2-pentanone; MIBK) was suggested as an outstanding discriminating solvent for acids and bases more than twenty years ago[1]. The figure of recording of a potentiometric titration of a mixture of perchloric, hydrochloric, salicylic, and acetic acids and phenol, documenting the resolving power of the solvent, has been since then reproduced in nearly all monographs dealing with nonaqueous solvents. Nonetheless, the number of theoretical as well as applied works concerned with neutralization titrations in MIBK is surprisingly small as compared with other ketones. Much more use has been made particularly of acetone and ethyl methyl ketone[2].

Juillard and Kolthoff[3] have measured some dissociation constants conductometrically, potentiometrically, and spectrophotometrically and suggested a procedure for the calibration of the glass electrode, thereby establishing a basis for the study of acid–base equilibria in MIBK. This solvent suits to the determination of weak acids of phenol type better than ethyl methyl ketone and is at least as good a medium as pyridine[1], although it is not a basic solvent. Potentiometric determinations have been reported of mineral acids[1], aliphatic monocarboxylic[1,4] and polycarboxylic[4] acids and aromatic monocarboxylic[1,5,8] and polycarboxylic[4,8] acids as well as hydroxy acids[1,6,7]. Metal electrodes are claimed[5] to afford a steeper curve in the titration end point range than the glass electrode. Pietrzyk and Belisle[9] titrated sulphonic acids with diphenylguanidine and compared their strength; they suggest that 2,4-dinitro- and 2,4,6-trinitrobenzenesulphonic acids can serve as reagents for the determination of bases in MIBK. Determined were also phenols[1,5,10,11], poly-

cyclic phenols (also conductometrically[12]), aromatic nitro compounds[13], and some heterocycles[14,15] (nitrotriazines and tetrazines).

Surprisingly enough, no titrations using indicators have been as yet performed and the dissociation constants of suitable indicators have not been determined. The object of the present study was therefore to determine the dissociation constants of some proven indicators from the nitrophenoxazine series[16,17] and to employ them in practical applications. A next aim of the work was to evaluate the effect of homoconjugation upon the shape of the potentiometric titration curves and to examine the relation between the curve shapes and the structure of the acids titrated.

EXPERIMENTAL

Solvents

Isobutyl methyl ketone (*purum*) was purified in the same manner for the equilibria study and for the titrations, although for routine titrations the purity is not a critical factor. One litre of MIBK was allowed to stand for 24 h above 80 g of anhydrous $CaCl_2$ with occasional stirring. The supernatant was poured over a column of neutral Al_2O_3 (4 × 25 cm) activated at 250°C prior to use. The effluent was collected in a vessel containing 50 g of anhydrous $MgSO_4$ (also dried at 250°C), and allowed to stand overnight. The solvent then was placed in a two-stage fractionation apparatus. The outlet from the head of the first column was connected *via* a molecular sieve column (Nalsit 4A, activated at 400°C) to the vessel for the second fractionation. During the distillation the whole apparatus was purged with nitrogen purified by means of anhydrone and ascarite, and protected by using tubes containing the same packing. The solvent obtained was stored in full bottles with perfectly ground-in stoppers. In addition, the bottle necks and stoppers were covered with a polyethylene foil.

If containing acetic acid in quantities so large that it could not be trapped completely by alumina, MIBK was first distilled on a column with 40–60 theoretical plates.

The final product was checked for water and acidic and basic impurities. Water was determined gas chromatographically by a modified procedure recommended for the determination of water in acetone[18]. The analysis was performed on a Chrom 4 apparatus applying the conditions as follows: column 120 × 3 mm, Porapak R packing, temperature 170°C (injection and detector temperature 200°C), detector: katharometer, carrier gas: hydrogen (40 ml/min), gain 1 : 2, injected volume 5 μl. The standard additions method enabled us to determine water in quantities of $10^{-3}\%$. In the four batches purified during the work, the water content was $1{\cdot}7 \cdot 10^{-3}\%$ to $5{\cdot}3 \cdot 10^{-3}\%$. The solvent with the lower water content was used in the equilibria study, that with $5 \cdot 10^{-3}\%$ water was applied to the titrations. Potentiometric titration of 50 ml of the solvent with 0·01M quaternary hydroxide was performed for checking for acidic impurities. A single drop (less than 0·03 ml) of the reagent induced a potential change of 700 mV. Titrations using indicators were carried out also in MIBK fractions with higher contents of acidic impurities. The presence of basic impurities was sought by observing colouration of 0·01M picric acid solution (the latter should remain colourless).

