Electronic Supplementary Material (ESI) for Soft Matter.

Supplementary Information - Monte Carlo simulation of the ionization and uptake behavior of cationic oligomers into pH-responsive polyelectrolyte microgels of opposite charge - a model for oligopeptide uptake and release

Christian Strauch[1] and Stefanie Schneider[1]

[1] *Institute of Physical Chemistry, RWTH Aachen University, 52056 Aachen, Germany*

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External stimuli can tune the uptake and release of guest molecules in microgels. Especially their pH responsiveness makes microgels exciting candidates for drug delivery systems. When both microgel and guest molecules are pH-responsive, predicting the electrostatically driven uptake can be complex since the ionization depends on many parameters. In this work, we performed Metropolis Monte Carlo simulations while systematically varying the pK of the monomers, the concentrations of microgel and guest molecules to obtain a better understanding of the uptake of weak cationic oligomers as a model for oligopeptides into a weak anionic polyelectrolyte microgel. Further, we varied the chain length of the oligomers. The polyelectrolyte networks can take up oligomers when both the network and the oligomers are charged. The presence of both species in the system leads to a mutual enhancement of their ionization. The uptake induces a release of counterions and results in complex formation between the oligomers and the network, leading to the collapse of the networks. Longer oligomers enhance the ionization of the network and, therefore, the complexation. A higher microgel concentration increases the uptake only around the isoelectric point but prevents the uptake due to lower entropy gain at counterion release at higher pH. The results give an insight into the uptake of cationic oligomers into oppositely charged polyelectrolyte microgels and provide hints for the design of anionic microgels as carriers for guest molecules e.g. antimicrobial peptides.

I. SIMULATION DETAILS

This section contains different tables with the simulation parameters.

TABLE I. Simulation parameters of the reference system

Parameter	Symbol	value
segments per chain (network)	$N_{\mathrm{seg,a}}$	10
segments per chain (oligomer)	$N_{\mathrm{seg,b}}$	6
number of chains (network)	$N_{\mathrm{chain,a}}$	184
number of chains (oligomer)	$N_{\mathrm{chain,b}}$	368
crosslinks	N_{cl}	71
charge crosslink	z_{cl}	0
charge network monomer	z_{a}	-1/0
charge oligomer bead	z_{b}	+1/0
charge counterion oligomer	$z_{\mathrm{c-}}$	-1/0
charge counterion network	$z_{\mathrm{c+}}$	+1/0
pK network	pK_{a}	7.0
pK oligomer	pK_{b}	7.0
radius of beads	R	1 σ
box length	L	750 σ
force constants of bonds	k	3.89 $\sigma^{-2}k_{\mathrm{B}}T$
zero force distance of bonds	r_{eq}	2.5 σ
Bjerrum length	l_{b}	3.58 σ
pH		4-10 in 0.5 steps

TABLE II. Simulation details of the varied parameters. In the simulations, the box size L, the pK values, the number of oligomer chains were varied.

simulation row	value
influence pK	p$K_\mathrm{b} = 5$, p$K_\mathrm{a} = 9$ (Δp$K = -4$)
	p$K_\mathrm{b} = 6$, p$K_\mathrm{a} = 8$ (Δp$K = -2$)
	p$K_\mathrm{b} = 7$, p$K_\mathrm{a} = 7$ (Δp$K = 0$)
	p$K_\mathrm{b} = 8$, p$K_\mathrm{a} = 6$ (Δp$K = 2$)
	p$K_\mathrm{b} = 9$, p$K_\mathrm{a} = 5$ (Δp$K = 4$)
influence concentration	$L = 250\sigma$, $N_\mathrm{chain,b} = 368$
	$L = 500\sigma$, $N_\mathrm{chain,b} = 368$
	$L = 750\sigma$, $N_\mathrm{chain,b} = 368$
	$L = 1000\sigma$, $N_\mathrm{chain,b} = 368$
	$L = 1500\sigma$, $N_\mathrm{chain,b} = 368$
	$L = 750\sigma$, $N_\mathrm{chain,b} = 184$
	$L = 1000\sigma$, $N_\mathrm{chain,b} = 872$
influence segment length	$N_\mathrm{seg,b} = 2$, $N_\mathrm{chain,b} = 1104$
	$N_\mathrm{seg,b} = 4$, $N_\mathrm{chain,b} = 552$
	$N_\mathrm{seg,b} = 6$, $N_\mathrm{chain,b} = 368$
	$N_\mathrm{seg,b} = 8$, $N_\mathrm{chain,b} = 276$
	$N_\mathrm{seg,b} = 10$, $N_\mathrm{chain,b} = 221$
	$N_\mathrm{seg,b} = 48$, $N_\mathrm{chain,b} = 46$

TABLE III. Simulation parameters of the "purification" run

simulation set	value
"purification"	$L = 250\sigma$, $N_\mathrm{seg,b} = 6$, Δp$K = 0$, pH 7
	$L = 750\sigma$, $N_\mathrm{seg,b} = 6$, Δp$K = 0$, pH 7
	$L = 750\sigma$, $N_\mathrm{seg,b} = 6$, Δp$K = 4$, pH 7
	$L = 750\sigma$, $N_\mathrm{seg,b} = 10$, Δp$K = 0$, pH 7
	strong PE, $L = 250\sigma$, $N_\mathrm{seg,b} = 6$, Δp$K = 0$, pH 7
	strong PE, $L = 750\sigma$, $N_\mathrm{seg,b} = 6$, Δp$K = 0$, pH 7

