

Molecular thermodynamics of complex coacervate systems. Part I: Modeling of polyelectrolyte solutions using pePC-SAFT

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ABSTRACT

Rigorous molecular modeling of polyelectrolyte solutions is complicated by several intrinsic challenges of those systems, such as the strong charge correlation and the complex cocktail of short-range and long-range interactions, which span over a broad length scale. On the other hand, there is an increasing interest in understanding and designing polyelectrolyte systems in biology, life science, medicine, and (bio)chemical engineering. Thermodynamics of polyelectrolyte solutions is rather underexplored, and the difficulties in describing polyelectrolytes at the molecular level as well as the lack and the uncertainty of experimental data might have hindered the development of accurate thermodynamic models for polyelectrolytes. In this work, the main phenomena of counterion condensation, complex formation and coacervate formation are discussed and considered for the further development of polyelectrolyte PC-SAFT (pePC-SAFT) as modeling framework in this work. The new development was then validated using experimental osmotic coefficients of aqueous polyelectrolyte solutions. Finally, liquid-liquid phase separation (LLPS) of complex coacervate systems (aqueous solutions containing oppositely charged polyions) were modeled with pePC-SAFT, and the results were in very good agreement with literature data.

1. Introduction

For more than a century, researchers have investigated polyelectrolyte solutions and phase behavior of mixtures containing multiple and oppositely charged polyions. The large amount of literature collected over the last seven decades (see Muthukumar [1] for an extensive overview) and recent reviews [1–5] confirm the strong interest in these fascinating systems. Polyelectrolytes are defined as homo- or copolymers carrying functional groups over the polymer chain which, in aqueous solution, usually undergo ionization due to (multiple) dissociation or protonation, releasing polyions and small counterions (such as Na^+ , Cl^- or OH^- ions) into the solution. Those counterions, always present with the polyions, strongly affect the thermodynamic properties of the polyelectrolyte solution. The special properties of polyelectrolyte solutions are conferred by the chain-like structure of polyions and the confinement of a relatively high number of charges within a small distance to each other. This gives rise of several interactions across multiple length scales, such as the solvent-mediated long range coulombic interaction at large intermolecular separation, strong short range coulombic interaction in the vicinity of each chain

due to charge correlation, interchain and intrachain dipole-dipole interactions between ion pairs, excluded volume effects and specific interactions, such as hydrogen bonding. These effects are nonlinearly coupled and the result can be synergistic or antagonistic [1] without obvious generalization. Caused by the mentioned complex behavior of polyelectrolytes at the molecular level, physical chemistry of polyelectrolyte solutions is considered one of the least understood topics in soft matter [1]. Research on polyelectrolytes is further motivated by their wide range of technical applications and scientific impact in biology, life science, medicine and (bio)chemical engineering. Numerous biologically relevant biomolecules (nucleic acids, natural and synthetic polypeptides or polysaccharides) as well as several industrially relevant synthetic macromolecules (poly(styrene sulfonate), polymethyl acrylate, polyacrylic acid) are polyelectrolytes [6,7]. Several phenomena in biological systems, such as the compaction of DNA [7] or the complexation of oppositely charged molecules [2], are attributed to the charged groups along the molecule's backbone. Mixtures of oppositely charged polyions might undergo complex coacervation, which is an electrostatically-driven LLPS leading to formation of a highly concentrated polyions solution, called coacervate phase, and a dilute aqueous

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solution, called supernatant. Early systematic studies from Bungenberg de Jong [8–10] on complex coacervation are almost a century old and focused on the system water + gum arabic + gelatin. Recently, complex coacervation has been found to be a ubiquitous phenomenon in living cells. Several membraneless organelles (MLO) consist of small droplets of negatively charged polynucleotides (mostly RNA) and positively charged polypeptides (see, for example [11,12]). Technical applications of polyelectrolytes are numerous, including drug delivery, molecules fractionation and flocculation, membranes, gels and as additives in cosmetics and detergents. Some recent studies aim at using complex coacervates of synthetic polyelectrolytes as extracting agents for biomolecules [13].

Several theoretical approaches were pursued to describe the thermodynamic properties (such as colligative properties or phase equilibria) and the observed conformational and transport properties of polyelectrolyte solutions, using different molecular models and mathematical approximations. It is known that a single polyion chain changes its configuration gradually from globular [14] to stretched [15] upon increased charges. This is reversed at high salt concentration due to electrostatic screening and reduced repulsion of the charged groups [16]. This phenomenon has far-reaching consequences for the different transport properties, resulting in different scaling laws between neutral and charged polymers [15,16]. On the other hand, it is known that thermodynamic properties of aqueous polyelectrolyte solutions are dominated by the interactions of the polyions with the surrounding counterions and less by the chain conformation [17]. Several theories were developed to describe colligative properties of solutions of single polyelectrolytes, for example by Lifson and Katchalsky [18,19], Alexandrowicz and Katchalsky [20–22] and Dolar [23] who solved the nonlinear Poisson-Boltzmann (PB) equation in the cylindrical geometry at different levels of approximation, and by the pioneering work of Manning [24–26] who included the concept of counterion condensation (this phenomenon was recognized also by other authors [27,28]) into one of the most widely accepted theories for polyelectrolyte solutions.

Polyelectrolyte systems have also been rigorously studied by means of molecular simulation at different levels of approximation of the polyions, counterions and solvent models. The group of Muthukumar has performed extensive studies using Langevin dynamic simulation with implicit solvent. The studied properties range from extent of counterion condensation [17,29–31], polyion end-to-end length and morphology [17,29–32], formation of soluble complexes as function of counterion concentration, ion valence, temperature and dielectric screening (dielectric constant) [32,33]. Radhakrishna et al. [34] used Monte Carlo (MC) simulation to calculate phase diagrams of complex coacervates and to study the effect of charge correlations and salt partitioning in coacervate solutions. Complex coacervation and the salting-in effect was also studied by Molecular Dynamics (MD) simulation using coarse-grain models [35,36]. Lytle et al. [37] proposed an hybrid approach to simulate complex coacervates, in which molecular-level MC simulation was used as input for a mean-field simulation with MC, which coarse-grains the system by lumping the monomers. In a series of subsequent works [38–40] the goal of the authors was to calculate phase diagrams of complex coacervates.

Whereas molecular simulation (whether MD or MC) provides a valuable tool to study polyelectrolyte systems up to complex coacervation in very detail, there is also a need of simplified models to describe phase equilibria with different polyions and salt concentrations. The model of complex coacervation developed by Voorn and Overbeek [41, 42] was used by Spruijt et al. [43] to model the phase envelope of a complex coacervate system as function of the salt concentration. More recently, Jiang et al. [44–48], developed an equation of state for mixtures of charged hard chains in the primitive model, which is capable of reproducing characteristic phase diagrams of complex coacervate systems [49–51]. Sing et al. [52] showed that almost all the models of complex coacervation share a Flory-Huggins mixing entropy term. Their difference can be linked to different approximations in the cluster

expansion of the residual Helmholtz energy. The current status in the development of theories for the description of physical properties of polyelectrolytes up to complex coacervation is reported in several reviews [1–3,5,52,53]. Almost all the models reported therein are very important from a theoretical point of view and provide valuable insights into features and trends of experimental results. However, very few of them have been used to model thermodynamic properties of polyelectrolyte solutions. A few models designed for engineering purposes (i. e. to correlate and predict thermodynamic properties of real systems) are reported in the literature, but they are limited to aqueous solutions of one single polyion and a counterion and do not account for complex coacervation [54–56].

The goal of the present work is to develop a thermodynamic model which is capable of correlating and predicting the phase behavior of polyelectrolyte systems (containing more than one polyion species as well as counterions) as function of compositions that are relevant for complex coacervate formation. The model is a further development of original pePC-SAFT by Naeem and Sadowski [53]. It is based on PC-SAFT to describe dispersion forces among the species and using the charged hard-chain model of Jiang et al. and the first-order Thermodynamic Perturbation Theory (TPT1) of Wertheim to incorporate the counterion condensation at low to moderate polyelectrolyte concentration. Furthermore, relevant questions to model polyelectrolyte solutions were addressed, including the nearest-neighbor approximation of the charge correlation in the charged hard chain term described within the TPT1 theory, the related necessity to invoke counterion condensation, and a comparison between the Debye-Hückel and the MSA theories in the development of the present model. The developed model was validated against experimental osmotic coefficients of aqueous polyelectrolyte solutions and the liquid-liquid equilibria encountered in complex coacervate systems.

2. Thermodynamics of polyelectrolyte solutions and complex coacervates

The main difference between polyelectrolyte solutions and classical “simple” electrolyte solutions is the internal structure of the polyions. The size of “simple” small ions is much smaller than the screening length at a typical electrolyte concentration, while the size l of the polyions is in general much larger than the Debye-Hückel screening length $1/\kappa_{DH}$. Exceptions might be found at extremely low concentrations which are rarely reported in the literature (and are of less interest in technical applications or experiments). In this work, the term “semi-dilute” region is used to refer to the relevant concentration range where $l \gg 1/\kappa_{DH}$. In this section, we review the main phenomena that occur in polyelectrolyte solutions that must be considered in a thermodynamic model for predicting thermodynamic properties and phase equilibria of aqueous polyelectrolyte solutions (containing multiple polyions and simple inorganic ions).

