# Determination of $pK_a$ Values for Acrylic, Methacrylic and Itaconic Acids by $^1$H and $^{13}$C NMR in Deuterated Water

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**Abstract:** Acrylic, methacrylic and itaconic acids have Brønsted acidity given by carboxylic groups, and they are extensively used in polymerization for modification of several soft-mater materials. By this reason it is important to propose better characterization studies and alternatives to obtain more of their physicochemical properties. In this work the $pK_a$ values of these acids are obtained by adjusting NMR chemical shifts for hydrogen and carbon nuclei as a function of pH with program HYPNMR, and compared with those obtained by potentiometric and conductometric titrations.

**Keywords:** $pK_a$ values, acrylic acid derivatives, HYPNMR, $^1$H NMR, $^{13}$C NMR.

## 1. INTRODUCTION

Unsaturated carboxylic acids are used to increase the solubility in water of several substances or confer it some specific properties by polymerization [1-6].

Some of these substances, preferred by its small size, are acrylic (AA), methaclrylic (MA) and itaconic acids (IA). The developed formulae of these substances are given in Figure **1**.

Recently some papers have reported the use of NMR to determine pKa values of drugs, like an alternative to other methods [7, 8]. This task could help to give, at the same time, structural information to characterize better the substances in other fields of research and industry.

The aim of the present work is to show the easiness of the NMR technique to determine pKa values for very soluble substances in water and compare it with those obtained with potentiometric and conductometric methods.

## 2. MODELING

### 2.1. Chemical Shifts of NMR Curves to Determine $pK_a$ Values

The protonation degree of a molecule has an effect over the chemical shifts of different nuclei of the molecule, which permit to obtain sigmoidal curves of chemical shift as a function of pH for each nucleus.

The inflexion point of a sigmoidal curve may be related with a $pK_a$ value for the simplest cases where there is only one acidity equilibrium, which is the case of AA and MA, in agreement with the Equation 1.

$$ {}_{X_i}\delta_{L'} = f_L({}_{X_i}\delta_L) + f_{HL}({}_{X_i}\delta_{HL}) \tag{1} $$

where $X_i$ represent the nucleus (H or C in this case) in the $i$-esim position of the molecule for $i \in \{1, 2, \dots, n\}$ and $n$ the number of active nuclei; $L$ and $HL$ represent the deprotonated and protonated species of the substance, respectively; $f_L$ and $f_{HL}$ represent the molar fractions of L species (Equation 2); and L´ takes in account all the L species with different protonation degrees in the system [8]. Electrical charges will be omitted in equations to simplify notation.

$$ f_L \equiv \frac{[L]}{[L']} = \frac{[L]}{[L]+[HL]} = \frac{1}{1+10^{(\mathrm{pK_a}-\mathrm{pH})}} $$

$$ f_{HL} \equiv \frac{[HL]}{[L']} = f_L \frac{[H^+]}{\mathrm{K_a}} = \frac{10^{(\mathrm{pK_a}-\mathrm{pH})}}{1+10^{(\mathrm{pK_a}-\mathrm{pH})}} \tag{2} $$

Equations 1 and 2, for each nucleus, may be used to fit experimental sigmoidal curves with a non-linear regression method to determine the $pK_a$ value of the species $HL$.

Nevertheless, for cases in which there are two or more acid-base equilibria, theoretically there are several inflexion points, which not necessarily

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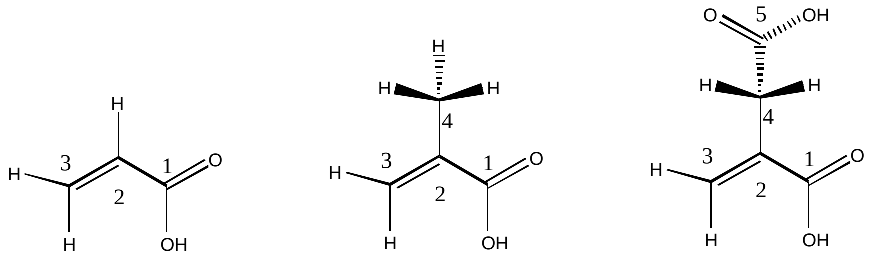


Acrylic acid (AA) Methacrylic acid (MA) Itaconic acid (IA)

**Figure 1:** Developed formulae for the carboxylic acids studied in this work with numbering to each nucleus or set of nuclei.

correspond to $pK_a$ values in the pH scale. For example, IA is a di-carboxylic acid with $pK_a$ values separated by less of two units [9]. The kind of sigmoidal curves of chemical shifts of their nuclei as a function of pH are described by equations 3 and 4.

$$ {}_{X_i}\delta_{L'} = f_L({}_{X_i}\delta_L) + f_{HL}({}_{X_i}\delta_{HL}) + f_{H_2L}({}_{X_i}\delta_{H_2L}) \tag{3}$$

Then, the fitting of sigmoidal curves for the nuclei in the different species of the system, by a non-linear regression method, can be used to determine $pK_{a1}$ and $pK_{a2}$ values –even though the inflexion points do not correspond with $pK_a$ values.

$$f_L \equiv \frac{[L]}{[L']} = \frac{[L]}{[L]+[HL]+[H_2L]} = \frac{1}{1+10^{(\mathrm{pK_{a2}-pH})}+10^{(\mathrm{pK_{a1}+pK_{a2}-2pH})}}$$

$$f_{HL} \equiv \frac{[HL]}{[L']} = f_L\frac{[H^+]}{\mathrm{K_{a2}}} = \frac{10^{(\mathrm{pK_{a2}-pH})}}{1+10^{(\mathrm{pK_{a2}-pH})}+10^{(\mathrm{pK_{a1}+pK_{a2}-2pH})}} \tag{4}$$

$$f_{H_2L} \equiv \frac{[H_2L]}{[L']} = f_L\frac{[H^+]^2}{\mathrm{K_{a1}K_{a2}}} = \frac{10^{(\mathrm{pK_{a1}+pK_{a2}-2pH})}}{1+10^{(\mathrm{pK_{a2}-pH})}+10^{(\mathrm{pK_{a1}+pK_{a2}-2pH})}}$$

The method explained in this subsection is that used in the present work, using HYPNMR program [8, 10, 11] to fit simultaneously all the sigmoidal curves useful to determine $pK_a$ values.