TABLE IV. System and Monte Carlo parameters

Parameter	value
Monte Carlo steps equilibration run	$1.5{\cdot}10^6$
Monte Carlo steps production run	$1.0{\cdot}10^6$
Monte Carlo steps production run (purification)	$0.1{\cdot}10^6$
max. displacement crosslink bead	2.2 σ
max. displacement network monomer bead	4.25 σ
max. displacement oligomer bead	4.25 σ
max. displacement oligomer chain	25.0 σ
max. displacement counterions	25.0 σ
probability single particle move crosslink	1.0
probability single particle move network monomer	0.995
probability charge-change network monomer	0.005
probability single particle move oligomer	0.895
probability charge-change oligomer bead	0.005
probability chain move oligomer	0.1
probability single particle move ion	1.0

II. FITTING THE DEGREE OF IONIZATION OF A PURE POLYELECTROLYTE NETWORK BY HOFZUMAHAUS ET AL.[1]

We compared our results with the ionization behavior of a pure polyelectrolyte network simulated by Hofzumahaus et al.[1] Please note that in our work, the number of beads per chain was 10, and in the compared work, it was 9. We used the following equation based on the Henderson-Hasselbalch equation for the fit and obtained for $\mathrm{p}K_\mathrm{a} = 9.70 \pm 0.02$.

$$\alpha = \frac{10^{\mathrm{pH}-\mathrm{p}K_\mathrm{a}}}{1 + 10^{\mathrm{pH}-\mathrm{p}K_\mathrm{a}}} \tag{1}$$

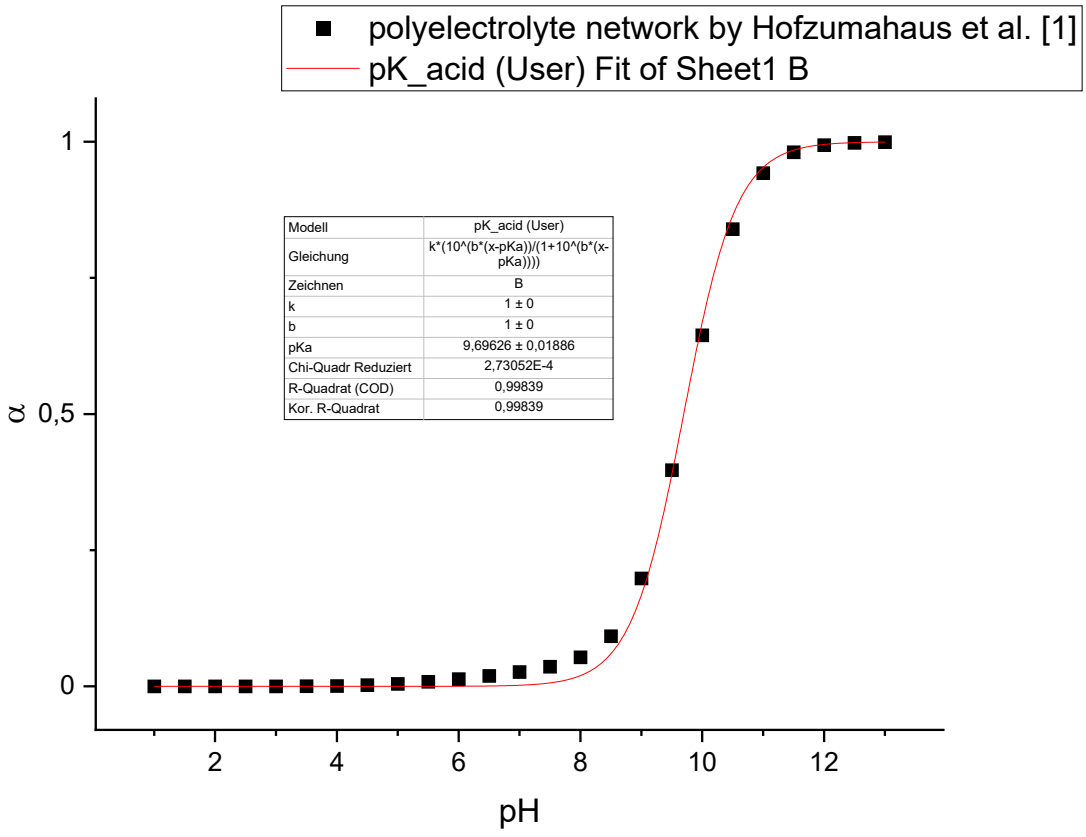

FIG. 1. Degree of ionization of a pure polyelectrolyte network by Hofzumahaus et al.[1] with a fit based on Henderson-Hasselbalch equation.

III. EFFECTIVE CHARGE

The charge of the microgel is important for the stability of the gels. Moreover, the charge becomes important in the application as a drug delivery system since positively charged gels could result in toxic effects. The effective charge was calculated in this work as the sum of all charges of the monomers, oligomers, and counterions taken up. Figure 2 shows the effective charge for different $\Delta \mathrm{p}K$ (top) and oligomer lengths (bottom) at different pH.

