ACS Macro Letters

Letter

Cite This: ACS Macro Lett. 2019, 8, 117−122

pubs.acs.org/macroletters

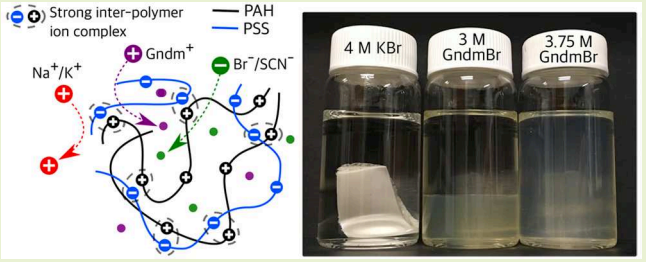
Guanidinium Can Break and Form Strongly Associating Ion Complexes

Kazi Sadman, Qifeng Wang, and Kenneth R. Shull*

Department of Materials Science and Engineering, Northwestern University, Evanston, Illinois 60208, United States

Supporting Information

ABSTRACT: Guanidinium is one of nature's strongest denaturants and is also a motif that appears in several interfacial contexts such as the RGD sequence involved in cell adhesion, cell penetrating peptides, and antimicrobial molecules. It is important to quantify the origin of guanidinium's ion-specific interactions so that its unique behavior may be exploited in synthetic applications. The present work demonstrates that guanidinium ions can both break and form strongly associating ion complexes in a context-dependent way. These insights into guanidinium's behavior are elucidated using polyelectrolyte complexes (PECs), where interpolymer ion pairs between oppositely charged polymers play an important role in determining material stability. Different polycation−polyanion combinations can span a large range of association affinities, where more strongly associating complexes can remain insoluble in concentrated salt solutions and in extreme pH conditions. This high stability is desirable in several application contexts for PECs, but also renders them challenging to process and, therefore, to study since they cannot be dissolved into polymer solutions. Here we demonstrate that guanidinium salts are very effective in dissolving the poly(styrenesulfonate)/poly(allylamine) (PSS:PAH) complex, which has one of the highest reported polycation−polyanion association affinities. We also demonstrate the importance of charge identity in complexation phenomena by functionalizing guanidinium directly into poly(allylamine), resulting in a complex that remains stable under highly denaturing conditions. The model system of PSS:PAH is used to glean insights into guanidinium's denaturing activity, as well as to broadly comment on the nature of ion-specific interactions in charged macromolecules.



Polyelectrolyte complexes (PECs) were difficult to process into functional materials before development of the layer-by-layer (LbL) assembly technique. This approach led to an explosion of work using these materials to obtain coatings for a variety of applications.[1,2] A similarly important advancement in the field was made when salt-mediated processing ("saloplastics") was introduced to process bulk PECs.[3,4] Here, salt is an analog for temperature where a solid-like PEC can be "melted" in appropriate salt concentrations into an associating polymer solution, commonly known as the coacervate phase. The liquid-like coacervate phase is more tractable from a processing standpoint, where the salt concentration can be tailored to modulate the viscosity and, ultimately, be cast into more useful formats such as films,[5] rods,[4] or fibers.[6] Since the number of potential polyelectrolyte combinations is large, a collective understanding of how the constituting polymer identities and the associated details, such as charge identity, topology, and hydrophobicity, dictate the observed macroscopic material response is only incipient. Given the vast number of applications to which polyelectrolyte complexes, or polyelectrolytes in general, are relevant, it is important to clearly correlate these molecular level details to measurable material parameters.

While different salts used to swell PECs result in a material response in a fairly predictable manner, according to ionic solvation,[5] different polycation/polyanion combinations exhibit more complex trends. Specifically, different constituting polyelectrolyte pairs have very different association affinities.[7] Weakly associating complexes have a low salt resistance, defined as the critical salt concentration needed to completely dissolve the material by charge screening.[8] On the other end of the spectrum, strongly associating complexes have a very high salt resistance and are frequently insoluble. Such strongly associating complexes are often found in nature, in protein−protein interactions for example.[9] The measured salt resistance of a specific complex is a nontrivial function of the ion-pairing strength,[7] chain topology,[10] hydrophobicity[5] and molecular weight.[8] Importantly, the salt resistance of a complex is also dependent on the specific salt being considered; a complex will have a low salt resistance against a salt that is effective for breaking that particular complex.[11] The most well-studied complex with high salt resistance is the pairing of poly(allylamine) with poly(styrenesulfonate) (PSS:PAH), which has been popular for LbL assemblies, precisely due to its high association affinity that makes processability simpler, but also precludes salt-mediated dissolution into a coacervate phase.[7,12,13] Indeed, PSS:PAH cannot be dissolved in