Chemicals and Solutions

Nitrophenoxazines were synthesized at our laboratory[19], their purity was checked by thin layer chromatography. Their solutions were so prepared that $A_{\lambda,max}$ was usually less than 1·0.

A 0·1M tetrabutylammonium hydroxide (TBAH) solution in a benzene–methanol 9 : 1 (*V*/*V*) mixture was prepared from fresh (CO_2-free) silver oxide and tetrabutylammonium iodide[20], and purified by using Amberlite IRA-410 anion exchanger in the OH^- cycle. Diluted solutions were prepared by adding benzene. The titre of the reagents was determined by titration of benzoic acid (standard for elemental analysis).

The measuring cells were calibrated by means of standard picrate buffers. The dissociation constants of nitrophenoxazines were determined by using a mixture containing picric acid and tetraethylammonium picrate in concentrations $5 \cdot 10^{-3}$ and $1 \cdot 10^{-2}$ mol l^{-1}, respectively; the pH* of the buffer was $10{\cdot}5_6$. Its capacity exceeded that of the equimolar mixture owing to the incomplete dissociation of the salt in MIBK. An equimolar mixture of picric acid and tetraethylammonium picrate in concentrations $5 \cdot 10^{-3}$ mol l^{-1} (pH* = $10{\cdot}3_8$) was used for the cell calibration prior to the titrations. The pH values of the two buffers were calculated according to the equation

$$a^3_{SH^+} y_\pm (K_a - K_s) - a^2_{SH^+} [y^2_\pm (K_a c_a + K_s c_s) + K_a (K_s - K_a)] +$$

$$a_{SH^+} y_\pm K_a c_a (K_s - 2K_a) + (K_a c_a y_\pm)^2 = 0 \qquad (1)$$

with the values of the constants $K_a = 1 \cdot 10^{-11}$ and $K_s = 5{\cdot}4 \cdot 10^{-4}$ (ref.[3]).

The mean activity coefficient was calculated from the limiting form of the Debye–Hückel equation,

$$\log y_\pm = -7{\cdot}36(\alpha c_s)^{1/2} \qquad (2)$$

$$\alpha = [-K_s + (K_s^2 + 4K_s c_s)^{1/2}]/2c_s \,. \qquad (3)$$

The acids titrated were mostly prepared at our laboratory; commercial chemicals were reagent grade purity.

Apparatus

Spectrophotometrically were the dissociation constants of the nitrophenoxazines determined on a Unicam SP 1800 spectrophotometer in 3·5 cm glass cells with the volume of 100 ml. The cell compartment was adapted after Karlíček[21] for simultaneous potentiometric and spectrophotometric measurements during titrations in inert atmosphere. Modifications were made for work with nonaqueous solutions. The measuring cell was plugged with a Teflon stopper fitted with openings for introducing the glass and reference electrodes, the burette tip, and a Teflon tube for feeding nitrogen freed from traces of humidity. The two cells were accomodated in the thermostated block at 25 ± 0·5°C.

The potential was measured on a PHM-26 pH-meter using an expanded scale. The titrant, TBAH, was added by means of a Radiometer ABU-12 burette (2·5 ml). The electrode system comprised a Beckman 40495 glass electrode and a calomel electrode (Laboratorní přístroje, Prague) filled with a saturated methanolic solution of KCl; in long-term tests its potential (against a silver chloride electrode) was steadier than that of Radiometer, Beckman, or Seibold electrodes (±1 mV over 48 h in MIBK).

The determination of acids was accomplished by using a Radiometer TTT 11 automatic titrator. Its electrode system was constituted by a Radiometer G 2222c glass electrode and a Radiometer K 401 calomel electrode containing a methanolic solution of KCl.

Dissociation Constants of Nitrophenoxazines

100 ml of an unbuffered solution of the acidic species of the indicator in MIBK and 100 ml of the solvent were placed in the measuring and reference cells, respectively. Purified nitrogen was bubbled through the solution to be measured, the absorption curve of the acidic species of the indicator was recorded in the 350—710 nm region, and the corresponding potential was measured. 0·01M-TBAH solution (0·1M-TBAH in the case of the weakest indicators) was then added in small increments; the absorption curves were recorded and the potentials read after each addition. Three or four analytical wavelengths were picked out from the curves. The experimental absorbance values were corrected for volume variations; the corrections were largely neglibigle.