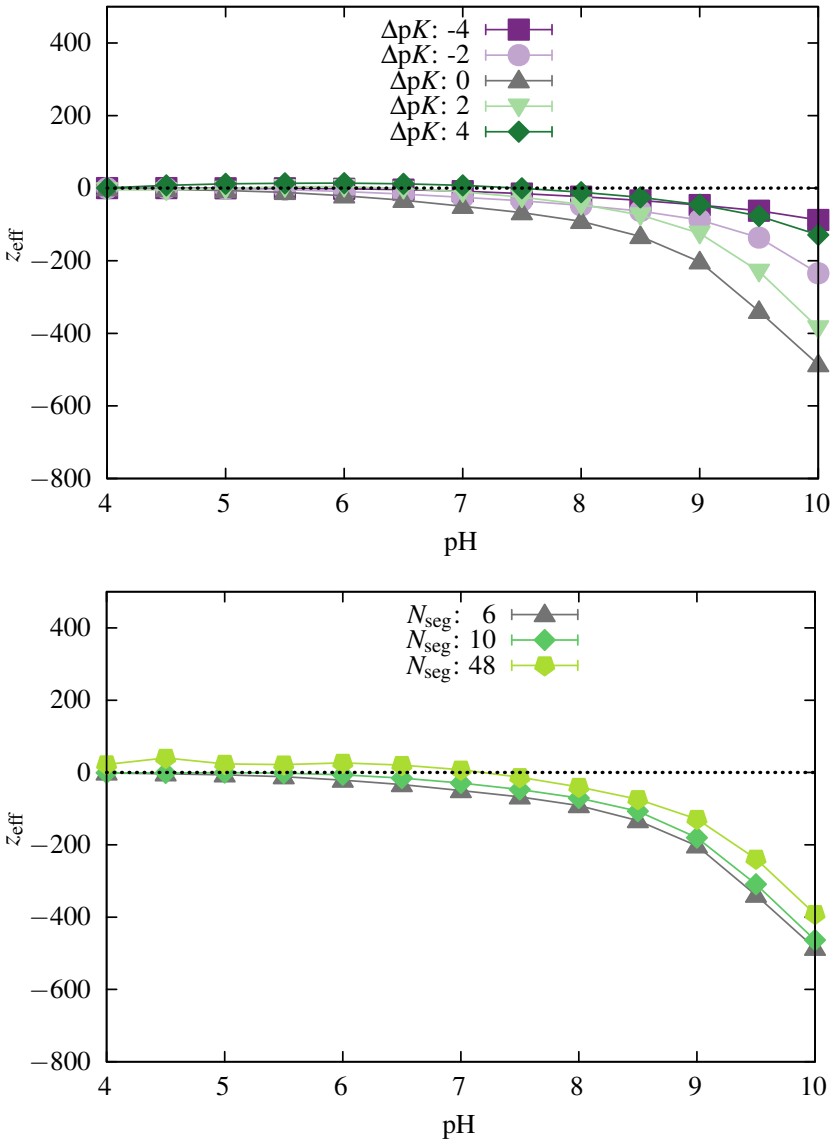

FIG. 2. Effective charge as a function of pH for systems with different oligomer lengths.

IV. INFLUENCE OF COUNTERIONS ON THE SWELLING BEHAVIOR

The counterions play an important role in the uptake of oligomers and swelling behavior. Figure 3 demonstrates for different $\Delta \mathrm{p}K$ that the networks are collapsed when no counterions were taken up. With an increasing number of counterions, the networks swelled.

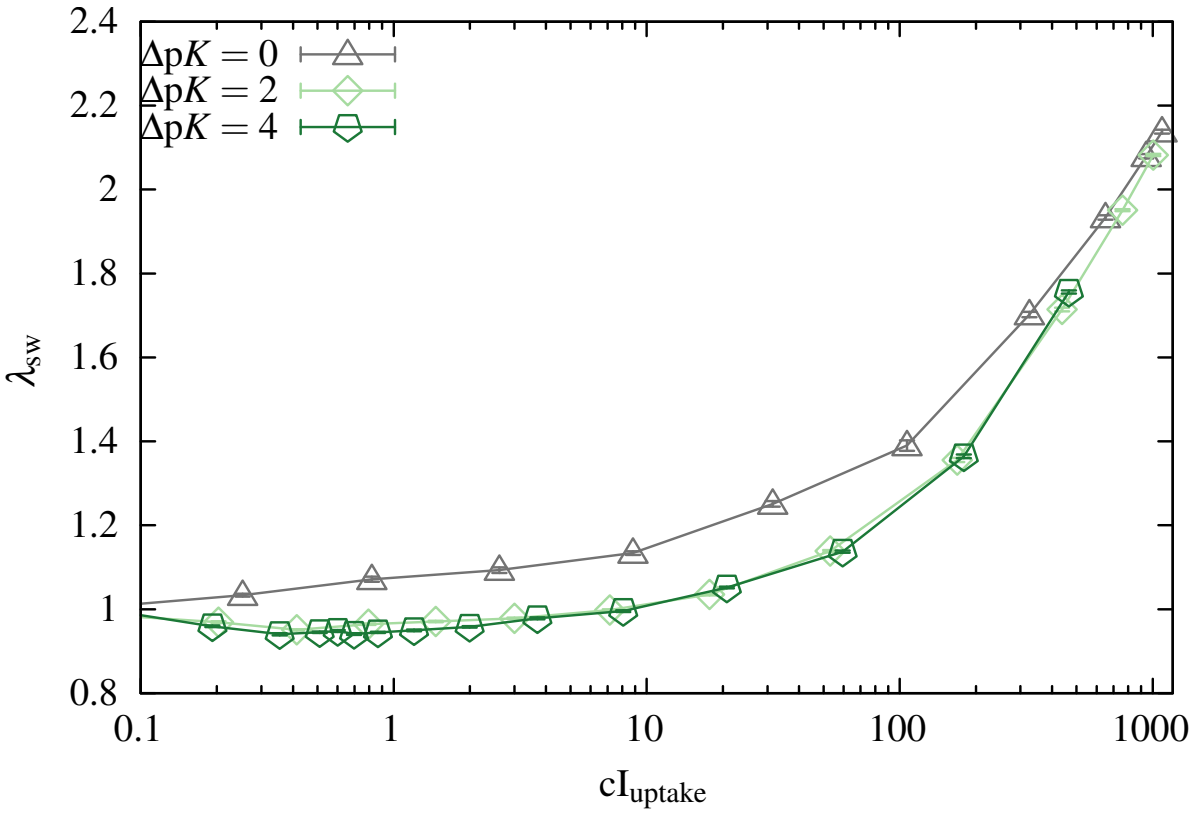

FIG. 3. Degree of swelling as a function of counterions uptaken for different $\Delta \mathrm{p}K$.

