

Prediction of pK_a Values for Oligo-methacrylic Acids Using Combined Classical and Quantum Approaches

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The pK_a values for polymeric acids are very useful quantities for many applications including separations using ion-exchange membranes and catalysis using polymeric acids. However, the pK_a value of a polymeric acid is typically different from the corresponding monomer value and is generally unknown. The pK_a value of a particular acid group is strongly dependent on the local environment of the dissociating acid group and the broad dielectric medium. The pK_a values for oligo-methacrylic acids were systematically determined as a function of degree of polymerization using combined classical and quantum mechanical approaches. The atomic charges were determined quantum mechanically, whereas the pK_a values were determined solving the Poisson–Boltzmann equation. The pK_a values were found to increase as the degree of polymerization (DP) increases and converge to a stable value after DP reaches 8. The predicted pK_a values agree very well with experimental results.

Introduction

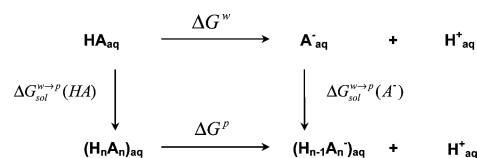
The acidity constant for macromolecules such as proteins and polymeric acids with multiple acid groups is complex due to each acid group's unique electrostatic environment.^{1–4} Polymeric acids with multiple acid groups have wide applications in specific bioseparations and catalysis. The pK_a values of the acid groups in a polymeric acid (e.g., poly(methacrylic acid), PMAA) are typically different from their corresponding monomer value due to the change in their electrostatic environment. Forsyth et al. show that two different carboxyl groups in the same protein can have pK_a values of 2 and 9.⁵ Since the pK_a values of the polymeric acids are typically unknown and expected to be different from their monomer values, it is therefore important to determine the pK_a values of polymeric acids used for ion-exchange-based separations (e.g., PMMA) and for catalysis (polysulfonic acids). The present work is an attempt to investigate the pK_a dependence on the chain length of the short oligomers of methacrylic acids (MAAs).

The classical continuum dielectric model based on the Poisson–Boltzmann equation (PBE) was used in this work to determine the pK_a values of the oligo-methacrylic acids.^{6–9} Georgescu et al. used this method to calculate the pK_a values of 166 ionizable groups in 12 proteins. The mean square error of their calculated pK_a values was 0.83 pH units, and only 3% of the calculated pK_a values are more than 2 pH units away from the corresponding experimental values.¹⁰ Our current work is to our best knowledge the first attempt to predict the pK_a values for polymeric acids, and their dependence on the degree of polymerization (DP).

Method

(1) Thermodynamic Cycle. The acidity constant, pK_a , of an acid group (HA) is determined by the free energy change of its

SCHEME 1: Thermodynamic Cycle for Determining the Free Energy Change of Proton Dissociation of the Carboxyl Groups in Oligo-MAA in Water



proton dissociation process in water, ΔG^w :

$$pK_a = \frac{1}{2.303RT}(\Delta G^w(\text{HA} \rightarrow \text{A}^- + \text{H}^+)) \quad (1)$$

In this study, a thermodynamic cycle (shown in Scheme 1) was used to calculate the relative pK_a change of MAA from the corresponding monomer value.

The free energy change ΔG^p for proton dissociation of the oligo-MAA (bottom reaction in Scheme 1) in water can be determined on the basis of the value of free energy change ΔG^w of the monomer, and the solvation free energy differences between the monomeric and oligomeric acids and their conjugate bases. The pK_a value of the oligo-MAA is

$$pK_{a,n} = pK_{a,1} + \frac{1}{2.303RT}(\Delta G_{\text{sol}}^{w \rightarrow p}(\text{A}^-) - \Delta G_{\text{sol}}^{w \rightarrow p}(\text{HA})) \quad (2)$$

where $pK_{a,1}$ is the acid constant of the monomer MAA, where the experimental acidity constant is used with $pK_{a,1} = \Delta G^w / 2.303RT$.

(2) Poisson–Boltzmann Equation. PBE solves for the electrostatic potential $\varphi(\vec{r})$ at position \vec{r} from contributions of all the charges in the system using Boltzmann distribution,