Prior to each measurement, the electrode system was allowed to stand for 20 min in a picrate buffer solution, $pH^* = 10{\cdot}5_6$, and the electromotive force was determined. Between the measurements the glass electrode had to be allowed to rest in 0·01M aqueous HCl for at least 1 h. For this reason two electrode systems were in alternate use. The mean electromotive force values for the two systems in the whole series of measurements were +325 and +345 mV, respectively; the deviations from the mean values for the individual measurements did not exceed ±7 mV. The measured potentials were corrected for the difference between the mean value for the 1st electrode system and the average value for the picrate buffer from measurements before and after the spectrophotometric titration using the pertinent electrode system, E_{Pi}:

$$E_{cor} = E - \Delta E = E - (E_{Pi} - 325) . \qquad (4)$$

For each addition of the TBAH titrant solution, the corrected absorbance at the wavelength chosen and the corrected potential were established and the half-neutralization potential (HNP) and the pH* and pK^*_{IH} values were calculated by using the relations

TABLE I

Absorption maxima of nitrophenoxazines in MIBK

Phenoxazine derivative	$c \cdot 10^5$ mol l^{-1}	$\lambda^{IH}_{max}(\varepsilon)^a$ nm	$\lambda^{I^-}_{max}(\varepsilon)^a$ nm	λ_i nm
1-Nitro	2·80	486 (5·8)	590 (10·7); 615 (11·0)	486, 590, 615
3-Nitro	1·50	444 (10·9)	574 (17·7); 612 (23·7); 664 (16·2)	444, 480, 612, 664
1,3-Dinitro	1·50	452 (11·6)	495 (17·8); 525 (17·7); 595 (12·2)	495, 525, 498
3,7-Dinitro	0·70	465 (14·7)	590 (15·9); >720 (—)	465, 590, 710
1,3,9-Trinitro	1·50	478 (12·7)	580 (22·1)	478, 550, 580
1,3,7-Trinitro	1·00	462 (18·6)	612 (32·1); 657 (41·7)	462, 624, 657
1,9-Dimethyl--3-nitro	1·30	438 (11·0)	545 (8·8); 590 (10·3); 618 (8·4); 672 (6·2)	438, 590, 618

[a] In 10^3 l mol^{-1} cm^{-1}.

$$\mathrm{HNP} = E_{\mathrm{cor}} - 59{\cdot}16 \log (|A - A_2|/|A_1 - A|) \qquad (5)$$

$$\mathrm{pH}^* = 10{\cdot}56 + (325 - E_{\mathrm{cor}})/59{\cdot}16 \qquad (6)$$

$$\mathrm{p}K^*_{\mathrm{IH}} = \mathrm{pH}^* + \log (|A - A_2|/|A_1 - A|) = \mathrm{pH}^* + (E_{\mathrm{cor}} - \mathrm{HNP})/59{\cdot}16\,, \qquad (7)$$

where A_1, A_2, and A are the absorbances of the acidic and basic species and of their mixture for the TBAH addition applied, respectively.

The K^*_{IH} data sets were statistically processed[22]; remote results were excluded based on the T-criterion and the arithmetic mean and the standard deviation estimate were calculated. The positions and intensities of the absorption maxima of the acidic and basic species, their concentrations, and the chosen λ_i values are given in Table I, the calculated $\mathrm{p}K^*_{\mathrm{IH}}$ dissociation constant values are summarized in Table II.

Titration of Acids in MIBK

a) A solution of $2 \cdot 10^{-5}$ to $8 \cdot 10^{-5}$ mol of the monobasic acid in 6 ml of MIBK was bubbled with nitrogen and titrated with 0·04M-TBAH with stirring. After every three titrations, benzoic acid was titrated. The electrode system was recalibrated by using the picrate buffer at the beginning and at the end of each series. Two glass electrodes were in alternate use in this case too. The titration end point was determined graphically. The HNP values were read from each titration curve, and the approximate dissociation constant values of the acids were calculated from them according to the relation

$$\mathrm{p}K_{\mathrm{A}} = 10{\cdot}38 + (263 - \mathrm{HNP})/59{\cdot}16\,; \qquad (8)$$

263 mV was the mean electromotive force in the picrate buffer solution. The HNP values were corrected with respect to this value.