V. CHARGE DISTRIBUTION OF OLIGOMERS

In our work, we plotted the average degree of ionization of all oligomers as a function of pH. However, there are distributions in the system. The degree of ionization is higher for oligomers taken up than for oligomers in solution. But also, within the network, the degree of ionization is not uniform. We explain the differences within the network by the distribution of the crosslinks. Since the crosslinks were set at the lattice points of the cubic diamond lattice at the beginning of the simulation, their distribution is not homogeneous. Around the crosslinks the density is higher, which reduces the ionization of the network. Therefore, also a reduced ionization of the oligomers can be seen around the crosslinks. Figure 4 shows the degree of ionization of the oligomers as a function of the distance to the center of mass of the network normalized by the radius of gyration of the network for the reference system at different pH. Figure 5 shows the distribution of the number of charges for the oligomers at different pH for the reference system.

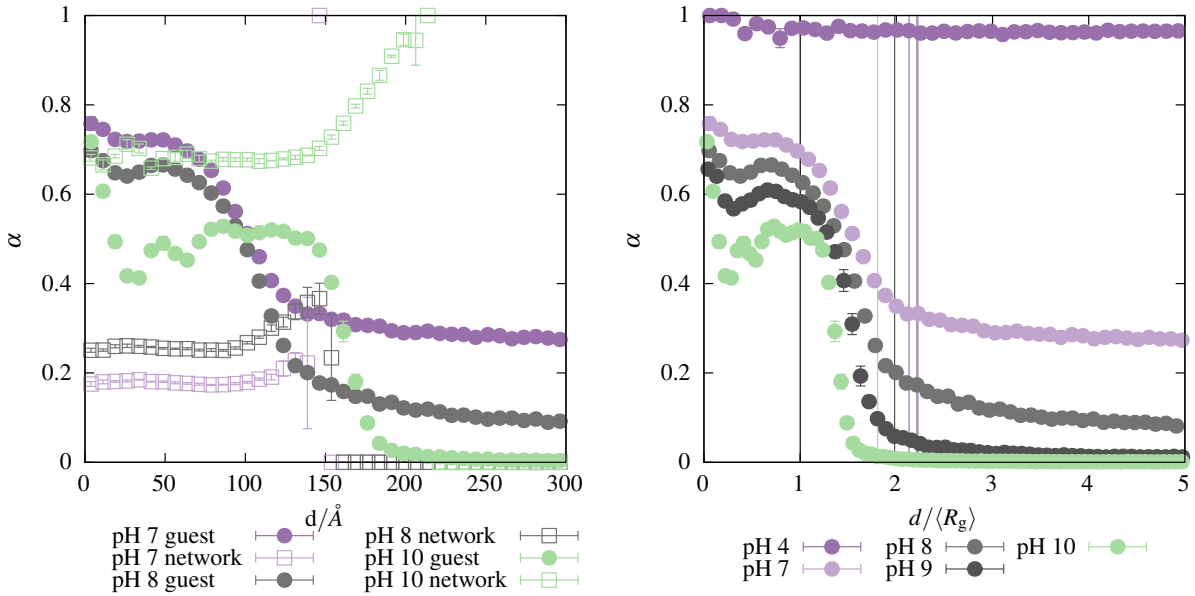

FIG. 4. Radial distribution functions of the degree of ionization of the network and the oligomers as a function of the distance to the center of mass of the network (left). Radial distribution functions of the degree of ionization of the oligomers as a function of the distance to the center of mass of the network normalized by the radius of gyration of the network for the reference system at different pH (right). The black vertical line represents the distance equal to the radius of gyration, and the colored lines are the distance to the network bead with the largest distance to the center of mass.

