Ionization behavior of nanoporous polyamide membranes

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Edited by Matthew V. Tirrell, The University of Chicago, Chicago, IL, and approved October 8, 2020 (received for review April 30, 2020)

Escalating global water scarcity necessitates high-performance desalination membranes, for which fundamental understanding of structure–property–performance relationships is required. In this study, we comprehensively assess the ionization behavior of nanoporous polyamide selective layers in state-of-the-art nanofiltration (NF) membranes. In these films, residual carboxylic acids and amines influence permeability and selectivity by imparting hydrophilicity and ionizable moieties that can exclude coions. We utilize layered interfacial polymerization to prepare physically and chemically similar selective layers of controlled thickness. We then demonstrate location-dependent ionization of carboxyl groups in NF polyamide films. Specifically, only surface carboxyl groups ionize under neutral pH, whereas interior carboxyl ionization requires pH > 9. Conversely, amine ionization behaves invariably across the film. First-principles simulations reveal that the low permittivity of nanoconfined water drives the anomalous carboxyl ionization behavior. Furthermore, we report that interior carboxyl ionization could improve the water–salt perme selectivity of NF membranes over fourfold, suggesting that interior charge density could be an important tool to enhance the selectivity of polyamide membranes. Our findings highlight the influence of nanoconfinement on membrane transport properties and provide enhanced fundamental understanding of ionization that could enable novel membrane design.

Significance

Novel membrane processes and materials are needed to combat global water scarcity. The advancement of membrane materials for water purification processes such as desalination is hindered by our limited understanding of structure–property–performance relationships. We address this knowledge gap by elucidating the mechanisms which govern the ionization behavior of nanoporous polyamide films and their influence on membrane performance. Polyamide ionization is key to enhancing the separation efficiency of charged constituents in aqueous solutions. Our results illustrate that a large portion of the ionizable moieties in polyamide films remain uncharged during typical operation due to extreme confinement effects, thus going unutilized. Complete ionization of state-of-the-art polyamide membranes offers selectivity improvements that could markedly improve desalination process efficiency.

Author contributions: C.L.R., J.R.W., and M.E. designed experimental research; H.J.K. carried out computational research; C.L.R., J.R.W., and M.E. analyzed data; C.L.R., M.W., and Z.Y. wrote the paper; and C.L.R., J.R.W., H.J.K., and M.E. edited the manuscript.

The authors declare no competing interest.

This article is a PNAS Direct Submission.

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This article contains supporting information online at https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2008421117/-/DCSupplemental.

First published November 12, 2020.

www.pnas.org/cgi/doi/10.1073/pnas.2008421117
will ionize during membrane operation. Given the paramount importance of charge density in membrane performance, gaining a fundamental understanding of R-COOH ionization could have vast implications on membrane operation, nanofluidic modeling, and novel membrane design.

In this work, we characterize the location-dependent charge density of nanoporous polyamide membranes and the impact of charge density on separation performance. Our analysis focuses on NF membranes, as Donnan exclusion generally plays a greater role in their performance than in RO membranes. To control film thickness, we extend the layered interfacial polymerization (LIP) technique to pipazine (PIP)-based polyamide TFC membranes, the state of the art for NF. Characterization of these films using the silver-binding method confirms the location-dependent behavior of R-COOH ionization in nanoporous polyamide films. We experimentally investigate the mechanisms governing R-COOH ionization behavior (i.e., local proton concentration or dielectric constant phenomena) and pair these insights with molecular dynamics (MD) simulations and density functional theory (DFT) to validate the mechanism behind the anomalous ionization behavior. We then evaluate the roles of fixed charged groups on the surface and within the film toward water–salt selectivity in NF. Finally, we assess the implications of our results for modeling nanofluidic transport through polyamide thin films, highlighting the intricate role of nanoconfinement effects and introducing opportunities for future membrane design.

**Results and Discussion**

**LIP to Control Polyamide Film Thickness.** We prepared several nanofilms of varying thickness (δ), with similar surface characteristics, to isolate changes in the interior R-COOH content, thus allowing direct comparison between the ionization behavior of R-COOH located on the surface and within the film. The validity of this technique holds only if physical—and chemical—similarity is preserved between the films, including the nanoporous structure. To accomplish this, we implemented an LIP technique to fabricate and compare PIP-based polyamide TFC membranes of varying thickness (Fig. 1A and Materials and Methods). Polyamide films fabricated by LIP are expected to maintain similar physicochemical characteristics, as the same surface conditions are maintained.