TABLE II

Dissociation constants of nitrophenoxazines in MIBK

Phenoxazine derivative	Colour change	HNP mV	$\mathrm{p}K^*_{\mathrm{IH}} \pm ts/\sqrt{n}$
1-Nitro	orange-blue	$(-533)^a$	$(25{\cdot}1)^a$
3-Nitro	yellow-blue	−531	$25{\cdot}0_3 \pm 0{\cdot}09$
1,3-Dinitro	yellow-violet	−376	$22{\cdot}4_1 \pm 0{\cdot}25$
3,7-Dinitro	yellow-bluegreen	−349	$21{\cdot}9_6 \pm 0{\cdot}17$
1,3,9-Trinitro	yellow-violet	−344	$21{\cdot}8_7 \pm 0{\cdot}17$
1,3,7-Trinitro	yellow-blue	−221	$19{\cdot}7_8 \pm 0{\cdot}04$
1,9-Dimethyl-3-nitro	yellow-violetblue	−478	$24{\cdot}1_3 \pm 0{\cdot}23$

[a] Unreliable value.

b) A solution of 0·02—0·1 mmol of the acid in 5 ml of MIBK was titrated with 0·05M-TBAH. The concentration of the nitrophenoxazine solutions in MIBK used as the indicator was $4 \cdot 10^{-3}$ mol l^{-1}, the volume of the indicator solution added was 0·1—0·3 ml. The values for the blanks of the indicators plus 5 ml of the solvent (0·006—0·037 ml) were subtracted. The indicator colour changes are from yellow to blue for the colourless titrates, and from yellow to blue-green yellow-green, or green, or from orange to dirty brown for coloured titrates.

The results of determination of several model substances and a series of 1,2,4-triazine derivatives (Types *I*—*VI*) by potentiometric titrations as well as titrations using selected indicators are summarized in Table III. The neutralization equivalent was in most cases determined three times for each compound, with the substance weights in ratios of approximately 1 : 2 : 2·5, so that constant errors, if any, could be disclosed. The arithmetic means along with the corresponding confidence intervals determined for a 95% probability level from the range[22] are given in the table.

RESULTS AND DISCUSSION

The shape of the absorption spectra of nitrophenoxazines in MIBK does not differ appreciably from that obtained with other solvents, particularly for the neutral molecules (acidic species). Anions (basic species) show a clearer separation of the complex long-wavelength band, particularly in comparison with solutions with 50% ethanol. This is due to the lower relative permittivity of MIBK and its incapability

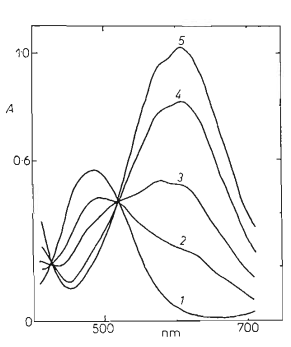


FIG. 1

Absorption curves of 1-nitrophenoxazine. $c = 2 \cdot 8 \cdot 10^{-5}$ mol l^{-1}, $d = 3 \cdot 5$ cm. *1* IH species, *2*, *3*, *4* IH + I^- mixture, *5* I^- species

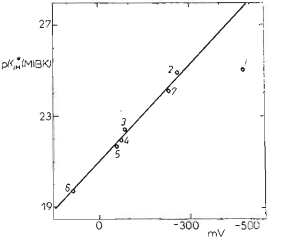


FIG. 2

Dependence of pK^*_{IH}(MIBK) and HNP(acetone) for nitrophenoxazines. Phenoxazine derivative: *1* 1-nitro, *2* 3-nitro, *3* 1,3-dinitro, *4* 3,7-dinitro, *5* 1,3,9-trinitro, *6* 1,3,7-trinitro, *7* 1,9-dimethyl-3-nitro

to form hydrogen bonds. In the measurements of the weakest acids (phenoxazine mononitro derivatives), condensation reactions in the solvent occurred in strongly alkaline systems, owing to which the solutions turned yellow and the absorption curves deformed in the region of lower wavelengths. This effect took place at pH* > > 25. Still satisfactory absorption curves could be obtained from rapid measurements, as documented by Fig. 1 showing the gradual dissociation of the weakest of the acids measured, *viz.* 1-nitrophenoxazine.