### 2.2. Potentiometric Titration Curves to Determine $pK_a$ Values

In order to fit the pH-metric titration curves is common to use a robust model, in which the volume is calculated for any pH [12, 13].

A valid equation to fit AA or MA pH-metric curves is presented in Equation 5.

$$V_{NaOH} = \frac{-V_oC_o\left[f_L\right]-V_o\left([\mathrm{H}^+]-\frac{K_w}{[\mathrm{H}^+]}\right)}{C_{NaOH}+[\mathrm{H}^+]-\frac{K_w}{[\mathrm{H}^+]}} \tag{5}$$

where $f_L$ is the molar fraction of the acrylate or methacrylate ion in agreement with Equation 2, $V_{NaOH}$ is the added volume and $C_{NaOH}$ the molar concentration of sodium hydroxide used as titrant, $V_o$ is the initial volume and $C_o$ the molar analytical concentration of AA or MA to be titrated, $K_w$ is the autoprotolysis constant of water and $[H^+] = 10^{-pH}$.

A valid equation to fit IA pH-metric curves is presented in Equation 6.

$$V_{NaOH} = \frac{-V_oC_o\left[2f_L+f_{HL}\right]-V_o\left([\mathrm{H}^+]-\frac{K_w}{[\mathrm{H}^+]}\right)}{C_{NaOH}+[\mathrm{H}^+]-\frac{K_w}{[\mathrm{H}^+]}} \tag{6}$$

where $f_L$ and $f_{HL}$ are the molar fractions of the itaconate and itaconate acid ions in agreement with Equation 4, and the other symbols have the same meaning that for Equation 5.

In order to determine $pK_a$ values by means of pH-metric curves the program SUPERQUAD [14] has been used.

### 2.3. Conductometric Fitting of Titration Curves

It is less common to use conductometric titration curves in order to determine $pK_a$ values. Nevertheless, the conductivity of solutions of AA or MA (in mixture with HCl) during titration may be written like is given in Equation 7.

$$\kappa = \lambda_{\mathrm{H}^+}[\mathrm{H}^+] + \lambda_{\mathrm{OH}^-}\frac{K_w}{[\mathrm{H}^+]} + \frac{V_oC_o}{V_o+V_{NaOH}}(\lambda_L f_L) + \lambda_{\mathrm{Na}}\frac{V_{NaOH}C_{NaOH}}{V_o+V_{NaOH}} + \lambda_{\mathrm{Cl}}\frac{V_oC_{HCl}}{V_o+V_{NaOH}} \tag{7}$$

where $\lambda_{H^+}$, $\lambda_{OH^-}$, $\lambda_{Na}$ and $\lambda_L$are the equivalent conductivities of hydronium, hydroxide, sodium and acrylate or methacrylate ions, respectively.The other symbols have the same meaning that they have in Equations 2 and 5.

In the same way, the conductivity of solutions of IA during titration may be written like it is shown in Equation 8.

$$\kappa = \lambda_{H^+}[H^+] + \lambda_{OH^-}\frac{K_w}{[H^+]} + \frac{V_o C_o}{V_o + V_{NaOH}}(2\lambda_L f_L + \lambda_{HL} f_{HL}) + \lambda_{Na}\frac{V_{NaOH} C_{NaOH}}{V_o + V_{NaOH}} \qquad (8)$$

where $\lambda_L$ and $\lambda_{HL}$ are the equivalent conductivities of itaconate and itaconate acid ions, respectively. The other symbols have the same meaning that they have in Equations 4 and 6.

Then, conductometric titrations for AA or MA solutions may be fitted by using the Equations 2, 5 and 7; while for the fitting of IA conductometric titrations Equations 4, 6 and 8 should be used.

## 3. RESULTS AND DISCUSSION

### 3.1. NMR

Figure **2** presents $^1$H NMR spectra of AA in acid and basic media, showing that chemical shift of several nuclei depends on pH. Additionally the assignation of signals to each nucleus could be easily achieved when there is multiplicity, which could be explained by the structure of molecule. In the case of AA, the signals observed are known as doublet of doublets [15] because each hydrogen nucleus of the vinyl group is coupled with the other two of the same group. Then, there is a strong coupling among the hydrogen nuclei placed in both sides of double bond followed by a weak coupling among geminal hydrogen nuclei. Also for that reason MA and IA $^1$H NMR spectra have only single

