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DETERMINATION OF DISSOCIATION CONSTANTS OF TWO QUINOLINE DERIVATIVES IN AQUEOUS SOLUTION AT 25^{O}C BY POTENTIOMETRIC TITRATION

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Abstract. In this study, the thermodynamic dissociation constants of two new quinoline derivatives including (6-hydroxyl-3-sulfoquinoline-7-yloxy) acetic acid and (5-bromo-6-hydroxyl-N-methyl-3-sulfoquinoline-7-yloxy) acetic acid were initially determined in an aqueous solution using potentiometric titration at (25.0 ± 0.1) ^{o}C in the ionic medium of 0.10 M KCl solution. From the results of this research, the dissociation constants of (6-Hydroxyl-3-Sulfoquinoline-7-yloxy) acetic acid are pK_{a1} = 4.15 ± 0.01 (for COOH group), pK_{a2} = 8.72 ± 0.02 (for NH^+ group) and pK_{a3} = 10.76 ± 0.03 (for OH group) while the pK_a values of 5-bromo-6-hydroxyl-N-methyl-3-sulfoquinoline-7-yloxy) acetic acid is pK_{a1} = 2.59 ± 0.02 (for the COOH group) and pK_{a2} = 5.41 ± 0.03 (for the OH group). To increase the reliability and accuracy of the results, the pK_a values could be calculated at different concentration levels. The structure of quinoline derivatives and data of potentiometric titration were analyzed in detail before calculating and assigning the pK_a values to suitable functional groups. These results will be applied to our further studies of these compounds.

Keywords: dissociation constants, potentiometric titration, (5-bromo-6-hydroxyl-N-methyl-3-sulfoquinoline-7-yloxy) acetic acid, (6-hydroxyl-3-sulfoquinoline-7-yloxy) acetic acid.

1. Introduction

In this report, two new acids (6-hydroxyl-3-sulfoquinoline-7-yloxy) acetic acid (**Q1**), (5-bromo-6-hydroxyl-N-methyl-3-sulfoquinoline-7-yloxy) acetic acid (**Q2**) were firstly studied to determine the acid dissociation constant. They are substituted quinolines that were synthesized from eugenol by Thi Hong Hai Le et al. [1] and Nguyen Huu Dinh et al. [2]. These compounds containing the quinoline skeleton have been known to be applied for manufacturing medicines. Moreover, these acids can also be used as ligands for determining metallic ions in analytical chemistry because they have a lot of functional groups that can form stable complexes with metallic ions [1, 3]. Additionally, the fluorescence properties of these acids will also be studied to apply in many branches of

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chemistry [1]. Compounds **Q1** and **Q2** were synthesized as the diagram of Figure 1 [1, 2].

The structures of **Q1** and **Q2** were studied in detail by some spectra such as IR, H^1NMR, D^2NMR, and MS [2]. Q1 has been determined as a triprotic acid in the aqueous solution while **Q2** is a diprotic acid [1, 2]. It was also confirmed that **Q1** and **Q2** are new acids and the dissociation constants of these acids have not been found in any literature. So, it is necessary to determine pK_a values for further research about their properties and applications.