Critical, however, is the fact that the expected potential value is not reached in such circumstances. After attaining a certain value, the potential of the measuring cell is virtually invariable with further additions of the reagent, and after a longer period of establishing it even becomes more positive. In the case of 3-nitrophenoxazine and 1,9-dimethyl-3-nitrophenoxazine, reliable pK^*_{IH} values could be derived from more than a half of the pH-curves, whereas for 1-nitrophenoxazine we failed to establish the correct value. The value given in Table II in parentheses is unlikely (it should be higher). This follows, in fact, also from the interdependence between the pK^*_{IH} values in MIBK and the HNP values found in acetone[23] (Fig. 2). The regression straight line equation for points 2–7 in Fig. 2 (with HNP in mV) is

$$pK^*_{IH}(\text{MIBK}) = -0{\cdot}014\ \text{HNP}(\text{acetone}) + 21{\cdot}05\,. \qquad (9)$$

The value for 1-nitrophenoxazine does not comply with the otherwise linear dependence anticipated for the two similar solvents.

As expected, polynitro derivatives are stronger acids than mononitro derivatives, and derivatives with the nitro groups in the *para* positions to the NH group (*i.e.* 3,7-dinitro- and 1,3,7-trinitrophenoxazine) are stronger acids than the corresponding isomers with the nitro groups in the *ortho* positions (hence, 1,3-dinitro- and 1,3,9-trinitrophenoxazine). Obviously, the nitro groups in the 1 and 9 positions are hydrogen bonding acceptors, thereby stabilizing the molecule of the nondissociated acid (weakening it). The corresponding anions are less conjugated systems with a weaker mesomeric stabilization, as indicated by the positions of the absorption maxima lying at lower wavelengths as compared with the 3,7-dinitro derivatives. This again results in a relatively lower acidity of the 1,9-dinitro derivatives.

Unexpected is the position in the seris of 1,9-dimethyl-3-nitrophenoxazine, which is a stronger acid than 3-nitrophenoxazine despite the fact that the acidity should be lowered due to the positive inductive effect of the methyl groups. The same unexpected effect of methyl groups has been observed in other solvents[23], and has been explained in terms of hyperconjugation of the methyl group.

Exhibiting contrasting colour changes, having no tendency to homoconjugation, and covering a wide pH range, nitrophenoxazines appear to be highly suitable indicators for systems in MIBK. Mononitro derivatives will suit to determination of weak acids, polynitro derivatives will be of limited use in determination of stronger acids.