Several techniques were used to characterize the polyamide films in an effort to validate the effectiveness of LIP. Depth profiles were measured via atomic force microscopy (AFM) of LIP-based polyamide films isolated on silicon wafers, with the selective layer of commercial NF270 membranes (DuPont Water) included for comparison (Fig. 1B and SI Appendix, Fig. S1). Selective layers for NF270 are formed by interfacial polymerization of PIP and trimesoyl chloride (TMC), suggesting similar chemistry as the LIP membranes. We found that the film thicknesses of the LIP membranes grew proportionally with the thicknesses of the LIP membranes increasing from 25.5 ± 1.3 nm to 13.2 ± 1.1 nm (Fig. 1C). The separation of the interior R-COOH content, thus following (19)

\[ J_w = A(\Delta p - \Delta \pi) = \frac{p_l^w}{\delta}(\Delta p - \Delta \pi), \]

where \( J_w \) is the water flux and \( \Delta p \) and \( \Delta \pi \) are the hydraulic and osmotic pressure differences across the membrane, respectively. The \( P^w_l \) of the LIP membranes were obtained by normalizing permeance by their respective thicknesses (Fig. 1H). A \( P^w_l \) of 0.11 ± 0.02 L mm⁻² h⁻¹ bar⁻¹ was determined from fitting Eq. 1, which is roughly 10-fold greater than the permeability of m-phenylenediamine (MPD)-based polyamide nanofilms (SI Appendix, Table S1) suggest that similar porous structures. To assess \( P^w_l \) we measured the pure water permeability, or water permeance (\( A \)), of our LIP and NF270 membranes with a pressure-driven, cross-flow filtration system (Fig. 1G). We find \( A \) is inversely proportional to the selective layer thickness (i.e., \( A \propto 1/\delta \)), thus following (19)

\[ J_w = A(\Delta p - \Delta \pi) = \frac{p_l^w}{\delta}(\Delta p - \Delta \pi), \]

where \( J_w \) is the water flux and \( \Delta p \) and \( \Delta \pi \) are the hydraulic and osmotic pressure differences across the membrane, respectively. The \( P^w_l \) of the LIP membranes were obtained by normalizing permeance by their respective thicknesses (Fig. 1H). A \( P^w_l \) of 0.11 ± 0.02 L mm⁻² h⁻¹ bar⁻¹ was determined from fitting Eq. 1, which is roughly 10-fold greater than the permeability of m-phenylenediamine (MPD)-based polyamide nanofilms (16). MPD-based chemistry produces less permeable polyamide membranes than PIP-based films due to a tighter porous structure, which also yields substantially higher water–salt selectivity (20).

The constant water permeability, in conjunction with the precisely controlled film growth and similar pore size estimated by HTM, suggests that the deposited polyamide layers are similar from a chemical structure perspective. We note that this does not imply isotropic conditions throughout the films, as heterogeneities across each layer are still possible (6). Given our limited ability to characterize the porous structure beyond these techniques, similar porous structures of the LIP membranes, although likely, are not definite. NF270, on the other hand, displayed a significantly higher \( P^w_l \) of 0.27 ± 0.02 L mm⁻² h⁻¹ bar⁻¹. The difference in \( P^w_l \) between commercial NF270 and the hand-cast LIP membranes is likely the result of optimized manufacturing conditions of the active and support layers of NF270.
Differentiating Surface- and Interior-Based Carboxyl Groups. Exploiting LIP to fabricate physically and chemically similar polyamide films of controlled thickness enables us to compare surface and interior R-COOH ionization. When comparing LIP membranes, surface R-COOH should remain roughly constant while interior R-COOH should scale linearly with film thickness (Fig. 2A). If the proposed interpretation for R-COOH ionization is correct—where \( pK_{a,1} \) represents R-COO\(^-\) on the surface and \( pK_{a,2} \) represents R-COO\(^-\) throughout the entire film (i.e., surface and interior)—then only R-COO\(^-\) associated with \( pK_{a,2} \) should scale with thickness, while R-COO\(^-\) associated with \( pK_{a,1} \) would be independent of film thickness. Therefore, quantifying R-COO\(^-\) with respect to solution pH for films of varied thickness will enable us to either validate or disprove this interpretation.

