8-13-2019

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Recommended Citation

Islam, N., Sharma, A., Gyawali, G., Kumar, R., & Rick, S. (2019). Coarse-Grained Models for Constant pH Simulations of Carboxylic Acids. *Journal of Chemical Theory and Computation*, 15 (8), 4623-4631.
<https://doi.org/10.1021/acs.jctc.9b00159>

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Coarse-grained models for constant pH simulations of carboxylic acids

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Abstract

A model for carboxylic acids, in both the protonated and de-protonated states, is developed in which hydrogen interaction sites are not used and all interactions are short ranged. A method for constant pH simulations, which exploits these features of the model, is developed. The constant pH method samples protonation states by making discrete Monte Carlo steps and is able to efficiently move between states in two steps. The method is applied to the polymer poly(methacrylic acid), a pH-responsive polymer that undergoes structural changes as a function of pH. The model is able to reproduce the structural changes induced by pH.

1 Introduction

The aggregation of acidic macromolecules is strongly influenced by pH. Long chain fatty acids have a rich phase diagram[?] and liposomes containing these molecules are potential drug delivery materials.^{???} Poly-acidic pH-responsive polymers show large reversible structural changes induced by pH and have a wide range of applications.[?] The structure of the acidic macromolecules is determined by the balance of the different interactions and how they shift as pH is changed. In addition to successfully reproducing these interactions, the models need to be computationally efficient for large-scale simulations of multiple macromolecules.

The coarse-grained (CG) approach based on the Stillinger-Weber (SW) potential[?] gains efficiency through an elimination of interaction sites on hydrogen atoms and a significant reduction in the range of the interactions. Despite the lack of hydrogen sites and Coulombic interactions, the SW approach has been shown to accurately model water,^{????} hydrophobic interactions,^{???} aqueous salt solutions,[?] and water soluble polymers.[?] The model uses a combination of two- and three-body interactions to establish nearest-neighbor coordination numbers, geometries, and energy scales. The models retain a molecular representation of the system, including water, unlike models which coarse-grain on a larger scale (typically mapping three or four heavy atoms onto one interaction site),^{??} while having similar computational efficiencies,[?] with the larger number of interaction sites (relative to other CG models) compensated for with the reduced range of the potential. The SW-based models are an appealing choice for simulating aqueous macromolecules, since they retain a molecular level description and the SW water model mW is of comparable accuracy to conventional all-atom models.[?]

In conventional molecular dynamics simulations, bonds are not broken or made, so

the protonation state of an acid or base remains constant. In constant-pH (CpH) simulations,[?] protonation states are allowed to change in response to pH and structural changes. These approaches can be grouped into types, depending on how the solvent is treated.[?] The simplest, most commonly used CpH method uses a continuum model for water and Monte Carlo moves between different protonation states are taken.^{??} This can work because the continuum solvent responds instantaneously to the protonation state change, so there is always equilibrium between solvent and solute. A second approach uses explicit solvent^{??} in which the protonation state changes continuously, in equilibrium with the slow solvent response. A third hybrid approach combines simulations with explicit solvent with protonation state moves based on continuum solvent models.^{???} CG models have been used with both implicit solvent models^{??} and CG water models.[?] A disadvantage of the explicit solvent CpH methods is that the use of continuous protonation states leads to significant time spent in unphysical states.[?] For a polymer or collection of acidic molecules near the pKa there is a very small chance that all acidic groups will be in a physical state and so structures that correspond to completely physical states will be rare. The SW approach is then well-suited for use with CpH simulations, since the lack of hydrogen sites means the solvent response will be quicker since it involves translational and not orientational motion. The difference between the protonated and de-protonated states in the CG model just involves a change in the potential parameters and not a change in the number of interaction sites. In this paper, we developed a CpH model in which transitions between protonated and de-protonated states are made through discrete jumps, with one intermediate states. This is intermediate method between implicit solvent models, which make the jump in one step, and atomistic solvent models, which use a continuous variable to make the jump.

In this work, we have developed SW models for protonated and de-protonated

carboxylic acids, which we apply to poly(methacrylic acid) (PMAA). In the PMAA studies, we show how the protonation states, tacticities, and counter ions influence the structure of the polymer. In CpH studies, we further explore the effects of local polymer structure and counter ions in the pH response.

