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Salt-Screened Transition toward Bulk-Like Water Dynamics near Polymeric Zwitterions

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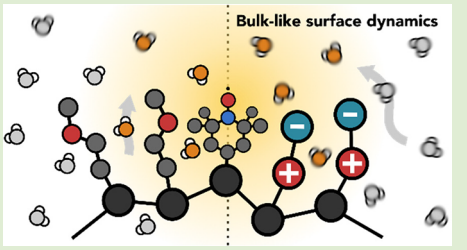
ABSTRACT: The superior antifouling performance of zwitterionic materials is commonly linked to their hydration structure, in which tight surface binding of water molecules inhibits solute adsorption. However, there is comparatively little direct experimental data on the hydration water structure and dynamics around zwitterionic moieties, including the longer-range behavior of the hydration shell that modulates the approach of solutes to the polymer surface. This work experimentally probes the dynamics of the diffusing hydration water molecules around a series of zwitterion chemistries using Overhauser dynamic nuclear polarization relaxometry. Surprisingly, water dynamics measured within ∼1 nm of the zwitterions were minimally inhibited compared to those near uncharged hydrophilic or cationic side chains. Specific dissolved ions further enhance the water diffusivity near the zwitterions, rendering the hydration shell bulk water-like. These results that the hydration of a zwitterion surface is nearly indistinguishable from bulk water suggest that these surfaces are "invisible" to biological constituents in a manner tunable by the ionic environment and the chemical design of the zwitterionic surface.



Polymeric zwitterions are a promising class of new materials defined by a stoichiometrically balanced set of positive and negative charges, tethered to a polymer backbone. The unique combination of high hydrophilicity and overall charge neutrality provides exceptional and nonspecific fouling resistance across a wide range of length scales appropriate for a diverse range of applications.[1−3] Ultralow protein binding makes these materials undetectable by the immune system, offering enhanced biocompatibility for implants and long-lasting drug formulations.[4,5] Sustained hydration, even in the presence of high salt concentrations, enables the design of environmentally benign marine antifouling coatings for ocean vessels.[6,7] Demonstrated high water permeability and metal ion selectivity in zwitterion functionalized membranes suggest potential for processing of industrial produced water streams.[8−10] The performance and design of zwitterionic materials for each of these applications is directly related to the modulation of ion-dipole interactions between the zwitterion and surface water molecules, which act as a thermodynamic barrier to foulant surface adsorption. Thus, understanding of the structure and dynamics of water molecules at the zwitterion surface is critical to the development of zwitterionic materials for targeted applications.

A growing body of literature attempts to understand the hydration behaviors of zwitterions but primarily probes only the structure of the closely bound surface water. Molecular dynamics simulations of zwitterions offer insights into the role of molecular design on water coordination number, water orientation, solvation correlation times, and hydrogen bonding character.[11−16] Experimental sum frequency generation (SFG) vibrational spectroscopy experiments[17−20] support these simulations, where enhanced SFG signal from zwitterionic surfaces indicates a net increase in the number of oriented water molecules at the interface, suggesting stronger hydration. Differential scanning calorimetry[21] and low-field nuclear magnetic resonance[22] further reveal that these surface waters are more tightly bound to zwitterionic polymers than uncharged hydrophilic polymers.

However, the current literature provides limited analysis of the role of the thermodynamic properties of water (i.e., enthalpic and entropic contributions) that would modulate the binding free energy of foulants.[11] To understand such solvation contributions to fouling susceptibility, local, but still collective properties of water near the zwitterionic sites must be examined to glean information about solvation thermodynamic properties. In fact, a series of experimental and computational studies of water near the surface of proteins and polymers have shown that water diffusion dynamics is an excellent proxy for the solvation thermodynamic properties of the same water population.[23−25] Furthermore, these studies have also shown that hydration dynamics are intimately related to the structural parameters of the hydrogen bond network and thus offer

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complementary insights into molecular ordering and interaction strength near a surface. How the ion-dipole interactions influence the local diffusion dynamics and structure of the network of water molecules near zwitterionic surfaces, however, has not been examined to date.