Counterion condensation: In an aqueous polyelectrolyte solution, a certain fraction of the small inorganic counterions will be locally bound along the chain of the polyion. This phenomenon is called counterion condensation and depends on the charge density of the polyion and on the excess of salt in the solution. Counterion condensation was largely studied by experimental and theoretical works [17,28,30,57,58], and it is known to be responsible for the strong non-ideality of aqueous polyelectrolyte solutions up to very low concentrations (cf. Section 4). Counterion condensation occurs only in an aqueous solution of equally charged polyions in the semi-dilute region (see the work of Ramanathan and Woodbury [59,60] for an extensive discussion of the concentration threshold where counterion condensation takes place) and its extent is caused by the interplay of the enthalpy gain (due to the strong bonding of the counterions to the polyion chain) and the negative entropy change (due to the loss of translational degrees of freedom of the counterions bound to the polyion) according to the general thermodynamic relationship $\Delta G = 0 = \Delta H - T\Delta S$. The real picture is more complicated,

since localizing counterions on the polyion chain also affects the chain conformation by relaxing the intrachain repulsion and increasing the mobility of the chain [61] (which, in turn, represents an increase in the degrees of freedom and an entropic gain in ΔS). However, it was shown that chain conformation effects have a marginal impact on thermodynamic properties compared to counterion condensation, proven by predictive theories (that explicitly neglect the chain conformation) as well as by MD studies that evaluated the chain conformation contribution to the Helmholtz energy [29]. In contrast, dynamic and transport properties are greatly affected by the chain conformation [62–64]. For this reason, several successful theories on colligative properties of polyelectrolyte solutions started from the simplified molecular model of the infinitely long rigid rod with charged surface and surrounded by counterions, which will be shortly introduced here. The configurational integral Z_1 of a rigid, uniformly charged rod of radius a and length l_p with charge density $l_p^{\text{ch}} = eN_p z_p / l_p$ (with N_p and z_p being the number of functional groups in the polyion and the respective charge) and with one counterion of charge z_i within the volume enclosed by a cylinder of radius R from the center of the rigid rod is given by Eq. (1).

$$Z_1(T, V) = l_p \int_0^R \exp\left(-\frac{u_{pi}(r)}{k_B T}\right) 2\pi r dr = 2\pi l_p \int_a^R r^{1+2z_p z_i \zeta} dr \quad (1)$$

In Eq. (1), $\zeta = N_p e^2 / 4\pi\epsilon_0 \epsilon_r l_p$. The contribution to Z_1 between 0 and a in the integral of Eq. (1) is zero due to the hard-core repulsion of the rod. Onsager noted that Z_1 diverges for all the values of $\zeta \geq |z_p z_i|^{-1}$ in the limit of $a \rightarrow 0$ [24]. Based on the objection of Onsager, Manning [24–26] derived a set of limiting laws for polyelectrolyte solutions in order to calculate osmotic coefficients, mean ionic activity coefficients of the mobile ions, and the Donnan factor. Manning stated that a certain number of counterions will condense on the surface of the polyion at given concentration, which lowers its effective charge until $\zeta = \zeta^* = |z_p z_i|^{-1}$ (thus preventing the divergence of Z_1). Then, the polyion interacts with the surrounding counterions via the effective charge density ζ^* according to the linearized PB equation [27]. The limiting laws derived by Manning have proved so far to be in excellent agreement with the experimental data in the region of validity of the theory, i.e. in the semi-dilute region. Levin et al. [65–71] investigated extensively the Debye-Hückel-Bjerrum (DHBj) theory, a cluster theory invoking ion-pair formation and formally representing a generalization of the Bjerrum theory for a given geometry [72]. Levin proved that the DHBj calculations (at small concentrations) is consistent with the Manning theory at ζ^* . Therefore, even though the Manning theory is apparently inconsistent (the theory was not derived invoking any law of mass action), it represents a very accurate limiting case reproduced by more elaborated theories. Inspired by Manning's theory, thermodynamic models have been developed to model thermodynamic properties of polyelectrolyte solutions, e.g., the extended Pitzer equation of Filho and Lammertz [56, 73,74], the previous versions of pePC-SAFT [55,75,76], and the NRTL model for polyelectrolytes [54].

Formation of polyelectrolyte complexes: The presence of oppositely charged polyions in the semi-dilute region might cause the formation of soluble polyanion-polycation pairs which in the literature are called “polyelectrolyte complexes” or “soluble complexes”. This is an extensively studied phenomenon due to the potential use of polyelectrolyte complexes as carrier systems for drugs, enzymes or DNA [77–81]. The formation of polyelectrolyte complexes is more probable for polyions with a high charge density and it is widely accepted that this phenomenon is predominantly entropy-driven [32,82–85]. The starting point is that a fraction of the inorganic counterions is reversibly bound to the polyion chain (and thus depleted of their translational degree of freedom). Upon addition of an oppositely charged polyion, the two polyions might condense to each other forming a polycation-polyanion ion pair. Depending on the charge ratio of the polyions and the presence of other added salts, non-stoichiometric pairs might also be

observed [86]. The main driving force for this phenomenon is not enthalpic, since it basically implicates replacing single counterions located on the polyion chain with a polyion, i.e. a species of similar number of charges as the inorganic salt but bound into a single chain. In fact, both positive or negative mixing enthalpies have been observed experimentally [84], but the order of magnitude points to a minor electrostatic contribution to the free energy of complexation. Thus, in contrast to counterion condensation, the main driving force for complexation is entropic due to the release of counterions, which re-gain translational degrees of freedom (as depicted in Fig. 1). Added salts in the system weaken the coulombic forces between both polyion-counterions and polycation-polyanion, decreasing the overall driving force for complexation [32,77,86]. To the best of our knowledge, there is no thermodynamic model that considers the formation of polyelectrolyte complexes.

Complex Coacervation: At higher polyelectrolyte concentration, macroscopic phase separation called complex coacervation might be observed. This phenomenon is also predominantly of entropic origin and can be explained by the large size of polyions (compared to water and counterions) and the resulting lower entropic penalty for liquid-liquid phase separating of a mixture of oppositely charged polyions. Several models which predict complex coacervate formation employs the Flory-Huggins form [87] in the mixing entropy (Eq. (2)) of the Helmholtz energy expression.

$$\alpha^{\text{FH}} = \frac{A^{\text{FH}}}{N k_B T} = -T s^{\text{FH}} \\ = x_{p+} \ln \Phi_{p+} + x_{p-} \ln \Phi_{p-} + x_{c+} \ln \Phi_{c+} + x_{c-} \ln \Phi_{c-} + x_w \ln \Phi_w \quad (2)$$

In Eq. (2), x_i and Φ_i are the molar fraction and the volume fraction (which is related to the size of the component i under consideration) of the polyions (p_+ and p_-), the counterions (c_+ and c_-) and water (w), respectively. The polyions and the counterions in the solution show a comparable magnitude of the volume fraction Φ_i . However, compared to the counterions, the polyions decrease much more the magnitude of the mixing entropy, according to Eq. (2), due to the much lower molar fraction x_p . Therefore, separating polyions from an aqueous solution into a highly concentrated phase is much easier than separating counterions. For this reason and because of the electroneutrality condition of each phase, phase-separation in a solution of a single polyelectrolyte is rarely observed: assuming monovalent counterions, the process of concentrating one single polyion with $|z_p|$ charges in one single phase requires concentrating $|z_p|$ single counterions (many of which are non-condensed in the polyion chain) into the same phase, and this process has a large entropic penalty. However, the situation becomes different if oppositely charged polyions and the respective counterions are present in the solution. Then, the polyanions and polycations might release the condensed counterions by forming soluble polyelectrolyte complexes (which is considered as precursor of coacervation [88,89]) and might even form a second phase which fulfills the electroneutrality condition with a very low entropic penalty. The total concentration of the polyions in the resulting coacervate phases can be up to three orders of magnitude higher than in the coexisting dilute aqueous phase (“supernatant phase”), while the counterions usually partition equally between the coacervate and the supernatant phases. The first and simplest model to study complex coacervation is credited to Voorn and Overbeek (VO) [41,42], and is given by a simple combination of the Flory-Huggins term of Eq. (2) with the limiting Debye-Hückel theory. Despite its simplicity and the non-consideration of several polyelectrolyte features (such as the volume of the ions, the chain connectivity in the polyions and all the assumptions in the Debye-Hückel limiting law, which is valid in the limit of infinite dilution only), the VO model qualitatively reproduces the topologies, the salt concentration dependency and chain-length dependency of complex coacervation and was found to be able to quantitatively match experimental data using empirical parameters [43]. The polyelectrolyte model of Jiang et al. [44–48] was derived by

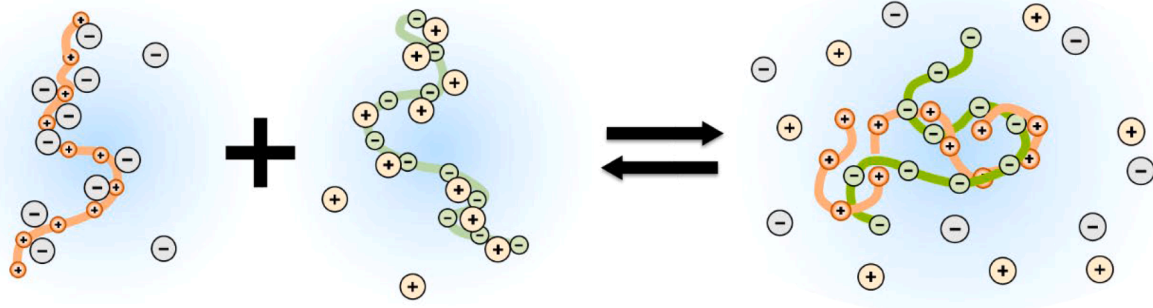


Fig. 1. Visualization of the phenomenon of polyelectrolyte complexes formation.

perturbation theory of a charged hard-sphere reference system. Although it does not involve the Flory-Huggins mixing entropy term, the hard-core part of the model reproduces the excluded volume and the different size of the species in solution (polyions, counterions, and water) and therefore resembles, in some extent, the mixing entropy of Eq. (2). Like the VO model, the model of Jiang et al. reproduces the feature of complex coacervation, as studied by several authors [35, 49–51,90]. However, it has never been validated by experimental data.