2 Methods

Potential model. The Stillinger-Weber potential⁷ uses two- and three-body potentials, as given by

$$E = \sum_i \sum_{j>i} \phi_2(r_{ij}) + \sum_i \sum_{j \neq i} \sum_{k>j} \phi_3(r_{ij}, r_{ik}, \theta_{jik}) \quad (1)$$

where r_{ij} is the distance between atoms i and j and θ is the angle between atom i and its neighbors j and k . The two-body term has this form,

$$\phi_2(r_{ij}) = A\epsilon_{ij}[B(\sigma_{ij}/r_{ij})^4 - 1] \exp(\sigma_{ij}/(r_{ij} - a_{ij}\sigma_{ij})) \quad (2)$$

and the three-body term has this form

$$\phi_3(r_{ij}, r_{ik}, \theta_{jik}) =$$

$$\lambda_{ijk}\epsilon_{ijk} [\cos \theta_{jik} - \cos \theta_0]^2 \exp(\gamma\sigma_{ij}/(r_{ij} - a_{ij}\sigma_{ij})) \exp(\gamma\sigma_{ik}/(r_{ik} - a_{ik}\sigma_{ik})) \quad (3)$$

Both terms are zero at r_{ij} greater than $a_{ij}\sigma_{ij}$. The three-body term is necessary for particles with highly directional interactions, like hydrogen bonds. There are no Coulombic interactions for the model, but for atoms with formal charges (sodium ions and the oxygens on the carboxylate group) a Yukawa potential is used between

pairs with the same charge, to treat charge repulsion. The Yukawa potential has the form[?]

$$\phi_Y(r_{ij}) = A_Y e^{-\kappa r_{ij}} / r_{ij} \quad r_{ij} < r_c \quad (4)$$

The parameters A, B, a_{ij} , γ , κ , and r_c are taken from previous studies (A=7.049556277, B=0.6022245583, a_{ij} =1.80, γ =1.20, κ =1.80 Å⁻¹, and r_c =7.0 Å).^{????} The well-depth, ϵ , and length scale, σ , parameters for ϕ_2 , the angle, θ_0 , and energy-scale, ϵ_{ijk} and λ_{ijk} , parameters for ϕ_3 , and the energy scale, A_Y , parameter for ϕ_Y are taken to be adjustable.

The bond stretch, $E = k_b(r - r_0)^2$, and bond angle terms, $E = k_\theta(\theta - \theta_0)^2$, we taken from OPLS-UA values[?] (Table ??). Bonded terms for oxygen atoms are taken to be independent of protonation state or bond order. In Table ??, CHn refers to all carbon atoms with two or three hydrogen atoms, CT is a quaternary carbon, CO is the carbon atom of the carboxyl group, and O* is all oxygens of the carboxyl group. The torsional parameters use the Fourier form

$$E(\theta) = V_1(1 + \cos \phi) + V_2(1 - \cos 2\phi) + \frac{1}{2}V_3(1 + \cos 3\phi) \quad (5)$$

The torsional parameters for CHn-CT-CO-O* are taken from the OPLS-AA value.[?] For the CO-CT-CHn-CT and CHn-CT-CHn-CT dihedral, which would have a hydrogen atom contribution to the dihedral energy, we modified the CG terms so that the CG torsional energies matched the all-atom (AA) energies. For four atoms along a bonded sequence ABCD, with atom B also bonded to two hydrogen atoms, then the condition that the CG and AA are equal is

$$E_{CG}(\phi) = E_{ABCD}(\phi) + E_{HBCD}(\phi + 120^\circ) + E_{HBCD}(\phi - 120^\circ) \quad (6)$$

where $E_{ABCD}(\phi)$ is the AA torsional energy for atoms A, B, C, and D. Using simple trigonometry identities leads to $V_1=V_{1A}-V_{1H}$, $V_2=V_{2A}-V_{2H}$, and $V_3=V_{3A}+2V_{3H}$, where V_{iA} is the dihedral parameter with the heavy atom A and V_{iH} is the parameter with the hydrogen atom. The torsional parameters are given in Table ??.