Received: October 30, 2018
Accepted: January 2, 2019
Published: January 14, 2019

DOI: 10.1021/acsmacrolett.8b00824
ACS Macro Lett. 2019, 8, 117−122

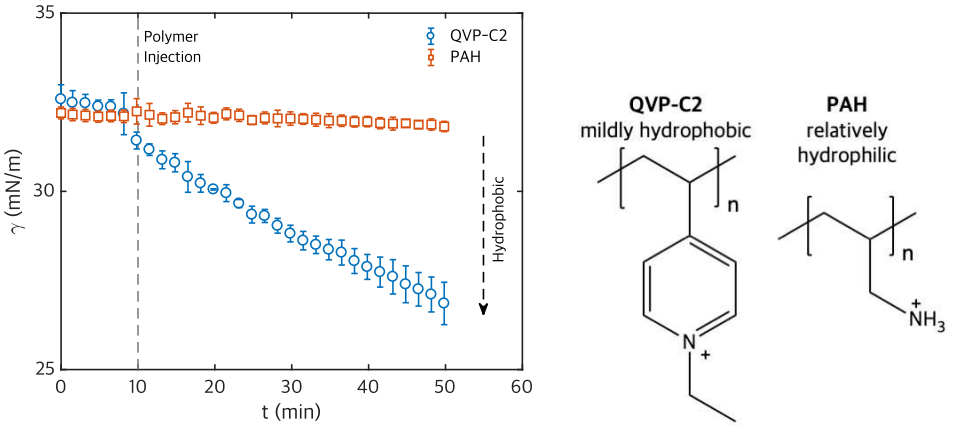


Figure 1. Effect of poly(allylamine) HCl (PAH) and poly(*N*-ethyl-4-vinylpyridinium) (QVP-C2) adsorption on the interfacial tension (γ) at a water/chloroform interface. More hydrophobic molecules adsorb to a greater extent, thus, lowering the tension from the pristine water/chloroform value of ≈32.8 mN/m. The polymers were added to the aqueous phase at a repeat unit concentration of 5 mM. A total of 5 mM $NaClO_4$ was also present in the aqueous phase.

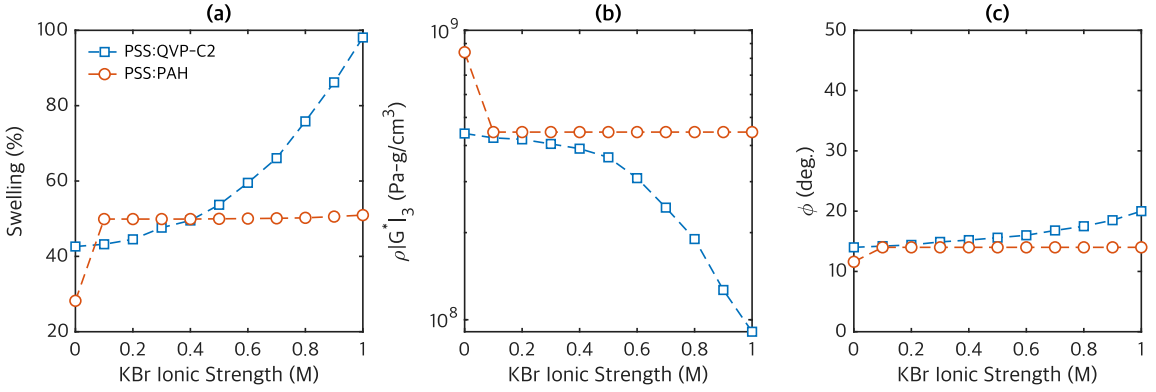


Figure 2. (a) Swelling behavior, (b) density-shear modulus product, and (c) viscoelastic phase angle (ϕ) as a function of ionic strength for spin-coated PSS:PAH films. Swelling % is calculated in reference to the dry film. PSS:PAH shows little sensitivity to increasing concentration of KBr, which is one of the most effective salts for dissolving polyelectrolyte complexes. PSS:QVP-C2 exhibits increased swelling and diminished mechanical properties with increasing salt concentration. Viscoelastic properties were measured at 15 MHz using the quartz crystal microbalance, as described previously.[5,14] For reference, polymer glasses have a shear modulus of ≈2×10^9 Pa and a $\phi \approx 1°$ at this frequency, and $|G^*| = |G' + iG''|$ and $\phi = \arctan(G''/G')$ as usual. pH of all solutions were ambient at ≈5.5−7.

potassium bromide solutions, which is one of the most effective salts in breaking ion pairs.[3,5,11] Yet, it remains desirable to be able to process PSS:PAH saloplastically since once it is formed into functional materials, the final product would be highly stable under many conceivable application environments.