TABLE III
Titrations of acids in MIBK

Compound — substituent X		Neutralization equivalent			ind.	HNP mV	pK_A
		calc.	potent.	visual			
I	*p*-Br	339·2	340·2 ± 2·0	339·3 ± 3·1	3-NO_2	−173	17·7
I	*p*-OCH_3	290·3	290·2 ± 4·1	295·1[a]	3-NO_2	−221	18·6
I	*p*-OC_2H_5	304·3	—	304·9 ± 6·1	1-NO_2	—	—
				305·7 ± 1·6	3-NO_2	—	—
I	*p*-$COOC_2H_5$	332·3	331·7 ± 3·1	337·0 ± 4·9	1-NO_2	−148	17·3
				337·3 ± 5·8	3-NO_2	—	—
I	*p*-H	260·3	261·7 ± 0·0	257·9[a]	3-NO_2	−189	18·0
II	*p*-CH_3	292·3	—	291·0 ± 4·8	1-NO_2	—	—
				289·7 ± 2·3	3-NO_2	—	—
II	*p*-Br	293·1	293·3 ± 5·7	297·6 ± 3·2	1-NO_2	−184	17·9
				291·4 ± 4·5	3-NO_2	—	—
III	—	421·4	421·3 ± 3·1	—	—	−197; −648	—
IV	CH_3	293·2	292·5 ± 2·0	—	—	−306	20·0
IV	H	279·2	279·9 ± 2·5	274·0 ± 3·9	3-NO_2	−276	19·5
IV	cyclohexyl	361·3	359·3 ± 3·2	—	—	−308	20·0
IV	benzyl	369·3	374·5 ± 3·8	—	—	−294	19·8
IV	phenyl	355·3	354·7 ± 0·0	—	—	−385	21·3
V	phenyl	285·3	277·8 ± 2·2	284·1 ± 1·4	1-NO_2	−469	22·8
V	*o*-tolyl	299·3	299·9 ± 2·8	—	—	−497	23·2
V	*p*-fluorophenyl	303·3	301·3 ± 3·4	—	—	−452	22·5
V	*p*-chlorophenyl	319·8	319·7 ± 1·8	—	—	−441	22·3
V	*p*-bromophenyl	364·2	365·9 ± 1·3	—	—	−429	22·1
V	*p*-iodophenyl	411·2	413·7 ± 3·7	—	—	−413	21·8
VI	phenyl	239·2	240·6 ± 0·9	238·7 ± 4·2	1-NO_2	−368	21·0
VI	*o*-tolyl	253·3	256·9 ± 2·1	—	—	−365	21·0
VI	*m*-nitrophenyl	284·2	285·9[a]	—	—	−363	21·0
VI	*p*-fluorophenyl	257·2	256·1 ± 1·6	—	—	−352	20·8
VI	*p*-chlorophenyl	273·7	(299·9 ± 2·6)[b]	—	—	—	—
VI	*p*-bromophenyl	318·2	320·8 ± 2·8	—	—	−354	20·8
VI	*p*-iodophenyl	365·2	368·8[a]	—	—	−340	20·6
α-(3-Pyridylhydrazono)--β-oxobutyric acid anilide		282·3	—	288·3 ± 0·4	1-NO_2	—	—
Phenylhydrazonomalonic acid diamide		206·2	—	205·6 ± 8·4	1-NO_2	—	—
Phenylhydrazonomalonic acid dinitrile		170·2	—	170·7 ± 1·4	3·7-$(NO_2)_2$	—	—
Phenylhydrazonomalon-cyanamide		188·2	—	188·8 ± 1·0	3-NO_2	—	—

TABLE III
(*Continued*)

Compound — substituent X	Neutralization equivalent			ind.	HNP mV	pK_A
	calc.	potent.	visual			
Phenylcinchoninic acid	249·3	248·9[a]	249·2 ± 1·6	1-NO_2	−306	20·0
			247·4 ± 2·3	3-NO_2	—	—
Salicylic acid	138·1	—	138·9 ± 1·4	1-NO_2	—	—
Picolinic acid	123·1	124·4 ± 1·1	126·1 ± 2·6	1-NO_2	−450	22·4
p-Carbethoxyphenol	166·2	165·8 ± 2·2	165·5 ± 2·7	1-NO_2	−561	24·3
p-Nitrophenol	139·1	137·5 ± 1·0	138·8 ± 3·4	1-NO_1	−378	21·2
m-Chlorophenol	128·6	129·6 ± 1·2	130·6 ± 0·1	1-NO_2	−627	25·4
3-Ethoxycarbonylamino-phenol	181·2	180·0 ± 2·4	—	—	−793	28·2
Benzoic acid	122·1	standard	standard	3-NO_2	−450	22·4

[a] Result of a single determination; [b] a low-soluble substance.

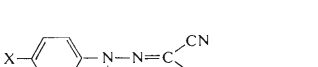
1,3,7-Trinitrophenoxazine is in MIBK nearly as strong an acid as 3,5-dinitrobenzoic acid.

In addition to several common model substances, a series of 1,2,4-triazine derivatives and the intermediates used in their synthesis have been chosen for determination of weak acids. These substances[24–26], recently studied as promising cancerostatics, are attracting attention owing to their coccidiostatic and antihelmintic activity[27]. By titrations in MIBK they can be quantitatively analyzed and their molecular weight can be determined; the method is also suitable for purity checking. Moreover, it turned out that the shape of the pontentiometric titration curve can often be of assistance in solving structure and other problems that for a synthesist are more interesting than a mere determination of the neutralization equivalent.