To quantify R-COO\(^-\) throughout our LIP membranes, we bound and eluted silver ions, which were then quantified by inductively coupled plasma mass spectrometry (ICP-MS) (4). The R-COO\(^-\) content of NF270 was also quantified for comparison. Areal R-COO\(^-\) densities of the polyamide films (Fig. 2B), fitted by Eq. 2 found in Materials and Methods, illustrate two important findings for LIP membranes: 1) areal R-COO\(^-\) densities associated with \( pK_{a,1} \) are low (0.3 to 0.9 sites per nm\(^2\)) and differences are statistically insignificant (one-way ANOVA, \( \alpha = 0.05 \)) and 2) areal R-COO\(^-\) density associated with \( pK_{a,2} \) increases significantly for thicker polyamide films, increasing from 6.9 to 23.6 sites per nm\(^2\) for 1L to 5L PIP membranes, respectively. Complete R-COO\(^-\) ionization is captured by a multi-\( pK_a \) model (Fig. 2D), which represents the superposition of the single-\( pK_{a,1} \) and \( pK_{a,2} \) models. The single-\( pK_{a,1} \) fits for areal R-COO\(^-\) densities (dotted lines) overlap one another, indicating that R-COO\(^-\) densities associated with \( pK_{a,1} \) are independent of film thickness. Conversely, the single-\( pK_{a,2} \) fits for R-COO\(^-\) densities (dashed lines) illustrate a distinct thickness dependence. This is exemplified by directly comparing experimental R-COO\(^-\) densities associated with \( pK_{a,1} \) and \( pK_{a,2} \) (Fig. 2F). R-COO\(^-\) densities associated with \( pK_{a,2} \) were isolated by subtracting out the contribution of R-COO\(^-\) found at pH 7 (i.e., all R-COO\(^-\) connected to \( pK_{a,1} \)) from the total R-COO\(^-\) density at pH 10.5. In this case, areal R-COO\(^-\) densities correlating with \( pK_{a,2} \) scale proportionally to film thickness, while the R-COO\(^-\) ionized at \( pK_{a,1} \) remain relatively unchanged. Further normalizing \( pK_a \)-specific areal R-COO\(^-\) densities by film thickness highlights that the LIP membranes have
for the separate ionization behavior of nanoporous polyamide films, verifies that the thickness-normalized active charge state of the membrane, as a function of pH for LIP membranes and NF270. (D) Impact of increased thickness on R-COO\(^{-}\) fitting. As illustrated for 1L and 5L PIP samples, increased thickness increases the \(pK_a\) intensity, while \(pK_a\) intensity remains constant. (E) Relative change in areal (Top) and volumetric (Bottom) R-COO\(^{-}\) densities with respect to membrane thickness for groups associated with the membrane surface (\(pK_a,1\)) and interior (\(pK_a,2\)). Interior R-COO\(^{-}\) density was determined by subtracting the surface R-COO\(^{-}\) density, measured at pH 10.5, from the total R-COO\(^{-}\) density, measured at pH 10.5. (F) Change in zeta potential with respect to pH for LIP membranes and NF270. All error bars represent one SD.

Membrane zeta potential was evaluated by streaming potential measurements (Materials and Methods) as another indicator of surface charge. Although this method does not provide a quantitative charge density, it captures the relative ionization state at the membrane surface (21). Thus, zeta potential is useful for comparing the surface charge of different membranes. At \(pK_a,1\) (i.e., pH 5), the zeta potentials of the LIP membranes closely overlap, while NF270 exhibits a much greater negative charge (Fig. 2F). This behavior mirrors trends for \(pK_a,1\) in Fig. 2B and corroborates our previous finding: \(pK_a,1\) is independent of film thickness. We also note the appearance of a second \(pK_a\) located around pH 9, which indicates that a small amount of interior R-COO\(^{-}\) contributes to the streaming potential measured at high pH (detailed analysis is provided in SI Appendix, Fig. S5).

Our analysis of LIP membranes, which exemplifies the unique ionization behavior of nanoporous polyamide films, verifies that the separate \(pK_a\) values distinguish surface and interior R-COO\(^{-}\). In other words, the thickness dependence of R-COO\(^{-}\) ionization at \(pK_a,2\), paired with the unchanging ionization behavior at \(pK_a,1\), strongly supports the location-dependent interpretation behind R-COO\(^{-}\) ionization—\(pK_a,1\) represents only surface R-COO\(^{-}\), whereas \(pK_a,2\) represents all R-COO\(^{-}\) throughout the film. Following this framework, comparison of the two \(pK_a\) populations for NF270 with LIP membranes shows comparable volumetric densities of interior R-COO\(^{-}\) (Fig. 2E). In contrast, the surface of NF270 is far more carboxyl-rich than the LIP membranes (Fig. 2E). Disparity between surface R-COO\(^{-}\) densities may be the result of additional posttreatment techniques during NF270 fabrication to enhance surface charge (22).

Shift in \(pK_a\) is Mainly due to Lower Dielectric Constant within Polyamide Pores. Ionization of the functional groups present in polyamide networks formed from PIP-based chemistry depend on local conditions of the pores. In particular, the local proton concentration and dielectric constant of a hydrated polymer matrix play critical roles in the ionization of weak-acid functional groups such as R-COO\(^{-}\) (23, 24). Disparity between local conditions (i.e., proton concentration or dielectric constant) within a pore and the bulk solution can shift the observed \(pK_a\) of functional groups positioned in the pores. The local proton concentration phenomenon is classically observed for ion exchange (IEX) resins at low ionic strength, where the proton concentration within the pores is higher than the bulk solution as protons act as counterions to satisfy electroneutrality (23). The increase in local proton concentration within a negatively charged pore can be further exacerbated by confinement effects (25). Extreme confinement may also influence dielectric interactions. Theoretical analyses of dielectric phenomena influencing ion transport indicate that confined charged groups fixed to dielectric walls have stronger electrostatic interactions with available counterions than in the bulk (26). Thus, a substantial decrease in local permittivity makes it less favorable for ionogenic groups to dissociate as their electrostatic charge is less readily stabilized by their surroundings (26, 27).