In this work, we quantify the translational diffusion of water molecules near hydrophilic and zwitterionic functional groups to better understand the fundamental differences in surface hydration of zwitterionic materials. Using a modular, sequence-defined polymer system, we directly compare the commonly studied sulfobetaine chemistry to hydrophilic ether and charged quaternary ammonium functionalities. The effect of molecular design on zwitterion hydration dynamics is probed through a series of zwitterionic side chain chemistries with varied cation charge delocalization. Water dynamics are measured over a range of salt concentrations and salt types to quantify the effects of free ion interactions in common application-relevant environments (Figure 1A).

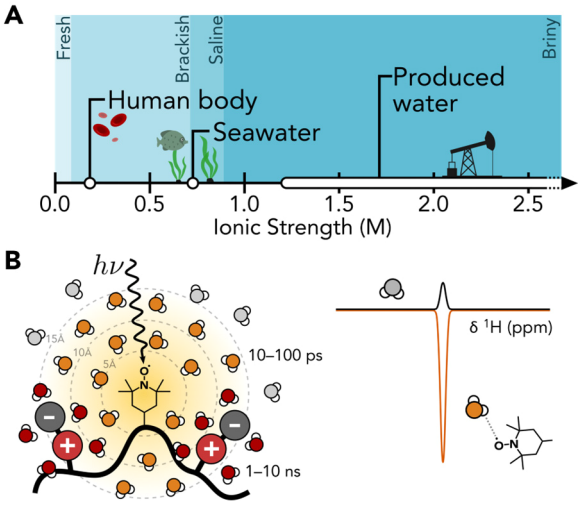


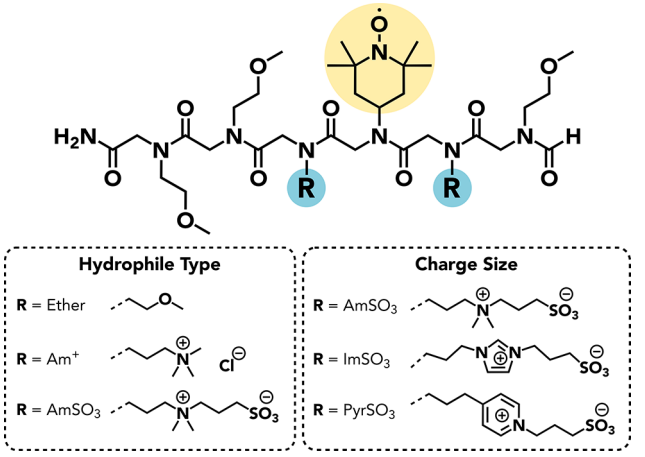
Figure 1. (A) Common applications of zwitterionic materials span a wide range of ion environments, requiring study of their interactions across this spectrum. (B) ODNP enhances the ^{1}H NMR signal of water molecules within 2−5 hydration shells of a free radical spin probe, enabling measurement of local water dynamics.

We employ Overhauser dynamic nuclear polarization (ODNP) relaxometry to measure water dynamics and interactions near the polymeric zwitterion surface. ODNP is a combined electron paramagnetic/nuclear magnetic resonance (EPR/NMR) technique that is unique in its ability to experimentally measure translational water diffusion within 5−15 Å (2−5 hydration shells) of a nitroxide-radical spin probe.[26] Studies have shown that ODNP captures the water dynamics determined by the local surface chemistry and curvature,[25,27,28] which are minimally affected by the presence of the nitroxide spin label. This is because the local diffusion dynamics are dictated by the cooperative effect of the local network of water, i.e., of water beyond the very first hydration shell. This technique has found notable use in the field of biophysics as a method to quantify heterogeneities in the surface hydration environment of proteins and nucleic acids, demonstrating the relationship of surface hydration to biomacromolecule function.[27,29,30] More recent application of ODNP to synthetic polymer systems provides important insights into the design of novel membrane materials with tunable catalytic activity and chemical surface patterning.[31−34]

In brief, ODNP utilizes magnetic dipolar cross-polarization between the saturated electron spin of a nitroxide label and the proton nuclear spins of nearby water molecules to quantify water motions on the time scale of the applied microwave radiation. At 9.8 GHz, ODNP measures the 10−100 ps time scale typical of bulk water's translational diffusion. These fast, bulk water motions (orange molecules in Figure 1B) are quantified through the relaxivity parameter k_σ, with larger values corresponding to faster dynamics and higher local water diffusivity relative to the spin probe. Combining ODNP measurements with separate T_1 relaxation measurements of the spin labeled and unlabeled polymer solutions provides a more comprehensive quantification of both the fast unbound (10−100 ps) and slower exchanging (1−10 ns) hydration dynamics through calculation of the coupling factor, ξ, which is commonly divided into specific regimes corresponding to different hydration environments.[35]