As mentioned earlier, hydrophobic effects, ion-pairing associations, molecular weights, and chain topology can all ascribe stability to PECs against salt solutions and pH changes. Since molecular weight effects are more pronounced at low degrees of polymerization and because the most common chain topology is linear, we focus here on the limit of linear high molecular weight chains, but note that these factors are important and have been considered elsewhere.[8,10] This leaves us to consider the roles of hydrophobicity and ion-pairing association in charged complexes, which are also two important factors determining protein stability. In our recent work, we demonstrated that more hydrophobic complexes are more salt resistant, showing greater and greater stability in salt solutions as the complex is made progressively more hydrophobic.[5] Let us now consider the polycations PAH and poly(*N*-ethyl-4-vinylpyridinium) (QVP-C2), where the latter is expected to be relatively more hydrophobic. The relative hydrophobicity/hydrophilicity of these two polyelectrolytes can be quantified by their propensity to segregate at water/chloroform interfaces, as measured from a drop in the interfacial tension. Figure 1 shows that QVP-C2 readily partitions to a water/chloroform interface due to its hydrophobic character, while poly(allylamine) has no observed interfacial affinity due to its relatively hydrophilic nature. If hydrophobicity is a dominating noncovalent interaction in complexes of these two polycations with the same polyanion, then one would expect the more hydrophilic complex involving poly(allylamine) to be more weakly associating with a lower salt resistance.[5] Yet, we find this not to be the case.

Figure 2 plots the salt responsiveness of PSS complexed with PAH and QVP-C2, showing that the more hydrophobic complex of PSS:QVP-C2 swells ≈40% in water, while PSS:PAH only swells ≈30%. These data were obtained with the quartz crystal microbalance, which is able to measure the linear viscoelastic behavior of PEC films (≈1.5 μm) at a frequency of 15 MHz.[5,14] This technique is advantageous because it allows precise mechanical characterization while simultaneously quantifying the swelling ratio of pore-free samples by measuring changes in the film thickness. The swelling ratio is directly related to the water content of the

DOI: 10.1021/acsmacrolett.8b00824
ACS Macro Lett. 2019, 8, 117−122

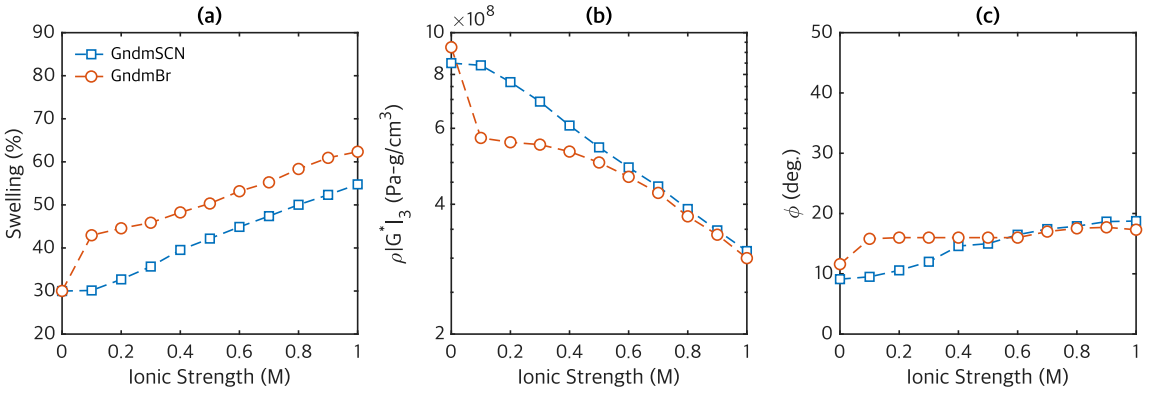


Figure 3. (a) Swelling behavior, (b) density-shear modulus product, and (c) viscoelastic phase angle in response to guanidinium salts for spin-coated PSS:PAH films. Both the bromide and thiocyanate salts of guanidinium (Gndm) are effective in swelling PSS:PAH, resulting in lower shear moduli and an increased phase angles, unlike the response for KBr in Figure 2. The mechanical properties are primarily a function of the water content,[5] as observed from well-defined swelling-modulus master curves (Figure S2). Viscoelastic properties reported at 15 MHz.