The presence of local proton concentration effects can be assessed by modulating the ionic strength of the solution (23). The addition of a salt which can penetrate the pore results in the
The appearance of two \( pK_a \) values in TFC polyamide membranes. We investigated the possibility of confinement-induced dielectric effects on the ionization of R-COOH by MD simulations and DFT as described in Materials and Methods. In particular, we applied MD simulations to assess the effect of nanoconfinement by a low-permittivity medium on the local dielectric constant of water. Several water models (e.g., SPC/E, SPC/Fw, and TIP4P/\( \varepsilon \)) were used to simulate water clusters and interactions, calculating the dielectric constant from the fluctuation in the water dipole moment along the MD trajectory (Eq. 4). Using this method, we calculated dielectric constants for bulk water that ranged from roughly 71 to 82, which is in good agreement with its measured value (\( \varepsilon_{\text{water}} \approx 78.2 \)) and validates our protocol for computing dielectric constants (Fig. 3C).

To induce confinement effects representative of the membrane pore, we constrained the water molecules by cylindrically shaped potential walls with a diameter of 2 nm (SI Appendix, Figs. S7 and S8). Constraining water by harmonic potential boundaries represented the simplest route to achieve the purpose of this simulation, namely, to demonstrate the intrinsic influence of confinement on the local dielectric constant of water (details in SI Appendix). The simulation was allowed to reach steady-state conditions (6 ns). An evident decrease in the dielectric constant of water from its bulk value was observed (Fig. 3C), as the confined water molecules displayed a dielectric constant approximately twofold less than bulk water (\( \varepsilon \approx 30 \) to 37). These simulations support the ability of a low-permittivity medium, such as polyamide (\( \varepsilon \approx 3 \)) (7), to reduce the local dielectric constant of water upon extreme confinement. For comparison, previous experimental characterization and transport modeling of polyamide NF
membranes found dielectric constants within the membrane pores to be 20 to 50, loosely matching our simulation results (7, 28).

DFT was then applied to evaluate the role of the intermediate dielectric constant in the ionization of semiaromatic polyamide-based R-COOH. To reduce the complexity of modeling a highly cross-linked polymer network, we selected 3,5-dicarbamoylbenzoic acid as a truncated molecular model of polyamide to study R-COOH ionization. We modeled the ionization of our R-COOH analog via DFT in solvents of varying dielectric constant and then corrected the calculated pK_a values based on experimental values of benzoic acid (Fig. 3D and Materials and Methods). We observed a notable increase in the corrected pK_a values of 3,5-dicarbamoylbenzoic acid experiencing lower dielectric constant, corroborating the viability of a dielectric-driven mechanism behind the upward shift in R-COOH pK_a.

Our theoretical simulations of a polyamide-based R-COOH analog suggest a possible mechanistic framework behind the ionization behavior of nanoporous polyamide films (Fig. 3E). Bulk water presents a favorable medium for R-COOH ionization, where highly polarizable water molecules can readily stabilize the electrostatic charge of R-COO− at neutral pH. However, extreme confinement induces ordering of water molecules that reduces their ability to polarize and thus decreases their dielectric constant (29). This confinement-based phenomenon has been observed in other areas of study, including polyelectrolyte interactions (30), protein electrostatics (31), and solid-state nanofluidics (29). The added difficulty for confined water—exhibiting a low local dielectric constant—to stabilize excess electrostatic charge is of particular importance in these subject areas as it can influence the structural and thermodynamic properties of the system as well as ion interactions. Relevant to our study, the lower local dielectric constant consequently increases the pK_a of R-COOH within single-digit nanopores. For nanoporous polyamide membranes, only R-COOH groups experiencing bulk water conditions are expected to ionize at neutral pH. R-COOH located in large pores >>2 nm or on the surface of the membrane would satisfy these conditions. However, considering that polyamide NF membranes comprise pores almost solely below 2 nm (32), the latter case is more tenable.

**Ionization of Piperazine-Based Amine Groups.** Similar to R-COO−, positively charged amine groups can impart hydrophilicity and influence electrostatic interactions between the membrane and charged constituents in the aqueous solution. Therefore, it is important to understand amine ionization when considering water and ion transport across nanoporous polyamide films. To our knowledge, the amine content and ionization of polyamide films has been quantitatively addressed in just one study (13). In this study, tungstate (WO_4^{2−}) was used as a probe to quantify ionized amine groups in fully aromatic polyamide NF and RO membranes (13), revealing a pK_a of ~4.1 (characteristic of aniline) and a low density relative to carboxylic groups.