3. Thermodynamic modeling framework using pePC-SAFT

pePC-SAFT (like the original PC-SAFT and all the SAFT-type EoS) is formulated as residual Helmholtz energy a^{res} of the system (at given temperature, volume, and composition) which, according to perturbation theory [91], can be written as sum of energy contributions (see Eq. (3)).

$$a^{res} = \frac{A^{res}}{Nk_B T} = a^{hs} + a^{ion} + a^{ch,hc} + a^{disp} + a^{assoc} + a^{Born} \quad (3)$$

$$a^{ch,hc} = \frac{A^{ch,hc}}{Nk_B T} = -x_r(r-1)\ln y_{ii}^{cc}(d_{ii}) \quad (4)$$

The contributions in Eq. (3) are the hard-sphere contribution a^{hs} , the ion-ion electrostatic contribution a^{ion} , the chain-formation contribution $a^{ch,hc}$, the dispersion contribution a^{disp} , the association contribution a^{assoc} and the Born contribution a^{Born} , which are described in the original [92–94] as well as in subsequent papers [95–97]. In Eq. (3) (as in Eq. (2) and in all other equations in this work as well) denotes N the total number of particles in the system and k_B the Boltzmann constant. Like in the previous version of pePC-SAFT [55,75], in this work the chain-formation contribution adopted by Jiang et al. [44,45] is employed as well. The previous version of pePC-SAFT employed the Manning theory to describe counterion condensation. The problem with this approach is that it is limited to solutions of single polyions, counterions and ions from an added salt. To extend the treatment to mixtures of oppositely charged polyions (in order describe counterion release and complex coacervation), we incorporate counterion condensation via the first-order perturbation theory (TPT1) of Wertheim [98–101] within the a^{assoc} contribution for charged hard spheres. The implementation of our approach will be detailed in the following, starting by revisiting the pePC-SAFT for mixtures of hard-sphere monomers (charged or non-charged) and r-mers (which means only accounting for $a^{hs} + a^{ion} + a^{ch,hc}$ of Eq. (3)) proposed by Jiang et al. prior to elucidating the requirement of explicitly invoking counterion condensation via TPT1. The rigorous mathematical derivation from perturbation theory, as well as the mathematical formulation of the levels of approximation adopted in this work, are reported in Appendix A. Besides the levels of

approximation included in the McMillan-Mayer [102,103] framework, which results in considering the solvent as continuum with an effective dielectric constant $\epsilon = \epsilon_0 \epsilon_r$, the *single-chain approximation* and the *nearest-neighbor correlation* were employed to derive pePC-SAFT (see Fig. 2 for a visualization of both approximations). The single-chain approximation (also called zeroth approximation in some publications [104,105]) results in considering $a^{ch,hc}$ as given by the residual Helmholtz energy of formation of a single r-mer, statistically averaged over the intrachain degrees of freedom and surrounded only by fully disconnected monomers, multiplied by the number density ρ_r of the r-mers. The nearest-neighbor correlation assumes that the residual Helmholtz energy of assembling an r-mer in a system of free monomers is equal to the residual Helmholtz energy of dimerization multiplied by $(r-1)$, i.e. the number of bonds. The resulting equation for $a^{ch,hc}$, which is derived in Appendix A, is given by Eq. (4). In Eq. (4), x_r is the molar fraction of the r-mer and $y_{ii}^{cc}(d_{ii})$ is the cavity correlation function between two monomers, evaluated at the distance of closest approach d_{ii} .

Both, the single-chain approximation and the nearest-neighbor correlation, have limitations. They have been proven to be accurate for a purely repulsive potential, such as the hard-sphere or square-well potential, as implemented in classical PC-SAFT (see, for example, the work of Chapman et al. [106], Fig. 2). However, those assumptions are at best adequate to describe a mixture of charged r-mers and free monomers in the high-density limit (i.e., when the interaction of each monomer with surrounding particles prevails the intrachain interactions) for the long-range coulombic potential. The effect of charge correlation and polyion architecture on complex coacervation was theoretically investigated by Qin and de Pablo [107], who found an increased tendency to coacervation when the chain connectivity was included. Similarly, our model predicts a smaller miscibility gap when the chain connectivity via nearest neighbor correlation (Eq. (4)) is neglected (results not shown). In contrast to the high-density concentration regime, in the low-density limit the strong intrachain correlation and the resulting intense local electrostatic field lead to pronounced chain enlargement. This causes counterion condensation and formation of polyelectrolyte complexes. By considering only nearest-neighbor correlations, all these intrachain correlations (and the resulting phenomena) will be neglected. Furthermore, the single-chain approximation leads to an overestimation of the number of free ions in solution (meaning ions that are able to build a screening atmosphere within the continuum), since most of the charged segments in the system are either bond together into r-mers or condensed to them, and therefore not available to contribute to the continuum. This will result in a significant overestimation of the screening strength of the continuum. To overcome the shortcoming of these approximations and to be able to account for counterion condensation in the low-density limit, the TPT1 theory of Wertheim is suggested here. In this new framework, one association site on the counterions and several association sites on the polyion are defined.

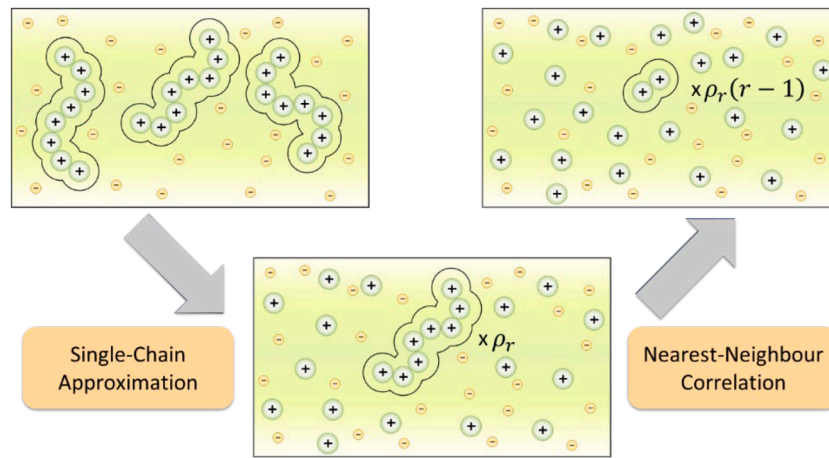


Fig. 2. Visualization of the approximations involved in the charged hard-chain energy contribution: each r -mer is considered to be formed alone in a mixture of disconnected monomers and counterions; furthermore, the single r -mer formation term is given as a sum of $(r-1)$ dimer formation terms.

Only association between sites on oppositely charged counterions and polyions, as well as between sites on polyanions and polycations (but not between polyions with the same charge), are considered. In the TPT1 theory, the fraction of non-bound sites A in component i , X_{A_i} , is required to calculate the association contribution a^{assoc} to the Helmholtz free energy. X_{A_i} is a function of the association strength $\Delta^{A_i B_j}$ between all couples of sites A_i and B_j of the species i and j , according to Eq. (5). In this work, the association strength between sites on charged spheres is given by Eq. (6)

$$X_{A_i} = \frac{1}{1 + \rho \sum_{B_j \in I} X_{B_j} \Delta^{A_i B_j}} \quad (5)$$

$$\Delta^{A_i B_j} = \kappa^{A_i B_j} \cdot \sigma_{ij}^3 \cdot [\exp(\epsilon^{A_i B_j} / kT) - 1] \cdot g_{ij}^{ch}(d_{ij}) \quad (6)$$

The unlike association volume between two sites $\kappa_{A_i B_j}$ is set to 0.04 whereas the corresponding association strength $\epsilon_{A_i B_j}$ is set to 5500 K (a value at which the resulting Helmholtz energy becomes insensitive to the association strength and only depends on the number of association sites). Thus, instead of treating $\epsilon_{A_i B_j}$ and $\kappa_{A_i B_j}$ as adjustable parameters, the number of association sites is used as an adjustable parameter within this work (fitted to experimental osmotic coefficients), similar to the approach of Filho et al. [56]. In Eq. (6), the pair correlation function of charged hard spheres is employed, whereas in the calculation of the association strength between neutral components (as in the original PC-SAFT [93]) the pair correlation function of hard spheres is used (see the work of Stell et al. [108], section IV, for a short discussion about using a long-range coulombic potential with hard core as reference potential in the Wertheim theory).

Two implicit approximations need to be mentioned within this approach. First, the TPT1 theory considers “sticky point” association sites, meaning that association originates from strong and highly directional short-range forces, which persist at any density range. In contrast, counterion condensation and polyelectrolyte complex formation originate from the strong electrostatic field in the vicinity of polyions, which depends on the particle density and is likely to be much weaker in the concentrated coacervate phase than in the dilute aqueous phase due to the screening of intrachain interactions. Second, the TPT1 theory is formulated at the same level of approximation that is employed also in $a^{ch, hc}$ (with the previous explained single-chain approximation and nearest-neighbor correlation required to derive Eq. (4)). That is, the association strength $\Delta^{A_i B_j}$ (required to determine X_{A_i}) is calculated by considering all the monomers as being disconnected. Thus, the theory does not consider the chain connectivity and therefore it also does not differentiate between the association of the monomer in a charged chain

with a counterion and the association of two monomers of two oppositely charged chains. Consequently, the strong entropy gain resulting from counterion release upon complexation (i.e., when oppositely charged polyions form a polyelectrolyte complex, as discussed in the previous section) is not fully considered by our modeling approach. The strategy of using the TPT1 theory to include counterion condensation resembles, in some extent, the approach of Friedowitz et al. [109], Ghasemi et al. [110], and Salehi et al. [111]. The authors described association between polyions and counterions by means of a law of mass action with an equilibrium constant that depends on a local binding strength (which, in the TPT1 theory, is described by $\epsilon_{A_i B_j}$ and $\kappa_{A_i B_j}$) and on an “exchange chemical potential” that considers the morphology of the polyion using a chosen molecular model (in TPT1 theory this is given by the radial distribution function g_{ij}^{ch} considering the charged hard-chain as being disconnected, according to Fig. 2). However, in a theoretically “perfect” model of polyelectrolytes that fully considers the strong charge correlations, no local binding strength would be required to incorporate the counterion condensation.

