SYNTHESIS OF SOME SALICYLIC ACID DERIVATIVES AND DETERMINATION OF THEIR ACIDITY CONSTANTS

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Several derivatives of salicylic acid have been synthesized by the condensation reaction of methyl salicylate with α,ω-diols and α,ω-diamines, and the acidity constants of five newly prepared derivatives have been determined in 61·10% aqueous ethanol using potentiometric titration method. In order to avoid calibration of pH-meter, the standard potential of glass electrode was determined from the titration data. The results obtained are discussed with regard to different resonance effects of the ester oxygen and the amide nitrogen atoms.

An increasing number of organic compounds have been recently studied with the aim of finding new ligands capable of binding selectively different cations or extracting them from very dilute solutions (various natural and waste waters). For a determination of the stability constant of a complex it is necessary to know the acidity constant of the corresponding ligand behaving as a weak acid. Many organic compounds which could serve as potential ligands are not sufficiently soluble in water; hence the ligand acidity constant and its complexing ability have to be studied in organic solvents or in their mixtures with water. In the present paper we have presented the results of determination of acidity constants of several newly prepared derivatives of salicylic acid (potential ligands) in 61·10% aqueous ethanol by potentiometric titrations of the mixtures of hydrochloric acid and corresponding organic acid.

The acidity constants of the newly synthesized derivatives of salicylic acid were determined by the potentiometric titration of a mixture of hydrochloric acid (strong acid in the given solvent) and the respective weak acid with a solution of LiOH at 25°C. In order to use concentrations instead of activities in the formulas for EMF and acidity constants, we added lithium chloride to all the solutions to make them 0·5 mol dm^{-3} in Li^+ or Cl^-. A glass electrode in combination with the half-cell: Ag|AgCl|0·5 mol dm^{-3} LiCl saturated with AgCl|0·5 mol dm^{-3} LiCl was used to determine the equilibrium concentration of H_3O^+.

Assuming the activity coefficients to be constant, we may represent the measured EMF by the equation:

$$E = E^0 + 59{\cdot}16 \log [H_3O^+] + E_j , \qquad (1)$$

where E^0 is a constant (the difference between the standard potential of glass electrode and the potential of the reference electrode), and E_j is the liquid junction potential, both in mV.

In each titration E^0 and E_j were obtained by a graphical method[1] in the most acidic part, where dissociation of the weak acid can be neglected.

On the basis of the titration data in the region of neutralization of hydrochloric acid, it was possible to determine its accurate concentration by Gran's method[2]. From the same data, i.e. the known equilibrium concentrations of H_3O^+ and the measured EMF (E, mV), the value for E^0 was obtained by extrapolating the straight line

$$E - 59{\cdot}16 \log [H_3O^+] = E^0 + E_j = f([H_3O^+]) \qquad (2)$$

to $[H_3O^+] = 0$ mol dm^{-3}.

The acidity constants of the given derivatives of salicylic acid were calculated by Schwarzenbach's method[3] using the expression:

$$K_2 = (B/AK_1) + B\,, \qquad (3)$$

where A and B are given by Eqs (4) and (5), respectively.

$$A = \frac{[H_3O^+] + c(OH^-) - c(H_2A) - [OH^-]}{([H_3O^+] + c(OH^-) - [OH^-])\,[H_3O^+]}\,, \qquad (4)$$

$$B = \frac{([H_3O^+] + c(OH^-) - c(H_2A) - [OH^-])\,[H_3O^+]}{2c(H_2A) + [OH^-] - [H_3O^+] - c(OH^-)}\,. \qquad (5)$$

The analytical concentration of the organic acid, $c(H_2A)$, was calculated with respect to dilution of the solution during titration. The analytical concentration $c(OH^-)$ of the base added reduced for the amount reacted with HCl was calculated from the expression:

$$c(OH^-) = \frac{c_0(LiOH)\,.\,(V - V_e(HCl))}{V_0 + V}\,, \qquad (6)$$

where $c_0(LiOH)$ is the concentration of the titrant, $V_e(HCl)$ is the volume of the base used for neutralization of HCl, V_0 is the starting volume of the titrated solution, and V is the volume of the base added.

