



PHYSICAL CHEMISTRY 2018

14th International Conference
on Fundamental and Applied Aspects of
Physical Chemistry

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Volume II

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THE EFFECT OF DIFFERENTLY CHARGED MICELLES ON PROTOLYTIC EQUILIBRIA OF MALEIC AND FUMARIC ACID

M. Popović-Nikolić¹, G. Popović², K. Stojilković², M. Dobrosavljević² and D. Agbaba¹

¹ Department of Pharmaceutical Chemistry,
(majap@pharmacy.bg.ac.rs)

² Department of General and Inorganic Chemistry, Faculty of Pharmacy,
University of Belgrade, Vojvode Stepe 450, 11000 Belgrade, Serbia

ABSTRACT

The pK_a values of maleic and fumaric acid have been determined potentiometrically in the presence and in the absence of differently charged micelles. The ionization of maleic acid has been significantly affected (ΔpK_a up to 1.91) by the presence of micelles, unlike the ionization of fumaric acid (ΔpK_a up to +0.30). Observed shift in equilibrium forms is most expressed in pH range 2 – 6.

INTRODUCTION

Maleic and fumaric acid are diastereoisomers that contain the same number and kinds of atoms, the same arrangement of bonds but differ in three-dimensional arrangement of atoms in space (Figure 1). Due to the presence of double bond, these organic diacids represent geometric isomers of ethylene dicarboxylic acid and exhibit different physico-chemical properties

[1]. Maleic and fumaric acid are among the most frequently used acids as salt formers in drug compounds, such as enalapril maleate, pheniramine maleate, domperidone maleate, bisoprolol fumarate, rupatadin fumarate, quetiapine fumarate, etc. Various pharmaceutical dosage forms are formulated to administer drug substances by different routes whereas the dosage form and the applicable technology depend on the physico-chemical properties profile of the chosen salt. One of the most important physico-chemical properties is pK_a value which allows us to calculate the relative percentages of ionized and unionized form of the compound for any given pH. In the solutions of

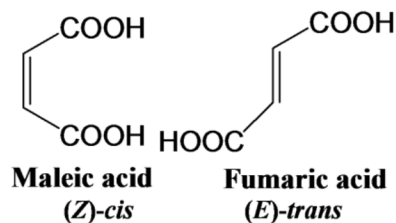


Figure 1. Chemical structures of examined compounds.

ionizable drugs formulated as salts with organic diacid, complex protolytic equilibria are established. Determination of the pK_a values of organic diacids helps in defining the ionization profile of the corresponding ionizable drug.

The aim of this study was the determination of the pK_a values of maleic and fumaric acid in "pure" water, as surfactant free media, and in micellar solutions of differently charged surfactants. Micelles express a solubilizing effect on the compounds sparingly soluble in water, but may influence protolytic equilibria, reaction rates, products, and stereochemistry that may be different from those observed in the surfactant free solutions [2]. The results obtained in this study provide a better insight into the behavior of investigated compounds in experimental conditions especially in analytical procedures important for drug compounds containing maleic and fumaric acid as salt formers.

EXPERIMENTAL

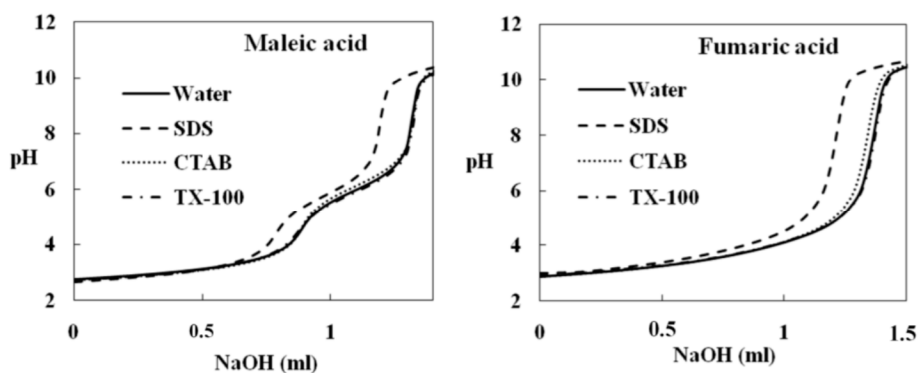


Figure 2. Potentiometric curves of maleic and fumaric acid solutions in the absence and in the presence of 10^{-2} M surfactant titrated with standard NaOH solution. $I = 0.1$ M (NaCl), $t = 25$ °C.

The pK_a values were determined potentiometrically on Automatic titrator 798 MPT Titrino (Metrohm, Switzerland) with a combined electrode LL unitrode Pt 1000 (Metrohm, Switzerland). Maleic and fumaric acid were kindly donated from Medicines and Medical Devices Agency of Serbia (Belgrade, Serbia). The surfactants, anionic, sodium dodecylsulphate - SDS (J.T. Baker); cationic, cetyltrimethylammonium bromide - CTAB (Acros Organic); and nonionic, 4-octylphenol polyethoxylate – TX-100 (Acros Organic) were used for the preparation of micellar solutions. All solutions

were prepared in double distilled water. Standard solutions of HCl and carbonate-free NaOH were standardized potentiometrically.