Parameter optimization. Parameter for water,[?] the carbon atom types CHn and CT,[?] and the sodium ion[?] are taken from previous studies. Non-bonded parameters for CT were taken to be equivalent to CH2. Interactions between the water and the carboxylic acid atom types are optimized to reproduce the water-solute pair correlations of all-atom models, for aqueous acetate and acetic acid. These atoms types are CO, COA, OH, O, and OA, where OH refers to the protonated oxygen, O to the oxygen with the double bond, OA to the carboxylate oxygen, CO to the carbon of the protonated acid and COA to the carbon atom of the de-protonated acid, as shown in Figure ??. For comparison, the TIP4P/2005[?] water and OPLS-AA[?] solute all-atom models are used. The free energy of hydration for acetic acid was also used to parameterize the model, against the experimental value.^{??} The interactions between OH-O, OH-OH, and OH-OA are taken to be similar to OH-water interactions, but slightly stronger. Experimental^{??} and simulation^{??} studies indicate the hydrogen bonds between carboxyl groups stabilize the self-assembly of PMAA at low pH, suggesting that they should be stronger than carboxyl-water hydrogen bonds. Interactions between OA atoms are taken to be purely repulsive, using the Yukawa potential. We took the full ion charge as modeled by the SW approach[?] and distributed it equally on the two oxygen atoms. Reducing the charge by a half, reduces $\phi_Y(r)$ by 1/4, so we take A_Y to be equal to the sodium or chloride A_Y divided by four. We did not otherwise optimize this parameter. Three-body interactions were only used for interactions treating hydrogen bonds, on water or the OH group on the carboxylic acids. Interactions between the OA and sodium ions were chosen so that

they reproduce the position and energy of the minimum of the potential of mean force between acetic acid and sodium.^{???}

Constant pH simulations. For each carboxylic acid group, there are two states, a protonated state with potential energy E_0 , and a de-protonated state with energy E_1 . With the λ -dynamics method,^{???} for continuous values of λ , the potential energy function is

$$E(\lambda) = (1 - \lambda)E_0 + \lambda E_1 - \lambda \Delta G_m + \lambda k_B T \ln(10)(pH - pK_{a_m}) \quad (7)$$

where ΔG_m is the pre-calculated free energy difference between the protonated and de-protonated states for the isolated monomer, k_B is Boltzmann's constant, and pK_{a_m} is the experimental pKa of the isolated monomer. In the present approach, rather than let λ be a continuous variable, we only allow it to have discrete values. The fewer intermediate states the better, since the simulation will spend less time in unphysical states, but with too few states, jumps between them can become too rare. For our application, we found that the method works with only one intermediate state. The choice of λ for the intermediate state can be optimized to maximize the number of transitions (see below). Intermediate states are defined with interaction parameters interpolated between the protonated and de-protonated parameters,

$$\alpha_\lambda = (1 - \lambda)\alpha_0 + \lambda\alpha_1 \quad (8)$$

where α represents a potential parameter, which includes ϵ , σ , and the three-body

parameters. The simulation then jumps between the states, with energies give by

$$E = \begin{cases} E_0 & 0 \\ E_\lambda - \Delta G_\lambda + \lambda k_B T \ln(10)(pH - pK a_m) & \lambda \\ E_1 - \Delta G_1 + k_B T \ln(10)(pH - pK a_m) & 1 \end{cases} \quad (9)$$

where ΔG_λ is the free energy of state λ relative to state 0 and ΔG_1 is the free energy of state 1 relative to state 0. (In equation ??, E_0 , E_λ , and E_1 refer potential energy functions, with the different force field parameters.) The constant pH simulations would jump between the states using the Metropolis algorithm. The free energies, ΔG_λ and ΔG_1 , for the monomer in water are found from standard free energy calculations. These were down using free energy perturbation theory with 11 intermediate states, each simulated for 1 ns, using the CG model. The values are $\Delta G_\lambda = -35.15$ kcal/mol and $\Delta G_1 = -41.95$ kcal/mol. The monomer is taken to be trimethylacetic acid, for the PMAA calculations, using the experimental value of 5.03 for $pK a_m$.

Sampling over protonation states can be helped using replica exchange, in which simulations at different pH are done simultaneously and configurations are swapped according to a Metropolis criterion.^{??} In this method, all the coordinates, the volume, and the protonation states of one simulation are swapped with another. Swaps between replicas i and j are accepted with a probability, P_{ij} , based on the energy difference ΔE_{ij} . From Equation ??, the exchange probability is

$$P_{ij} = \min[1, e^{(N_i - N_j) \ln 10 (pH_i - pH_j)}] \quad (10)$$

where N_i is the sum over the N_p protonation states of replica i ,

$$N_i = \sum_{k=1}^{N_p} (1 - n_{i,k}) \quad (11)$$

The quantity $n_{i,k}$ gives the protonation state value (as given by the numbers 0, λ , or 1) of the k^{th} titratable group for replica i . The implementation used follows this sequence:

- For a range of pH values, run at fixed protonation states for 100 steps (0.5 ps).
- Attempt a change in protonation state, for every ionizable group, in random order. For each group, attempt to move to a neighboring state (between 0 and λ or λ and 1). For the middle λ state, randomly choose to move to the 0 or 1 state. For the de-protonated state, randomly choose one of the two carboxyl oxygens to attempt to protonate. Accept or reject this protonation state move, and change the protonation state if the move is accepted, then move on the next randomly chosen group.
- After 1000 cycles of constant pH simulations (0.5 ns total), attempt a replica exchange swap between replicas at adjacent pH values. We alternate between a swap step involving the first and second, third and forth, and so on, and the second and third, forth and fifth, and so on.
- The constant pH replica exchange cycle was repeated 50 times, so that each pH value was simulated for a total of 25 ns.