PEC films (see Experimental section). Here, the modulus of PSS:PAH initially is nearly glass-like at ≈9 × 10^8 Pa (for reference, polystyrene at room temperature is ≈2 × 10^9 Pa). Even more surprisingly, PSS:PAH appears resistant to swelling with increasing KBr ionic strength, after an initial response at low salt concentrations (a similar response is also observed for other common salts, see Figure S1), but PSS:QVP-C2 keeps swelling with a corresponding modulus decrease, as one would expect.[3,5] During the initial swelling response of PSS:PAH, the complex was observed to swell to 40−50% from the initial swollen state of about 30% in pure water. While this initial swelling response at low ionic strengths is somewhat peculiar, conflicting reports exist in literature where similar behavior has been observed in some polyelectrolyte multilayers involving poly(allylamine),[15,16] but not in others.[17,18] In our experiments, we observe that this initial swelling at 0.1 M occurs over several hours (Figure S6), consistent with at least one study explicitly reporting it.[15] Therefore, the slow time scales associated with this phenomenon could be a reason for the experimental discrepancies, as the measurement time scale becomes critical, and more detailed investigations are required to elucidate the underlying mechanisms.[19] However, the majority of studies acknowledge PSS:PAH's relatively high modulus/lower water content[18,20] and insensitivity to salt,[17,18,21,22] consistent with our own observations in the present work. The relatively high modulus and low water content of the PSS:PAH complex, even though it is quantifiably more hydrophilic, may be attributed to the tighter/stronger ion pairs that form between the two monomers. This observation is complementary to other reports that have found PSS:PAH to be highly stable in a variety of salt solutions.[7] Understanding this stability is desirable since materials and soft assemblies formed using this unique ion pair would also be highly stable.

Thus far, intuition has misled expectations in terms of PEC stability, and it appears that processing PSS:PAH remains difficult. Numerous publications have focused on the interaction of Hofmeister series of salts to study interaction with PECs, usually focused on the anions.[23] Poorly solvated salt species are generally found to interact more strongly with complexes, and well-solvated species such as lithium typically interact weakly.[5] KBr is one of the best salts for dissolving PECs since the bromide ion can efficiently break ion pairs, but does not precipitate polycations at high concentrations. More poorly solvated anions such as perchlorate and thiocyanate tend to precipitate out some polycations.[24] However, we speculate that it may be possible to use a more poorly solvated cation than potassium to process PECs. This speculation was inspired by observing the well-known role of guanidinium ions in protein denaturation.[25,26] Guanidinium thiocyanate is one of the strongest known denaturants and also happens to be a very weakly solvated salt.[25] Many essential molecular details that contribute to protein stability are also relevant to PECs, and therefore, it can be expected that salts that are strong denaturants would also be strong dopants for PECs. Figure 3 shows that, when subjected to increasing concentration of guanidinium bromide (GndmBr) or guanidinium thiocyanate (GndmSCN), PSS:PAH complexes swell significantly with a corresponding decrease in the modulus, unlike the response observed for KBr. Importantly, the mechanical properties of these complexes are ultimately determined by the amount of water inside the complex, as plotted in Figure S2 and as we have reported previously.[5] The rheological response of a highly swollen coacervate phase (≈ 16 wt % PEC), obtained at an overall GndmBr concentration of 3.25 M is shown in Figure 4,

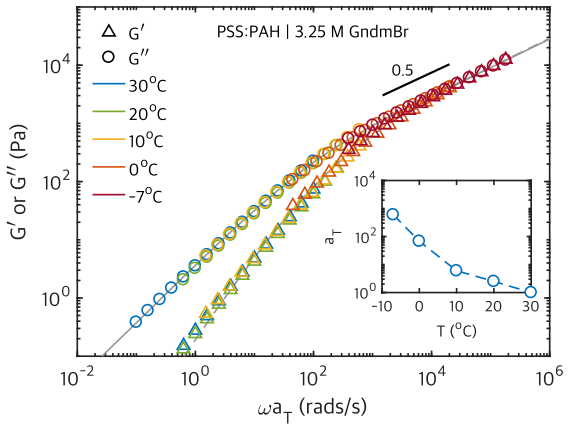


Figure 4. Time−temperature superposition of PSS:PAH coacervate formed at a overall GndmBr concentration of 3.25 M. Here, the polymer concentration is ≈16 wt % in the coacervate phase. A typical polymer solution response is observed even at this high salt concentration. The lowest temperature of −7 °C could be measured before the onset of freezing effects. The associated relaxation spectrum ($H(\lambda)$) is plotted in Figure S4.[5]