The equilibrium concentration of OH^- ion is given as

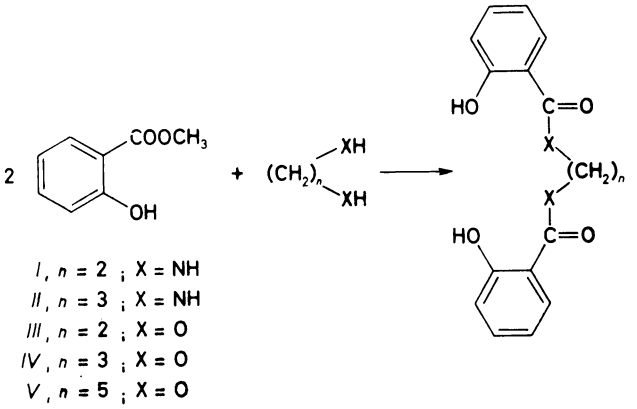
$$[OH^-] = K_w/[H_3O^+]\,. \qquad (7)$$

The value of $pK_w = 15{\cdot}04$ was taken for the autoprotolytic constant of water[4].

EXPERIMENTAL

The synthetic part of the present paper forms a continuation of our earlier work[5] describing the preparation of the simplest representatives of the newly designed tetradentate ligands based on salicylic acid.

Now we report the preparation of N,N′-disalicyloyl-1,3-propanediamine *II*, 1,3-bis(salicyloyloxy)propane *IV* and 1,5-bis(salicyloyloxy)pentane *V* according to Scheme 1.



I, *n* = 2 ; X = NH
II, *n* = 3 ; X = NH
III, *n* = 2 ; X = O
IV, *n* = 3 ; X = O
V, *n* = 5 ; X = O

SCHEME 1

The IR spectra (in cm^{-1}) were measured with a Perkin–Elmer 457 spectrometer. The chemical shifts are given in ppm, the symbols s, d, t, q, m, denoting singlet, doublet, triplet, quartet, and multiplet, respectively; the NMR spectra were recorded with a Varian 60A apparatus. The mass spectra were measured with a Varian CH-5 spectrometer (the first number denotes the *m/z* value, and the ion abundances are given in parentheses). The melting points were determined with a Büchi SMP-20 apparatus and are not corrected.

The potentiometric measurements were carried out on a Beckman digital pH-meter model 4500 with the accuracy of ±0·1 mV. A glass electrode Beckman No. 40498 and a reference electrode Ag/AgCl (prepared after Brown[6]) were employed. The titrations were carried out in a magnetically stirred plain-bottom titration vessel (300 cm^3) with four necks connecting it to a burette, nitrogen gas supply, the glass electrode and the reference electrode by means of the Wilhelm bridge[7]. During the measurement the titration vessel and the Wilhelm bridge were immersed in a paraffin oil thermostat at 25·0 ± 0·1°C. The room temperature was held at 25 ± 1°C. The preparation of solutions and other experimental details are similar to those described in our previous communication[8].

N,N′-*Disalicyloyl-1,3-propanediamine* II. 1,3-Propanediamine (7·99 g, 0·11 mol) was carefully added to 30·68 g (0·20 mol) methyl salicylate placed in a distillation flask in an ice bath. The reaction mixture was left to stand in the ice bath at 0–5°C for half an hour and then heated gradually (in an oil bath at the atmospheric pressure) to 150°C, whereupon methanol was gradually distilled off. The total reaction time was 2 h. After the reaction was finished, 30·81 g (97%) raw product was obtained. This product (0·50 g) was purified by means of column chromatography (50 g silica gel; benzene–ethyl acetate 4 : 1) to give 0·40 g (78%) pure product *II*. Recrystallization from 95% ethanol gave 0·30 g (58%) pure compound *II*, m.p. 184–185°C. IR