The cavity correlation function for the calculation of Eq. (4) is given as the ratio of the two-body radial distribution function in the real system and that in an ideal gas, i.e. when there are no interactions with other particles. For an electrostatic potential with hard-sphere repulsion at the distance of closest approach d_{ii} , the cavity correlation function at d_{ii} is given by Eq. (7).

$$y_{ii}^{cc}(d_{ii}) = \frac{g_{ii}^{ch}(d_{ii})}{g_{ii}^{ch, ig}(d_{ii})} = g_{ii}^{ch}(d_{ii}) e^{\frac{z_i^2 e^2}{4\pi\epsilon_0 d_{ii} k_B T}} \quad (7)$$

For a chain containing both, charged as well as neutral monomers, with “cc” being the ratio between the number of charged to the total number of monomers, Eq. (7) is approximated by an “effective” cavity correlation function $y_{ii}^{eff}(d_{ii})$ estimated according to Eq. (8).

$$y_{ii}^{eff}(d_{ii}) = cc \cdot y_{ii}^{cc}(d_{ii}) + (1 - cc) \cdot g_{ii}^{hs}(d_{ii}) \quad (8)$$

Here, $g_{ii}^{hs}(d_{ii})$ describes the radial distribution function for neutral hard spheres. In this work, the radial distribution function of charged hard spheres $g_{ii}^{ch}(d_{ii})$ is estimated from the so-called *exponential approximation* (EXP) given by Andersen et al. [112]. The exponential approximation gives a much better representation of computer simulations of charged hard-spheres than linearized models such as the Debye-Hückel or the Mean Spherical Approximation (MSA) theory, and basically results in assuming additivity of the hard-sphere potential of mean force w^{hs} and the coulombic potential of mean force w^{el} , as given by Eq. (9).

$$g_{ii}^{ch}(d_{ii}) = e^{-\frac{w^{hs}(d_{ii}) + w^{el}(d_{ii})}{k_B T}} \quad (9)$$

w^{hs} and w^{el} are functions of the temperature T , the density ρ and the composition $\bar{x}$. In this work, w^{hs} is calculated from the Carnahan-Starling [113] radial distribution function and w^{el} is calculated using either the MSA or the Debye-Hückel theory. Results with both will be compared in the next section. The coulombic potential of mean force at contact estimated by the Debye-Hückel theory $w^{el,DH}$ is given by the screened two-body electrostatic interaction potential in a continuum with dielectric constant $\epsilon = \epsilon_0 \epsilon_r$, according to Eq. (10).

$$w^{el,DH}(d_{ij}) = -\frac{z_i^2 z_j^2 e^2}{4\pi\epsilon_0 \epsilon_r d_{ij}} e^{-\kappa_{DH} d_{ij}} \quad (10)$$

With κ_{DH} being the inverse of the Debye-Hückel screening length. According to the MSA theory [114], the coulombic potential of mean force at contact is given by Eq. (11). Γ is a scaling parameter as reported elsewhere [115].

$$w^{el,MSA}(d_{ij}) = -\frac{z_i^2 z_j^2 e^2}{4\pi\epsilon_0 \epsilon_r d_{ij}} \frac{1}{(1 + \Gamma d_{ij})^2} \quad (11)$$

Throughout in our work, the temperature-dependent segment diameter $d_{ij} = d_{ij}(T)$ described in [92] is employed. This term accounts for the “softness” of the repulsive part of the square-well potential of PC-SAFT and thus represents, for the other terms as well, an effective distance of closest approach. The only exception is the temperature-independent segment diameter σ_{ii} in Eq. (6).

Fig. 3 shows a comparison between the exponential approximation of the radial distribution function at contact, calculated using the MSA and the Debye-Hückel theories, and results of Monte Carlo simulation of a system of charged hard spheres in the primitive model.

The exponential approximation of $g_{ij}(d_{ij})$ with MSA matches the MC simulations almost quantitatively, whereas the estimation based on the Debye-Hückel theory leads to remarkable deviations from MC, especially at higher salt concentrations. This is probably due to neglecting the excluded volume of the surrounding ions in the continuum by the Debye-Hückel theory. However, as shown in the next section, the small deviations in the reported calculations of osmotic coefficients with MSA and Debye-Hückel do not justify the preferential use of one of both models. The Debye-Hückel theory has the advantage of simplicity and easier implementation compared to the MSA theory, and does not

require any internal iteration step, thus speeding up the phase-equilibrium calculation compared to MSA. In the following sections, calculation with MSA will be shown only once, for the sake of comparison with Debye-Hückel, namely in Fig. 5. All the other calculations, comprising osmotic coefficients (Figs. 4 and 6) and phase diagrams of complex coacervates (Figs. 7–11), are performed using pePC-SAFT exclusively with the Debye-Hückel theory. For modeling osmotic coefficients of polyelectrolyte solutions (Figs. 4–6), each of the monomers of the polyions was modeled as one single charged hard-sphere (i.e. with a segment number $m = 1$), meaning that the number of segments of each polyion m_i^{seg} is equal to the degree of polymerization $\bar{n}$; the segment

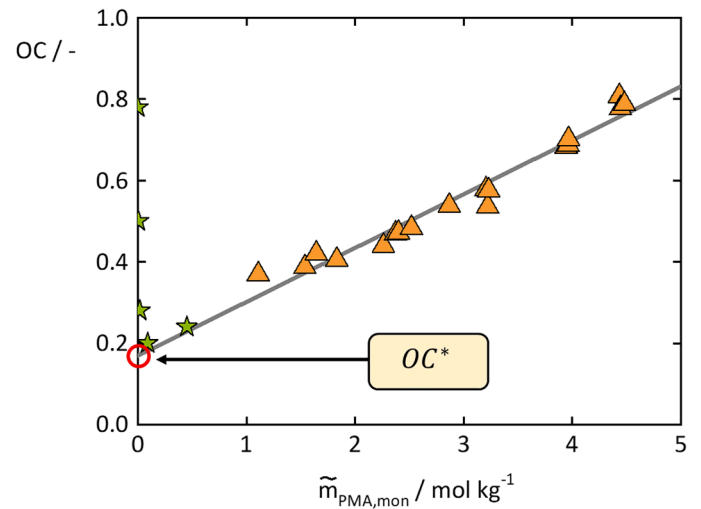


Fig. 4. Osmotic coefficients of an aqueous single polyelectrolyte solution (NaPMA with an average of $n_p = 56$ monomer units). Concentration is expressed as molality of polyion monomers. Experimental data (symbols) are from Lammertz et al. [74] (orange triangles) complemented with data of Alexandrowicz et al. [118] (green stars) at low NaBr concentration. Depicted is the linear extrapolation of experimental osmotic coefficients at high to zero polyelectrolyte concentration. For the calculation, a temperature $T = 298.15$ K and a pressure of $p = 1.013$ bar were assumed.

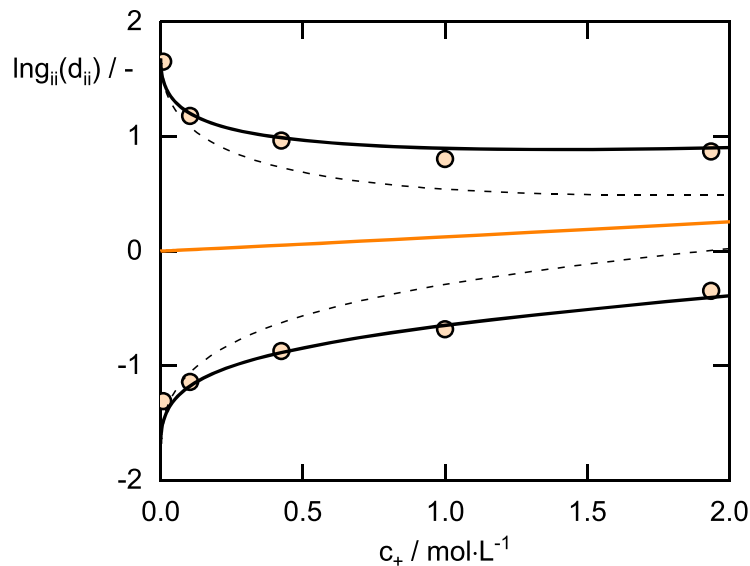


Fig. 3. Comparison of the pair correlation function of two charged hard spheres at contact, in the primitive model, determined by Monte Carlo simulations (solid circles, data from [116]), calculations with the exponential approximation of the MSA (solid line) and of the Debye-Hückel (dashed line) theories with the same parameters as [116] ($T = 298$ K, $\epsilon_r = 78.5$, $\sigma = 4.25$ Å). The middle solid, orange curve represents calculation with the Carnahan-Starling EoS. Upper values represent calculations of two oppositely charged spheres, lower values are calculations of two equally charged spheres. The same diagram was shown by Jiang et al. [48], but only with comparisons between MSA and Monte Carlo values.