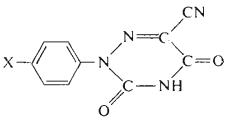
The precision of the determination in MIBK (Table III) is sufficient, although poorer than in acetone or pyridine[16]. This can be explained in terms of MIBK being a relatively low polar solvent, so that complicating protolytic side reactions of the homoconjugation and heteroconjugation types, association phenomena, and the like can at the same time take place in it[28]. On the other hand, owing to its outstanding discriminating power, mixtures of substances can be analyzed and polybasic acids determined. Occurrence of marked homoconjugation permits some structure problems to be solved in a simple manner. For instance, in the case of the acid of the structure *III*, which had been assumed to be an easily hydrolyzing ester of substituted cinnamic acid, it could not be decided based on elemental analysis and infrared spectroscopy (a complicated situation in the region of OH and NH groups vibrations)

whether the substance is an ester or the free acid. Titrations in MIBK in conjunction with the determination of water proved unambiguously that the compound is a dibasic acid, *viz.* α-benzoylamino-*p*-(5-cyano-6-azauracil-1-yl)cinnamic acid monohydrate, and not an ester (Fig. 3, curve 3).

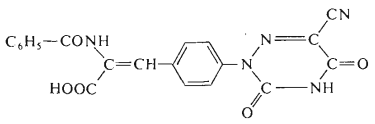
Type *II* compounds are cyclized products of compounds of the *I* series, and similarly, substances of the *VI* structure are products of cyclization of substances *V*. As follows from Table III, compounds *II* and *VI* are stronger acids than compounds *I*



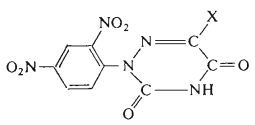
I



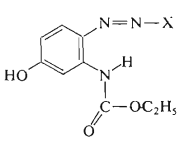
II



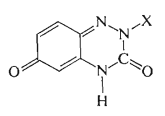
III



IV



V



VI

(*I*) Arylhydrazonocyanacetylurethanes

(*II*) 1-Aryl-6-azauracil-5-carboxylic acids nitriles

(*III*) α-Benzoylamino-*p*-(5-cyano-6-azauracil-1-yl)cinnamic acid

(*IV*) 2-(2′,4′-Dinitrophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazines

(*V*) 4-Arylazo-3-ethoxycarbonylaminophenols

(*VI*) 2-Aryl-2,3,4,6-tetrahydro-1,2,4-benzotriazine-3,6-diones

and *V*, respectively. The difference is not high enough to permit the two components to be separately determined in equimolar mixtures, but if the fraction of the weaker (noncyclized) product is small (1–5%), a two-step titration curve is obtained. Use was made of this fact for purity checks and for approximate determination of the noncyclized products in *II* and *VI* type compounds. The phenomenon can be explained in terms of the low polarity of MIBK; the salt formed during the titration is not dissociated completely, the degree of dissociation decreasing (association increasing) with increasing concentration of the substance titrated. In the equation

$$paH^* = pK_a + \log([A^-]/[HA]) + \log y_{\pm}\,, \qquad (10)$$

the two logarithmic terms decrease with increasing concentration. As a result, the main component is amplified more than the impurities *I* and *V*. Moreover, structure *V* compounds are in the second half of their titration curves weakened due to their homoconjugation.

As it has been demonstrated[17], acids with the dissociable proton bonded at a nitrogen atom show in acetonitrile practically no tendency to homoconjugation, whereas OH-acids homoconjugate appreciably. The difference in the shape of the titration curves can be of assistance in solving OH, NH tautomerism problems. Homoconjugation effects are considerably more marked in MIBK, and very subtle structure information can be derived from the shape of the potentiometric titration curve. Homoconjugation in OH-acids is suppressed by steric hindrance, intramolecular hydrogen bonds, and resonance stabilization of the anion. Types *I*, *II*, and *VI* compounds exhibit "classical" titration curve shapes without an enhanced steepness in the middle part, hence they are NH-acids. In contrast to this, the compound *V* is a phenol with homoconjugation effects as marked as those of *e.g.*, *m*-chlorophenol (Fig. 3, curve *1*). Comparing the titration curve shapes for type *V* substances with those for *m*-chlorophenol and 3-ethoxycarbonyl aminophenol (Fig. 3, curve *2*)

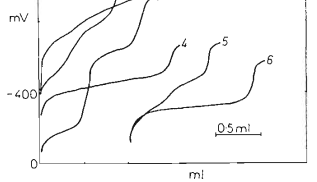


FIG. 3

Selected titration curves in MIBK. *1* *m*-chlorophenol, *2* 3-ethoxycarbonylaminophenol, *3* compound *III*, *4* picolinic acid, *5* compound *IV* (R = C_6H_5), *6* compound *IV* (R = CH_3)

we conclude that the compound *V* does not form strong hydrogen bonds, whereas 3-ethoxycarbonylaminophenol clearly does. All the conclusions are borne out by infrared spectroscopy data.