WO_4^{2−} is not an ideal probe for polyamide films, including PIP-based NF membranes, as it is a large ion that may not be able to access many R_2-NH_2^+ sites within the membrane. Furthermore, the stoichiometric binding ratio between an ionized amine and the divalent WO_4^{2−} is unclear, making it difficult to interpret data. Therefore, to quantify R_2-NH_2^+ in our membranes, we employed DFT calculations to predict which monovalent anions would express the most favorable binding (Fig. 4A). Binding favorability was quantified by the binding enthalpy (ΔH) between the anion and acetylated piperazine (Ace-PIP), which we selected as the molecular analog for R_2-NH_2^+ in polyamide films. DFT revealed metaborate (BO_3^−) binds the most favorably with Ace-PIP; however, due to the tendency of metaborate’s conjugate acid to form metabolic acid, BO_3^− was considered unsuitable for quantifying R_2-NH_2^+ over a wide pH range. As such, bromide (Br^−) was selected as the most suitable counterion for probing R_2-NH ionization. The same bind-and-elute technique used for determining R-COO− content was adopted here but with slight modifications (Materials and Methods).
Fig. 5. Influence of R-COOH and R2-NH ionization on membrane swelling and performance. (A) Change in the pure water permeability coefficient and swelling of NF270 with respect to solution pH (Top). Starting from pH 7, the solution pH was decreased to pH 3.5 by HCl addition before being incrementally increased to pH 10.5 by NaOH. Swelling of the polyamide layer, which was quantified by the relative change in wet film thickness compared to the dry film, can be ascribed to the (de)ionization of R-COOH and R2-NH throughout the membrane (Bottom). (B and C) Dependence of solute rejection on the number of sequential PIP layers and pH for (B) 2 mM and (C) 20 mM NaCl feed solutions. Measurements for all feed solutions were collected under a constant water flux ($J_w = 10$ L m$^{-2}$ h$^{-1}$) to mitigate differences in concentration polarization between membranes of varying permeability. (D and E) Increase in salt resistance, taken as the inverse salt permeance (i.e., $B^{-1}$), related to ionization of interior R-COOH groups at (D) 2 mM and (E) 20 mM NaCl. Results are based on measurements found in B and C. The interior volumetric R-COO$^{-}\$ density was determined by subtracting the surface R-COO$^{-}\$ density, measured at pH 7, from the ionized R-COO$^{-}\$ densities measured above pH 7. Salt resistances were normalized to the salt resistance at pH 7 ($B_0^{-1}$) to assess the sole influence of interior R-COO$^{-}\$ on salt transport. All error bars represent one SD.

Areal R$_2$NH$^+$ densities of the LIP and NF270 membranes illustrate single-pK$_a$ (pK$_a$ $\approx$ 9.5) ionization of R$_2$-NH (Fig. 4B), similar to that of the simple analog piperidine (pK$_a$ of $\sim$11). The lack of multiple pK$_a$ values suggests that the difference observed between the ionization of surface and interior R-COOH does not hold for R$_2$-NH. In this case, R$_2$-NH$^+$ densities would be representative of the total R$_2$-NH content (i.e., surface and interior). The roughly constant value for Br$^{-}$ uptake below pH 7 also suggests that the counterion probe is associating with ionized amine groups rather than being cosorbed alongside protons, as has been recently proposed for fully aromatic polyamides (33–35). If proton uptake was the predominant means by which Br$^{-}$ was associated into the membrane, one would instead expect an exponential increase in Br$^{-}$ uptake as pH decreases.

We find consistently less total R$_2$-NH than R-COOH in LIP membranes, which is expected for polyamide films (20, 36). The disproportionating swelling between total R$_2$-NH content and film thickness in our LIP membranes likely stems from the grouped contributions of surface and interior R$_2$-NH$^+$.

Results from Fig. 4B imply that decrements to the local dielectric constant within the polyamide pore have negligible effect on the charge stability of R$_2$-NH$^+$. DFT calculations on the ionization of Ace-PIP in solvents of varying dielectric constant support this notion (Fig. 4D). Specifically, the projected increase (rather than a decrease) in the pK$_a$ of Ace-PIP at lower dielectric constants indicates that lower-permittivity media do not inhibit R$_2$-NH ionization. In other words, Ace-PIP can remain ionized over a wide pH range—regardless of its dielectric environment. This theoretical insight reinforces the notion that R$_2$-NH ionization behavior for varying pH is similar across the film thickness (Fig. 4E).

Influence of Ionization on Membrane Performance. The added hydrophilicity and exclusion of coions that coincide with R-COOH and R$_2$-NH ionization are inextricably linked with membrane performance. The enhanced hydrophilicity of ionized groups typically increases water uptake by the polymer matrix, leading to swelling and increased water permeability (19). In general, polymers that absorb more water also absorb more salt, leading to a permeability–selectivity trade-off where higher water permeability comes at the cost of reduced water–salt selectivity (37). The swelling behavior of polyamide thin films was previously reported to be pH-dependent (38), but this was largely based on the comparison of just two data points. The bulk of membrane research still lacks a thorough investigation into the pH-dependent swelling behavior of polyamide thin films and its subsequent influence on membrane performance.