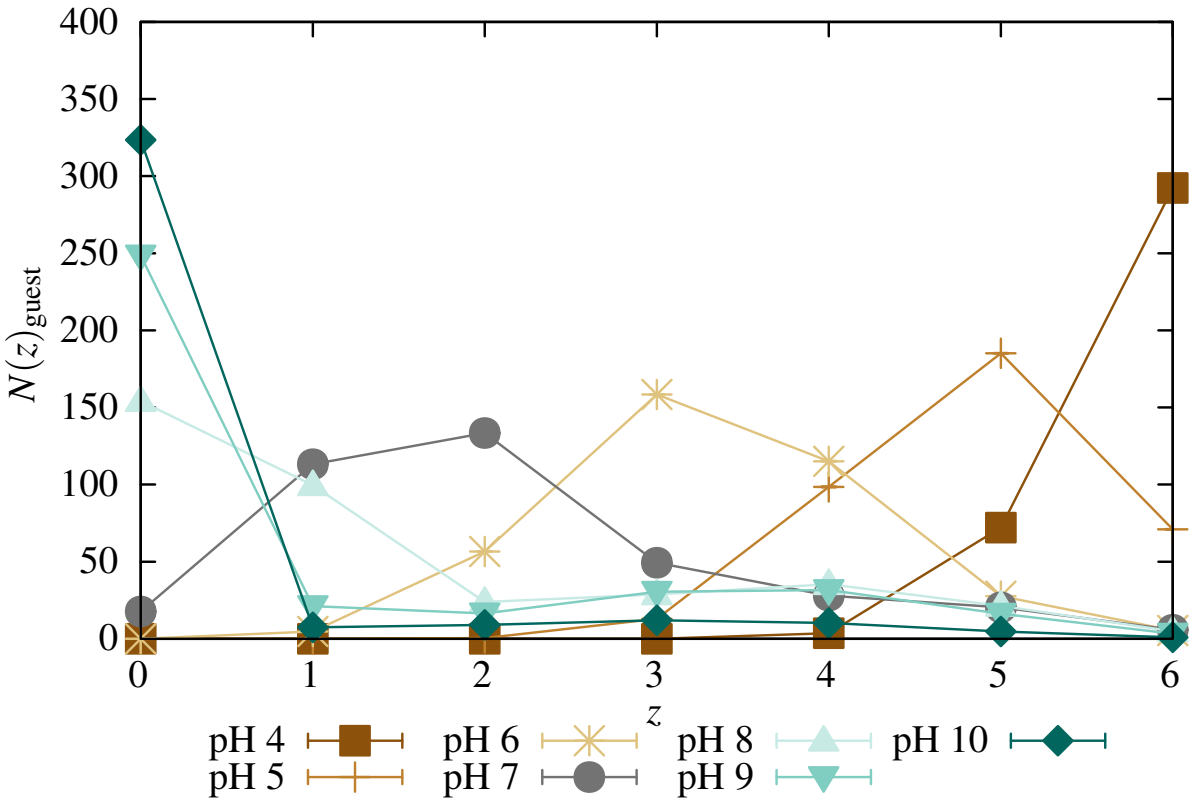

FIG. 5. Number of oligomer chains as a function of their charge for the reference system at different pH values.

VI. NUMBER OF CHARGES TAKEN UP

In our work, we plotted the number of chains taken up as a function of pH. As the total number of chains is 46 for chains with 48 beads, it is also interesting to plot the number of oligomer charges taken up instead. The plots in Figures 6 and 7 show that the network took up more charges with increasing number of beads per oligomer chain.

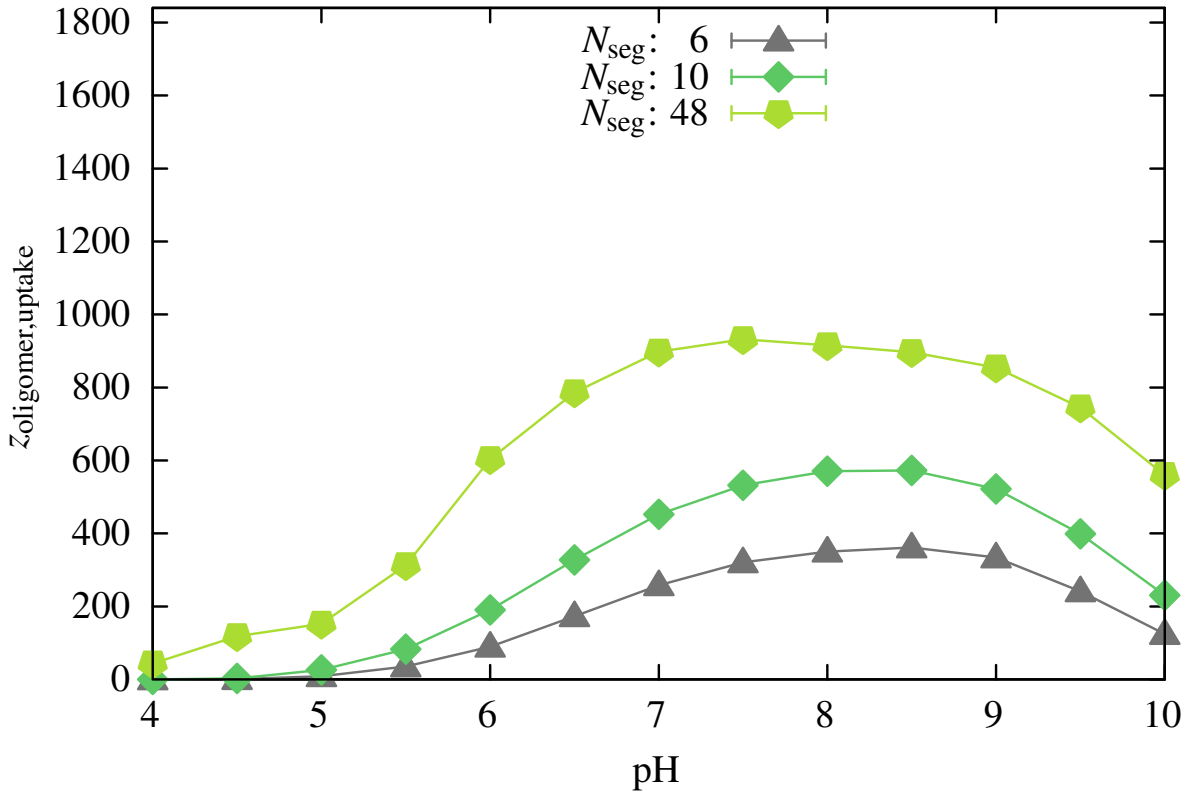

FIG. 6. Number of charges in the oligomers taken up as a function of pH for systems with different oligomer lengths.