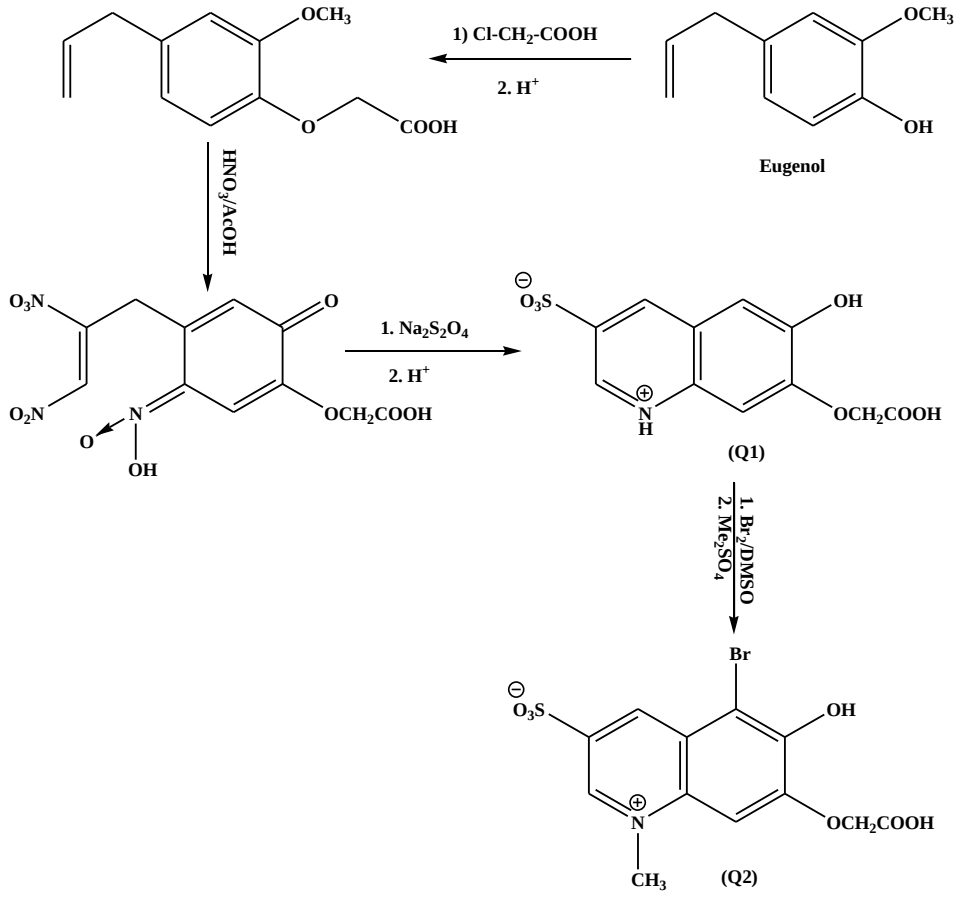


Figure 1. The synthesized diagram of Q1 and Q2 from Eugenol

There are a lot of known methods to determine the thermodynamic parameters such as potentiometric titration, UV-Vis absorption spectroscopy, chromatography, etc. [4]. In this research, potentiometric titration is still being used for determining the thermodynamic dissociation constants because of its convenience [4]. The principles of potentiometric titration involve the measurement of the pH of acid solutions as a function of titrant volume [5].

It is easy that the experimental data is treated by linear statistics based on the least square method. Therefore, a linear equation containing dissociation constant values is required to construct. This relationship was constructed based on the theory of analytical chemistry and our previous research [5-7].

2. Content

2.1. Theoretical fundamental for calculating the pK_a values of acids

Based on our previous research [5, 6] and the theory of chemistry equilibria [7], we have constructed a theory for calculating pK_a values from the experimental data.

For a potentiometric titration, V_0 mL of a multiprotic acid solution (H_mA, C_0 mol.L^{-1}) was titrated with V mL of KOH standard solution (C mol.L^{-1}) at a given ionic strength (I) which was maintained by KCl. At all times during the titration process, we always have:

$$[H^+] + [K^+] = [OH^-] + \sum_{i=1}^{m} i \times [H_{m-i}A^{i-}] \quad (1)$$

Rearranging Equation (1) and using φ term as a reverse form of activity coefficient, we obtain

$$\left(h - \frac{K_w}{h}\right)\varphi_1 \frac{V+V_0}{C_0V_0} + \frac{CV}{C_0V_0} = \frac{h^{m-1}\varphi_1K_{a1} + 2h^{m-2}\varphi_2K_{a1}K_{a2} + ... + m\varphi_m\prod_{i=1}^{m}K_{ai}}{h^m + h^{m-1}\varphi_1K_{a1} + h^{m-2}\varphi_2K_{a1}K_{a2} + ... + \varphi_m\prod_{i=1}^{m}K_{ai}} \quad (2)$$

where, $[H^+]$ and h = (H^+) are equilibrium concentration and activity of H^+ ion, respectively; φ_1, φ_2, ..., φ_m are the reverse forms of activity coefficients which were estimated by Davies equation [8]:

$$\lg\varphi_i = 0.5115 \times Z_i^2 \times \left(\frac{\sqrt{I}}{1+\sqrt{I}} - 0.2 \times I\right) \quad (3)$$

where I is ionic strength and Z_i is the ionic charge

The left hand of Equation (2) was defined as

$$N = \left(h - \frac{K_w}{h}\right)\varphi_1 \frac{V+V_0}{C_0V_0} + \frac{CV}{C_0V_0} \quad (4)$$