Feed solution pH should only influence the ionization of fixed functional groups throughout the film. Therefore, interpreting the effect of pH from an ionization perspective is reasonable. We assessed the effect of pH—and consequently membrane charge—on the swelling and water permeability of NF270 (Fig. 5A). We find the observed trends in water permeability coincide remarkably well with
the swelling of the NF270 selective layer, measured by comparing nanofilm thickness in liquid water with thickness in air (Fig. 5A). Our data suggest that polyamide swelling can be interpreted by breaking R-COOH and R₂-NH ionization into three stages: 1) pH <5, 2) pH 5 to 9, and 3) pH >9. In the first stage (pH <5) there is no change in R₂-NH ionization (i.e., all are R₂-NH⁺), which accounts for most of the swelling. As the solution pH approaches 5, the gradual ionization of surface R-COOH causes electrostatic repulsion between R-COO⁻ near each other, thus increasing the swelling from 15.7 to 32.2%. Entering the second stage (pH 5 to 9), surface COOH are fully ionized. During this stage, the hydrophilicity of the membrane decreases as R₂-NH⁻ gradually deprotonate, thus reducing the swelling to 14.2%. For the final stage (pH >9), R₂-NH⁻ have completely deprotonated (i.e., all are R₂-NH), while interior R-COO⁻ are subsequently ionized. Despite the neutralization of the amines, the introduction of a high density of hydrophilic R-COO⁻ increases film swelling sharply to 31.7%. The pH-dependent swelling measurements reported here are qualitatively similar to vapor swelling of semiaromatic polyamide selective layers (20 to 45% at 95% relative humidity), measured using X-ray reflectivity (39). While the observed trends in water permeability and swelling appear to mirror each other, the change in swelling does not produce a 1:1 change in water permeability. For instance, the roughly twofold increase in swelling (15.7–32.2%) from pH 3.5 to pH 5 results in a 10% increase in the water permeability, which runs counter to typically large increases in permeability with increased water sorption (19). The limited effect on permeability may be due to heterogeneous swelling behavior, such as localized swelling near the top surface with minimal change in the dense center of the nanofilm, owing to the nonuniform ionization behavior.

The salt separation efficacy of the LIP and NF270 membranes was assessed in a cross-flow filtration system (Fig. 5B and C). All membranes were tested under a constant water flux (Jw = 10 L·m⁻²·h⁻¹) in an effort to maintain similar solute boundary layers at the membrane–solution interface for membranes of varying water permeability. Chloride (Cl⁻) rejection of 2 mM NaCl feed solution from pH 3.5 to pH 9 (Fig. 5B) mirrored trends observed in previously published works on NF separation (40, 41). Below pH 5, Cl⁻ rejection is governed via Na⁺ exclusion by R₂-NH⁺ to maintain solution electroneutrality. As the pH increases to 5, NaCl rejection approaches a minimum with the ionization of surface R-COO⁻. Diminished Cl⁻ rejection at this point likely stems from increased salt sorption into the membrane due to the high degree of swelling at pH 5 (19). Cl⁻ rejection did not increase substantially until pH ≥9, where the deprotonation of R₂-NH⁻ and interior R-COO⁻ greatly enhanced Cl⁻ exclusion. To our knowledge, this behavior has not been observed until now, likely due to the lack of published rejection data beyond pH 9 (21, 41, 42). Trends in Cl⁻ rejection generally mirror the opposite behavior of membrane swelling and appear to be explained well by R₂-NH and R-COO⁻ ionization.

From the solution-diffusion model, the salt flux, J, can be represented as $J = B \cdot \Delta \cdot \rho$, where $B$ is the salt permeance and $\Delta \cdot \rho$ is the salt concentration difference across the active layer. The salt permeance can be considered as the reciprocal of salt resistance, $R_s$, across the membrane (i.e., $R_s = B^{-1}$) (43). Based on the rejection data presented in Fig. 5B, we determined salt permeance (SI Appendix, Fig. S9) and the corresponding salt resistance (SI Appendix, Fig. S10). The overall resistance increased 4- to 13-fold from pH 7 to pH 10.5, suggesting that interior R-COO⁻ groups play a prominent role in salt separation, highlighting high pH. We further compared the normalized salt resistance of our LIP and NF270 membranes against interior volumetric R-COO⁻ densities (Fig. 5D and E). Resistances (i.e., $B^{-1}$) were normalized to the salt resistance at pH 7 (i.e., $B_0^{-1}$), where interior R-COO⁻ groups remain neutrally charged. Our data suggest that salt resistance increases linearly with R-COO⁻ density. This behavior matches relevant models that describe ion transport in NF and RO membranes (e.g., steric–dielectric–Donnan and ion association models) (44, 45). While these models are principally different, in the limiting forms for high cation exclusion, both relate salt permeance to the volumetric charge density of the film, X, by $B \propto X^{-n}$. The value of $n$ depends only on the symmetry of the electrolyte (i.e., $n$ describes the ratio of counterions to coions in the salt). For the monovalent, symmetric electrolytes studied here, our data suggest that $n \approx 1$ under the given experimental conditions, which agrees with the physical interpretation of $n$. More work is needed to elucidate which model is most appropriate to explain the transport mechanisms across nanoporous polyamide. Experimental insight from this study may provide further clarity.

Implications for the Design of Desalination Membranes. Our work demonstrates the intricate relationship between polyamide ionization, film morphology, and membrane performance. While understanding the unique ionization of nanoporous polyamide films was the primary goal of our study, it is increasingly apparent that an improved understanding of polyamide ionization can help develop fundamental structure–property–performance relationships. Such frameworks could lead to improved nanofluidic transport modeling and novel membrane design.