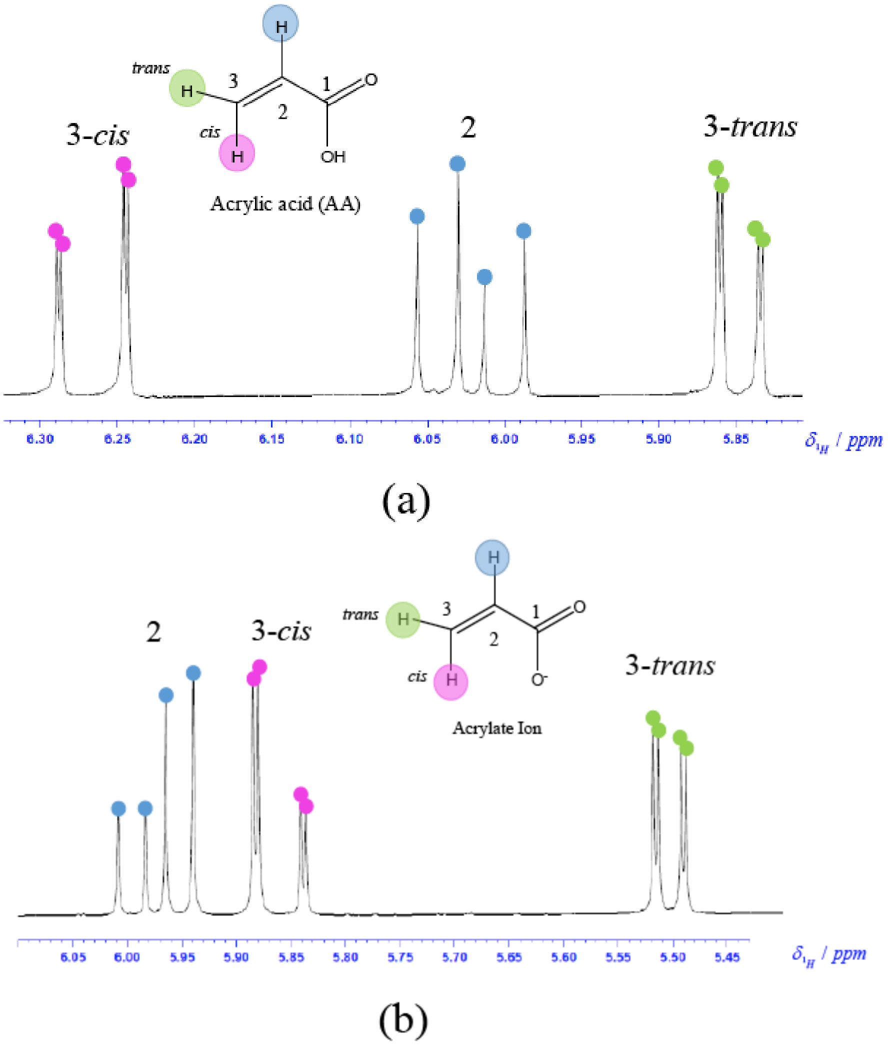


**Figure 2:** $^1$H NMR spectra for AA in **a**) pH = 1.28 and **b**) pH = 12.45. The signals of each hydrogen nucleus are a doublet of doublets (or double of doubles).

signals. From Figure **2**, it can be shown that the signal of the hydrogen in position 2 of AA is practically independent on pH.

Sets of spectra of hydrogen and carbon as a function of pH have been obtained for the three carboxylic acids studied in the present work.

Like an example, Figure **3** shows the dependence of the signals of carbon nuclei with pH with the aid of some $^{13}$C NMR spectra of the set obtained for MA.

It is clear (Figure **3**) that the carbon signals of methyl group of MA (or those of methylene group of IA) are less dependent on pH than the others.

The chemical shift values of the nuclei of carboxylic acids studied in the present work are presented in Table **1** at acid and basic pH values.

Like an example of sigmoidal curves that may be obtained, Figure **4** shows the chemical shifts as a function of pH for the carbon nucleus of carboxylate ion in position 1 of the molecules for AA, MA and IA. Markers represent experimental points while solid lines represent the fitting with the corresponding model using data of Table **2** for AA and MA, and of Table **3** (Model I) for IA. It is evident that the model of one acid-base equilibrium is not enough adequate for IA, because the residuals show a trend: the calculated points in the model before inflexion point are greater than the experimental ones, but after inflexion point the calculated points are lesser.

Although one of this kind of curves may be used to obtain an estimator of pK$_a$ value, statistically is better fitting simultaneously all the sigmoidal curves useful for the same group of experiments. This has been achieved for AA, MA and IA with program HYPNMR. Like an example, Figure **5** shows all the fitted curves for IA with Model II.

Tables **2** and **3** show that better results for the fit are obtained when more points are used with the more meaningful model for AA, MA and IA, as well as the good agreement with pK$_a$ values previously reported. Figure **5** shows the very good fitting achieved of the experimental data for the case of IA.

In order to compare the quality of pK$_a$ values obtained by NMR, potentiometric and conductometric titrations have been obtained.

### 3.2. Potentiometry and Conductometry

The potentiometric titrations (with an automatic titrator for AA and MA and manual for IA) are shown in Figures **6a**, **7a** and **8a**, respectively. More points have been acquired when an automatic titrator has been used, as expected.

The shape of AA and MA titrations is that expected for monoprotic acids, with a titration reaction very quantitative (Figures **6a** and **7a**).

The IA titration also has the expected shape for a diprotic acid, with pKa values near one of each other, for which the first titration reaction is few quantitative and the second is very quantitative (Figure **8a**).

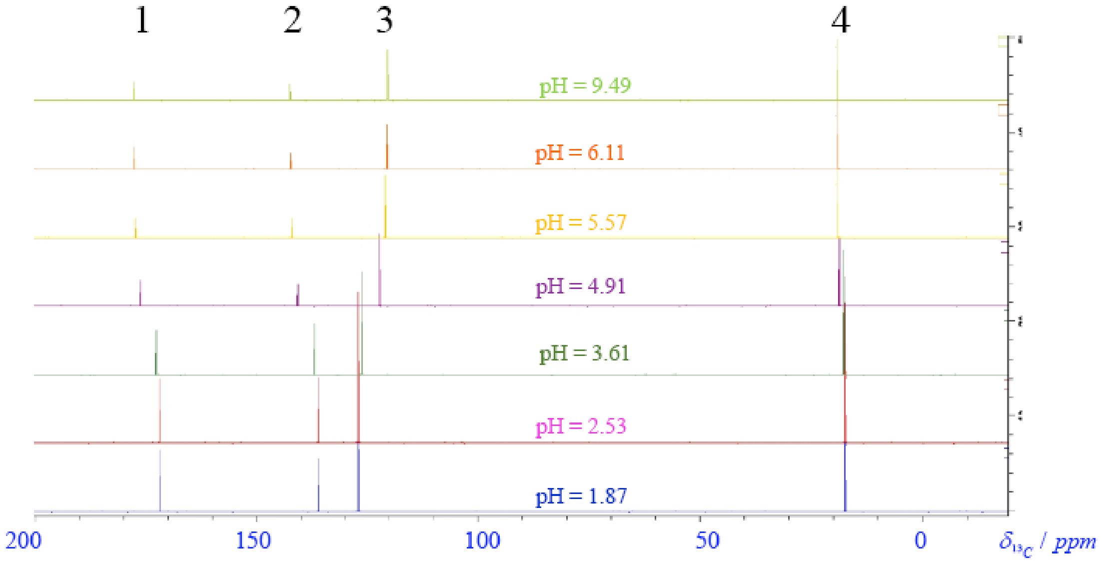


**Figure 3:** $^{13}$C NMR spectra for MA at several pH values.Numbers in top of figure indicate the position of the carbon atom in the developed formulae.