All solutions (10^{-3} M) of investigated compounds with and without the presence of 10^{-2} M surfactants (SDS, CTAB, and TX-100) were titrated with 0.0997 M NaOH at a 25°C and a constant ionic strength (0.1 M NaCl) (Figure 2). Surfactants were used at a concentration higher than their critical micellar concentrations. Experimental data obtained by potentiometric titration were analyzed by the program Hyperquad.

RESULTS AND DISCUSSION

The ionization profiles are defined for surfactant free media and obtained pK_a values are $pK_{a1}=2.32$ and $pK_{a2}=6.03$ for maleic acid and $pK_{a1}=2.86$ and $pK_{a2}=4.26$ for fumaric acid. The intramolecular hydrogen bond in maleic acid facilitates the ionization of the first carboxyl group by the stabilization of carboxylic anion (lower pK_{a1}) but e^-e^- repulsion between carboxylic groups, when are both deprotonated, hinders the ionization of the second group (higher pK_{a2}). The carboxylic groups are too far from each other to form hydrogen bond in fumaric acid and there are no e^-e^- repulsions between carboxylic anions.

Table 1. The pK_a values obtained potentiometrically in the presence of 10^{-2} M surfactants. ΔpK_a - differences in relation to pK_a values obtained in surfactant-free media. MA-maleic acid; FA-fumaric acid.

Acid	pK_a	SDS	ΔpK_a	CTAB	ΔpK_a	TX-100	ΔpK_a
MA	pK_{a1}	1.23 ± 0.05	-1.09	1.11 ± 0.0 6	-1.21	1.88 ± 0.0 2	-0.44
	pK_{a2}	6.25 ± 0.05	+0.22	5.81 ± 0.0 6	-0.22	5.97 ± 0.0 2	-0.06
FA	pK_{a1}	2.87 ± 0.04	+0.01	2.74 ± 0.0 2	-0.12	2.93 ± 0.0 1	+0.07
	pK_{a2}	4.56 ± 0.04	+0.30	4.28 ± 0.0 2	+0.02	4.25 ± 0.0 1	-0.01

On the basis of the values obtained in the presence of micelles (Table 1), the shift in protolytic equilibria (ΔpK_a) can be noticed. More pronounced effect is observed for maleic acid, ΔpK_a from -1.21 for pK_{a1} in the presence of CTAB, to +0.22 for pK_{a2} in the presence of SDS. The pK_a values of fumaric acid are not significantly affected by the presence of micelles, whereas ΔpK_a range from -0.12 for pK_{a1} in the presence of CTAB to +0.30 for pK_{a2} in the presence of SDS. Electrostatic and nonspecific hydrophobic interactions could be dominant in interaction with ionic SDS and CTAB micelles. The

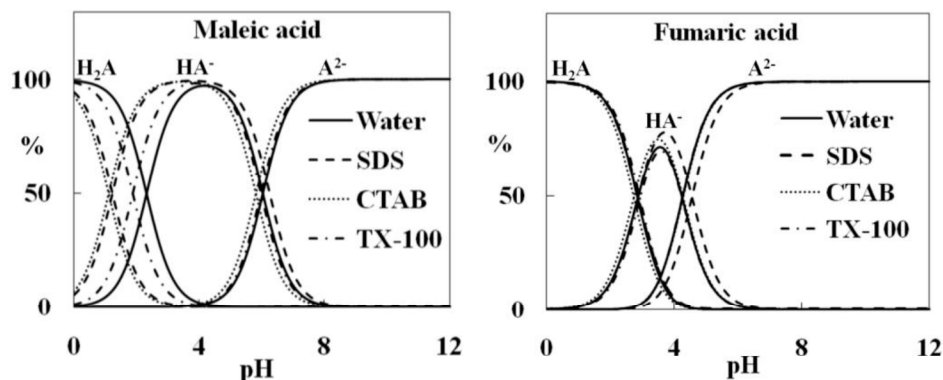


Figure 3. Distribution of maleic and fumaric acid equilibrium forms as function of pH.

nonionic micelles are not charged, but contain hydrophilic surface layer in which hydrogen bond forming and dipole interactions with carboxylic groups of examined diacids are possible (ΔpK_a up to -0.44).

The effect of micelles on protolytic equilibria can be clearly seen on the distribution diagrams of equilibrium forms as function of pH (Figure 3). Obtained shift in distribution of the equilibrium forms is the most expressed in a pH range 2 – 6.

CONCLUSION

The difference in pK_a values has been observed for geometric isomers, maleic and fumaric acid. The protolytic equilibria of maleic acid is shifted in the presence of micelles, especially anionic and cationic. The presence of differently charged micelles does not significantly affect the ionization of fumaric acid. Obtained results could be observed together with corresponding drug molecules under the different experimental conditions.

Acknowledgement

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