Solid phase synthesis of sequence-defined polypeptoids enables site-specific measurement of hydration dynamics local to the zwitterion side chains. This work utilizes 6-mer polypeptoids comprised of a centrally located TEMPO spin label (Scheme 1, yellow circle). The neighboring residues on

Scheme 1. Sequence-Specific Polypeptoids Chemistry Allows for Precise Placement of Functional Groups in Proximity of the Spin Probe, Enabling Study of Local Hydration Dynamics[a]



[a]Testing of different side chain chemistries provides insights into the unique behaviors of zwitterions and the role of charge size on zwitterionic water dynamics.

either side of the spin label (Scheme 1, blue circles) are functionalized with a pair of uncharged ether, cationic, or zwitterionic side chains. Placement of these functional groups directly adjacent to the TEMPO maximizes their effect on the local hydration environment measured by the spin probe. This design allows for direct comparison of the zwitterionic side chains to other common hydrophilic groups (uncharged ether and cationic Am+) as well as comparison of different zwitterion chemistries on hydration dynamics. The sulfobetaine ($AmSO_3$) zwitterion is chosen as a starting point due its widespread use in existing theoretical and experimental studies of zwitterionic materials.[7,12,17,22,36−38] The quaternary ammonium (Am+) chemistry closely mimics the structure of the

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sulfobetaine, minus the sulfonate anion, and is similarly popular among the antifouling and membrane literature.[39,40] The relatively short length of these polypeptoids minimizes larger conformational changes, allowing us to focus solely on the behavior of lone zwitterionic functionalities on the local water network. Recall that the ODNP technique captures the collective dynamics of the extended hydration shell around the spin label, as indicated in Figure 1B. Additional methoxyethyl glycine residues (labeled "ether" in Scheme 1) induce slower tumbling of the molecule, which simplifies the interpretation of ODNP water diffusion rates.[35,41,42]

As shown in Figure 2, comparison between the different hydrophile types indicates that water near zwitterions exhibit

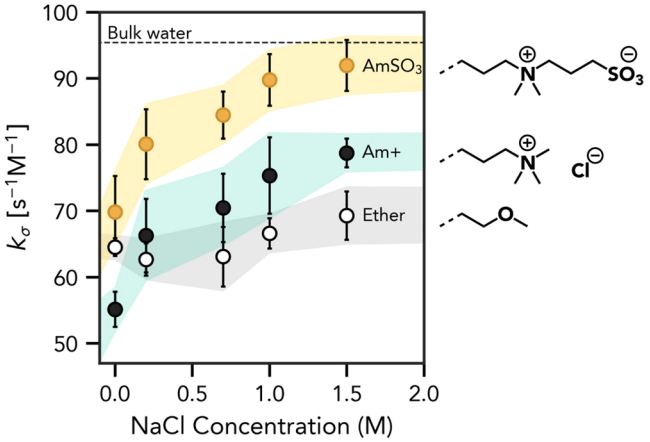

Figure 2. k_σ water dynamics near the cationic Am+ (black filled) and zwitterionic $AmSO_3$ (yellow) side chains are accelerated at high sodium chloride concentration, while the neutral ether (white) side chains are unaffected.

faster hydration dynamics. ODNP measurements of water near polypeptoids with uncharged hydrophilic (ether), cationic (Am+) and charge neutral zwitterionic ($AmSO_3$) functional groups were taken over a range of aqueous sodium chloride solutions from 0 to 1.5 M. At the low screening limit (I = 0 M), the strong ion-dipole interaction of the cationic sample slows the water diffusion dynamics of the local hydration shell, resulting in lower k_σ values relative to the ether control. In contrast, the zwitterionic sample shows significantly greater k_σ values (faster water dynamics) than the cationic sample and similar or even slightly faster dynamics than the ether control.