**Table 1: NMR Chemical Shifts for Hydrogen and Carbon Nuclei of Different Carboxylic Acids Studied in this Paper, in Acid and Basic Media**

| **Acrylic Acid (AA)** | **pH = 1.28** | **pH = 12.45** |
|---|---|---|
| Position of H nucleus | $\delta_{^1H}$ /ppm | $\delta_{^1H}$ /ppm |
| 3-*trans* | 5.848 | 5.503 |
| 2 | 6.043 | 5.952 |
| 3-*cis* | 6.266 | 5.861 |
| Position of C nucleus | $\delta_{^{13}C}$ /ppm | $\delta_{^{13}C}$ /ppm |
| 3 | 132.74 | 126.62 |
| 2 | 127.76 | 133.7 |
| 1 | 170.37 | 175.44 |
| **Methacrylic acid (MA)** | **pH = 1.87** | **pH = 11.00** |
| Position of H nucleus | $\delta_{^1H}$ /ppm | $\delta_{^1H}$ /ppm |
| 4 | 1.698 | 1.704 |
| 3-*trans* | 5.518 | 5.191 |
| 3-*cis* | 5.912 | 5.485 |
| Position of C nucleus | $\delta_{^{13}C}$ /ppm | $\delta_{^{13}C}$ /ppm |
| 4 | 17.32 | 18.91 |
| 3 | 126.93 | 120.38 |
| 2 | 135.90 | 142.24 |
| 1 | 171.62 | 177.40 |
| **Itaconic acid (IA)** | **pH = 1.94** | **pH = 12.00** |
| Position of H nucleus | $\delta_{^1H}$ /ppm | $\delta_{^1H}$ /ppm |
| 4 | 3.260 | 2.999 |
| 3-*trans* | 5.728 | 5.227 |
| 3-*cis* | 6.210 | 5.702 |
| Position of C nucleus | $\delta_{^{13}C}$ /ppm | $\delta_{^{13}C}$ /ppm |
| 4 | 37.37 | 41.96 |
| 3 | 130.55 | 121.94 |
| 2 | 133.52 | 141.68 |
| 1 | 170.08 | 175.78 |
| 5 | 176.00 | 180.59 |

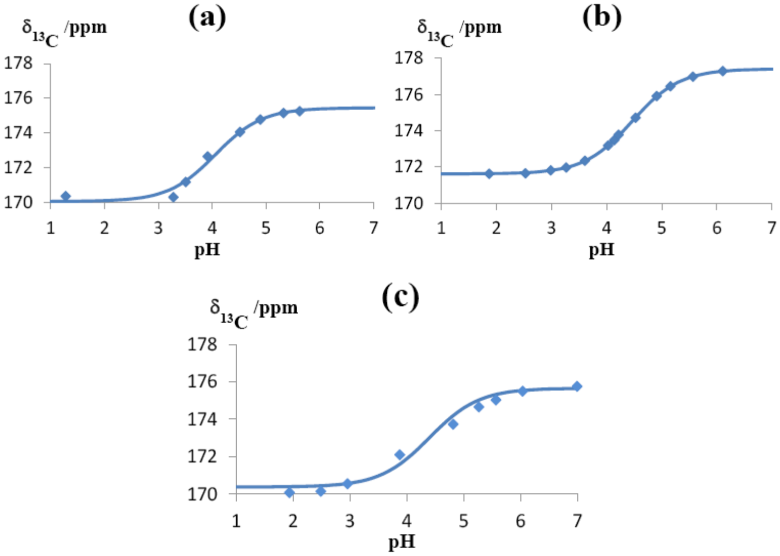


**Figure 4:** Chemical shifts of carbon nucleus of carboxylate group 1 as a function of pH for: **a**) AA. **b**) MA. **c**) IA. Markers represent experimental data and solid line is calculated with a model of one equilibrium of acidity with the parameters shown in Table **2**, for AA and MA, and in Table **3**, Model I, for IA.

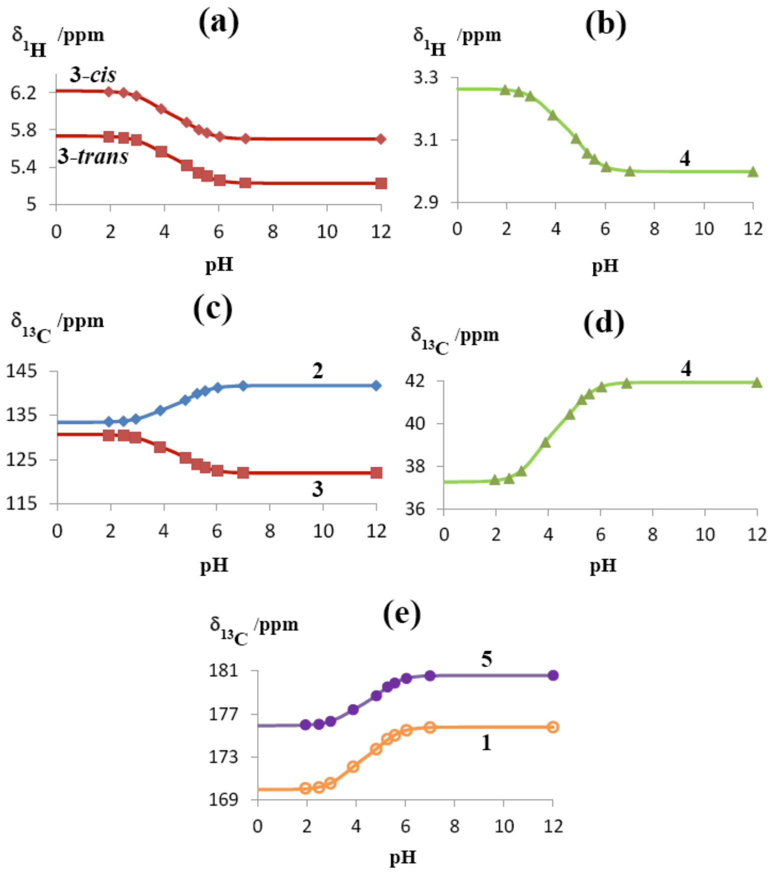


**Figure 5:** Behavior of chemical shifts of hydrogen and carbon atoms of IA with pH. Markers represent experimental data and lines fitting achieved using Model II in Table **3**, obtained in the same procedure, with two pKa values and chemical shifts of nuclei for three different species given in Table **3**. (**a**) Vinylic hydrogen nuceli. (**b**) Methylene hydrogen nuclei. (**c**) Vynilic carbon nuclei. (**d**) Methylene carbon nucleus. (**e**) Carboxylic carbon nuclei.