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$$\nabla \cdot \epsilon(\vec{r}) \nabla \varphi(\vec{r}) = -4\pi \rho_0(\vec{r}) - 4\pi \sum_{\lambda} q_{\lambda} \rho_{\lambda} \exp[-\beta q_{\lambda} \varphi(\vec{r})] \quad (3)$$

where $\epsilon(\vec{r})$ is the position dependent dielectric constant, ρ_0 the charge distribution of the solute, and q_{λ} and ρ_{λ} the charge and concentration of salt ion λ , respectively. It has been shown that PBE can accurately predict the pK_a values of proteins.^{6,10–13} Using the continuum dielectric model under PBE, the system is divided into the solute and structureless solvent parts. The solvation free energy of the solute comes from all of the electrostatic interactions including the Coulombic interactions between the solute and the induced charges in solvent, and any additional interactions due to the presence of an external field and any salt in solution,

$$\Delta G_{\text{sol}} = \sum_j q_j \varphi_{\text{coul}}(\vec{r}_j) + \sum_j q_j \varphi_{\text{react}}(\vec{r}_j) + \sum_j q_j \varphi_{\text{solv}}(\vec{r}_j) \quad (4)$$

In this study, the PBE was solved for both the neutral oligomers and their conjugate bases. Only the intrinsic pK_a values of the oligo-MAAs are determined; i.e., only one acid group is ionized, while all other acid groups are at their neutral states. With one acid group in the ionized state, further ionizations become increasingly more difficult due to electrostatic repulsions, and thus are not expected to contribute significantly to the acid strength. Moreover, as the DP value increases, the number of calculations needed to determine the atomic charges quantum mechanically increases dramatically for double or multiple ionizations. These more complex situations will be subject to future investigations.

(3) Computational Details. The PBE of the oligo-MAA was solved numerically using the Delphi code.¹⁴ It utilizes a finite-differential method and is capable of treating multiple solvent media with different dielectric constants. In order to take into account the conformations of oligo-MAA, the multiconformation continuum electrostatics (MCCE) program based on the Delphi code developed by Gunner's group is used.^{6,15} The structures and atomic charges of oligo-MAA were obtained by using the Car–Parrinello molecular dynamics (CPMD) simulations.¹⁶ For oligomers with DP ≥ 10 , charges from the 8-mer were used. The details of atomic charge calculations are given in the Supporting Information.

In MCCE, each of the oligo-MAAs is divided into three types of residues: CH₃-capped, H-capped, and middle residue, as shown in Figure 1. The COOH group in the residues was allowed to rotate. The solvent is a mixture of water with a dielectric constant (ϵ) of 80 and the oligomers have $\epsilon = 3$. The latter value was taken from the dielectric constants of small carboxylic acids, which are in a range of 2.58–3.44.¹⁷

Results and Discussion

Table 1 lists the calculated pK_a values for oligo-MAA with DP = 2–20. Also listed for comparison are the pK_a values for the dimer and trimer in our earlier study using *ab initio* calculations.¹⁸ Our earlier studies yield pK_a values of 6.08 and 5.27 for the CH₃-capped and H-capped residues, respectively, for the dimer. The pK_a values calculated using MCCE are 5.22 and 5.23, respectively, in good agreement with our previous results. For the two end residues of the MAA trimer, the MCCE pK_a values of 6.51 and 6.90 are larger than the previously

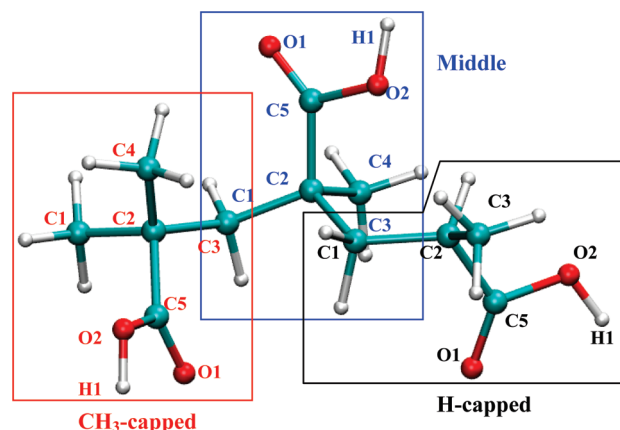


Figure 1. Residues of the MAA trimer.

TABLE 1: Calculated pK_a Values for Methacrylic Acid Oligomers with DP = 2–20 Given by the Multiconformation Continuum Electrostatics (MCCE) Program

		pK_a		
		CH ₃ -capped	H-capped	mid (average)
dimer	MCCE	5.22	5.23	
	Gaussian	6.08	5.27	
trimer	MCCE	6.51	6.90	5.52
	Gaussian	5.46	5.37	5.64
4-mer		6.06	5.92	5.68
5-mer		7.61	6.74	6.26
6-mer		6.71	6.88	6.16
7-mer		7.36	8.24	6.88
8-mer		7.14	8.46	6.99
12-mer		7.05	8.54	7.42
16-mer		7.40	8.84	7.50
20-mer		7.86	8.79	7.44
exp.	7.3			

predicted values of 5.46 and 5.37. However, the pK_a values for the middle residue agree well (5.52 and 5.64, respectively).