Therefore, Eq. (2) is

$$N = \frac{h^{m-1}\varphi_1 \times K_{a1} + ... + m\varphi_m \times \prod_{i=1}^{m}K_{ai}}{h^m + h^{m-1}\varphi_1 \times K_{a1} + ... + \varphi_m \times \prod_{i=1}^{m}K_{ai}} \quad (5)$$

When rearranged, Eq. (5) becomes

$$h^mN = h^{(m-1)}\varphi_1(1-N)\times K_{a1} + h^{(m-2)}\varphi_2(2-N)\times K_{a1}K_{a2} + \ldots + \varphi_m(m-N)\times\prod_{i}^{m}K_{ai} \quad (6a)$$

Equation (6) is like a linear equation

$$Y = a_1X_1 + a_2X_2 + ... + a_mX_m \quad (6b)$$

where Y, X_1, X_2, ..., X_m and a_1, a_2, ..., a_m were defined as

$$\begin{cases} Y = h^m N \\ X_1 = h^{m-1}\varphi_1(1-N) \\ X_2 = h^{m-2}\varphi_2(2-N) \\ \ldots\ldots\ldots\ldots\ldots\ldots \\ X_m = \varphi_m(m-N) \end{cases} \text{ and } \begin{cases} a_1 = K_{a1} \\ a_2 = K_{a1}K_{a2} \\ \ldots\ldots\ldots\ldots\ldots \\ a_m = \prod_{i=1}^{m} K_{ai} \end{cases} \quad (6c)$$

The values of N, Y, X_1, X_2, …, and X_m will be obtained from data of potentiometric titration such as h, C_0, C, V_0, V, φ. A linear least-square method will be done for n experimental points ($n > m$) and the pK_a values will be obtained from a_1, a_2, …, a_m. This research uses $m = 3$ for **Q1** acid and $m = 2$ for **Q2** acid.

2.2. Experiment

2.2.1. Chemicals and Instrument

Two acids **Q1** and **Q2** were synthesized, re-crystallized in a strong acid medium, and dried [1, 2]. Their purity was confirmed by H^1NMR and thermal analysis. Chemicals that are used without further purification include KOH, KCl, and $H_2C_2O_4.2H_2O$. All titrations were carried out by a pH meter (SI Analytics, Lab 850, Germany) with a combined glass electrode. The electrode system was standardized by standard buffer solutions (pH = 4.01, 7.01, and 10.01).

2.2.2. Sample Preparation and Procedure

The Q1, Q2, and KOH solutions were prepared in 0.10 M KCl solution that will maintain a given ionic strength (see Table 1).

Table 1. The studied concentrations of Q1, Q2, and KOH solutions

Compound	C_1 (M)	C_2 (M)	C_3 (M)	C_{KOH} (M)	Ionic strength	V_0 mL
Q1	1.14×10^{-3}	1.46×10^{-3}	1.68×10^{-3}	1.04×10^{-2}	0.10	25.00
Q2	7.65×10^{-4}	8.33×10^{-4}	-	6.19×10^{-3}	0.10	20.00

Pipette V_0 mL of each acid solution into a 100-mL beaker. Add a given volume of KOH solution (C_{KOH} M) to the studied solution, mix well, and record the pH values. All titrations were conducted in an aqueous solution with a constant ionic strength, maintained by adding 0.1 M of KCl solution, under the N_2 atmosphere at (25 ± 0.1) ^oC. Each studied solution was titrated 3 times to get an average value of pH. The V_0, C, and ionic strength (I) values are shown in Table 1.

2.3. Results and Discussion

The titrated results of **Q1** and **Q2** solutions were shown in Table 2 and the titration curves were shown in Figures 2 and 3.