**Table 2: Results of the Fitting Achieved of Chemical Shifts as a Function of pH for the Different Nuclei of AA and MA with Program HYPNMR to Characterize their Equilibria of Acidity and the Species Involved**

| | | |
|---|---|---|
| **Acrylic acid ($\sigma_{fitting}$ = 0.20)*** | | |
| Chemical equilibrium | $pK_a$ | |
| $HL \leftrightarrows H^+ + L^-$ | 4.060 ± 0.032 | |
| Position of H nucleus | $\delta_{^1H}$ /ppm in HL | $\delta_{^1H}$ /ppm in $L^-$ |
| 3-*cis* | 6.27 ± 0.12 | 5.873 ± 0.087 |
| 3-*trans* | 5.85 ± 0.12 | 5.514 ± 0.087 |
| Position of C nucleus | $\delta_{^{13}C}$ /ppm in HL | $\delta_{^{13}C}$ /ppm in $L^-$ |
| 1 | 170.06 ± 0.12 | 175.447 ± 0.085 |
| 2 | 127.39 ± 0.12 | 133.673 ± 0.085 |
| 3 | 133.05 ± 0.13 | 126.656 ± 0.089 |
| **Methacrylic acid ($\sigma_{fitting}$ = 0.02)**** | | |
| Chemical equilibrium | $pK_a$ | |
| $HL \leftrightarrows H^+ + L^-$ | 4.462 ± 0.002 | |
| Position of H nucleus | $\delta_{^1H}$ /ppm in HL | $\delta_{^1H}$ /ppm in $L^-$ |
| 3-*cis* | 5.913 ± 0.008 | 5.493 ± 0.008 |
| 3-*trans* | 5.520 ± 0.008 | 5.188 ± 0.008 |

**(Table 2). Continue.**

| **Methacrylic acid ($\sigma_{fitting}$ = 0.02)**** | | |
|---|---|---|
| Position of C nucleus | $\delta^{13}_{\mathrm{C}}$ /ppm inHL | $\delta^{13}_{\mathrm{C}}$ /ppm in $L^-$ |
| 1 | 171.615 ± 0.007 | 177.410 ± 0.008 |
| 2 | 135.875 ± 0.007 | 142.246 ± 0.008 |
| 3 | 126.970 ± 0.009 | 120.376 ± 0.008 |

*Model with one equilibrium of acidity fitting simultaneously 5 sigmoidal curves (one for each nucleus) with 10 points in each one as a function of pH. The data of hydrogen nucleus in position 2 was omitted in the refinement due to the invariance of its chemical shift. Reported $pK_a$ = 4.06 at 25°C [16].

**Model with one equilibrium of acidity fitting simultaneously 5 sigmoidal curves (one for each nucleus) with 16 points in each one as a function of pH. The data of hydrogen nucleus in position 4 was omitted in the refinement due to the invariance of its chemical shift. Reported $pK_a$ = 4.66 at 20°C [17].

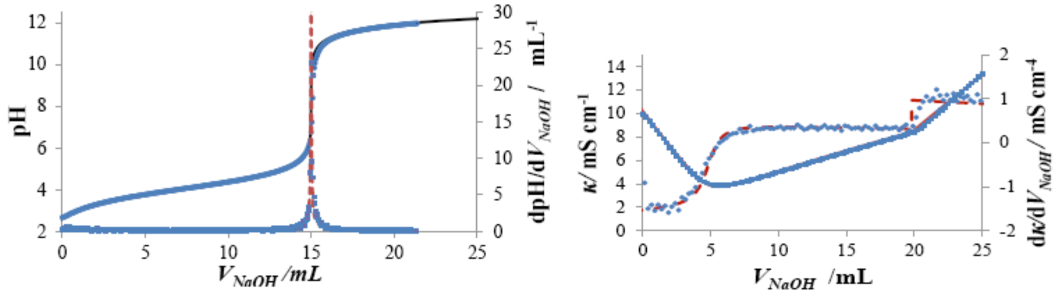
**Table 3: Results of the Fitting Achieved of Chemical Shifts as a Function of pH for the Different Nuclei of IA with Program HYPNMR to Characterize their Equilibria of Acidity and the Species Involved**