Differences in dynamics between the cationic Am+ and zwitterionic $AmSO_3$ likely originate from the different ordering of water near these moieties and interaction strengths between the side chains and water. Ether moieties are known to strongly interact with water (e.g., in poly(ethylene oxide)) with the water hydrogen facing toward the polymer surface, while water tend to be oriented with its oxygen toward the tertiary ammonium surface moieties. In contrast, water in the hydration shell of the zwitterionic groups would resist a simple unidirectional ordering given that it must adopt different orientations of water near the spatially proximal oppositely charged groups of the zwitterion that are embedded within a system subject to dynamic conformational changes. The proximity of the oppositely charged cation and anion in the zwitterion may further lead to self-screening of each charge's respective electric field. This effect creates a fundamentally sharper, r^{-3} decay (dipole−dipole interaction) in the pair potential with nearby water molecules compared to the r^{-2} decay of a purely ionic interaction with water, as experienced near the cationic Am+.[43] The longer-range interactions of the cationic Am+ hence slow water diffusion within the hydration shell more effectively relative to near the zwitterion.

The nearly indistinguishable dynamics of the $AmSO_3$ and ether functionalities in pure water (I = 0 M) are more interesting, as the large dipole moment of the zwitterion yields stronger interactions with nearby water molecules than the ether sample. Comparable, and slightly faster k_σ values for $AmSO_3$ counter expectations based on binding strength alone as rationalized by differences in the side chains' expected dipole moments. This may therefore suggest differences in hydration structure around the zwitterionic versus ether side chains which facilitate water diffusion. Indeed, recent molecular dynamics simulations provide additional nuances to zwitterion-water interactions, indicating an increase in icosahedral hydration structure relative to bulk water that is counter to changes in local water structure around uncharged, polar solutes.[16] Such increases in icosahedral structure (and reduction in tetrahedral water structure) are linked to increased water diffusivity caused by disruption of the hydrogen bond network relative to the uncharged functional groups.[24] Agreement with this ODNP result thus supports the theory that zwitterions alter the hydrogen bond structure of water at the surface at all ionic strengths.

At the high ionic strength limit (I = 1.5 M), interactions with salt ions compete with those between the charged polymer side chains ($AmSO_3$ and Am+) and surrounding water molecules, leading to increased translational mobility. For the $AmSO_3$ sample specifically, k_σ dynamics closely approach those of bulk water, which is rare in ODNP studies, and has only been observed near DNA surfaces.[29] In contrast, the dynamics of the uncharged ether sample minimally changes with ionic strength (adopting values that are largely within error). The interactions between free Na^+ and Cl^- ions and the tethered charges are significantly stronger than the interactions with water molecules, suggesting the formation of transient ion contact pairs with charged side chains which may weaken their impact on water motion. Indeed, chloride ions are known to selectively pair with chemically similar protein surfaces due to their low water affinity, aiding protein assembly and crystallization.[44] 1.5 M NaCl also exceeds the overlap concentration of the individual ions' first hydration shells.[45] At such high salt concentrations, it is likely that overlapping and transient electric fields of the free ions will disrupt the structure of the charged polypeptoids' hydration layers, further contributing to the increased dynamics observed in Figure 2 for both $AmSO_3$ and Am+ functionalities.

Simulations and experimental antifouling assays of polymeric zwitterions show that molecular design can further influence application-specific performance.[11−14,17,20,36,46−48] Most notably, Jiang et al. identified that shorter distances between the cation and anion maximize protein fouling resistance and salt resistance, which has been hypothesized to be related to a balance between water binding and salt ion interactions with the zwitterions.[11,20] Similarly, zwitterion charge volume has been linked to water coordination number,[12,49] which is an important factor in marine antifouling performance.[18]

The ODNP-derived water dynamics around a series of zwitterions with increasing cation charge delocalization ($AmSO_3$, $ImSO_3$, and $PyrSO_3$) indicate that more diffusely charged cations dampen the influence of sodium chloride salt

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screening on water diffusion (Figure 3). Indeed, while the smallest alkylammonium zwitterion ($AmSO_3$) approaches bulk