spectrum (KBr, ν_{max}): 3 500—3 380, 3 070, 2 940, 1 655, 1 595, 1 545, 1 500, 1 445, 1 365, 1 340, 1 305, 1 250, 1 135, 1 050, 890, 820, 790, 750 cm^{-1}. NMR spectrum ($(CD_3)_2CO$): 1·85 m, 2 H; 3·35 m, 4 H; 6·85 m, 4 H; 7·32 m, 2 H; 7·87 dd, 2 H; 8·86 t, 2 H; 12·65 s, 2 H. Mass spectrum (*m/z*, rel. %): 314 (M^+, 17), 194 (8), 193 (5), 177 (9), 165 (5), 164 (17), 151 (49), 150 (29), 138 (6), 122 (8), 121 (100), 120 (17), 93 (17), 92 (9), 65 (20), 57 (9), 56 (26). For $C_{17}H_{18}O_4N_2$ (314·3) calculated: 64·97% C, 5·73% H, 8·92% N; found: 65·04% C, 5·71% H, 9·12% N.

1,3-Bis(salicyloyloxy)propane IV. 1,3-Propanediol (8·38 g, 0·11 mol), methyl salicylate (30·40 g, 0·20 mol), and sodium (0·25 g, 0·011 mol) were mixed in a distillation flask. The reaction mixture was heated gradually in an oil bath at the atmospheric pressure; methanol and the excess of 1,3-propanediol were removed by vacuum distillation. The total reaction time was 2 h. After the distillation was completed, 150 cm^3 distilled water and hydrochloric acid (1 : 1, to make the pH 6—7) were added to the distillation residue. The reaction product was extracted with ether, and the extract was dried with anhydrous sodium sulfate. After removing Na_2SO_4 and ether, 26·85 g (85%) crude product *IV* was obtained. Recrystallization from 95% ethanol (150 cm^3) gave 15·14 g (48%) partly purified product, and a repeated recrystallization gave 11·89 g (38%) pure compound *IV*, m.p. 76—77°C. IR spectrum (KBr, ν_{max}): 3 500, 3 150, 2 980, 1 670, 1 615, 1 590, 1 490, 1 470, 1 350, 1 300, 1 255, 1 215, 1 160, 1 140, 1 090, 1 035, 985, 770, 700 cm^{-1}. NMR spectrum ($CDCl_3$): 2·00 q, 2 H; 4·60 t, 4 H; 6·60 m, 4 H; 7·20 m, 2 H; 7·75 dd, 2 H; 8·90 s, 2 H. Mass spectrum (*m/z*, rel. %): 316 (M^+, 21), 265 (3), 198 (7), 181 (10), 180 (70), 179 (14), 166 (7), 123 (7), 122 (100), 120 (31), 94 (10), 93 (12), 88 (7), 75 (16), 65 (12). For $C_{17}H_{16}O_6$ (316·3) calculated: 64·55% C, 5·10% H; found: 64·75% C, 5·16% H.