| **Itaconic Acid*** | | | |
|---|---|---|---|
| **Model I ($\sigma_{fitting}$ = 0.29)**** | | | |
| **Chemical equilibrium** | **$pK_a$** | | |
| $HL \leftrightarrows H^+ + L^-$ | 4.540 ± 0.040 | | |
| Position of H nucleus | $\delta^{1}_{\mathrm{H}}$ /ppm in HL | $\delta^{1}_{\mathrm{H}}$ /ppm in $L^-$ | |
| 3-*cis* | 6.18 ± 0.15 | 5.71 ± 0.13 | |
| 3-*trans* | 5.70 ± 0.15 | 5.24 ± 0.13 | |
| 4 | 3.25 ± 0.15 | 3.01 ± 0.13 | |
| Position of C nucleus | $\delta^{13}_{\mathrm{C}}$ /ppm in HL | $\delta^{13}_{\mathrm{C}}$ /ppm in $L^-$ | |
| 1 | 170.39 ± 0.15 | 175.65 ± 0.13 | |
| 2 | 133.83 ± 0.15 | 141.37 ± 0.13 | |
| 3 | 130.22 ± 0.15 | 122.28 ± 0.13 | |
| 4 | 37.67 ± 0.15 | 41.91 ± 0.13 | |
| 5 | 176.16 ± 0.15 | 180.41 ± 0.13 | |
| **Model II ($\sigma_{fitting}$ = 0.03)** | | | |
| **Chemical equilibrium***** | | | |
| $HL \leftrightarrows H^+ + L^{2-}$ | $pK_{a2} = \log\beta_1 = 5.079 \pm 0.015$ | | |
| $H_2L \leftrightarrows 2H^+ + L^{2-}$ | $pK_{ag} = \log\beta_2 = 8.623 \pm 0.038$ | | |
| Position of H nucleus | $\delta^{1}_{\mathrm{H}}$ /ppm in $H_2L$ | $\delta^{1}_{\mathrm{H}}$ /ppm in $HL^-$ | $\delta^{1}_{\mathrm{H}}$ /ppm in $L^{2-}$ |
| 3-*cis* | 6.219 ± 0.021 | 5.957 ± 0.035 | 5.702 ± 0.018 |
| 3-*trans* | 5.735 ± 0.021 | 5.507 ± 0.035 | 5.227 ± 0.018 |
| 4 | 3.263 ± 0.021 | 3.153 ± 0.035 | 2.999 ± 0.018 |
| Position of C nucleus | $\delta^{13}_{\mathrm{C}}$ /ppm in $H_2L$ | $\delta^{13}_{\mathrm{C}}$ /ppm in $HL^-$ | $\delta^{13}_{\mathrm{C}}$ /ppm in $L^{2-}$ |
| 1 | 169.966 ± 0.021 | 172.842 ± 0.034 | 175.785 ± 0.017 |
| 2 | 133.387 ± 0.021 | 136.905 ± 0.034 | 141.675 ± 0.017 |
| 3 | 130.669 ± 0.021 | 127.040 ± 0.035 | 121.937 ± 0.018 |
| 4 | 37.261 ± 0.021 | 39.829 ± 0.034 | 41.964 ± 0.017 |
| 5 | 175.925 ± 0.021 | 177.859 ± 0.034 | 180.589 ± 0.017 |

*Models fitting simultaneously 8 sigmoidal curves (one for each nucleus) with 10 points in each one as a function of pH. Model II is the meaningful model with better statistical parameters.

**Meaningless model that has been included only for didactic reasons in discussion.

***$H_2L \leftrightarrows H^+ + HL^-$:$pK_{a1} = \log\beta_2 - \log\beta_1 = 3.544 \pm 0.041$ and $pK_{a2} = \log\beta_1 = 5.079 \pm 0.015$. Reported values: $pK_{a1}$ = 3.69, $pK_{a2}$ = 5.22 at 25°C [9].



(a) (b)

**Figure 6:** Titration curves acquired by an automatic titrator. Markers represent experimental points, while solid line represents the fitted curve calculated with a robust model: and segmented line represents the first-derivative of the titration curve, obtained approximately as the quotient of finite differences. (**a**) Potentiometric titration of 100 mL aqueous solution of 0.075M AA with 0.500M of NaOH. (**b**) Conductometric titration of 100 mL aqueous solution of 0.075M AA and 0.024M HCl with 0.500 M of NaOH. Fitting achieved with $\lambda_{H^+}$ = 340 S cm$^2$eq$^{-1}$, $\lambda_{OH^-}$ = 199 S cm$^2$eq$^{-1}$, $\lambda_{Na^+}$ = 50 S cm$^2$eq$^{-1}$, $\lambda_{Cl^-}$ = 76 S cm$^2$eq$^{-1}$, $\lambda_{L^-}$ = 43 S cm$^2$eq$^{-1}$, and p$K_a$ = 4.06.

Then, in all cases only one break is shown in the titration curve (pH = f($V_{NaOH}$)), giving a sharp maximum in its first-derivative curve. The points used for p$K_a$ determination were those before the equivalence point, where there is more information to determine these parameters.

The results obtained for p$K_a$ values using the program SUPERQUAD are presented in Table **4**. These values are in good agreement with those reported previously [9, 16, 17] and with the p$K_a$ values determined by HYPNMR, as it is shown in the same Table **4**, even though the ionic strength (I) is different for the potentiometric and NMR experiments.The good fitting achieved for the p$K_a$ values refined with SUPERQUAD is shown in Figures. **6a**, **7a** and **8a** for AA, MA and IA, respectively.

Like an additional proof of the good quality of the p$K_a$ values determined by potentiometric titrations, they have been used to fit conductometric curves of AA, MA or IA with NaOH. These fittings are shown in Figures. **6b**, **7b** and **8b** for AA, MA and IA, respectively. The equivalent conductivity used for the fittings are shown in the foot of each Figure and the known values, for $\lambda_{H^+}$, $\lambda_{OH^-}$, $\lambda_{Na^+}$ and $\lambda_{Cl^-}$, are practically the same that those reported [18] for AA and MA. For IA they show a deviation of approximately -15%, may be due to the temperature and the ionic strength values of the system in these experiments.

It must be noted that conductometric titration curves for AA and MA (Figures **6b** and **7b**) show almost linear trends (solid line), reflected in its first-derivative curve like almost constants (segmented line).

The first-derivative of the conductometric titration curve for IA (Figure **8b**) is much more complex before the second equivalence point, due to the fact that pKa values are near, one of each other; then, the curve in this region is non-linear. Nevertheless, the robust model used to calculate the conductometric curve and the good estimators of p$K_a$ values allow a very good fitting of experimental curve.

## 4. CONCLUSIONS

In the present work it has been shown that curves of sigmoidal chemical shift (of many nuclei) as a function of pH may be used to determine p$K_a$ values on an exact and precise way, using non-linear least squares programs (like HYPNMR) and giving a structural characterization of the system. The values obtained are comparable to those determined by potentiometric methods. This could be an alternative method when the substances under study are very soluble in water.

## 5. MATERIALS AND METHODS

### 5.1. NMR Determinations

### *5.1.1. Instrumentation*

Natural abundance spectra were recorded on an AVANCE Bruker 400 spectrometer, operating at 400 MHz with PABBO probe. All spectra were acquired at 25 °C.