DOI: 10.1021/acsmacrolett.8b00824
ACS Macro Lett. 2019, 8, 117−122

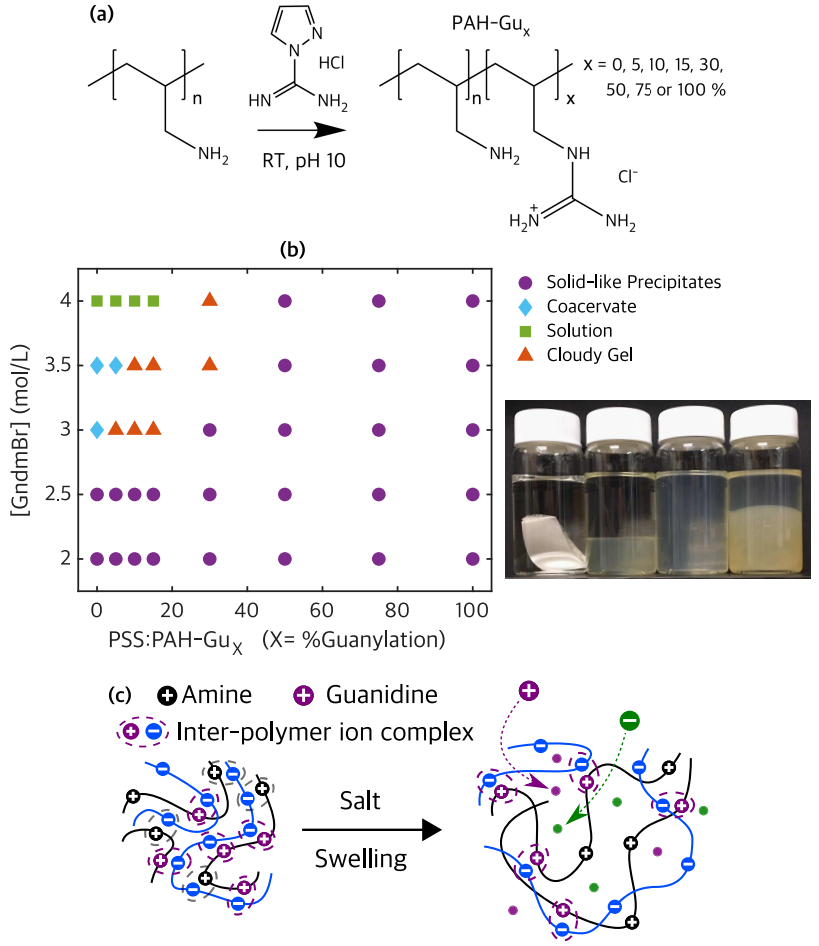


Figure 5. (a) Reaction scheme for systematic guanylation of poly(allylamine), (b) phenomenological phase behavior of PSS:PAH-Gu complexes as a function of guanylation percent at pH ≈ 6, and (c) schematic representation of a possible explanation for the observed phase behavior. Guanidinium is able to break the relatively strong ion-complex of styrenesulfonate with allylamine, but not allylguanidine.

where we have used time−temperature superposition to access a broad range of time scales. Here, the typical response of a coacervate is observed, with a liquid-like behavior at high temperatures and low frequencies and a power-law behavior of ≈0.5 at low temperatures and high frequencies. A comparison of GndmBr to other salts for swelling PSS:QVP-C2 is also made in Figure S3, where GndmBr also appears to be a strong dopant.

Polyanions and polycations associate due to the large entropy gain from counterion release. While entropy is the dominant driving force for association, a polyelectrolyte complex's responsiveness and strength are primarily determined by ion and polymer specific interactions. This importance of polymer specific interactions was highlighted in this work by noting that PSS:PAH is stronger and more stable than PSS:QVP-C2, even though the later is quantitatively more hydrophobic. Ion-specific interactions allow guanidinium ions to break PSS:PAH complexes when all other common salts fail to do so. Since guanidinium is an organic cation ubiquitous in biology as part of the amino acid arginine, the following question can be posed: how would the complex respond if guanidinium charges were introduced directly into the PAH backbone? Alternatively, what is the role of charge identity in amine versus guanidine in determining the physical properties of the complex? This simple difference can have significant implications in the development of effective antimicrobial agents with low toxicity and low drug resistance.[22,27,28] For a polypeptide, this would correspond to quantifying the difference in association of lysine versus arginine with a common polyanion. In the present case it is straightforward to convert PAH into a statistical copolymer with amine and guanidine using the scheme in Figure 5a. Due to the molecular simplicity of poly(allylamine) and poly(allylguanidine), this approach is attractive for studying the differences between primary amines (lysine-like) and guanidinium (arginine-like) charges.