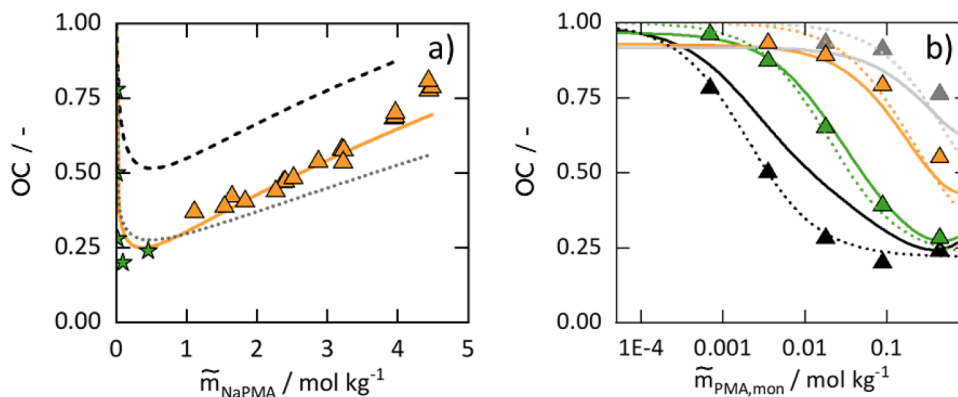


Fig. 5. Comparison between experimental (symbols) and modeled (lines) osmotic coefficients of polyelectrolyte solutions. (a) System water-NaPMA. Solid, orange line represents modeling using the Debye-Hückel theory; gray dotted line represents modeling with the MSA theory and the same set of pePC-SAFT parameters; black, dashed line is calculated with the Debye-Hückel theory and the same set of parameters as the orange line, but without considering counterion association. Experimental data are from Lammertz et al. [74] and Alexandrowicz et al. [118]. b) System water-PMA-NaBr in the low concentration region of the polyion and at different concentrations of NaBr (black: 0.001 mol kg⁻¹; green: 0.01 mol kg⁻¹; orange: 0.1 mol kg⁻¹; gray: 0.3 mol kg⁻¹). Solid lines are predicted with pePC-SAFT (using the Debye-Hückel theory) with the same model parameters as in Figure (a) (meaning using the model predictively, without fitting any parameters to the data in b)), dotted lines are predicted by the Manning theory. Experimental data are from Alexandrowicz et al. [118]. Model parameters are reported in Table S1. For all the calculations, a temperature $T = 298.15$ K and a pressure of $p = 1.013$ bar were assumed.

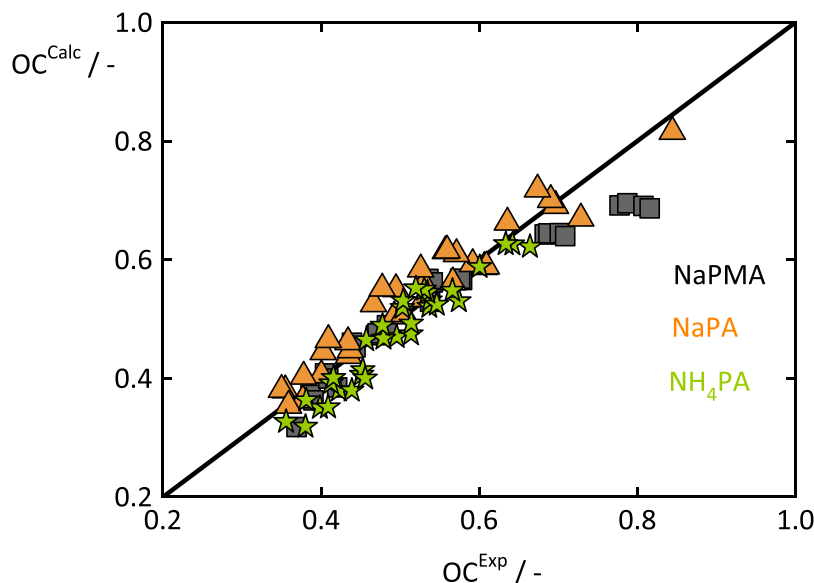


Fig. 6. Parity plot of experimental osmotic coefficients and values calculated by pePC-SAFT. Experiments and calculations are performed at $T = 298.15$ K and $p = 1$ bar. The points reported of each system comprises different degrees of polymerization $\bar{n}$ (and thus molecular weights) of the polyelectrolyte (between $\bar{n} = 26$ and $\bar{n} = 132$). Data are from Lammertz et al. [74].

Table 1

Pure-component parameters of water, polyanions, counterions and inorganic ions used in this work to model osmotic coefficients.

Component	m_i^{seg}	$\sigma_i / \text{\AA}$	$u_i/k_B / \text{K}$	$N / -$	$\epsilon^{\text{AiBi}} / \text{K}$	κ^{AiBi}	$z_i / -$	$\epsilon_i / -$	Refs.
Water	1.2047	*1	353.95	2:2	2425.7	0.04509	—	78.50	[117]
PMA ⁻	*2	4.1250	250.0	$0.45\bar{n} : 0 \text{ (ch)}^{*3}$	5500.0	0.004	*2	8	This work
PA ⁻	*2	3.5300	350.0	$0.25\bar{n} : 0 \text{ (ch)}^{*3}$	5500.0	0.004	*2	8	This work
Na ⁺	1	2.8232	230.0	$0:1 \text{ (ch)}^{*3}$	5500.0	0.004	+1	8	[95] ^{*4}
NH ₄ ⁺	1	3.5740	230.0	$0:1 \text{ (ch)}^{*3}$	5500.0	0.004	+1	8	[95] ^{*4}
Br ⁻	1	3.0707	190.0	0:0	—	—	-1	8	[95] ^{*4}

*1 $\sigma = 2.7927 + (10.11 \cdot e^{-0.01775 T} - 1.417 \cdot e^{-0.01146 T})$.

*2 The segment number m_i^{seg} , as well as the number of charges $|z_i|$, of each polyanion is equal to the reported degree of polymerization $\bar{n}$.

*3 The number of donors (or acceptors) of polyions is given as the closest integer of the expression $\alpha \cdot \bar{n}$, where α is a factor which only depends on the polyion species (but not on its length). “(ch)” in the Table means that this association is only between oppositely charged species, and all other cross-associations were set to zero.

*4 All the values of the parameters are retrieved from the reference, except the association strength and association volume, which were introduced in this work and implemented, for charged hard spheres, according to the methodology explained in Section 3.

diameter σ_i , dispersion energy u_i/k_B and number of “charged” association sites N of each polyelectrolyte, as well as the binary interaction parameters k_{ij} between each polyelectrolyte, water and the counterions were fitted to experimental osmotic coefficients by minimizing the objective function $OF = \sum_{i=1}^{N_{exp}} (1 - OC^{calc,i}/OC^{exp,i})^2$. All the other pure-component parameters and binary interaction parameters are reported, respectively, in [s 1 and 2](#).

The dielectric constant ϵ of the homogeneous phases was estimated from the dielectric constant of the pure components (reported in [Table 1](#)) by a segment-based mixing rule, given by Eq. (S-5). It must be mentioned that for the systems studied in this work the exact value of the dielectric constant ϵ (arising from the adopted mixing rule) has a marginal influence on the modeling results since water is the most abundant component and therefore dominantly determines the value of ϵ (this is in contrast to the LLPS of water, an apolar organic solvent and a salt, as studied in our previous work [\[97\]](#)). For the same reason, the Born term has a marginal influence on the modeling results as well.

4. Results and discussion

4.1. Osmotic coefficients

First, pePC-SAFT was validated against experimental osmotic coefficients of single polyelectrolyte solutions. The influence of counterion condensation on the thermodynamic behavior of polyelectrolyte solutions can be seen in [Fig. 4](#), which shows the characteristic dependence of the osmotic coefficient on the polyelectrolyte concentration, starting at $OC = 1$ (per definition), steeply decreasing until reaching a minimum, and then increasing almost linearly with the concentration.

As it can be seen, a linear extrapolation of experimental osmotic coefficients from high to zero polyelectrolyte concentration yields a certain y-axis interception. We denote this by OC^* , which is only obtained by this linear extrapolation (otherwise $OC = 1$ at zero concentration, per definition). This value OC^* has a significance, as discussed by Filho et al. [\[56\]](#), since OC data are then connected to the extent of counterion condensation α as given by [Eq. \(16\)](#).

$$OC = \frac{\ln x_w \gamma_w}{\ln x_w} \text{ and } OC^* = OC_{\tilde{m}_{polyions} \rightarrow 0} \approx \left. \frac{osm}{\tilde{m}_{all \text{ ions}}} \right|_{\tilde{m}_{polyions} \rightarrow 0} \rightarrow OC^* = \frac{\nu \cdot \alpha + 1}{\nu + 1} \quad (16)$$

In [Eq. \(16\)](#), x_w and γ_w are the molar fraction and activity coefficient of water, respectively, $\tilde{m}_{sol}$ is the molality of all the solutes in solution (polyions and counterions), osm is the osmolality of the solution, ν is the number of counterions per polyion and α the fraction of free (non-condensed) counterions. The osmolality in the dilute region can be simplified as the effective molality $\tilde{m}_i^{eff}$ of free ions in the solution, $osm = \sum_{i=ion} \nu_i \tilde{m}_i^{eff}$, and the osmotic coefficient can thus be interpreted as the ratio between the number of free and the total (bound and free) number of ions in solution. Consistently, osmotic coefficients approach $OC = 1$ at zero total solute molality. As can be seen in [Fig. 4](#), even at very low molality of the polyion, a fraction of the counterions (which can be estimated by [Eq. \(16\)](#) for $\tilde{m}_{polyel} \rightarrow 0$) remains condensed to the polyion. This can be used to estimate the fraction of free ions for $\tilde{m}_{polyel} \rightarrow 0$, which

was used by Filho et al. [\[56\]](#) to parameterize their modified Pitzer equation for polyelectrolyte solutions. In the present work, we adopted a similar approach by using the number of association sites on the polyions as an adjustable integer variable. Modeling results for the system water-NaPMA 56 (sodium polymethacrylate, i.e. the sodium salt of polymethacrylic acid, with an average degree of polymerization $\bar{n} = 56$ defined as the average number $\bar{n}$ of monomers forming the polyion) are reported in [Fig. 5](#).