Insufficient understanding of R₂-NH and—more importantly—R-COO⁻ ionization in nanoporous polyamide films is evident in nearly all ion transport models for NF and RO. The effective charge density is a critical component in these models; however, most models assume homogeneous functional group ionization across the entire film, regardless of pH (7, 11, 12). Our work highlights the critical flaws in current models, which do not account for the separate ionization of the polyamide surface and pore, while also introducing the techniques and experimental benchmarks necessary to improve them. Quantifying R-COO⁻ densities on the membrane surface and interior will establish more realistic frameworks for transport modeling, thus improving our comprehensive understanding of nanofluidic transport across polyamide NF and RO membranes.

Charge-based exclusion is broadly recognized as a primary rejection mechanism for NF membranes and has commonly been exploited to improve NF performance (21, 40, 42). While the influence of charge-based exclusion on membrane performance has primarily been conceptualized as a surface-based phenomenon (7, 21, 41), our findings suggest that interior R-COO⁻ could play a significant role if ionized. Notably, we find the complete ionization of interior R-COO⁻ results in a greater than fourfold increase in the water–salt permselectivity of NF270 (SI Appendix, Table S2 and Fig. S11). This fundamental insight has important implications for future membrane design. Furthermore, similarities observed in the R-COO⁻ ionization behavior of fully aromatic polyamide RO membranes indicate that comparable performance enhancements could be exploited in brackish water RO (4).

Although these proposed benefits are intriguing, desalination typically occurs far below pH 10.5 (usually around pH 8) (3), where interior R-COO⁻ would not ionize. Therefore, the advantage of interior R-COO⁻ cannot be captured under typical operating conditions given current membrane materials. Several methods may be available to increase the effective charge density within TFC membranes at operationally relevant pH. Increasing the membrane pore size could increase the local dielectric constant, allowing R-COO⁻ to ionize more readily. However, this would come at a significant cost to steric hindrance of solutes. Likely more feasible is the tailoring of membrane pores with highly acidic functional groups (e.g., sulfonate) that will readily deprotonate in most environments (generally $pK_a < 1$) (46). Incorporating sulfonate groups into polymers has been a popular route for introducing additional charge and hydrophilicity (19). While the added charge in the membranes studied here resulted in increased water permeability and water–salt selectivity, sulfonation of polymers has produced
mixed results (19). The addition of excessive charge can lead to significant swelling and, consequently, reduced salt exclusion. This trade-off necessitates a balance, where enough fixed charges must exist to exert sufficient resistance to ion mobility and maintain adequate salt exclusion without overswelling the polymer matrix.

**Materials and Methods**

LIP. Layered TFC NF membranes were fabricated by forming several sequential polyamide selective layers atop prewetted PS20 (Sepro) support membranes via LIP (SI Appendix, A method previously used for polyethylenimine- and MPD-based TFC membranes (16, 47). The aqueous amine solution used for forming the polyamide layer consisted of 1.0 wt % PIP, 0.5 wt % triethylenamine, and 0.15 wt % NaOH in deionized water. We denote our layered membranes as “nL PIP,” where n represents the number of PIP-based polyamide layers deposited on the membrane.

**Material Characterization of Polyamide Films.** SEM (10 kV SU8230; Hitachi) was used for qualitatively analyzing the surface morphology and roughness of the film. Membrane samples were sputter coated with 2 nm of iridium (208HR Sputter Coater; Cressington) to prevent charging. Images were captured at 10,000x magnification. TEM was performed with an FEI Tecnai G2 Spirit BioTWIN to analyze cross-sectional features of the polyamide film. An 80-kV electron source was applied with a LaB6 filament. Samples were microtomed prior to TEM imaging (SI Appendix).

The film thickness and roughness of isolated polyamide films were quantified via AFM (SI Appendix) based on previously published methods (38, 48). A 10L PIP membrane was fabricated only for AFM analysis to substantiate the relationship between the number of deposited layers and the membrane thickness. Image analysis was performed with Nanoscope Analysis v1.9 (Bruker) software. The same method used to quantify film thickness in AFM was extended to determine swelling in the polyamide film (details in SI Appendix). After measuring the dry film thickness ($d_0$), we pipetted water of controlled pH (ranging from pH 3.5 to 10.5) onto the film. We allowed the film to equilibrate at each pH (~5 min) before measuring the thickness of the swollen film. Swelling was calculated as the relative change in thickness of the wet film ($d_w$) compared to the dry film, $(d_w - d_0)/d_0$.

**Quantification of Ionized Carboxylic Amine Functionalities.** The silver-bridging/CP-M5 method (details in SI Appendix) was employed to determine R-COO$^-$ throughout the polyamide film (4). We did not remove the fabric backing of the LIP membranes in an effort to avoid altering their R-COOH density. Instead, we calibrated our measured values by subtracting the average silver quantity found in our control support membranes (SI Appendix, Fig. S12). The same procedure was repeated when assessing amine ionization, but with slight modifications (SI Appendix).

