Titration Curve Generation for SAMPL8 Physical Properties Analysis

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This document describes the procedure of using the relative microstate free energies to find the macro-pK_a values. This procedure involves the generation of titration curves based on the work by Selwa et. al and Gunner et. al for SAMPL6. This methodology was used for the SAMPL8 physical properties pK_a analysis.

0.1 Microstates and Macrostates

Macrostates: Each microstate corresponds to a tautomer of a given molecule. For example, in an acid dissociation reaction below,the tautomers of HA and A^- are considered microstates.

$$HA_{(s)} \rightleftharpoons H^+_{(s)} + A^-_{(s)} \tag{1}$$

Macrostates: The set of microstates with the same total number of protons is called a macrostate.($Ni = N$ where N is the total number of protons)

0.2 Relation between Free Energy Change and pK_a

From equation 1 we can derive the acid dissociation constant as follows-

$$K_a = \frac{[A^-][H^+]}{[HA]} \tag{2}$$

The pK_a can be estimated from equation 2 as follows-

$$pK_a = -log_{10}\frac{K_a}{c_0} \tag{3}$$

where $c_0 = 1\frac{mol}{liter}$ measures the thermodynamic acidity (This constant is used to ensure that the pK_a has appropriate units.

The microscopic pK_a can be defined as the as the free energy change for deprotonation reaction (i.e acid dissociation reaction) at the standard state (concentration of 1 mol/liter and T = 298.15 K)

$$pK_a = \frac{\Delta G^*_{(s)}}{RTln10} \tag{4}$$

The relationship between pH and pK_a is given by the Henderson-Hasselbalch equation-

$$pK_a = pH - log_{10}\left(\frac{[A^-]}{[HA]}\right) \tag{5}$$

where $[HA]$ and $[A^-]$ is its conjugate base. This can also be seen as protonated and deprotonated states respectively.

Equation 5 can be rewritten based on first principles of statistical mechanics as follows-

$$pK_a = pH - \frac{1}{ln10} ln \left(\frac{P(N-1)}{P(N)} \right) \tag{6}$$

where P(N) and P(N-1) are the probabilities that N and N-1 charged states exist.

Equation 6 can be rewritten in terms of free energy change for a deprotonation reaction as follows-

$$\Delta G_{N,N-1} = -\Delta G_{N-1,N} = -\beta^{-1} ln \left(\frac{P(N-1)}{P(N)} \right) \tag{7}$$

Using Equation 6 and Equation 7 we can derive the relationship between the relative free energy and the pK_a-

$$pK_a = pH - \frac{\beta \Delta G_{N-1,N}}{ln10} \tag{8}$$

We can re-write Equation 8 as follows-

$$\Delta G_{N-1,N} = (pH - pK_a) \frac{ln10}{\beta} \tag{9}$$

where $\beta = \frac{1}{RT}$

Equation 9 gives the relationship between the free energy change and the pK_a for a deprotonation reaction. However, given that in each SAMPL submission we are given the standard relative free energy changes, we can use the above equations to derive a relationship between relative free energy changes as a function of pH and standard relative free energies. Note-Standard here means that pH values are computed at T=300 K.

0.3 Relationship between Relative Free Energy Change and pK_a as a function of pH

For this section we will consider a reference state for calculating the relative free energy state. This reference state can be an tautomeric state of the molecule. All free energy change calculations will be made relative to this state.

The relationship between standard free energy change and the pK_a is as follows-

$$\Delta G^{pH}_{AB} = \Delta m_{AB} C_{units}(pH - pK_{AB}) \tag{10}$$

Note: Here B is the reference state and ΔG^{pH}_{AB} refers to the free energy change going from state B to state A as a function of pH at a standard temperature.

In the case of SAMPL8, all standard relative free energies are computed at pH=0 and a temperature of 300K. Hence these are the stanadrd conditions. Based on these criteria Equation 10 can be modified as follows-

$$\Delta G^0_{AB} = \Delta m_{AB} C_{units}(-pK_{AB}) \tag{11}$$

To find the relative free energy change at any pH we can use the equation below-

$$\Delta G^{pH}_{jB} = \Delta G^0_{jB} + \Delta m_{jB} C_{units}(pH - pH_{ref}) \tag{12}$$

Since our standard relative free energy changes are computed at pH=0 we can further simplify Equation 12 to-

$$\Delta G^{pH}_{jB} = \Delta G^0_{jB} + \Delta m_{jB} C_{units} pH \tag{13}$$

Equation 13 is the relationship needed to compute relative free energy changes at any given pH.

0.4 Using charged population fractions to construct titration curves

Given a relative free energy changes and using first principles of statistical mechanics , an equation can be derived to estimate the population fraction of that specific charge state at a given pH. This can be estimated using the standard expression-

$$N^{pH}_j = \frac{e^{-\beta \Delta G^{pH}_{jB}}}{\sum_i e^{-\beta \Delta G^{pH}_{iB}}} \tag{14}$$

where $\beta = \frac{1}{RT}$

Equation 14 can be used to construct titration curves showing the transition

from one macrostate to the other for a molecule. The intersection of these transition state curves are the macro-pK_a's.

Macro-pK_a's are the points on a titration curve where the relative free energy difference between two formal charged states is 0.