The interaction of poly(styrenesulfonate) as the model polyanion with poly(allylamine-*co*-allylguanidine) (PSS:PAH-Gu) can now be studied as a function of the salt concentration by observing whether the resulting complexes remain solid-like or can be dissolved into polymer solutions. Figure 5b provides a phenomenological phase map of the formed complexes as a function of the guanidinium fraction on the polycation. The complex is classified as solid-like if it appears insoluble, a coacervate if a liquid−liquid phase separation occurs, and a polymer solution if it is dissolved completely. We discover that the phase behavior of PSS:PAH-Gu is extremely sensitive to the guanidinium fraction on the backbone. At just 10% guanidinium, the complex forms a cloudy gel instead of a coacervate, indicating the presence of insoluble aggregates. The rheological response of this "cloudy gel" is atypical of complex coacervate's polymer solution response, such as in Figure 4,

DOI: 10.1021/acsmacrolett.8b00824
ACS Macro Lett. 2019, 8, 117−122

but is characteristic of colloidal gels, as shown in Figure S5.[29] At higher guanidinium fraction the complex only forms solid-like complexes, suggesting that guanidinium has a higher affinity for poly(styrenesulfonate) than poly(allylamine), consistent with a recent study reporting guanidinium containing polyelectrolyte multilayers to be more rigid.[30] However, it is quite possible these complexes may be far from their thermodynamic equilibrium, and more detailed investigations are needed to corroborate these preliminary observations. Such unique behavior of guanidinium has been observed and utilized in other self-assembling macromolecular systems,[31−33] and the present work here provides fundamental insights into those observations.

In the current work, we have demonstrated that ion-specific interactions play a key role in determining the stability and responsiveness of charged complexes. These interactions can be exploited to both disassemble complexes, or to increase their stability, depending on the context. In this particular case, guanidinium was a powerful agent for disassembling the otherwise strongly associating PSS:PAH complex. This ability to break strong ion-pairs likely compliments other proposed mechanisms for guanidinium's denaturing activity.[25,26,34−36] While guanidinium is a strong denaturant as a free salt, it is a strong binding agent when incorporated into the polymer itself, rendering complexes with anionic moieties highly stable, suggesting a mechanism for its interfacial adhesion promoting properties.[37] Therefore, the context in which ion-specific interactions are considered is extremely important for rationalizing observations. Lastly, given guanidinium's biological relevance, its behavior in synthetic macromolecular systems could be better explored because of its technological significance.[28] The present work introduces PAH-Gu polyelectrolytes as a simple and accessible model platform for future investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmacrolett.8b00824.

Experimental procedures, polymer functionalization techniques, instrumentation, supporting figures (S1−S7), and characterization (PDF).

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: k-shull@northwestern.edu.

ORCID

Kazi Sadman: 0000-0003-2872-752X

Qifeng Wang: 0000-0002-6010-2178

Kenneth R. Shull: 0000-0002-8027-900X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Yaoyao Chen for NMR analysis of the guanylation reactions. This work was supported by the U.S. Department of Energy Office of Science under Contract DE-AC02-06CH11357, by the National Institute of Standards and Technology (NIST) as part of the Center for Hierarchical Materials Design (CHiMaD), and by the National Science Foundation (NSF DMR-1710491). This work made use of the MatCI Facility which receives support from the MRSEC Program (NSF DMR-1121262) of the Materials Research Center at Northwestern University. Also, this work made use of the IMSERC at Northwestern University, which has received support from the Soft and Hybrid Nanotechnology Experimental (SHyNE) Resource (NSF NNCI-1542205); the State of Illinois and International Institute for Nanotechnology (IIN).

■ REFERENCES

(1) Hammond, P. T. Engineering materials layer-by-layer: Challenges and opportunities in multilayer assembly. *AIChE J.* **2011**, *57*, 2928−2940.

(2) Tang, Z.; Wang, Y.; Podsiadlo, P.; Kotov, N. A. Biomedical Applications of Layer-by-Layer Assembly: From Biomimetics to Tissue Engineering. *Adv. Mater.* **2006**, *18*, 3203−3224.

(3) Wang, Q.; Schlenoff, J. B. The Polyelectrolyte Complex/Coacervate Continuum. *Macromolecules* **2014**, *47*, 3108−3116.

(4) Schaaf, P.; Schlenoff, J. B. Saloplastics: Processing Compact Polyelectrolyte Complexes. *Adv. Mater.* **2015**, *27*, 2420−2432.

(5) Sadman, K.; Wang, Q.; Chen, Y.; Keshavarz, B.; Jiang, Z.; Shull, K. R. Influence of Hydrophobicity on Polyelectrolyte Complexation. *Macromolecules* **2017**, *50*, 9417−9426.

(6) Meng, X.; Schiffman, J. D.; Perry, S. L. Electrospinning Cargo-Containing Polyelectrolyte Complex Fibers: Correlating Molecular Interactions to Complex Coacervate Phase Behavior and Fiber Formation. *Macromolecules* **2018**, *51*, 8821−8832.