The diagram in [Fig. 5a](#) shows that a non-consideration of counterion condensation significantly overestimates the osmotic coefficients. Only by including the association of counterions described by our modeling approach via a^{assoc} reduces the modeled osmotic coefficients to bring it to complete agreement with the experimental data at higher concentrations ($\tilde{m}_{PMA,mon} > 1 \text{ mol}\cdot\text{kg}^{-1}$). Further, including counterion condensation via a^{assoc} is also decisive for the modeling at smaller concentrations ($\tilde{m}_{PMA,mon} < 0.1 \text{ mol}\cdot\text{kg}^{-1}$), since up to this concentration association forces between counterions and the polyion mainly dictate the osmotic-coefficient behavior. At $\tilde{m}_{PMA,mon} > 1 \text{ mol}\cdot\text{kg}^{-1}$, the association sites on the polyion are completely occupied by counterions, and the other non-electrostatic contributions of pePC-SAFT dominate the osmotic-coefficient behavior. Further, [Fig. 5a](#) compares modeling results with pePC-SAFT using either MSA or Debye-Hückel energy expressions for a^{el} . It can be observed that there are only small differences in the modeled osmotic coefficients. Since the Debye-Hückel theory has the advantage of simplicity and easier implementation compared to the MSA theory, we decided to use the Debye-Hückel theory energy expressions for a^{el} , $a^{ch,hl}$ and a^{assol} in pePC-SAFT from now on.

[Fig. 5b](#) illustrates osmotic coefficients in the low concentration range of the polyion ($\tilde{m}_{PMA,mon} < 0.1 \text{ mol}\cdot\text{kg}^{-1}$) at different concentrations of added NaBr. The modeling by pePC-SAFT is compared with experimental data as well as with predictions by the Manning theory (using [Eq. \(40\)](#) from [\[24\]](#)). The screening of electrostatic forces due to the added salt causes increased osmotic coefficients, which is correctly predicted by pePC-SAFT and by the Manning theory. Interestingly, Manning's theory performs slightly better than pePC-SAFT, especially at the lowest considered NaBr concentrations. However, the TPT1 theory of Wertheim employed in pePC-SAFT to describe counterion association is an established theory for engineering models: in contrast to the Manning theory, the Wertheim theory can be extrapolated to mixtures of several species and holds over the whole concentration range, while Manning's theory is not able to handle mixtures of oppositely charged polyions (interactions between polyions are completely neglected) and highly concentrated phases. This is relevant for modeling the coacervate phase, where the TPT1 theory can reproduce counterion release (which is a precursor of complex coacervation) through the competitive association between polyions-counterions and polyions-polyions (where the latter prevails over the former in the coacervate phase).

The parity plot in [Fig. 6](#) shows a comparison of the experimental osmotic coefficients and modeling results for three polyelectrolyte systems with different degrees of polymerization $\bar{n}$ of each polyion: those are sodium polymethacrylate (NaPMA, with $\bar{n} = 56, 132$), sodium polyacrylate (NaPA, with $\bar{n} = 28, 73$) and ammonium polyacrylate (NH₄PA, with $\bar{n} = 26, 82, 87$). The number of segments m_{seg} (i.e. the chain length) of the modeled polyions is proportional to the degree of polymerization $\bar{n}$. Model parameters used to calculate all the osmotic coefficients are shown in [Tables 1 and 2](#). Experimental osmotic coefficients are from Lammertz et al. [\[74\]](#). The charge density and counterion condensation have the largest influence on the osmotic coefficient of a polyelectrolyte solution (when the concentration is expressed in a monomer basis), whereas the chain length has only a marginal influence. This is because thermodynamic behavior in the semi-dilute region is mainly affected by the interaction of the polyion with the surrounding ions, and for long polyions those interactions are barely affected by the chain length and by end-chain effects.

Table 2

Binary interaction parameters used in this work to model osmotic coefficients, valid at 298.15 K.

	PMA ⁻	PA ⁻	Na ⁺	NH ₄ ⁺	Br ⁻
Water	-0.095	0.08	-	-	-
PMA ⁻	-	-	-	-	-
PA ⁻	-	-	-	-0.15	-
Na ⁺	-	-	-	-	0.29
NH ₄ ⁺	-	-	-	-	-
Br ⁻	-	-	-	-	-

4.2. Complex coacervation

pePC-SAFT was further tested for the prediction of complex coacervation, i.e. of liquid-liquid phase separation in mixtures of oppositely charged polyions at different counterion concentrations. In contrast to osmotic properties, the LLPS due to complex coacervation is greatly affected by both, the charge density ($\rightarrow$ counterion condensation) and the chain length of the polyions ($\rightarrow$ mixing entropy (See Eq. (5)). Fig. 7a shows for a hypothetical mixture a characteristic phase diagram of an aqueous polyelectrolyte mixture containing polycations, polyanions, as well as the respective counterions. The procedure to calculate this and all the following diagrams is explained in our previous work [119] and is elucidated in Appendix B. The 3D phase diagram (Fig. 7a) was calculated with pePC-SAFT for this hypothetical system with the same chain length of the polycation and the polyanion. The set of parameters for

polyanion and polycation was assumed to be equal but opposite charges were applied, and even the counterions were assigned with the same parameters (and opposite charges) but only with one segment; these parameters can be found in Table S1. Those complex coacervate systems contain at least five species: the solvent water, polycation and polyanion, and their respective counteranion and counteranion. However, due to the electroneutrality and summation conditions ($\sum_{i=1}^N \zeta_i = \text{const}$, with ζ_i being a concentration unit, e.g., molar or mass fraction; the same holds for the molality) only three independent variables need to be provided to completely specify the system (at a given pressure and temperature). In Fig. 7a, these independent variables are the segment fraction of the polycation Φ_{Polycat} (X axis), of the polyanion Φ_{Polyan} (Y axis) and the sum of the segment fractions of both the counteranion and the counteranion $\Phi_{\text{Cat+An}}$ (Z axis). The segment fraction of a component i is defined as the fraction of the total segments in the system (i.e. from

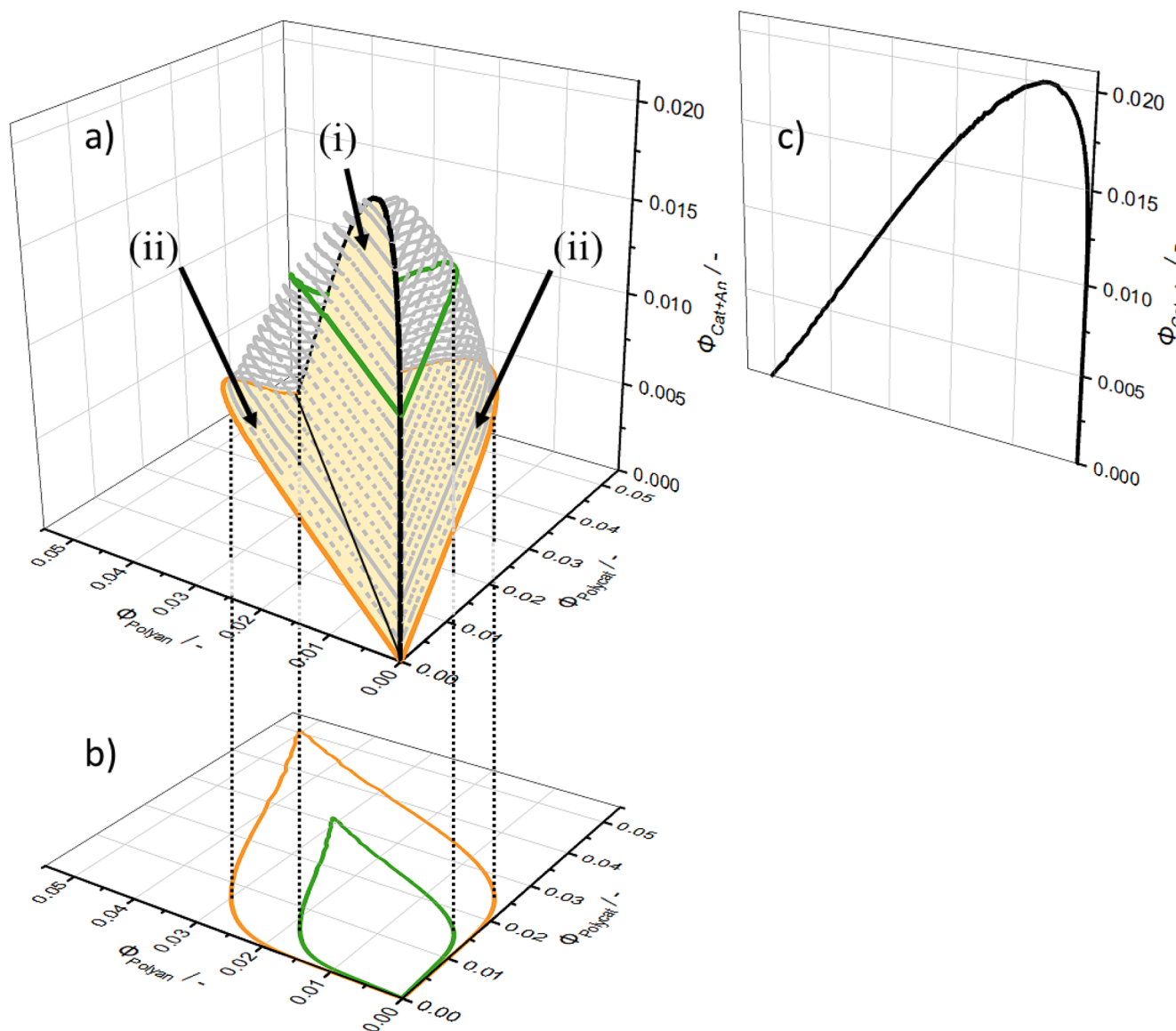


Fig. 7. (a) 3D phase diagram of a chain-length symmetric complex coacervate system calculated with pePC-SAFT. The Z axis shows the segment fraction $\Phi_{\text{Cat+An}}$ of both the counteranion and the counteranion, the X and Y axis represent, respectively, the segment fraction of polycation Φ_{Polycat} and polyanion Φ_{Polyan} (Φ_i defined according to Eq. (17)). In a), the vertical yellow surface (i) and the yellow surfaces (ii) at the bottom left and right pointed by black arrows represent, respectively, manifolds of tie-lines at constant $C_{\text{Polycat}}/C_{\text{Polyan}}$ ratio and at minimal counterion concentration. The green curve on the same diagram is built, from a point in the yellow surfaces at the bottom and at a fixed ratio of both phases, by adding a constant amount of both counterions at stoichiometric ratio. b) Phase envelope of the system in 2D illustration, which represents projections of the orange curve (binodal at minimal salt concentration) and the green curve from the 3D diagram of a), on the XY plane (without the salt). c) Phase envelope of the system in 2D illustration which represents a projection from the vertical yellow area of the diagram of a) on the XZ plane of the same diagram. Calculation for $T = 298.15$ K and $p = 1$ bar pePC-SAFT parameters are given in Table S1.