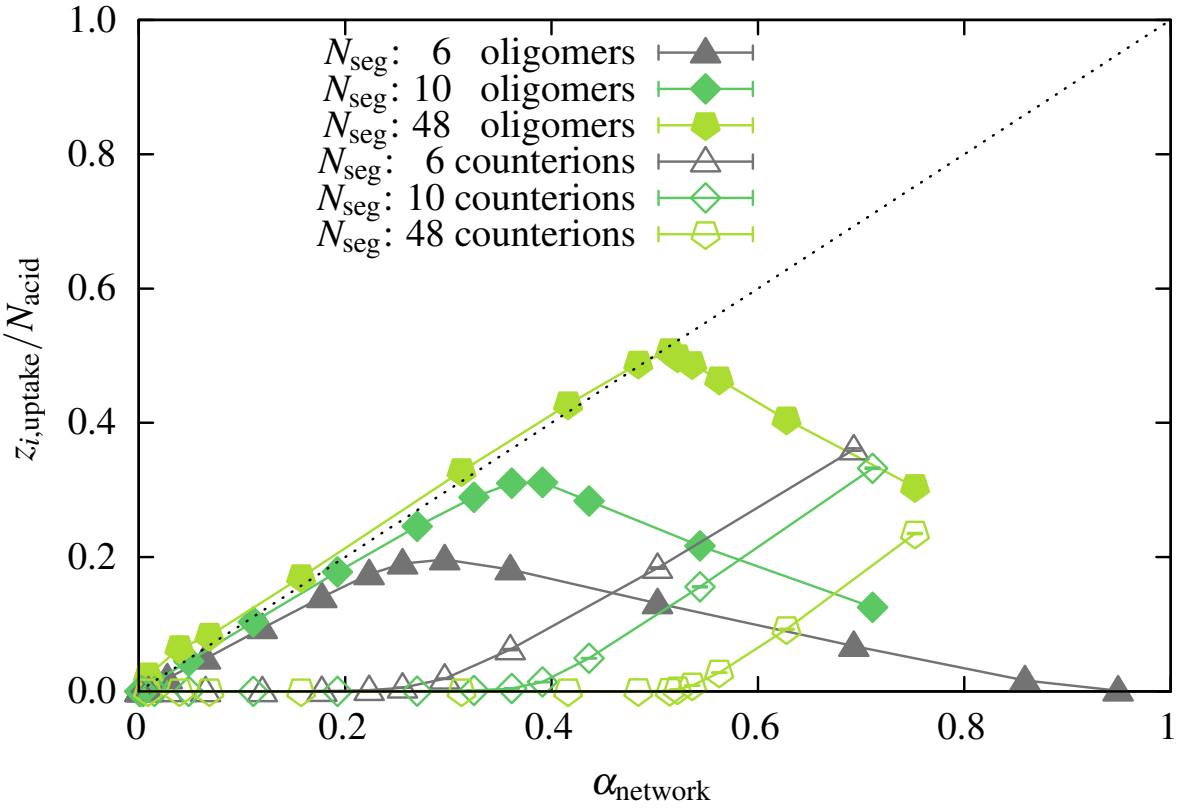

FIG. 7. Number of charges taken up normalized by the total number of acidic beads in the network as the function of the degree of ionization of the network. Oligomers (filled symbols) and counterions of the network (hollow symbols) were investigated separately. The dashed line represents the number of charges taken up equal to the degree of ionization.

VII. CONCENTRATION PROFILES

The concentrations as a function of the distance to the center of mass give insights into the distribution of oligomers and counterions taken up. Further, the swelling behavior can be seen. At pH 6, the network is slightly ionized and a few oligomers were taken up in the regime where the network is ionized. At pH 8, the number of oligomers taken up increases. Counterions were not found within the network. At pH 9, the number of oligomers decreases and counterions were within the network for charge compensation.