It was important to use a different random number seed to assign velocities at the beginning of each simulation. Otherwise the constant pH simulations, resulting from a

number (40 times 1000) of short simulations, will not reproduce the results of a single long simulation for the highest and lowest pH. At these pH values, the protonation states are essentially constant and the constant pH results should be the same as conventional simulations.

Simulation details. The CG simulations used LAMMPS,[?] with a 5 fs time step in the isothermal-isobaric (TPN) ensemble, with temperature and pressure controlled using a Nosé-Hoover thermostat, with a 100 fs damping constant, and a barostat, with a damping parameter of 1000 fs, at a temperature of 300 K and a pressure of 1 bar, respectively. The all-atom simulations used the Gromacs simulation package[?] using TIP4P/2005[?] water and OPLS-AA[?] solute models. The free energy calculations for the hydration free energy of acetic acid were done using finite difference thermodynamic integration (FDTI),[?] using a soft core potential to avoid singularities.[?] The subroutines necessary to implement FDTI using LAMMPS with the SW potentials are available on github.[?] The constant pH simulations were carried out using bash shell scripts, which calls LAMMPS with the appropriate input files for the specific protonation state, and accepts or rejects protonation state changes and replica swaps as described above. The sodium-acetate potential of mean force calculations were run for 2.5 microseconds. The constant pH simulations used a number of sodium ions equal to the number of acidic groups, at a concentration of 0.25 M. Simulations for the de-protonated 20mer were ran at a number of sodium ion concentrations, by varying the number of water molecules.

3 Results

The potential parameters are given in Tables ??, ?? and ??. Two-body parameters not given are obtained from the Lorentz-Berthelot combining rules: $\epsilon_{AB} =$

$(\epsilon_{AA}\epsilon_{BB})^{1/2}$ and $\sigma_{AB} = (\sigma_{AA} + \sigma_{BB})/2$. Three-body parameters not given are zero. The coarse-grained models were parameterized to reproduce the pair correlations of all-atom models, for aqueous acetate and acetic acid (Figure ??). The CG model does fairly well at reproducing the water structure near the three different oxygen types, in terms of the positions of the first solvation shell and the peak heights. There is not a large peak around the acetic acid oxygen atoms, particularly for the carbonyl oxygen. The pair correlation function between the methyl carbon on (protonated) trimethylacetic acid and water can be used to check how the model captures the hydrophobic interaction (Figure ?? (D)). For these interactions, we used previously published values, optimized for alkanes.[?] The CG and AA models show similar small peaks in about the same positions, giving us some confidence that the CG potential will model the hydrophobic part of PMAA with sufficient accuracy. The free energy of hydration for acetic acid was also used for parameterization. The model gives a value of -6.6 ± 0.1 kcal/mol. The experimental value is -6.69 kcal/mol.[?] ?

The potential of mean force (PMF) between the central carbon of the acetate ion and the sodium ion (Figure ??) shows both a bidentate minimum at $2.7 \text{ \AA}$ and a slightly deeper monodentate minimum at $3.3 \text{ \AA}$, as well as a shallow solvent-separated minimum around $5 \text{ \AA}$. The PMF from *ab initio* molecular dynamics for the acetate-sodium PMF finds that the contact pair is stable by 1 kcal/mol over the solvent-separated pair, similar to CG model.[?] Other simulations, with polarizable potentials[?] and non-polarizable force fields optimized to reproduce the osmotic pressure,[?] find a similarly shallow contact pair minimum. The free energy difference between the mono- and bidentate states is small and depends on the force field or *ab initio* method.[?]

Structural changes are examined both on the length scale of the entire polymer through the radius of gyration and at local, nearest-neighbor scale, through the

fraction of proximal neighbors.[?] The distance between neighboring carboxylic acid groups fall into two groups, depending on the backbone conformation. The carbonyls can be on the same side, in a conformation termed proximal, or on opposite sides (at a dihedral angle equal to 120 degrees), termed distal. For the syndiotactic polymer, if all backbone dihedral angles are equal to 180 degrees, then the carboxyl groups are distal and for the isotactic polymer, this extended backbone conformation puts the carboxyl groups as proximal. The local structure can be described by the fraction of neighboring groups that are proximal, $f_{proximal}$. This fraction was found using the distance between the carbonyl carbon atoms. If that distance is less than 3.7 Å, then the conformation is proximal, otherwise it is distal.