all the components which are present) that comes from the component i and is defined, from the segment number m_j and mole fraction x_j of each component $j = 1, \dots, N$, according to Eq. (17).

$$\Phi_i = \frac{m_i x_i}{\sum_j m_j x_j} \quad (17)$$

Due to the electroneutrality condition, the exact ratio between the volume fraction of counteranions and counteranions depends on the value of Φ_{Polycat} and Φ_{Polyan} . Three surfaces are highlighted in yellow in Fig. 7a and marked by black arrows: (i) the vertical surface framed by the bold black line at stoichiometric polycation-polyanion concentration ratio (from now referred as $C_{\text{Polycat}/\text{Polyan}}$ ratio) and increasing counterions concentrations (i.e. increasing $\Phi_{\text{Cat}+\text{An}}$), and (ii) two surfaces on the bottom left and bottom right of the diagram, which are encompassed by bold orange lines and which intersect the vertical plane (i) at the polycation-polyanion stoichiometric tie-line at $\Phi_{\text{Cat}+\text{An}} = 0$. These two surfaces (ii) represent manifolds of tie-lines in the two-phase region at varying non-stoichiometric $C_{\text{Polycat}/\text{Polyan}}$ ratio, when the concentration of counterions is minimal. In this context, “minimal” means that no more counterions are present in the system than those required to not violate the electroneutrality condition (of the system and of both phases) at the given $C_{\text{Polycat}/\text{Polyan}}$ ratio. For example, when the polycation is present in excess, a minimal amount of only the counteranion (given as the difference in charge concentration between polycation and polyanion in each phase) must be present to compensate for the excess of positive charges in each phase. If $C_{\text{Polycat}/\text{Polyan}}$ is stoichiometric, the polyions mixture is electroneutral and no additional counterions is required (corresponding to the condition $\Phi_{\text{Cat}+\text{An}} = 0$). It must be pointed out that the condition $\Phi_{\text{Cat}+\text{An}} = 0$ cannot be realized experimentally, since no solution containing a mixture of polyions can be prepared without adding the respective counterions. The whole binodal surface of the 3D diagram, depicted by a manifold of gray lines, ends at those two surfaces (ii), which represent the limiting case. Below the surfaces (ii), thermodynamic states are not possible since they would violate the electroneutrality condition.

Since the lower limiting curves (orange curves) are now defined for which phases might exist physically, the question is now what happens to the demixed phase region if the counterion concentration increases. Here, Fig. 7a provides an answer by highlighting a green curve that is of similar shape as the orange curve but of smaller size. The green curve is representative of one of the grey curves, i.e. curves of the binodal surface but with concentrations higher than in the limiting case (orange curve). Such lines are hypothetically prepared from any tie-line at minimal counterion concentration (i.e. from the yellow surface at the bottom) by adding a constant amount of both counterions, at stoichiometric ratio, to a composition point within this tie-line at fixed ratio of both phases (i.e. from a point at a fixed length ratio within the tie-line). Since increasing the concentration of small inorganic ions (either counterions or additional ions) in the system leads to salting-in, the resulting green curve in the diagram of Fig. 7a is smaller in size compared to the orange one. Fig. 7b projects points on the orange and green curves to the XY (polycation-polyanion) plane from the diagram of Fig. 7a. However, this representation in Fig. 7b leads to a loss of information about the concentration of the counterions; in the literature, equilibrium concentrations at different $C_{\text{Polycat}/\text{Polyan}}$ ratio are usually reported in the form of this 2D phase envelope of Fig. 7b (see, for example, Fig. 5 from [50]), only showing the polycation and polyanion concentration, without providing any information on the concentration and partitioning of the counterions. A particularity in the 2D representation is the appearance of a discontinuity in the diagram, in the form of a peak, in the point of maximal polycation and polyanion concentration. This is, of course, thermodynamically non-existent and this discontinuity is explained by the counterion-free illustration of the XY projection of the diagram of Fig. 7a. Another representation often found in the literature is the so-called polyelectrolyte-salt diagram, which is given by the 2D diagram

of Fig. 7c. This diagram is generated as a projection of the vertical surface of the diagram of Fig. 7a in one of the XZ (polyanion-counterions) or YZ (polycation-counterions) planes. In this diagram, which represents a complex coacervate system at a stoichiometric $C_{\text{Polycat}/\text{Polyan}}$ ratio with increasing counterion concentration, the overall salt concentration (Y axis) and the concentration of one of the polyions (X axis) is reported (the concentration of the other polyion, as well as of both counterions, is often assumed to be the same, see [49–51]). In the following, this diagram will be used to closer investigate the qualitative features of pePC-SAFT in predicting LLPS in complex coacervate systems, as well as the influence of the physical parameters of the model on the calculated phase diagram (c.f. effect of the chain length, of the charge density as well as of the consideration or neglecting of polyion-counterion and polycation-polyanion association).

The phase envelope of polyelectrolyte-salt-water systems at $T = 293$ K and $p = 1$ bar at different degrees of polymerization are illustrated in Fig. 8. Fig. 8b shows a manifold of envelopes, calculated with pePC-SAFT, for a hypothetical chain-length symmetric coacervate system (i.e. with polyanion and polycation having the same chain length and present at stoichiometric ratio) at three different chain lengths of both polyions, as function of the counteranion concentration. Since the same parameters were used for both polyanions, as well as for both counterions (except for the sign of their charges), the concentration of both polyions is the same, as is the concentration of both counterions. Therefore, it is enough to provide the concentration of one of the polyions (X-axis) and one of the counterions (Y-axis), and the system is fully specified at the given temperature and pressure. The pePC-SAFT parameters are reported in Table S1. Fig. 8a then compares the findings of the calculated diagram in Fig. 8b with experimental data of a coacervate system determined by Spruijt et al. [43] for the system PAA (polyacrylic acid)-PDMAEMA (poly-N,N-dimethylaminoethyl methacrylate)-KCl. Further, Fig. 8a shows the prediction of the coacervate system with the VO model for the different degrees of polymerization of both polyanion and polycation.

Direct comparison of the experimental data with pePC-SAFT predictions was not possible in Fig. 8a due to the lack of pePC-SAFT parameters for PDMAEMA. Nevertheless, some qualitative statements between the modeling results and the experimental data can be drawn: i) pePC-SAFT correctly reproduces the enlargement of the miscibility gap with increasing chain length of the polyions. This behavior, which is known from experiments (such as that from Spruijt et al. [43] or Li et al. [120]) and is predicted also by the VO model [41,42], can be fully explained by the Flory-Huggins mixing entropy of chain-like molecules such as polyions: an idealized mixture of chain-like molecules consisting of ν_p monomers in a solvent of small molecules (such as water) has a much lower mixing entropy than the corresponding mixture of disconnected monomers, due to the loss of translational degrees of freedom of the single monomers upon chain formation. For this reason, the entropic penalty for phase separation is lower the longer the chain is, i.e. this penalty is maximally great for the small inorganic counterions. ii) The same arguments explain that the counterions tend to partition approximately equally into both, the coacervate phase and the dilute aqueous supernatant phase (see the predicted tie-lines on the right diagram of Fig. 8), which is also correctly predicted by pePC-SAFT. The reason behind this predictive power is that the hard-chain part of pePC-SAFT can be interpreted as a non-lattice equivalent of the Flory-Huggins model (the hard-chain term of pePC-SAFT shows, however, a non-vanishing enthalpic contribution, in contrast to the athermal chain described by the Flory-Huggins model). Fig. 9 shows the predicted dependence of the total polyion concentration (in segment fraction) in the coacervate phase, without added salt, on the fraction of charged segments of each polyion (i.e. the number of charged versus the total number of segments) across different values of dispersion energy between the polyions and water. Reported in the diagram are also experimental values of Neitzel et al. [121] of the total weight fraction of

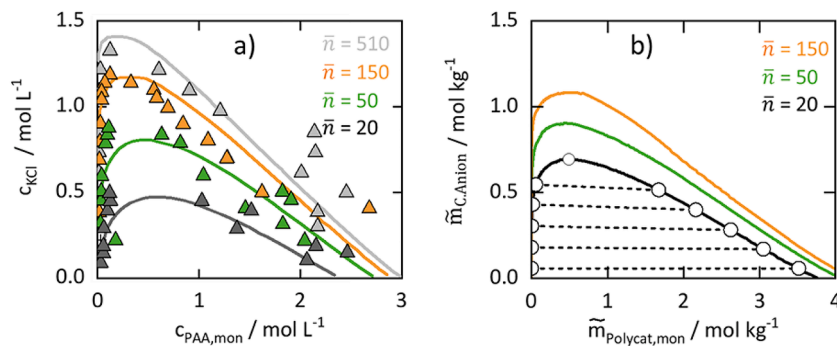


Fig. 8. Polyelectrolyte-salt-water phase envelopes at $T = 293$ K and $p = 1$ bar at different degrees of polymerization $\bar{n}$ a) showing experimental points of the binodal (symbols) in the system water/PAA/PDMAEMA/KCl vs. modeled results using the VO model (solid lines), adapted from Spruijt et al. [43]. b) of an hypothetical chain-length symmetric coacervate system, calculated with pePC-SAFT, together with tie-lines of the phase diagram of the shortest polyion with $\bar{n} = 20$ (connected symbols). Concentrations are expressed as monomer basis. Model parameters are reported in Table S-1.