(7) Fu, J.; Fares, H. M.; Schlenoff, J. B. Ion-Pairing Strength in Polyelectrolyte Complexes. *Macromolecules* **2017**, *50*, 1066−1074.

(8) Li, L.; Srivastava, S.; Andreev, M.; Marciel, A. B.; de Pablo, J. J.; Tirrell, M. V. Phase Behavior and Salt Partitioning in Polyelectrolyte Complex Coacervates. *Macromolecules* **2018**, *51*, 2988−2995.

(9) Borgia, A.; Borgia, M. B.; Bugge, K.; Kissling, V. M.; Heidarsson, P. O.; Fernandes, C. B.; Sottini, A.; Soranno, A.; Buholzer, K. J.; Nettels, D.; Kragelund, B. B.; Best, R. B.; Schuler, B. Extreme disorder in an ultrahigh-affinity protein complex. *Nature* **2018**, *555*, 61−66.

(10) Johnston, B. M.; Johnston, C. W.; Letteri, R. A.; Lytle, T. K.; Sing, C. E.; Emrick, T.; Perry, S. L. The effect of comb architecture on complex coacervation. *Org. Biomol. Chem.* **2017**, *15*, 7630−7642.

(11) Ali, S.; Prabhu, V.; Ali, S.; Prabhu, V. M. Relaxation Behavior by Time-Salt and Time-Temperature Superpositions of Polyelectrolyte Complexes from Coacervate to Precipitate. *Gels* **2018**, *4*, 11.

(12) Harris, J. J.; Stair, J. L.; Bruening, M. L. Layered Polyelectrolyte Films as Selective, Ultrathin Barriers for Anion Transport. *Chem. Mater.* **2000**, *12*, 1941−1946.

(13) Stanton, B. W.; Harris, J. J.; Miller, M. D.; Bruening, M. L. Ultrathin, Multilayered Polyelectrolyte Films as Nanofiltration Membranes. *Langmuir* **2003**, *19*, 7038−7042.

(14) Sadman, K.; Wiener, C. G.; Weiss, R. A.; White, C. C.; Shull, K. R.; Vogt, B. D. Quantitative Rheometry of Thin Soft Materials Using the Quartz Crystal Microbalance with Dissipation. *Anal. Chem.* **2018**, *90*, 4079−4088.

(15) Sukhorukov, G. B.; Schmitt, J.; Decher, G. Reversible swelling of polyanion/polycation multilayer films in solutions of different ionic strength. *Berichte der Bunsengesellschaft für physikalische Chemie* **1996**, *100*, 948−953.

(16) Feldötö, Z.; Varga, I.; Blomberg, E. Influence of Salt and Rinsing Protocol on the Structure of PAH/PSS Polyelectrolyte Multilayers. *Langmuir* **2010**, *26*, 17048−17057.

(17) Dubas, S. T.; Schlenoff, J. B. Swelling and Smoothing of Polyelectrolyte Multilayers by Salt. *Langmuir* **2001**, *17*, 7725−7727.

(18) Jaber, J. A.; Schlenoff, J. B. Counterions and Water in Polyelectrolyte Multilayers: A Tale of Two Polycations. *Langmuir* **2007**, *23*, 896−901.

(19) Fares, H.; Wang, Q.; Schlenoff, J. Swelling and inflation in polyelectrolyte complexes. *Macromolecules* **2018**, DOI: 10.1021/acs.macromol.8b01838.