The properties of PMAA with 20 repeat units show that the model undergoes a structural transition induced by the change in the protonation states (Table ??). The radius of gyration, R_G , changes from about 6 Å for the protonated state to 10 Å for the de-protonated state. Similar changes have been reported using all-atom simulations.^{???} Table ?? compares our results with simulations of PMAA of the same length, but different force fields, tacticities and counter-ion concentrations.^{??} Sulatha and Natarajan[?] give values for two different force fields. The R_G for the de-protonated form shows a small dependence on sodium concentration, decreasing as the sodium concentration increases. The local structure changes from mostly proximal for the isotactic form and mostly distal for the syndiotactic form to about mostly distal for both tacticities. The fraction of proximal values for both protonation states and tacticities are similar to all-atom studies.[?]

Sodium ions are taken to be associated with the polymer if they are less than 4.0 Å from a carboxylate carbon. The amount of sodium ion in contact with the polymer increases from about 3 at 0.25 M to about 5 at 0.5 M.

Constant pH simulations. Using one intermediate state, as defined by Eq. ??,

the method can jump between protonation states (Fig. ??). Using trimethylacetic acid as a test case, we found that value of λ equal to 0.70 gives even transitions between the two states. A larger λ value results in more transitions between the intermediate and the final state, but fewer transitions between the intermediate and the initial state. A smaller λ value does just the opposite, with more transitions between the initial and intermediate state. This is the value used for subsequent constant pH simulations, for which we found that λ samples between protonation states effectively. Calculations were run for chain lengths, ranging from 1 to 20. For the 20mer, we simulated both the syndiotactic and isotactic form. The simulations used a number of sodium counter ions equal to the length of the chain, at a concentration of 0.25 M. The titration curves are shown in Figure ???. The results are fit to the Hill equation

$$\text{fraction de - protonated} = 1/(10^{n(pK_a - pH)} + 1) \quad (12)$$

where pKa is minus the log of the acid dissociation constant and n gives the degree of cooperativity. Those values are given in Table ??. The pKa of the monomer, trimethylacetic acid, is, by construction, close to the experimental value of 5.03. The pKa of the dimer increases by about 0.8 pH units and n is near one. The 20mer has a pKa, for both tacticities, around 8.4 and a cooperativity near 0.6. For comparison, the experimental value for PMAA has been reported to be 5.5,[?] 6.25[?] and 7.3.[?] A large conformation change of PMAA has been observed over the pH range from 5 to 6, suggesting the pKa is about 5.5.[?] Quantum calculations give a pKa of 5.22 for the dimer and 6.06 for the tetramer.[?] All-atom constant pH simulations give a pKa for the 20mer close to 5.[?]

As the simulation jumps between protonation states, intermediate states are visited, so some of the structures generated do not correspond to physical, real states.

The fraction of states that correspond to completely physical states (that is, those with no intermediate states on any acidic groups) is shown in Figure ???. In all cases, this fraction is above about 0.45. As might be expected, there are the most un-physical states near the pKa, when transitions between states are frequent. The number of unphysical configurations does not increase as the number of groups increase; we get no more unphysical states for the 20mer than for the monomer. For a monomer, transitions between states are governed only by solvent fluctuations. For the longer chains, transitions are also induced by polymer motion, which are slower. This decreases the frequency of transitions, leading to fewer intermediate states. In the data presented below, we only use the physical states in generating averages, even though the averages generated with all the configurations and those just with the physical configurations are very similar.

To further characterize the pH response, each carboxylic acid group can be grouped according to its local structure. If a carboxyl group has all neighbors in a distal geometry then the pKa is less than if it has at least one proximal neighbor (Table ???). For the dimer, the difference in the distal and proximal pKa is about 1 and for the 20mer, the difference is 0.5 for the isotactic and 0.7 for the syndiotactic. This shift is about the same as the all-atom constant pH results.[?] In the distal geometry n is about 1, indicating no cooperativity, and changes to about 0.5 in proximal geometries, as repulsions between adjacent groups lead to negative cooperativity. When the groups are close, the loss of a proton, creating the negatively charged carboxylate, makes it more difficult for a neighboring group to lose a proton. Sodium ions also affect the pKa. By comparing structures which had a sodium ion near a carboxylate carbon with those that do not, the pKa shows a large decrease when a sodium ion is near. For the 20mers, this is over 2.5 pH units.