Table 2. The potentiometric titration results of Q1 and Q2 solutions with KOH

V_{KOH} (mL)	pH_{A11}	pH_{A12}	pH_{A13}	pH_{A21}	pH_{A22}
0.00	3.641	3.541	3.474	3.269	3.258
0.20	3.713	3.599	3.531	-	-

V_{KOH} (mL)	pH_{A11}	pH_{A12}	pH_{A13}	pH_{A21}	pH_{A22}
0.40	3.793	3.673	3.598	3.354	3.340
0.60	3.881	3.747	3.651	-	-
0.80	3.974	3.821	3.715	3.455	3.434
1.00	4.071	3.901	3.775	-	-
1.20	4.176	3.981	3.846	3.574	3.541
1.40	4.290	4.060	3.917	-	-
1.60	4.412	4.149	3.980	3.720	3.675
1.80	4.556	4.243	4.057	-	-
2.00	4.734	4.327	4.129	3.904	3.841
2.20	4.932	4.446	4.200	-	-
2.40	5.246	4.565	4.284	4.129	4.045
2.60	5.782	4.680	4.364	-	-
2.80	6.494	4.849	4.456	4.373	4.259
3.00	7.168	5.053	4.552	-	-
3.20	7.547	5.334	4.651	4.619	4.512
3.40	7.780	5.810	4.772	-	-
3.60	7.959	6.575	4.895	4.863	4.745
3.80	8.111	7.114	5.078	-	-
4.00	8.247	7.420	5.348	5.139	4.985
4.20	8.370	7.650	5.732	-	-
4.40	8.486	7.831	6.161	5.467	5.278
4.60	8.603	7.980	6.780	-	-
4.80	8.723	8.109	7.102	6.051	5.685
5.00	8.841	8.220	7.415	-	-
5.20	8.963	8.321	7.585	7.620	6.423
5.40	9.091	8.419	7.737	-	-
5.60	9.217	8.517	7.862	9.300	8.045
5.80	9.350	8.612	7.977	-	-
6.00	9.484	8.701	8.077	9.753	9.376
6.20	9.617	8.806	8.159	-	-
6.40	9.749	8.898	8.237	9.999	9.768
6.60	9.872	8.991	8.324	-	-
6.80	9.989	9.096	8.401	10.169	9.989
7.00	10.096	9.201	8.473	-	-
7.20	10.190	9.304	8.549	10.281	10.136
7.40	10.277	9.425	8.623	-	-
7.60	10.351	9.522	8.691	10.391	10.247
7.80	10.420	9.624	8.773	-	-
8.00	10.478	9.746	8.837	10.468	10.330

V_{KOH} (mL)	pH_{A11}	pH_{A12}	pH_{A13}	pH_{A21}	pH_{A22}
8.20	10.532	9.836	8.923	-	-
8.40	10.580	9.961	8.992	10.532	10.403
8.60	10.624	10.048	9.072	-	-
8.80	10.663	10.139	9.156	10.587	10.460
9.00	10.699	10.225	9.228	-	-
9.20	-	10.297	9.304	10.630	10.512
9.40	-	10.368	9.387	-	-
9.60	-	10.428	9.457	10.671	10.554
9.80	-	10.477	9.544	-	-
10.00	-	10.521	9.633	10.706	10.594

where pH_{Aij} is the pH value of the $\mathbf{Q_i}$ solution at the C_j concentration level. For example, pH_{A12} is the pH of the **Q1** solution at the C_2 concentration level.

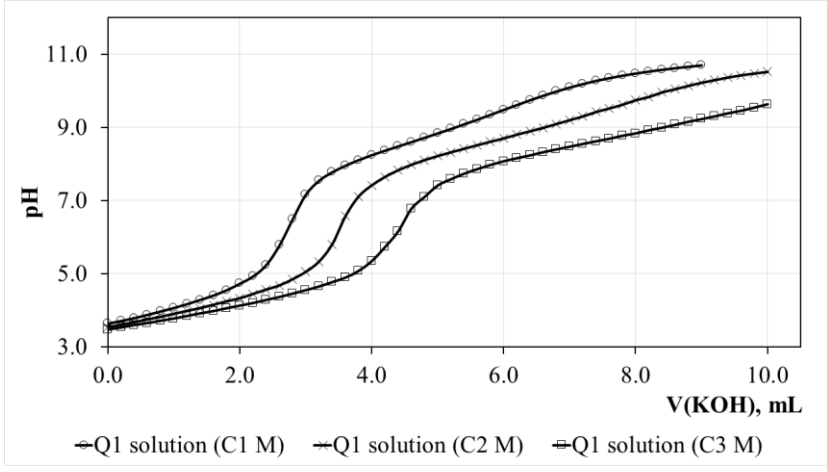


Figure 2. The titration curve of Q1 solutions with 1.04×10^{-2} mol/L KOH solution

