

pK_a s in Dicarboxylic Acids by Constant- pH Molecular Dynamics Simulations

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A method for performing constant- pH molecular dynamics, where pH is one of the external parameters of the solution, is applied for computation of protonation equilibria in a series of small dicarboxylic acids. Proton dissociation constants for succinic, glutaric, adipic and cork acids were determined. Very good agreement with experimental measurements is achieved.

Key words: pK_a ; Constant- pH Molecular Dynamics;
Dicarboxylic Acid.

1. Introduction

The physical and chemical properties of molecules depend on the pH of the solution. Inclusion of the proton exchange phenomena can be crucial for the results of computer simulations of molecules [1, 2]. We analysed the ionization equilibria of a series of dicarboxylic acids as test of a simulation method we are developing. Our algorithm employs molecular dynamics (MD) simulations with an implicit, dielectric continuum solvent, in connection with Poisson-Boltzmann electrostatics calculations (constant- pH MD). A detailed description of our approach is presented in [3].

2. Methods and Results

We choose monocarboxylic butyric acid for adjusting the model pK_a [4] appropriate for dielectric constants of the interior (value of 1.5) and the exterior (value of 80.0) of the molecules and sets of partial charges assigned to model the ionized (deprotonated) and neutral (protonated) state of the carboxylic group shown in Figure [1].

For this purpose we generated constant- pH MD trajectories of butyric acid at several pH values. Trac-

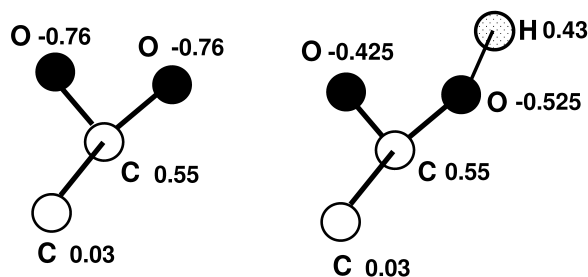


Fig. 1. Schematic view of the carboxylic group showing the partial charges in the ionized (left) and the protonated (right) state.

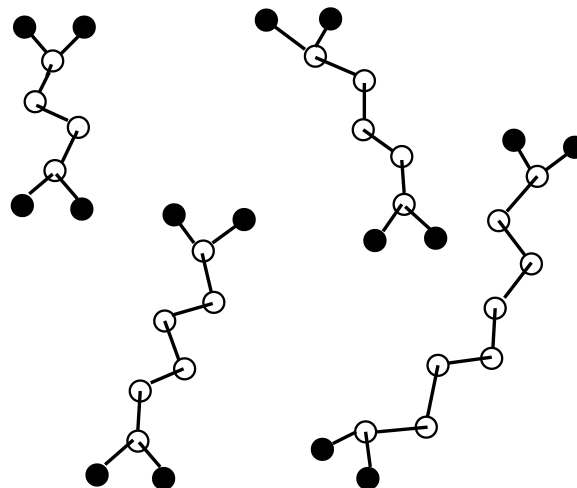


Fig. 2. Heavy atoms representations of dicarboxylic acids: succinic (upper left), glutaric (upper right), adipic (lower left), cork (lower right).

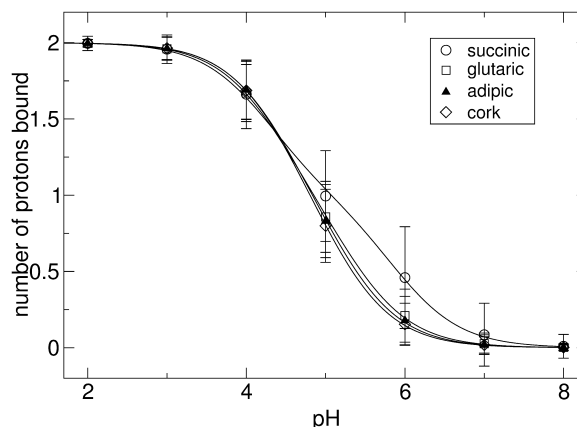


Fig. 3. Titration curves for dicarboxylic acids.

Table 1. Values of proton dissociation constants determined experimentally [9–11] and by the constant-*pH* MD.

Acid	Experiment			Computation		
	<i>pK</i> ₁	<i>pK</i> ₂	Δ	<i>pK</i> ₁	<i>pK</i> ₂	Δ
butyric	4.8	—	—	4.7	—	—
succinic	4.2	5.6	1.4	4.3	5.9	1.6
glutaric	4.3	5.3	1.0	4.3	5.4	1.1
adipic	4.4	5.3	0.9	4.4	5.3	0.9
cork	4.5	5.4	0.8	4.4	5.2	0.8

ing the trajectory-averaged charge of the molecule as a function of the *pH*, we found that the model *pK*_a value of 4.5 reproduces the experimental *pK*_a for butyric acid with an accuracy of 0.1 *pH* units. We adopted this value of the model *pK*_a for the studied dicarboxylic acids.

Having this parametrization, we performed constant-*pH* MD simulations for *pH* values in the range from 1 to 8 of the molecules of interest, using the protocol described in [3].

The average number $\langle N \rangle$ of protons bound to the molecule computed based on the ensemble of struc-

tures taken from the constant-*pH* trajectory for a given *pH* value can be described by [5]

$$\langle N \rangle = \frac{10^{pK_2 - pH} + 2 \times 10^{pK_1 + pK_2 - 2pH}}{1 + 10^{pK_2 - pH} + 10^{pK_1 + pK_2 - 2pH}}. \quad (1)$$

This equation represents the titration curve of the dibasic molecule and is sufficient to determine the apparent *pK*_a values of its titratable groups.

Our results, summarized in Table 1 and Fig. 3, indicate that the constant-*pH* MD simulation gives reasonable agreement with experimental data. Previously presented approaches to an analysis of the ionization equilibria of dibasic aliphatic acids [6, 7] ignored the conformational flexibility of molecules and possible relations between conformational transitions and the ionization equilibria [8].

Acknowledgements

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