Structural changes for the 20mer as a function of pH are shown in Figure ???. The

radius of gyration shows an abrupt change near the pKa. The fraction of proximal neighbors show a more gradual change. The local change, as given the fraction proximal, begins at a lower pH than the global change, as given by the radius of gyration.

4 Conclusion

The CG model is able to reproduce properties of both the protonated and de-protonated states. For PMAA, the models capture the pH response on both the local level, with a change in the number of fractional neighbors, as well as the larger scale change as given by the radius of gyration (Table ?? and Figure ??). Neighboring carboxylate groups get further from each other and the entire polymer expands due to repulsive interactions. For all-atoms models, the expansion is induced by Coulombic repulsions between the charged groups and a strong attraction to the solvent, which can draw the groups away from each other and into solution. For the CG model, the repulsions are due to the Yukawa potential and the three body terms involving the carboxylate oxygens and water molecules. These interactions are short-ranged, by design. In order to make repulsive interactions to cause the structural change, they need to be sufficiently strong over their short range. The model overestimates the pKa of the polymers, and the structural pH response occurs at a larger pH, possibly because it overestimates the strength of the short-ranged interactions in order to compensate for the lack of long-ranged interactions.

The constant pH method is able to use the lack of hydrogen interaction sites to result in an efficient method for sampling over protonation states. The method enable Monte Carlo moves between the protonated and de-protonated state using one state in between (Figure ??). The method is intermediate between the methods which use

continuum solvent methods, and can switch directly between the two states,²² and those that use explicit solvent, which use a continuous coordinate representing the protonation state.²² The present method allows for a molecular treatment of the solvent, while still enabling an efficient sampling of protonation states, without spending much time in unphysical states. The method also allows for either of the equivalent carboxylate oxygens to become protonated, using a single coordinate, unlike other methods which treat the possible protonation of the two oxygens by introducing an additional coordinate.²²

The protonation state is strongly dependent on the local geometry. If the neighboring groups are rotated so that they are distal, the pKa of that group is about 1 pH unit less than if one or more neighboring groups are proximal (Table ??). Previous all-atom constant pH simulations found a similar change in the pKa.² Proximity to a sodium ion has a large affect on the protonation state also, changing the pKa by over 1 pH unit (Table ??). A constant pH simulation of fatty acids, find that the addition of sodium ions decreases the pKa of the carboxylic acid head group by 0.8 pH units relative to simulations without counter ions.² For the de-protonated polymer, representing the high pH limit, simulations were ran at different sodium ion concentrations, by varying the amount of water. As the sodium concentration increases, the radius of gyration decreases (Table ??). Experimental studies on polymers seem to find mixed results on the effects of sodium on polymer conformation.²² Light scattering experiments, on polyacrylic acid (PAA), find that the hydrodynamic radius, R_H , does not change at all as a function of NaCl concentration, up to 1 M.² This study used polymers with molecular weight 82 and 120 KDaltons, or about 1000 to 1400 monomers. Flourescence correlation spectroscopy experiments on PMAA find that R_H decreases as the sodium concentration increases to 1 M.² This was done for polymers of 25, 72 and 105 KDaltons, or 250, 720, and 1050 monomers. Our results,

even though the polymers are much smaller, are consistent with the PMAA results, showing a similar small decrease in conformational size.

The CG model for the carboxylic acids captures fairly well many properties, despite the approximations made by the model, including the lack of hydrogen interaction sites and the lack of any long-ranged interactions. The models presented here can be combined with similar models for water,[?] ions,[?] alkanes,[?] ethers,[?] and peptoids,[?] to allow the simulation a larger range of polymeric materials.

5 Acknowledgements

This material is based upon work supported by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, under EPSCoR Grant No. DE-SC0012432 with additional support from the Louisiana Board of Regents. We gratefully acknowledge computer time allotted by the Louisiana Optical Network Initiative (LONI).