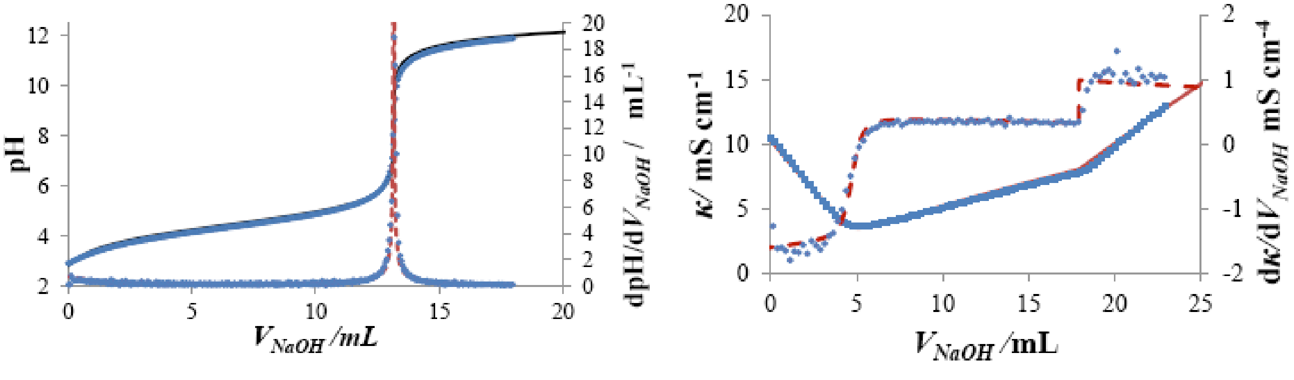
### *5.1.2. Reagents*

$D_2O$ (Cambridge Isotope Laboratories, Inc.), KOH (J.T. Baker), HCl (J.T. Baker), acrylic acid (Dow Chemical), methacrylic acid (Dow Chemical) and itaconic acid (Sigma Aldrich), pH buffers 7, 4 and 10 (Thermo Scientific) and Deionized water.

**Table 4: Comparison of Results for the Acidity Constants (p$K_a$) Obtained by Fitting of Potentiometric Titration Curves or Chemical Shifts/pH Curves for AA, MA and IA with the Aid of Programs SUPERQUAD or HYPNMR, Respectively**

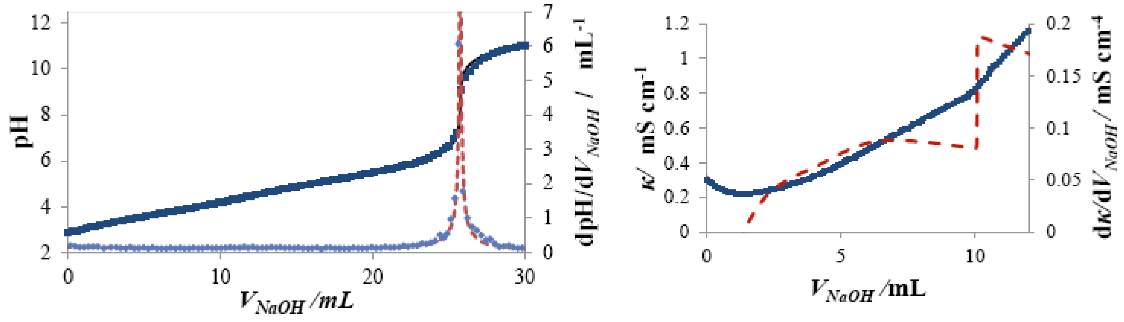
| | SUPERQUAD | HYPNMR | REPORTED |
|---|---|---|---|
| **AcrylicAcid (AA)** | | | |
| Chemical equilibrium | T = 25°C,<br>I ≈ 0.08 M<br>($\sigma_{fitting}$ = 0.88)<br>N = 300 points | T = 25°C,<br>I ≈ 0.1 M<br>($\sigma_{fitting}$ = 0.20)<br>N = 50 points | T = 25 °C,<br>I = 0.1 M<br>[16] |
| $HL \leftrightarrows H^+ + L^-$ | 4.064 ± 0.001 | 4.060 ± 0.032 | 4.08 |
| **Methaacrylic Acid (MA)** | | | |
| Chemical equilibrium | T = 25°C,<br>I ≈ 0.07 M<br>($\sigma_{fitting}$ = 3.1)<br>N = 261 points | T = 25°C,<br>I ≈ 0.01 M<br>($\sigma_{fitting}$ = 0.02)<br>N = 80 points | T = 20 °C,<br>I = not available<br>[17] |
| $HL \leftrightarrows H^+ + L^-$ | 4.381 ± 0.003 | 4.462 ± 0.002 | 4.66 |
| **Itaconic Acid (IA)** | | | |
| Chemical equilibria | T = 23°C,<br>I ≈ 0.01 M<br>($\sigma_{fitting}$ = 5.4)<br>N = 86 points | T = 25°C,<br>I ≈ 0.01 M<br>($\sigma_{fitting}$ = 0.29)<br>N = 80 points | T = 25 °C,<br>I = not available<br>[9] |
| $H_2L \leftrightarrows H^+ + HL^-$ | 3.58± 0.03* | 3.544 ± 0.041* | 3.69 |
| $HL \leftrightarrows H^+ + L^-$ | 5.21± 0.02 | 5.079 ± 0.015 | 5.22 |
| $H_2L \leftrightarrows 2H^+ + L^{2-}$ | 8.79± 0.02 | 8.623 ± 0.038 | |

* determined by the difference $\log\beta_2 - \log\beta_1$.



(a) (b)

**Figure 7:** Titration curves acquired by an automatic titrator. Markers represent experimental points, while solid line represents the fitted curve calculated with a robust model: and segmented line represents the first-derivative of the titration curve, obtained approximately as the quotient of finite differences. (**a**) Potentiometric titration of 100 mL aqueous solution of 0.0661M MA with 0.500 M of NaOH. (**b**) Conductometric titration of 100 mL aqueous solution of 0.0661M MA and 0.024M HCl with 0.500 M of NaOH. Fitting achieved with $\lambda_{H^+}$ = 350 S cm$^2$ eq$^{-1}$, $\lambda_{OH^-}$ = 199 S cm$^2$ eq$^{-1}$, $\lambda_{Na^+}$ = 50 S cm$^2$ eq$^{-1}$, $\lambda_{Cl^-}$ = 76 S cm$^2$ eq$^{-1}$, $\lambda_{L^-}$ = 45 S cm$^2$ eq$^{-1}$, and p$K_a$ = 4.46.