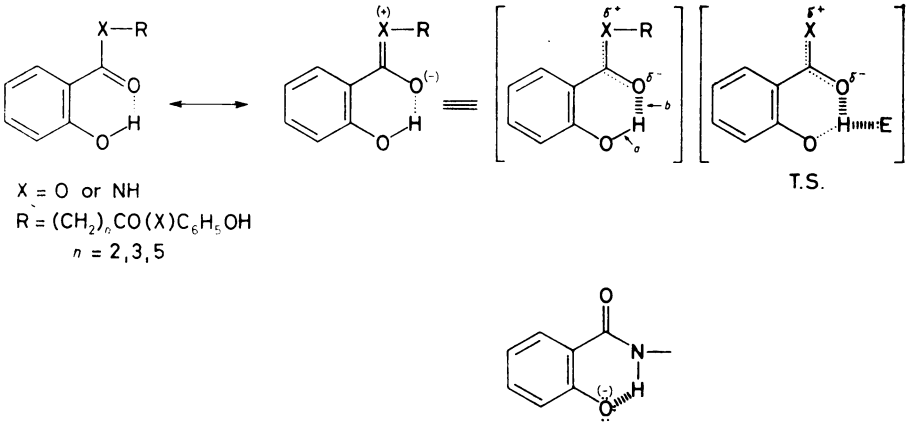
1,5-Bis(salicyloyloxy)pentane V. The synthesis of this compound was analogous to the previous one, 33·95 g (99%) crude product *V* being obtained from 11·42 g (0·11 mol) 1,5-pentanediol, 30·40 g (0·20 mol) methyl salicylate, and 0·27 g (0·012 mol) sodium. Yields of two repeated recrystallizations were 10·87 g (32%) and 9·81 g (29%), m.p. of the final compound *V* was 60 to 61°C. IR spectrum (KBr, ν_{max}): 3 430, 3 110, 2 950, 2 860, 1 670, 1 615, 1 590, 1 490, 1 470, 1 405, 1 330, 1 300, 1 250, 1 220, 1 160, 1 090, 1 030, 965, 870, 760, 730, 700 cm^{-1}. NMR spectrum ($CDCl_3$): 1·80 m, 6 H; 4·34 t, 4 H; 6·80 m, 2 H; 6·93 dd, 2 H; 7·40 m, 2 H; 7·80 dd, 2 H; 10·78 s, 2 H. Mass spectrum (*m/z*, rel. %): 344 (M^+, 8), 207 (7), 139 (10), 138 (26), 122 (8), 121 (100), 120 (36), 93 (8), 92 (9), 69 (18), 68 (9), 65 (8). For $C_{19}H_{20}O_6$ (344·6) calculated: 66·27% C, 5·81% H; found: 66·35% C, 5·80% H.

RESULTS AND DISCUSSION

The acid concentration chosen for determination of the acidity constants depends on the solubility and degree of dissociation of the organic acid. The solubility limits of the ligands synthesized are $6 \cdot 10^{-3}$ to $1 \cdot 10^{-1}$ mol dm^{-3}. At concentrations of $(3{\cdot}8 \text{ to } 8) \cdot 10^{-3}$ mol dm^{-3} H_2A the changes of potential were ca 10 mV after particular increments of the base solution added.

Three to five parallel titrations were carried out for determination of each acidity constant; in each titration seven points were used for calculation of a particular acidity constant value from the data corresponding to 30—70% dissociation of the organic acid. The values obtained for the acidity constants are presented in Table I. Differences in the acidity constants, especially in the case of the amides *I* and *II* compared with the esters *III*—*V* can be explained as follows. All the compounds examined (*I*—*V*) having the general formula shown in Scheme 2 are stabilized by

resonance (in all the cases only one half of the molecule is represented, the structure of the second half being the same due to molecular symmetry). The degree of resonance stabilization is obviously dependent on the nature of the group X (oxygen



SCHEME 2

or imino group): the resonance energy is larger for X = NH than for X = O. This is easily seen, e.g., from the positions of the IR bands corresponding to stretching vibrations of the carbonyl groups in amides and esters[9] (cf. Experimental of the present paper – the positions of the IR bands of carbonyl groups in the compounds *I* – *V*). Thus in the case of the amides *I* and *II* the hydrogen bond (*b*) (see Scheme 2) is stronger and, consequently, the OH bond (*a*) is weaker than in the esters *III* – *V*.

TABLE I

The acidity constants of the compounds *I* – *V* in 61·10% aqueous ethanol at (25·0 ± 0·1)°C and μ = 0·5 mol l^{-1} (LiCl)

Compound	Concentration 10^3 mol dm^{-3}	pK_1[a]	pK_2[a]
I	8	8·48 ± 0·01	9·28 ± 0·01
II	6–7	8·53 ± 0·01	9·17 ± 0·01
III	3·8–5	9·45 ± 0·07	9·85 ± 0·05
IV	7	9·64 ± 0·01	10·03 ± 0·05
V	8	9·66 ± 0·04	10·10 ± 0·01

[a] The limits shown are the average deviations.

This means that the dissociation of the phenolic OH is facilitated in the case of amides (as compared to the esters) due to a lower free energy of the transition state (see T. S. in Scheme 2) which must be passed during the deprotonation process. In addition, the phenoxide ions formed are extra-stabilized in the case of amides as a result of a new intramolecular hydrogen bond (Scheme 2).

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