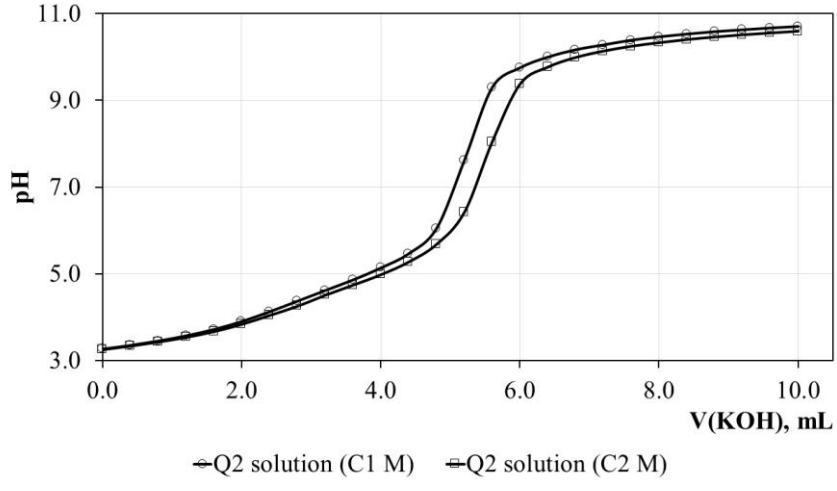


Figure 3. The titration curve of Q2 solutions with 6.19×10^{-3} mol/L KOH solution

On these titration curves, only one titration jump was observed in which the estimated pH range of titration jumps of **Q1** and **Q2** are (5.6 to 7.3) and (6.0 to 9.0), respectively. Based on the titration data, we have estimated the equivalent volume (V_E, mL) of KOH for each titration. Then, the titration ratio of KOH and each acid at the equivalent point was calculated for all studied solutions. For example, for the first solution of **Q1** acid ($C_1 = 1.142\times10^{-3}$ M), the determined equivalent volume is $V_{E,\,KOH} = 2.75$ mL. Thus, the number of reacted moles of KOH and **Q1** acid, in this case, are $2.75\times1.04\times10^{-2} = 2.86\times10^{-2}$ mmol and $25.00\times1.14\times10^{-3} = 2.86\times10^{-2}$ mmol, respectively. Therefore, the mole ratio of KOH and **Q1** acid at the equivalent point is 1:1. Similarly, the other titration ratios of KOH and the studied acids were also calculated. The results show that at the equivalent point, the titration ratio of KOH and **Q1**, and **Q2** acids are 1:1 and 1:2, respectively. This means that in the titration process to the equivalent point, only one proton of **Q1** has been neutralized while two protons of **Q2** have reacted with OH^-. Based on these results and our previous research [5], we have chosen some suitable ranges from titration data for calculations of the pK_a values of three acids. For **Q1** acid, the range of pH < 5.6 was chosen to calculate the pK_{a1} value, and the range of pH > 7.3 was used to estimate the pK_{a2} and pK_{a3} values. In the same way, for **Q2** acid, the range of pH < 6.0 was chosen to estimate both values of dissociation constants. In these ranges, the composition of the studied solutions is the buffer. So, the calculation using the titration data of these ranges is more accurate.

By using the principle that has been mentioned above, we have calculated the values of dissociation constants of **Q1** and **Q2**. The results are shown in Table 3.

Table 3. The results of thermodynamic dissociation constants of Q1 and Q2

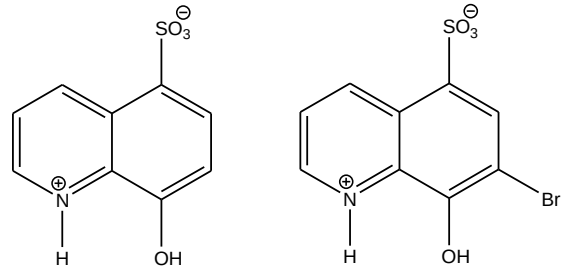
Compound	***C***	**pK_{a1}**	**pK_{a2}**	**pK_{a3}**
Q1	C_1	4.19 ± 0.01	8.69 ± 0.03	10.74 ± 0.04
	C_2	4.16 ± 0.01	8.74 ± 0.03	10.74 ± 0.06
	C_3	4.11 ± 0.01	8.73 ± 0.02	10.79 ± 0.05
	Mean	*4.15 ± 0.01*	*8.72 ± 0.02*	*10.76 ± 0.03*
Q2	C_1	2.52 ± 0.02	5.32 ± 0.04	-
	C_2	2.65 ± 0.02	5.50 ± 0.05	-
	Mean	*2.59 ± 0.02*	*5.41 ± 0.03*	-

The results in Table 3 indicate that the dissociation constants that have been determined have great repeatability and reliability.