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Table 1: Bonded parameters.

bond stretch parameters			
atoms	force constant (kcal mol ⁻¹ Å ⁻²)	equilibrium distance (Å)	
CHn-CT	268.0	1.529	
CT-CO	317.0	1.522	
CO-O*	570.0	1.229	
bond angle parameters			
atoms	force constant (kcal mol ⁻¹ degrees ⁻²)	equilibrium angle (degrees)	
CHn-CT-CHn	58.35	112.7	
CHn-CT-CO	63.00	111.1	
CT-CO-O*	75.00	119.0	
O*-CO-O*	80.00	122.0	
dihedral angle parameters			
atoms	V ₁ (kcal mol ⁻¹)	V ₂ (kcal mol ⁻¹)	V ₃ (kcal mol ⁻¹)
CHn-CT-CO-O*	0	0.273	0
CHn-CT-CHn-CT	0.3223	-0.1072	0.3891
CO-CT-CHn-CT	-1.5925	-0.4125	0.1465

Table 2: Two-body potential parameters for the carboxylic acids, previously published parameters for water,[?] sodium[?] and methyl carbons.[?]

		σ (Å)	ϵ (kcal/mol)
CH ₃	CH ₃	4.64	0.10
CH ₂	CH ₂	5.08	0.072
CO	CO	4.50	0.141
COA	COA	4.20	0.010
COA	CH ₃	4.50	0.200
COA	CH ₂	4.70	0.180
OA	OA	4.0	0
O	O	3.1	0.05
OH	OH	2.2	0.6
O	OH	2.05	1.0
OA	OH	2.20	2.18
OA	O	3.10	0.05
CH ₃	OA	3.60	0.400
CH ₃	O	4.0	0.120
CH ₃	OH	3.90	0.130
CH ₂	OA	3.70	0.380
CH ₂	O	3.70	0.110
CH ₂	OH	3.70	0.120
COA	OA	4.20	0.010
COA	O	3.80	0.100
COA	OH	4.00	0.220
CO	OA	3.675	0.280
CO	O	3.655	0.260
CO	OH	3.675	0.210
CH ₃	H ₂ O	4.250	0.165
CH ₂	H ₂ O	4.290	0.1222
COA	H ₂ O	3.70	1.3
CO	H ₂ O	4.10	0.025
OA	H ₂ O	2.15	7.00
O	H ₂ O	3.1	0.340
OH	H ₂ O	2.6	0.800
CH ₃	Na ⁺	3.700	0.220
CH ₂	Na ⁺	3.800	0.140
COA	Na ⁺	2.600	0.010
CO	Na ⁺	4.100	0.025
OA	Na ⁺	1.900	3.100
O	Na ⁺	1.900	1.100
OH	Na ⁺	1.850	0.700
H ₂ O	H ₂ O	2.3925	6.189
Na ⁺	H ₂ O	1.850	16.0

Table 3: Yukawa potential parameters for the acetate ion and previously published parameters for sodium.[?]

		κ (Å ⁻¹)	A (kcal/mol)
O(acetate)	O(acetate)	1.8	276.75
Na ⁺	Na ⁺	1.8	1107

Table 4: Three-body potential parameters for the acetate ion and previously published parameters for water and sodium.^{??} The central atom is given first.

			ϵ (kcal/mol)	λ	$\cos(\theta_0)$
OH	OH	OH	0.6	10	-1/3
O	OH	OH	1.0	10	-1/3
OH	O	OH	1.0	10	-1/3
O	O	OH	1.0	10	-1/3
OH	O	O	1.0	10	-1/3
OH	OH	OA	2.18	8	-1/3
OH	OA	OA	2.18	8	-1/3
OH	O	OA	1.38	8	-1/3
O	OH	OA	1.0	8	-1/3
OA	OH	OH	2.18	8	-1/3
OA	OA	OH	2.18	8	-1/3
OA	O	OH	1.0	8	-1/3
OH	CO	OH	1.0	10	-1/3
OH	CO	O	1.0	10	-1/3
OH	CO	OA	2.18	8	-1/3
OH	CO	H ₂ O	0.8	8	-1/3
OA	OA	H ₂ O	7.0	2.85	-1/3
H ₂ O	OA	OA	7.0	8	-1/3
OA	H ₂ O	H ₂ O	7.0	8	-1/3
H ₂ O	OA	H ₂ O	7.0	8	-1/3
O	O	H ₂ O	0.340	8	-1/3
O	OH	H ₂ O	0.340	8	-1/3
H ₂ O	O	O	0.340	8	-1/3
O	H ₂ O	H ₂ O	0.340	8	-1/3
H ₂ O	O	H ₂ O	0.340	8	-1/3
OH	OH	H ₂ O	0.80	8	-1/3
OH	O	H ₂ O	0.80	4	-1/3
H ₂ O	OH	OH	0.800	8	-1/3
OH	H ₂ O	H ₂ O	0.800	8	-1/3
H ₂ O	OH	H ₂ O	0.800	8	-1/3
H ₂ O	OH	O	0.4	8	-1/3
OA	H ₂ O	OH	3.0	8	-1/3
OA	H ₂ O	O	1.54	5	-1/3
OH	OA	H ₂ O	1.02	8	-1/3
H ₂ O	OA	O	1.54	8	-1/3
H ₂ O	OA	OH	2.37	8	-1/3
O	OA	H ₂ O	1.54	5	-1/3
OA	H ₂ O	Na ⁺	3.1	2	-1/3
H ₂ O	OA	Na ⁺	3.1	2	-1/3
Na ⁺	OA	H ₂ O	3.1	2	-1/3
H ₂ O	O	Na ⁺	1.1	2	-1/3
O	H ₂ O	Na ⁺	1.1	2	-1/3
Na ⁺	O	H ₂ O	1.1	2	-1/3
H ₂ O	H ₂ O	H ₂ O	6.189	23.15	-1/3
Na ⁺	H ₂ O	H ₂ O	16.0	7	-1/3
H ₂ O	Na ⁺	H ₂ O	16.0	7	-1/3
H ₂ O	Na ⁺	Na ⁺	16.0	7	-1/3
Na ⁺	H ₂ O	Na ⁺	16.0	7	-1/3