An even more interesting result was obtained from the study of type *IV* compounds; none of them homoconjugates (Fig. 3, curve *6*) with a single exception of the phenyl derivative (Fig. 3, curve *5*). The bonding of aryl in the 6 position obviously induces a conjugation displacement associated with the conversion of the NH tautomer into the more stable OH tautomer in MIBK.

Comparing the values in Tables II and III it can be claimed that in MIBK, weak acids are best titrated using an indicator whose HNP is no less than 200 mV more negative than the HNP of the substance titrated. Of the compounds studied, 1-nitrophenoxazine and 3-nitrophenoxazine satisfy most this requirement. Very weak acids, such as 3-ethoxycarbonylaminophenol, cannot be determined reliably by using indicators, as even the least acidic indicator from the series tested, 1-nitrophenoxazine, is too strong an acid for this purpose. An example of acid that is amenable to determination is *m*-chlorophenol (HNP = −627 mV).

Of the carboxylic acids examined, picolinic acid is the only one that does not homoconjugate in MIBK; it might thus suit to the preparation of buffers and calibration of cells with junction in MIBK.

REFERENCES

1. Bruss B. D., Wyld G. E. A.: Anal. Chem. *29*, 232 (1957).
2. Kreshkov A. P., Bykova L. N., Kazaryan N. A.: *Kislotno-Osnovnoe Titrovanie v Nevodnykh Rastvorakh*, p. 102. Khimiya, Moscow 1967.
3. Juillard J., Kolthoff I. M.: J. Phys. Chem. *75*, 2496 (1971).
4. Kreshkov A. P., Yarmakovskaya L. C.: Zh. Anal. Khim. *29*, 572 (1974).
5. Greenhow E. J., Al-Mudarris B. F.: Talanta *22*, 417 (1975).
6. Rink M., Riemhofer M.: Deutsch. Apoth. Ztg. *101*, 1600 (1961).
7. Lin S., Blake M. I.: J. Pharm. Sci. *55*, 781 (1966).
8. Sestrienková M., Šingliar M.: Petrochémia *17*, 113 (1977).
9. Pietrzyk D. J., Belisle J.: Anal. Chem. *38*, 969 (1966).
10. Diembeck S., Granger E., Jaeger H.: Arch. Pharm. (Weinheim) *301*, 628 (1968).
11. Miron R. R., Hercules D. M.: Anal. Chem. *33*, 1770 (1961).
12. Mitra R. P., Chaterjee S. K.: Indian J. Chem. *1*, 63 (1963).
13. Sarson R. D.: Anal. Chem. *30*, 932 (1958).
14. Fauth M. I., Frandsen M., Havlík B. H.: Anal. Chem. *36*, 380 (1964).
15. Sinha S. K., Kulkarni R. M., Rao K. R. K.: Anal. Chem. *36*, 894 (1964).
16. Stránský Z., Grúz J.: Chem. Zvesti *26*, 507 (1772).
17. Stránský Z., Čáp L., Slouka J.: This Journal *38*, 2712 (1973).
18. McDonald J. C., Brady C. A.: Anal. Chem. *47*, 947 (1975).
19. Grúz J., Stránský Z.: Acta Univ. Palacki. Olomuc., Fac. Rerum Natur. *27*, 321 (1968).
20. Kucharský J., Šafařík L.: *Titrace v nevodných prostředích*, p. 82. Published by SNTL, Prague 1961.

21. Karlíček R.: This Journal *40*, 3825 (1975).
22. Eckschlager K.: *Chyby chemických rozborů*, 2nd Ed., pp. 109, 123, 155. Published by SNTL, Prague 1971.
23. Stránský Z.: Acta Univ. Palacki Olomuc., Fac. Rerum Natur. *37*, 401 (1972).
24. Slouka J.: Monatsh. Chem. *94*, 258 (1963).
25. Slouka J.: Monatsh. Chem. *96*, 134 (1965).
26. Slouka J., Stránský Z.: Pharmazie *28*, 309 (1973).
27. Brit. P. 1 206 698.
28. Stránský Z., Dostál V.: Acta Univ. Palacki. Olomuc., Fac. Rerum Natur. *61/65*, 219 (1979/1980).

Translated by P. Adámek.