(a) (b)

**Figure 8:** Titration curves acquired manually. Markers represent experimental points, while solid line represents the fitted curve calculated with a robust model: and segmented line represents the first-derivative of the titration curve, obtained approximately as the quotient of finite differences. **a**) Potentiometric titration of 100 mL aqueous solution of 0.0104M IA with 0.0801M of NaOH. **b**) Conductometric titration of 30 mL aqueous solution of 0.0068M AA with 0.0405M of NaOH. Fitting achieved with $\lambda_{H^+}$ = 315 S cm$^2$ eq$^{-1}$, $\lambda_{OH^-}$ = 165 S cm$^2$ eq$^{-1}$, $\lambda_{Na^+}$ = 41.8 S cm$^2$ eq$^{-1}$, $\lambda_{HL^-}$ = 20 S cm$^2$ eq$^{-1}$, $\lambda_{L^{2-}}$ = 39 S cm$^2$ eq$^{-1}$, pK$_{a1}$ = 3.83, and pK$_{a2}$ = 5.37.

### *5.1.3. Solutions*

1.0 M HCl stock solution, diluted with 10% $D_2O$ (i.e., 90% $H_2O$).

1.0 M KOH stock solution, diluted with 10% $D_2O$.

250 µL of acrylic acid or methacrylic acid and 9.75 mL of 10% $D_2O$ were mixed well with a small magnetic stir bar and magnetic stirring plate.

119 mg of itaconic acid with 10 mL of 10% $D_2O$ were mixed well with a small magnetic stir bar and magnetic stirring plate.

The rest of the samples were acquired splitting the work solution (acrylic acid, methacrylic acid or itaconic acid) in two portions, add the 1.0 M HCl stock solution dropwise to adjust for the lower pH. To the other portion, add 1.0 M KOH stock solution dropwise to adjust for the higher pH. Various samples were prepared to cover pH range of approximately 1 – 13.

The ionic strength was not imposed to the solutions because in this work it is emphasized the possibility of the determination of pKa values by NMR signals, more than to obtain these values with very high precision.

### *5.1.4. pH Measurements*

pH values were measured in accord with the procedure ISO 4316, with a potentiometer 716 DMS Metrohm equipped with a glass combined electrode, 60259.100 Metrohm.

### *5.1.5. Spectroscopic Procedures*

Typical one-dimensional $^1$H and $^{13}$C NMR spectra were acquired with standard pulse programs for unequivocal assignment of chemical shifts to nuclei. Tetramethylsilane (TMS) was used to calibrate chemical shifts of $^1$H or $^{13}$C as internal standard.

## 5.2. Titration Determinations with Automatic Titrator

### *5.2.1. Instrumentation*

The potentiometric and conductometric titrations of acrylic, methacrylic or itaconic acid were acquired with Automatic Tritino 808 (Metrohm), equipped with glass combined electrode, 60259.100 Metrohm, (Conductometer 712 Metrohm), Dosing devices (808 and 805 Metrohm), Exchange unit with data chip of 20 mL, Magnetic stirring plate (804 Metrohm) and TiamoSotware 2.4 (Metrohm).

### *5.2.2. Reagents*

NaOH (J.T. Baker), potassium biphthalate (J.T. Baker), acrylic acid (Dow Chemical), methacrylic acid (Dow Chemical) and itaconic acid (Sigma Aldrich), pH buffers 7,4 and 10 (Thermo Scientific) and deionized water.

### *5.2.3. Solutions*

0.5 M stock NaOH solution, 0.01M KCl solution.

### *5.2.4. Potentiometric Titrations*

The potentiometric titrations were obtained at 25 °C in a titration vessel filled with 0.5 g of acid (acrylic, methacrylic or itaconic) and 100 mL of deionized water, this solution was continuously stirred. Solution of 0.5 M NaOH was used as titrant. The precise concentration of base was obtained by titrating with primary standard potassium biphtalate. The data of titration were acquired automatically by Tiamo 2.4 Software (Metrohm).

### *5.2.5. Conductometric Titrations*

The conductometric titrations were obtained at 25 °C in a titration vessel filled with 0.5 g of acid (acrylic, methacrylic or itaconic), a volume of HCl 1 M and 100 mL of deionized water, in order to have an initial pH near to 2.0 and a narrower beginning of carboxylic acids titration, this solution was continuously stirred. Solution of 0.5 M NaOH was used as titrant. The precise concentration of base was obtained by titrating with primary standard potassium biphtalate. The data of titration were acquired automatically by Tiamo 2.4 Software (Metrohm).

In both kind of titrations, the ionic strength was also variable.

## 5.3. Manual Titrations for IA

### *5.3.1. Instrumentation*

For manual potentiometric titrations a sens ION+ PH31 potentiometer of Hach was employed, equipped with a 5010T combined electrode with temperature sensor. For conductometric titrations a Radiometer CDM230 conductometer equipped with a CDC641T cell with a constant H = 1 $cm^{-1}$ was used.

### *5.3.2. Reagents*

NaOH (J.T. Baker), potassium biphthalate (J.T. Baker), and itaconic acid (Sigma Aldrich), pH buffers 7,4 and 10 (Radiometer) and deionized water.

### *5.3.3. Solutions*

0.5 M stock NaOH solution, 0.01M KCl solution.

### *5.3.4. Potentiometric Titrations*

pH-metric titrations were achieved for IA, titrating 100 mL of 0.0104 M of IA with 0.0810 M of NaOH at room temperature: (23.00 ± 0.50)°C. Calibration was achieved by a method reported previously, considering the electrochemical cell efficiency [19, 20].

### *5.3.5. Conductometric Titrations*

Conductometric titrations were achieved for IA, titrating 30 mL of 0.0068 M of IA with 0.0405 M of NaOH at room temperature: (22.60 ± 0.63)°C.

In both kind of titrations, the ionic strength was also variable.

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