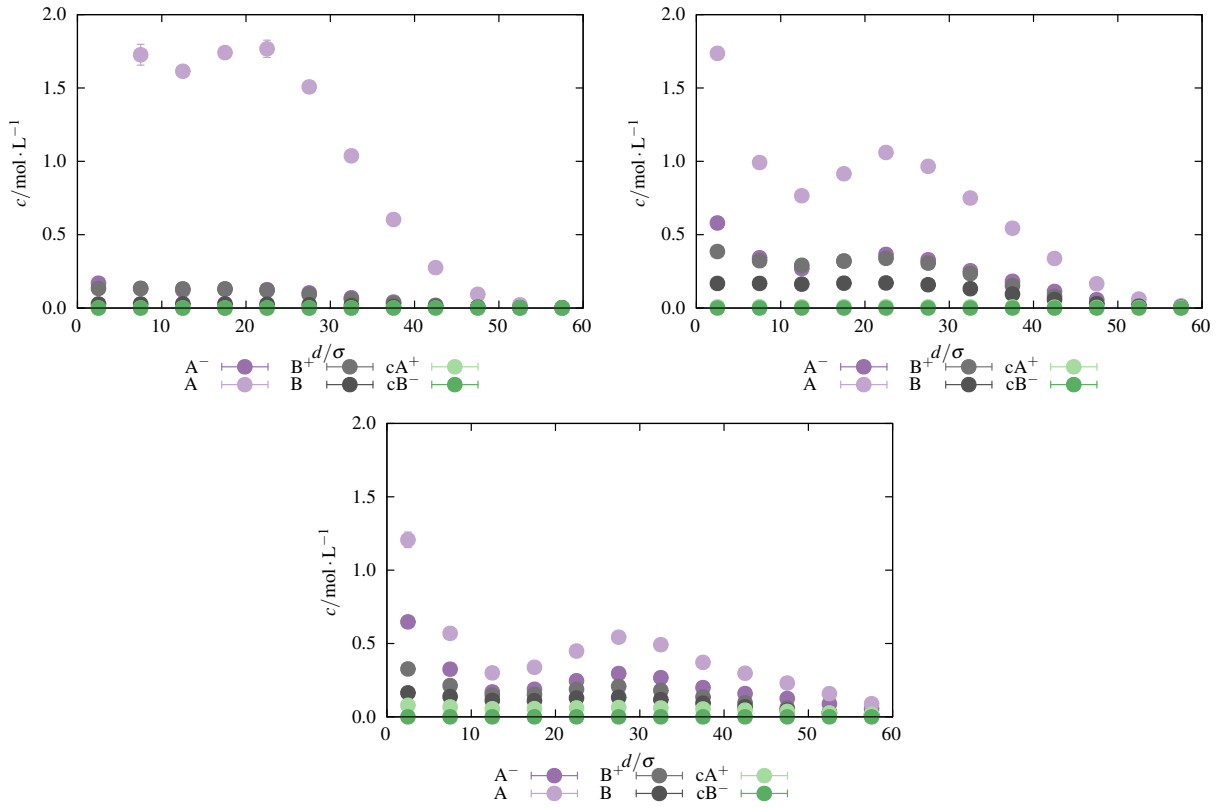

FIG. 8. Concentrations of network monomers, oligomer beads (charged and uncharged), and counterions in the reference system as a function of the distance to the center of mass at a) pH 6, b) pH 8, and c) pH 9

VIII. INFLUENCE OF OLIGOMER CONCENTRATION ON THE IONIZATION, SWELLING, AND UPTAKE BEHAVIOR

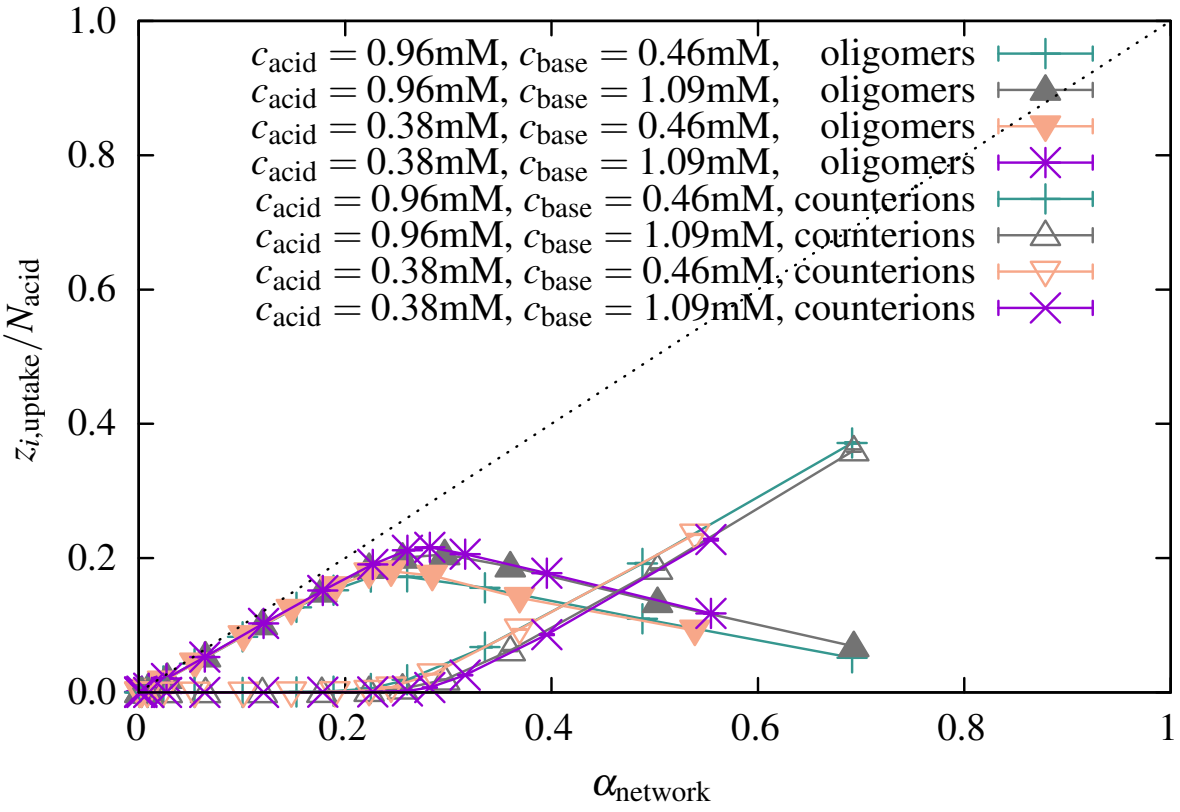

FIG. 9. Number of charges taken up normalized by the total number of acidic beads in the network as the function of the degree of ionization of the network. Oligomers (filled symbols) and counterions of the network (hollow symbols) were investigated separately. The dashed line represents the number of charges taken up equal to the degree of ionization.

Simply varying the simulation box size changes the microgel and oligomer concentration. Therefore, we applied for two different microgel concentrations also two different oligomer concentrations. Figure 9 and 10 give additional insights of the influence of the concentration on the uptake and swelling behavior and the effective charge of the network-oligomers-complexes. Note that the systems $c_{\mathrm{acid}} = 0.96$ mM, $N_{\mathrm{chain}} = 184$ and $c_{\mathrm{acid}} = 0.38$ mM, $N_{\mathrm{chain}} = 368$ have the same oligomer concentration, as like the systems $c_{\mathrm{acid}} = 0.96$ mM, $N_{\mathrm{chain}} = 368$ and $c_{\mathrm{acid}} = 0.38$ mM, $N_{\mathrm{chain}} = 872$.