Table 5: Properties of a 20 unit long PMAA for the protonated and de-protonated form at various sodium concentrations.

	[Na ⁺]	radius of gyration (Å)		fraction proximal		number of contact Na ⁺	
		syndiotactic	isotactic	syndiotactic	isotactic	syndiotactic	isotactic
protonated	0 m	5.78±0.04	5.67±0.04	0.28±0.01	0.77±0.02	N/A	N/A
protonated	0.25 m	5.80±0.03	5.73±0.05	0.30±0.01	0.80±0.02	0.03±0.02	0.03±0.02
de-protonated	0 m	10.8±0.6	9.7±0.4	0.20±0.02	0.30±0.02	N/A	N/A
de-protonated	0.25 m	10.7±0.5	9.7±0.3	0.19±0.03	0.35±0.02	3.0±0.5	3.2±0.3
de-protonated	0.50 m	10.2±0.4	8.8±0.4	0.22±0.02	0.39±0.02	5.6±0.5	4.9±0.5

Table 6: Radius of gyration for n=20 PMAA from different simulation studies.

tacticity	[Na ⁺]	radius of gyration (Å)	
		protonated	de-protonated
syndiotactic, this work	0.25 m	5.80±0.03	10.7±0.5
isotactic, this work	0.25 m	5.73±0.05	9.7±0.3
syndiotactic [?]	0	7.3±0.1	12.0±0.1
isotactic [?]	0	7.0±0.5	12.4±0.1
atactic [?]	0.2 m	6.4,6.7	9.9,10.0

Table 7: Values of the pKa and the Hill cooperativity parameters.

chain length	total		Na ⁺ far		Na ⁺ close		distal		proximal	
	pKa	n	pKa	n	pKa	n	pKa	n	pKa	n
1	5.04±0.06	1	5.09±0.06	1	4.3±0.2	1				
2	5.8±0.1	0.91±0.09	5.9±0.1	0.93±0.05	5.2±0.2	1.3±0.2	5.7±0.1	1.02±0.05	6.7±0.2	0.5±0.1
20 isotactic	8.4±0.3	0.55±0.08	8.5±0.3	0.5±0.1	6.2±0.6	0.7±0.2	7.8±0.5	0.8±0.2	8.2±0.5	0.4±0.1
20 syndiotactic	8.4±0.3	0.65±0.07	8.5±0.3	0.6±0.1	6.4±0.6	0.6±0.2	8.1±0.2	0.8±0.1	8.9±0.4	0.4±0.1

Figure 1: Two units of the poly(methacrylic acid) structure, showing the protonated and de-protonated forms and the coarse-grained groups (circles).

Figure 2: Coarse-grained and all-atom pair correlation functions between water oxygen and oxygen atoms on the acetic acid (A and B) and the acetate ion (C), and between water oxygen and the methyl carbon on trimethylacetic acid (D).

Figure 3: Potential of mean force between the acetate and sodium ions, relative to the distance between the carboxylate carbon and the sodium ion.

Figure 4: The protonation state variable, λ , as a function of time for aqueous trimethylacetic acid.

Figure 5: Titration curves for oligomers of various lengths.

Figure 6: The fraction of physical states as a function of pH.

Figure 7: Radius of gyration (A) and fraction proximal nearest neighbors (B) as a function of pH for the isotactic and syndiotactic 20mer.