In the electron structure of the **Q1** molecule, the positive mesomeric effect (+M) of the OH and the OCH_2 groups and the intramolecular hydrogen bond between the H atom of the OH group and the O atom of the OCH_2 group lead to a decrease in the acidic strength of the OH group. We predicted that the acidic strength of this group is weaker than the OH group of phenol (C_6H_5OH, $pK_a = 10.00$ [9]). So, we have assigned the value pK_{a3} = 10.76 ± 0.03 for the OH group. This effect also leads to a decrease in the negative inductive effect (−I) of the OCH_2 group to the COOH group compared with the effect in the molecule of glycolic acid ($HOCH_2COOH$, pK_a = 3.83 [9]). For this reason, we have assigned the value pK_{a1} = 4.15 ± 001 for the COOH group. For the NH^+ group, the positive

mesomeric effect (+M) of the OH and OCH_2 groups leads to a strong increase in the electron density in the quinoline ring. So, the basic strength of the N atom is increased, or the acidic strength of NH^+ is decreased compared with the quinolinium ion ($pK_a = 4.80$ [9]). Therefore, the value $pK_{a2} = 8.72 \pm 0.02$ has been assigned for the NH^+ group.

For the **Q2** molecule, the positive charge center (CH_3N^+) in the quinoline ring will strongly shift electrons into the ring and this effect has no change for all dissociated steps of this acid. So, the acid strength of both OH and COOH groups increases much more than in **Q1**. In addition, due to the negative inductive effect of the bromine (Br) atom next to the OH group (*ortho* position), the acid strength of the OH group will be increased strongly. The influence of the bromine atom on the acidic strength of the OH group (linked to the quinoline ring) can be shown as an example of 8-hydroxyquinoline-5-sulfonic acid and 7-bromo-8-hydroxyquinoline-5-sulfonic acid [9].



$pKa_1 = 4.09$ (N-H)
$pKa_2 = 8.78$ (O-H)

8-HydroxyQuinoline-5-Sulfonic Acid

$pKa_1 = 2.51$ (N-H)
$pKa_2 = 6.70$ (O-H)

7-Bromo-8-HydroxyQuinoline-5-Sulfonic Acid

Figure 4. The influence of bromine on the acidic strength of the OH group

The influence of both the positive charge center (CH_3N^+) and bromine (Br) leads to a great increase in the acidic strength of the OH group. Therefore, the $pK_{a1} = 2.59 \pm 0.02$ was assigned for the COOH group, and the $pK_{a2} = 5.41 \pm 0.03$ for the OH group.

3. Conclusions

We have applied successfully the potentiometric titration method to determine the thermodynamic dissociation constants of two quinoline derivatives in the aqueous solution at 25 ^oC. This is the first time that the dissociation constants of (6-hydroxyl-3-sulfoquinoline-7-yloxy) acetic acid and (5-bromo-6-hydroxyl-N-methyl-3-sulfoquinoline-7-yloxy) acetic acid) are announced. By analyzing in detail the structure of two new acids, the calculated dissociation constants of (6-hydroxyl-3-sulfoquinoline-7-yloxy) acetic acid are $pK_{a1} = 4.15 \pm 0.01$ (for COOH group), $pK_{a2} = 8.72 \pm 0.02$ (for NH^+ group) and $pK_{a3} = 10.76 \pm 0.03$ (for OH group) while the pK_a values of 5-Bromo-6-Hydroxyl-N-Methyl-3-Sulfoquinoline-7-yloxy) Acetic acid is $pK_{a1} = 2.59 \pm 0.02$ (for the COOH group) and $pK_{a2} = 5.41 \pm 0.03$ (for the OH group).

Because of the simple procedure, saving time, and easy calculation, the potentiometric titration method is a convenient method for determining the pK_a values of new acids. The received results are so highly accurate and reliable that they can be used as a reference for other researches.

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