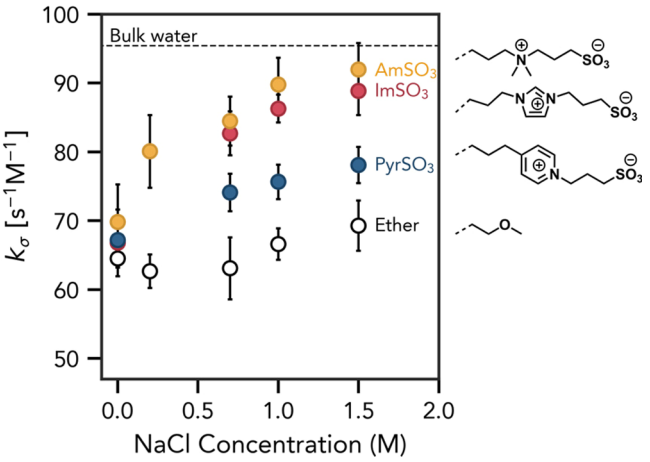

Figure 3. Larger, more diffuse zwitterions exhibit smaller changes in local water dynamics with increasing sodium chloride concentration.

water dynamics at high ionic strength, the bulkier pyridinium zwitterion ($PyrSO_3$) shows a relatively modest increase and more closely resembles the uncharged ether control.

We hypothesize that differences between the zwitterion types are a result of varied strength in ion pairing between dissolved salt ions and the tethered zwitterions, which in turn modulate water-zwitterion interactions. Dissolved ions are known to selectively interact and pair with counterions of similar hydration enthalpies to form stronger ion pairs, as evidenced by their reduced solubility in water.[44] Selective ion pairing between the charges of the zwitterion and dissolved ions may hence further reduce the effective charges of the zwitterion, shrinking the zwitterion dipole moment and water binding strength.

Water dynamics near these different zwitterions are strongly sensitive to dissolved ion identity but notably do not follow the Hofmeister or lyotropic series.[50] Additional ODNP measurements were made on the $AmSO_3$ and $PyrSO_3$ zwitterions, replacing either the Na^+ or Cl^- ions with the more weakly hydrated ClO_4^- or more strongly hydrated SO_4^{2-} and Mg^{2+} ions, maintaining a constant ionic strength of 0.7 M.[50] As shown in Figure 4, the ordering of the zwitterion types is highly salt dependent, although there is no trend matching the solvation properties of the ions. In both $NaClO_4$ and Na_2SO_4, the more diffuse $PyrSO_3$ zwitterion shows faster k_σ dynamics than $AmSO_3$, a reversal from the behavior in aqueous NaCl. The faster dynamics are potentially related to increased zwitterion-salt pairing, which may weaken water-zwitterion interactions, resulting in more bulk-like water dynamics. The exact mechanism of this effect is unclear, but it is remarkable that the choice of dissolved ion species, in this case $NaClO_4$ or Na_2SO_4 salt, renders the dynamics, structure, and presumably thermodynamic property of hydration water around the diffuse $PyrSO_3$ zwitterion side chains indistinguishable from or very close to bulk-like water dynamics.

Zwitterion selectivity toward specific ion types has previously been reported in simulations and experiments.[10,36] Further study of salt interaction effects on water dynamics is necessary to potentially use zwitterionic groups as powerful tools to mitigate salt screening and provide improved ion selectivity in separation processes.[10]

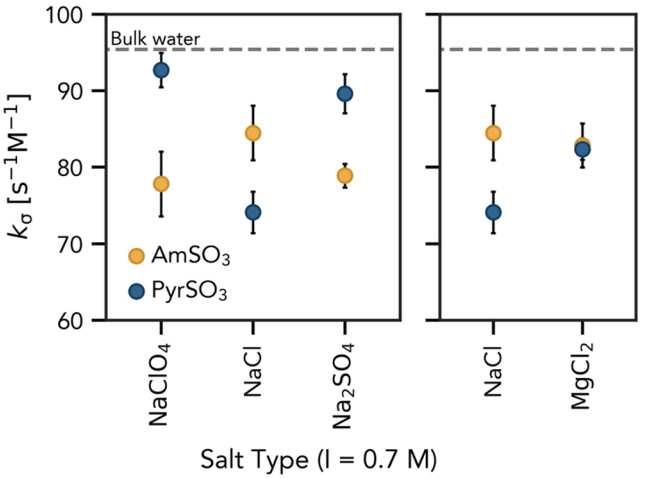

Figure 4. Zwitterions with different cation sizes show opposing trends in water dynamics in different aqueous salt solutions. Changes in water dynamics are not linked to expectations from the Hofmeister series. The salts are ordered by anion (left) and cation (right) hydration enthalpies.[46]

Another NMR parameter, the coupling factor ξ, for the hydration shell of the different peptoid chemistries studied here (Figure 5) can further quantify the weakening interactions