IC-ESMS (ELAN DRCII; PerkinElmer) was utilized to quantify eluted silver, using a calibration curve ranging from 0 to 200 μg L$^{-1}$. Indium nitrate (40 μg L$^{-1}$) was used as the internal standard. Ion chromatography (90A Compact IC Flex with Metrosep A Supp 5-150/4.0 column and conductivity detector; Metrohm) was used to analyze eluted bromide, using a calibration curve ranging from 0 to 100 μg L$^{-1}$. Counterion concentrations were converted to areal R-COO$^-$ and R$_i$NH$_4^+$ densities (SI Appendix). Carboxylic and amine ionization were fitted using multi-pK$_a$ and single-pK$_a$ functions, respectively (4, 5).

$$[R-COO^-] = C_{R-COO^+} \sum_i n_i \frac{K_{a_i}}{[H^+]^{i+} + K_{a_i}}$$

$$[R_i-NH_4^+] = C_{R_i-NH_4^+} \frac{[H^+]^{i+} + K_{a_i}}{[H^+]^{i+} + K_{a_i}}$$

where $C_{R-COO^+}$ and $C_{R_i-NH_4^+}$ are the total densities of residual carboxylic and amine groups throughout the film. $[H^+]$ is the molar proton concentration, $K_a$ is the acid-base equilibrium constant, and w is the fraction of groups with different $K_a$. Two $K_a$ values (i.e., $n = 2$) were used to fit carboxyl ionization for the polyamide membranes.

The zeta potential of the membrane surface was evaluated by a streaming potential analyzer utilizing an asymmetric clamping cell (EKA; Brookhaven Instruments) as reported previously (49). Measurements were performed with a solution containing 1 mM potassium chloride (KCl) and 0.1 mM potassium bicarbonate (KHCO$_3$). The streaming potential induced by flowing the electrolyte solution over the membrane surface at pressures ranging from 0 to 300 mbar was measured using Ag/AgCl electrodes mounted at each end of the clamping cell.

A carboxylate-based weak acid IEX resin (Dowex MAC-3; DuPont) was used to demonstrate the effect of ionic strength on carboxylic pK$_a$ (SI Appendix), as shown previously (23).

**First-Principles Simulations of Dielectric Phenomenon.** Classical MD simulations were performed to determine the dielectric constant of bulk and confined water using the LAMMPS (50) (7 Aug 2019) package (details in SI Appendix, Table S3 and Fig. S13). The dielectric constants of bulk and confined water models were computed using the PyLAT (51) package from the fluctuations dynamics according to

$$ε = 1 + \frac{(M^2_ν – M^2_0)}{3νC_0V_{eff}}$$

where $T$ is the absolute temperature, $k_B$ is the Boltzmann constant, $V$ is the volume of the solvent system, and $M$ is the dipole moment of the solvent system.

DFT calculations were performed using Q-Chem 4.2 (52) to estimate pK$_a$ values and compute binding energies (details in SI Appendix, Tables S4–S7). The pK$_a$ values were calculated using a thermodynamic cycle approach (SI Appendix, Fig. S14). The binding enthalpy of Ace-PIP with a range of anions (i.e., ClO$_4^-$, ClO$_4^-$, NO$_3^-$, F$^-$, Cl$^-$, Br$^-$, I$^-$, and SO$_4^{2-}$) was computed as $ΔH_{binding} = H_{complex} − H_{An} + H_{Pip} − H_{Ion}$,

where the $H$ refers to the zero-point vibrational energy-corrected electronic energy (SI Appendix, Table S8). The isolated Ace-PIP, anion, and anion-Ace-PIP complex were each geometry-optimized in implicit water solvent.

**Characterization of NF Performance.** A custom three-cell bench-scale filtration system operating in cross-flow mode with a flat sheet membrane cell was used for salt rejection and water permeability tests (details in SI Appendix). Observed salt rejection ($R_{salt}$) was determined by comparing the salt concentration in the feed ($C_f$) and permeate ($C_p$) solutions (i.e., $R_{salt} = 1 - C_p/C_f$). Salt separation experiments were evaluated separately with 2 mM and 20 mM feed solutions of sodium chloride (NaCl). Feed solution pH was monitored and adjusted between 3.5 and 10.5 with sodium hydroxide (NaOH) and sulfuric acid (H$_2$SO$_4$). Feed and permeate samples were collected for ion analysis, where ion chromatography was used to measure anion concentrations with a Dionex DX-500 ion chromatograph equipped with an AS14A IonPac column.

**Data Availability.** Raw images and tabulated measurement data have been deposited in Zenodo (https://zenodo.org/record/3974975#.XSHHceu10PY).

ACKNOWLEDGMENTS. This work was supported as part of the Center for Enhanced Nanofluidic Transport, an Energy Frontier Research Center funded by the US Department of Energy, Office of Science, Basic Energy Sciences under Award DE-SC0019112. We also acknowledge the NSF Graduate Research Fellowship awarded to C.L.R.

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