DOI: 10.1021/acsmacrolett.8b00824
ACS Macro Lett. 2019, 8, 117−122

(20) Nolte, A. J.; Rubner, M. F.; Cohen, R. E. Determining the Young's Modulus of Polyelectrolyte Multilayer Films via Stress-Induced Mechanical Buckling Instabilities. *Macromolecules* **2005**, *38*, 5367−5370.
(21) Lulevich, V. V.; Vinogradova, O. I. Effect of pH and Salt on the Stiffness of Polyelectrolyte Multilayer Microcapsules. *Langmuir* **2004**, *20*, 2874−2878.
(22) Gabriel, G. J.; Madkour, A. E.; Dabkowski, J. M.; Nelson, C. F.; Nüsslein, K.; Tew, G. N. Synthetic Mimic of Antimicrobial Peptide with Nonmembrane-Disrupting Antibacterial Properties. *Biomacromolecules* **2008**, *9*, 2980−2983.
(23) Salomäki, M.; Kankare, J. Specific Anion Effect in Swelling of Polyelectrolyte Multilayers. *Macromolecules* **2008**, *41*, 4423−4428.
(24) Li, Y.; Wang, Y.; Huang, G.; Ma, X.; Zhou, K.; Gao, J. Chaotropic-Anion-Induced Supramolecular Self-Assembly of Ionic Polymeric Micelles. *Angew. Chem., Int. Ed.* **2014**, *53*, 8074−8078.
(25) Mason, P. E.; Neilson, G. W.; Dempsey, C. E.; Barnes, A. C.; Cruickshank, J. M. The hydration structure of guanidinium and thiocyanate ions: Implications for protein stability in aqueous solution. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 4557−4561.
(26) Heyda, J.; Okur, H. I.; Hladílková, J.; Rembert, K. B.; Hunn, W.; Yang, T.; Dzubiella, J.; Jungwirth, P.; Cremer, P. S. Guanidinium can both Cause and Prevent the Hydrophobic Collapse of Biomacromolecules. *J. Am. Chem. Soc.* **2017**, *139*, 863−870.
(27) Locock, K. E. S.; Michl, T. D.; Valentin, J. D. P.; Vasilev, K.; Hayball, J. D.; Qu, Y.; Traven, A.; Griesser, H. J.; Meagher, L.; Haeussler, M. Guanylated Polymethacrylates: A Class of Potent Antimicrobial Polymers with Low Hemolytic Activity. *Biomacromolecules* **2013**, *14*, 4021−4031.
(28) Chin, W. A macromolecular approach to eradicate multidrug resistant bacterial infections while mitigating drug resistance onset. *Nat. Commun.* **2018**, *9*, 917.
(29) Won, Y.-Y.; Meeker, S. P.; Trappe, V.; Weitz, D. A.; Diggs, N. Z.; Emert, J. I. Effect of Temperature on Carbon-Black Agglomeration in Hydrocarbon Liquid with Adsorbed Dispersant. *Langmuir* **2005**, *21*, 924−932.
(30) Cao, Z.; Gordiichuk, P. I.; Loos, K.; Sudhölter, E. J. R.; Smet, L. C. P. M. d. The effect of guanidinium functionalization on the structural properties and anion affinity of polyelectrolyte multilayers. *Soft Matter* **2016**, *12*, 1496−1505.
(31) Hunt, J. N.; Feldman, K. E.; Lynd, N. A.; Deek, J.; Campos, L. M.; Spruell, J. M.; Hernandez, B. M.; Kramer, E. J.; Hawker, C. J. Tunable, High Modulus Hydrogels Driven by Ionic Coacervation. *Adv. Mater.* **2011**, *23*, 2327−2331.
(32) Robison, A. D.; Sun, S.; Poyton, M. F.; Johnson, G. A.; Pellois, J.-P.; Jungwirth, P.; Vazdar, M.; Cremer, P. S. Polyarginine Interacts More Strongly and Cooperatively than Polylysine with Phospholipid Bilayers. *J. Phys. Chem. B* **2016**, *120*, 9287−9296.
(33) Hori, M.; Cabral, H.; Toh, K.; Kishimura, A.; Kataoka, K. Robust Polyion Complex Vesicles (PICsomes) under Physiological Conditions Reinforced by Multiple Hydrogen Bond Formation Derived by Guanidinium Groups. *Biomacromolecules* **2018**, *19*, 4113−4121.
(34) Ma, C. D.; Wang, C.; Acevedo-Vélez, C.; Gellman, S. H.; Abbott, N. L. Modulation of hydrophobic interactions by proximally immobilized ions. *Nature* **2015**, *517*, 347.
(35) Wang, C.; Ma, C.-K. D.; Yeon, H.; Wang, X.; Gellman, S. H.; Abbott, N. L. Nonadditive Interactions Mediated by Water at Chemically Heterogeneous Surfaces: Nonionic Polar Groups and Hydrophobic Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 18536−18544.
(36) Vazdar, M.; Heyda, J.; Mason, P. E.; Tesei, G.; Allolio, C.; Lund, M.; Jungwirth, P. Arginine "Magic": Guanidinium Like-Charge Ion Pairing from Aqueous Salts to Cell Penetrating Peptides. *Acc. Chem. Res.* **2018**, *51*, 1455−1464.
(37) Stanzl, E. G.; Trantow, B. M.; Vargas, J. R.; Wender, P. A. Fifteen Years of Cell-Penetrating, Guanidinium-Rich Molecular Transporters: Basic Science, Research Tools, and Clinical Applications. *Acc. Chem. Res.* **2013**, *46*, 2944−2954.

DOI: 10.1021/acsmacrolett.8b00824
ACS Macro Lett. 2019, 8, 117−122