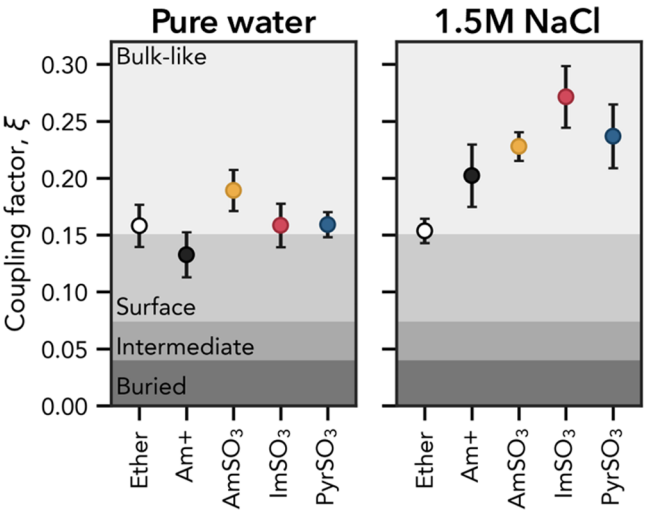

Figure 5. At all salt conditions, both the zwitterionic and uncharged peptoids exhibit near-bulk water dynamics. Increasing ionic strength accelerates dynamics of the charged polymers through screening of ion−dipole interactions.

and fast dynamics of water near salt screened polypeptoids. The k_σ derived water dynamics capture only the fast, picosecond time scale of freely diffusing water molecules near a surface. The ODNP coupling factor on the other hand offers a more comprehensive view of hydration dynamics by accounting for both the freely diffusing water and slower, exchanging, waters at the surface. For all four charged side chains, the addition of aqueous sodium chloride leads to an increase in the coupling factor toward more bulk-like hydration behavior, consistent with the faster k_σ dynamics observed (see Figures 2 and 3). Meanwhile, the uncharged ether sample remains unaffected by salt concentration, but still shows highly dynamic hydration water that is slower than water near other

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zwitterionic groups within the bulk-like regime. Deeper interpretation of coupling factor values and differentiation between charged chemistries is complicated by the fast rotational dynamics of these relatively short polymers (see SI for discussion of the ODNP parameter, k_{low}, for these samples).

To conclude, the application of Overhauser dynamic nuclear polarization spectroscopy allowed us to characterize the diffusion dynamics of water hydrating short zwitterionic polypeptoids over a range of relevant saline environments. This led to our discovery of fast, bulk-like, water diffusion that is accentuated at high salt concentration owing to charge screening effects, in a highly ion-specific manner. At low ionic strengths (closer to physiological conditions), zwitterions possess similar dynamics to uncharged side chains, indicative of moderate interactions with nearby water molecules compared to cationic side chains. At the high salt limit (marine and industrial brine conditions), significant charge screening accelerates water diffusion, resulting in bulk-like water dynamics near the polymer surface decorated with zwitterionic groups. The increase in dynamics is demonstrated both by near-bulk k_σ values and an increase in the overall coupling factor for all charged polypeptoid samples considered here. The water dynamics near different zwitterions show strong sensitivity for the size and/or charge density of the zwitterion groups, as well as toward dissolved ion identity, providing a practical and sensitive handle to tune water's dynamical and thermodynamic property at zwitterion-water interfaces. While one can speculate that a surface that gives rise to bulk-like water dynamics will be the least immunogenic, what kind of surface water property is ideal for antifouling is not clear and requires further studies. However, the ability to tune water dynamics over a wide range offers the opportunity to optimize zwitterionic materials for the specific ionic environment and performance metrics of a given application.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.4c00347.

Experimental methods for small molecule and polypeptoid synthesis/characterization, ODNP sample preparation, ODNP data collection, and further ODNP analysis (PDF)

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Author Contributions

CRediT: **Shawn Mengel** conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing-original draft, writing-review & editing; **Audra J DeStefano** conceptualization, formal analysis, methodology, supervision, writing-review & editing; **Thomas R. Webber** methodology, resources, software, validation, writing-review & editing; **Anton Semerdjiev** investigation; **Songi Han** methodology, resources, software, supervision, writing-review & editing; **Rachel A. Segalman** conceptualization, funding acquisition, project administration, resources, supervision, writing-review & editing.

Notes

The authors declare no competing financial interest.

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