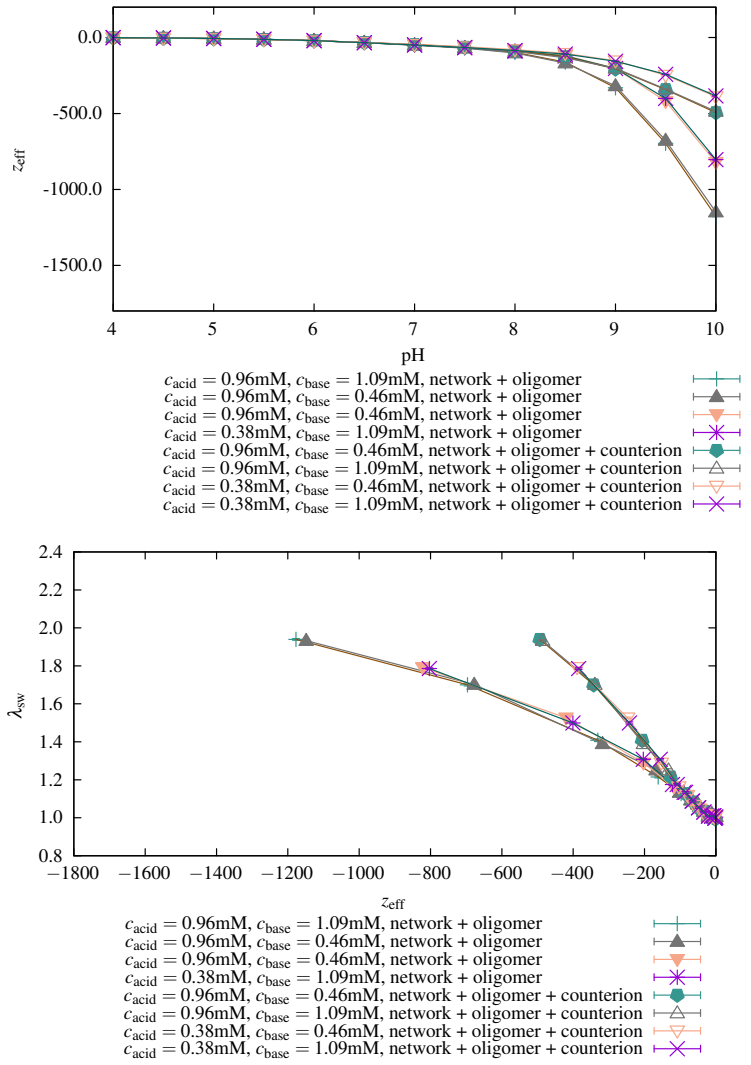

FIG. 10. Effective charge defined as the sum of network charges and oligomer charges taken up (hollow symbols) and counterion included (filled symbols) as a function of pH (top). Degree of swelling as a function of effective charge (down).

IX. RELATION TO EXPERIMENTAL UPTAKE AND RELEASE STUDIES

As supporting information, we provide simulation snapshots in Figure 11 to show the different uptake behavior of the reference system at pH 7 for the first uptake simulation and the "final purification" simulation.

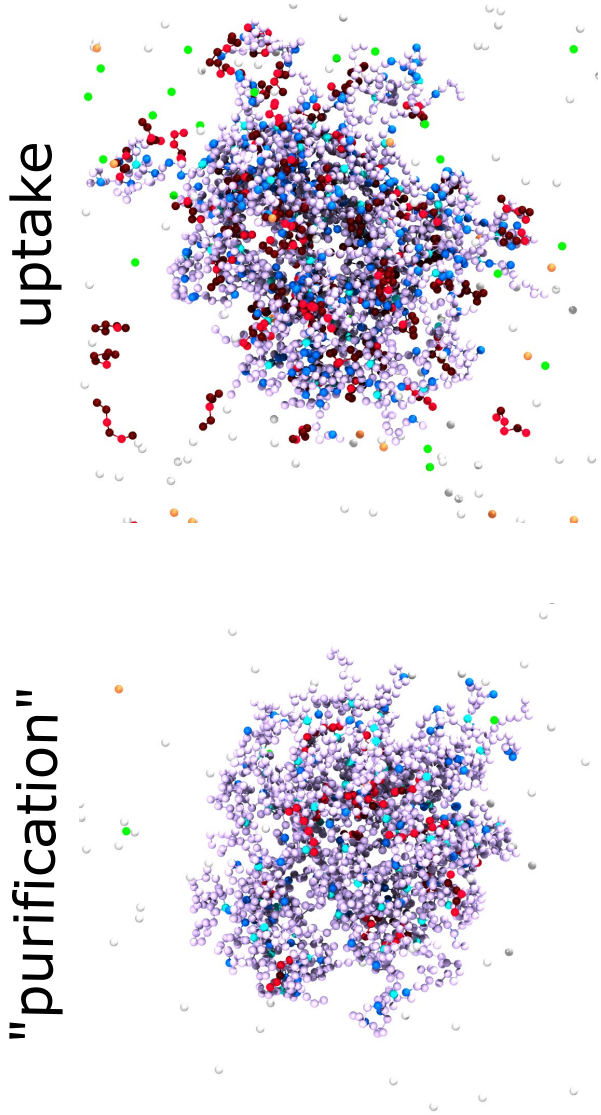

FIG. 11. Snapshots of the reference system at pH 7 for the first uptake simulation and the "final purification" simulation.

X. REFERENCES

[1] Hofzumahaus, C.; Hebbeker, P.; Schneider, S. Monte Carlo simulations of weak polyelectrolyte microgels: PH-dependence of conformation and ionization. *Soft Matter* **2018**, *14*, 4087–4100.