The overall agreement between the two methods indicates that the continuum dielectric model of the PBE can adequately describe the electrostatic environment of oligo-MAA at an accuracy level similar to *ab initio* methods. Both methods predict an increase in the pK_a values for the oligo-MAA. In our previous study, the calculated pK_a value of methacrylic acid was 4.83 (exp. = 4.65). The calculated pK_a values for the dimer and trimer using the same method are 0.73 higher on average. In this work, the experimental pK_a value of 5.03 for pivalic acid was used as the monomer value for comparison. For the H-capped residue, 2-methyl propanoic acid ($pK_a = 4.83$) was used instead. For the CH₃-capped and middle residues in the dimer and trimer, MCCE calculations predict an average of 0.72 increase in the pK_a values. For the H-capped residues, the shift is 0.69. These results are in excellent agreement with our earlier data.

The pK_a values for the oligo-MAA with DP = 4–20 by MCCE are also listed in Table 1. Their pK_a values are all higher than their respective monomer values. Figure 2 shows the pK_a values averaged over all residues (blue diamonds) for the oligo-MAA with DP = 2–20. The average pK_a values show a significant increase from the dimer ($pK_a = 5.22$) to 7-mer ($pK_a = 7.14$). This near 2 pK_a unit increase suggests that the electrostatic environments of the ionizing carboxyl groups become very different upon polymerization. Further DP increase has no apparent additional impact on the pK_a values. The pK_a values averaged over all middle residues (light blue triangles in Figure 2) show a similar trend. Both series of calculated pK_a

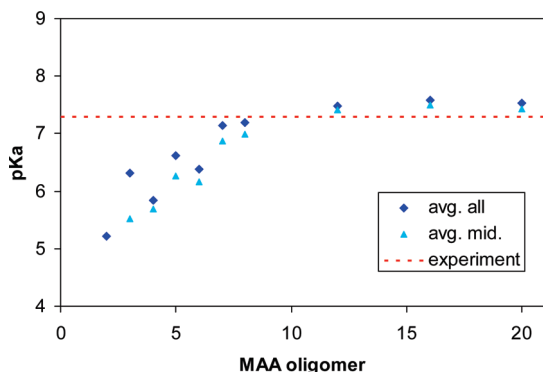


Figure 2. Average pK_a values for methacrylic acid oligomers with DP = 2–20 given by the multiconformation continuum electrostatics (MCCE) program. The red dotted line represents the experimental pK_a of PMAA ($pK_a = 7.3$).

values converge to 7.5, which is in excellent agreement with the experimental pK_a value of 7.3 for PMAA (the red dotted line in Figure 2).¹⁹

The pK_a values by MCCE show that the proton dissociation process of the oligo-MAA becomes less favorable upon polymerization. The electrostatic effect of increasing the DP value is to shift the ionization equilibrium further to the direction of disfavoring the anions up to DP 7.

It is also interesting to examine the spatial variations of pK_a values along the oligo-MAA chains. The MCCE results show that the middle residue gives a slightly lower pK_a value than the two end residues. The pK_a difference between the middle residues and the CH_3 -capped residues becomes smaller as the DP increases. On the other hand, the pK_a value of the H-capped residue increases up to DP = 16. For DP > 8, the pK_a values of the H-capped residues are above 8.4, which is higher than the other pK_a values. This variation in pK_a along the polymer chain indicates that the electrostatic environment around the ionizing residues is different depending on the position of the residues. As the chain becomes longer, this variation becomes less significant.

The agreement of MCCE-derived pK_a values with experimental measurements indicates that the continuum dielectric model is able to capture the essence of the electrostatic properties of the oligo-MAA. However, the conformations and the atomic charges of the oligo-MAA in our calculations were obtained from the gas phase. These may not reflect the true conformations and charges of oligomers in water. Here, the oligomers adopt a fully extended chain conformation. Also, only the intrinsic acidity constant of the ionizing group was considered in the present study. The more complex multiple ionization constants, which involve interactions between various neutral and ionized acid groups, were not studied.

Conclusion

The continuum dielectric model of the Poisson–Boltzmann equation has been used to predict the intrinsic pK_a values of oligomers of methacrylic acid with DP = 2–20. The calculated pK_a values agree well with *ab initio* results for the dimer and trimer. A converged pK_a value of 7.5 is reached for DP > 12. This value agrees well with the experimental measurement of 7.3. The results confirm that the acid strength of polymeric acids becomes weaker with respect to their corresponding monomer values.

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Supporting Information Available: Description of the CPMD calculation details and effects of the dielectric constant, table showing calculated pK_a values for methacrylic acid oligomers, and figure showing average pK_a values for methacrylic acid oligomers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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