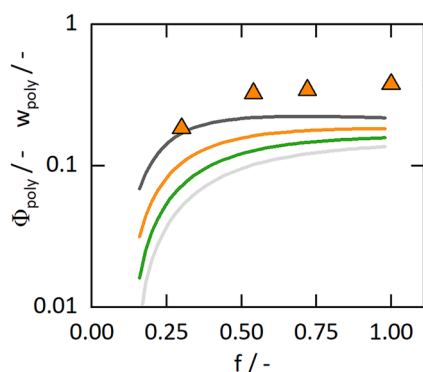


Fig. 9. Total polyion concentration in the coacervate phase as function of the charge fraction of the polyions. Symbols are experimental data of Neitzel et al. (in weight fraction), lines are prediction of pePC-SAFT (in segment fraction) using parameters from Table S-1 for a chain of 50 segments and different values of the dispersion energy between the polyions and water (black: $k_{ij} = -0.07$; orange: $k_{ij} = -0.1$; green: $k_{ij} = -0.13$; gray: $k_{ij} = -0.16$).

polyions in the coacervate phase of the coacervate system containing two differently functionalized Poly(allyl glycidyl ethers).

The data of Neitzel et al. and our prediction show the same dependence of the coacervate phase concentration on the charge density for $f > 0.5$. Below this value, the concentration of the coacervate shows a strongly pronounced decrement, and our model predicts no

electrostatic-driven phase separation at all for $f < 0.15$. Interestingly, Neitzel et al. found no phase separation in the system prepared with a charge density of $f = 0.10$, in agreement with our calculations.

Particularly interesting is to compare the effect of counterion-polyion association (i.e. counteranion-polyanion and counteranion-polycation) and polyanion-polycation association, introduced within our approach to treat counterion condensation and soluble complex formation, and the effect of the charge density on the resulting miscibility gap, which are shown in Fig. 10a and 10b. Increasing the number of association sites on the polyanion and on the polycation chains leads to an enlargement of the miscibility gap, while the partitioning of the counterions between coacervate phase and supernatant phase is nearly not affected. However, as the number of association sites increases, the qualitative picture of the phase envelope remains unchanged. In contrast, increasing the charge density of the polyions has a very strong effect on the size of the miscibility gap (and, slightly, also on the partitioning of the counterions) as shown in the diagrams of Fig. 10a and of Fig. 9.

The diagrams of Fig. 10a and 10b show only a slight change of the partitioning of small ions between both phases across different charge densities and considering association with the polyions. Overall, the concentration of counterions remains similar in magnitude in both phases, and preferential partitioning into the supernatant or the coacervate phase is not generalizable and is mainly dictated by specific interactions with the polyions [121]. Fig. 11 shows the same phase envelope as that of Fig. 7b at given chain length of the polycation but with different chain lengths of the polyanion (i.e. a chain-length asymmetric mixture). Decreasing the chain length of one of the polyions

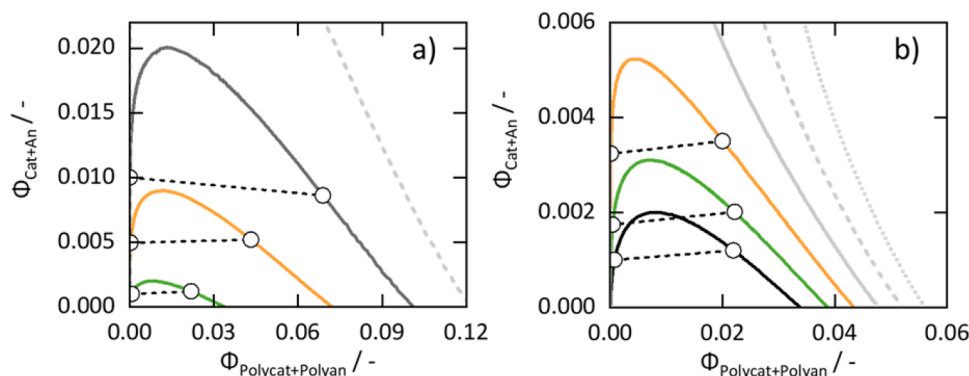


Fig. 10. Polyelectrolyte-salt-water phase envelopes, calculated with pePC-SAFT for a chain length of 50 segments at $T = 298.15$ K and $p = 1$ bar a) binodal curves for different number of charges along the chains of both the polyanion and the polycation (green: 10; orange: 15; black: 20; dashed gray: 25). b) binodal curves for different number of counterion that are allowed to associate on the chain of both the polycation and the polyanion, for a chain of 50 segments and 10 charges (black: no association sites; green: 1; orange: 2; solid gray: 3; dashed gray: 4; dotted gray: 5). Model parameters are shown in Table S-1.

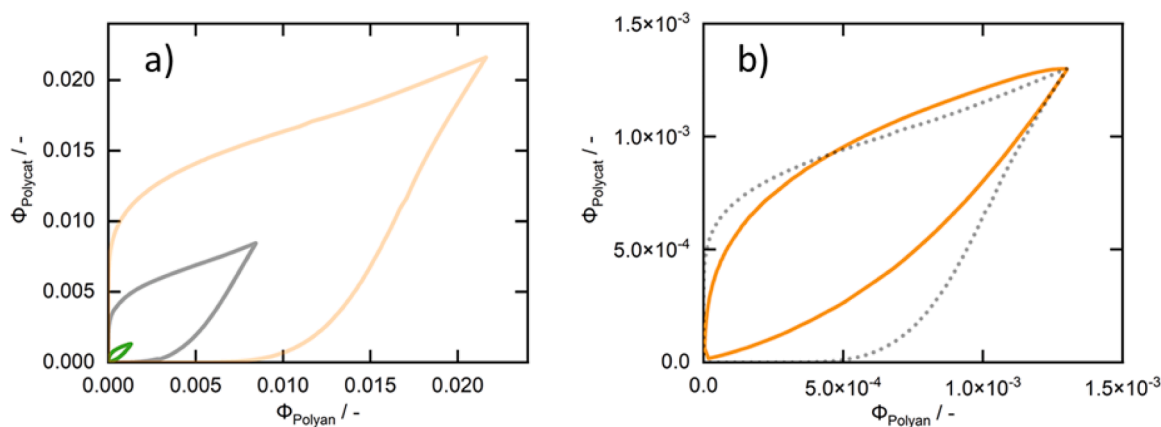


Fig. 11. Polyelectrolyte-salt-water phase envelopes of a chain length asymmetric system, calculated with pePC-SAFT.

(a) polycation-polyanion phase envelope for salt-free systems at fixed polycation length of $\bar{n} = 20$ and different lengths of the polyanion (orange: $\bar{n} = 20$; gray: $\bar{n} = 10$; green: $\bar{n} = 5$).

(b) phase envelope of the system with a polyanion length of $\bar{n} = 5$; the dotted line represents the phase envelope of the symmetric system, which is scaled to the size of the asymmetric system for the purpose of comparison. Model parameters are shown in Table S-1.

reduces the size of the miscibility gap, according to the increased entropic penalty for phase separation of shorter chains. The qualitative shape of the phase envelopes only slightly changes, and the miscibility gap becomes smaller if the shorter polyion is present in excess.

5. Conclusion

It was the aim of this work to understand the behavior of single polyelectrolyte solutions and of complex coacervates in order to develop a thermodynamic model which is valid to cover a wide range of concentrations and compositions of polyions and counterions. In this work, the pePC-SAFT EoS was revised and the leading assumptions in the electrostatic term were carefully discussed to assess the capability of the model in reproducing the most important phenomena that occur in aqueous solutions of single polyelectrolytes and in complex coacervate systems. The key phenomena of counterion condensation, formation of polyelectrolyte complexes and complex coacervation were discussed and strategies were derived to consider them in pePC-SAFT. To the best of our knowledge, no engineering-oriented thermodynamic model ever attempted to consider all of these three phenomena. Both the Debye-Hückel and MSA theories were compared and used in the electrostatic, charged hard-chain and association terms of pePC-SAFT, leading to similar results which do not justify the superiority of one particular theory in the final model. Caused by simplicity, it is suggested to use Debye-Hückel in the modeling framework, which was also followed in this work. Modeling polyelectrolytes requires accounting for counterion condensation. This was explicitly accounted for by employing the TPT1 theory of Wertheim for charged hard spheres. The formation of polyelectrolyte complexes was then described by the TPT1 theory as well.

Using pePC-SAFT within this new approach allowed accurately predicting osmotic coefficients of polyelectrolyte solutions. This confirmed the assumption that the thermodynamic behavior of solutions of single polyelectrolytes in the semi-dilute region is dominated by electrostatic interactions between polyions and counterions. Further,

pePC-SAFT was used to model phase equilibria of complex coacervates. pePC-SAFT was found to be able to accurately reproduce several features of the LLPS in complex coacervates, such as the salting-in effect upon increase the concentration of counterions, as well as the chain-length dependence of the resulting LLPS.

The model allows to predict phase behavior of coacervate systems in the future, which are relevant for understanding cellular processes as well as engineering applications (e.g. using complex coacervates as extraction systems).

CRediT authorship contribution statement

Moreno Ascani: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Gabriele Sadowski:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Christoph Held:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.fluid.2024.114304](https://doi.org/10.1016/j.fluid.2024.114304).

Appendix A. Derivation and Assumptions of the Chain-Formation Term

In this Section, an exact expression of the Helmholtz energy of a mixture of chain molecules of equal-sized spherical-symmetric monomers, each

containing r monomers (r -mer), and unbound monomers (with the same size as the monomers in the r -mers) is derived as perturbation of the Helmholtz energy of the mixture of pure monomers. The assumptions employed in this work are then re-derived and discussed. The Helmholtz energy A of a system of N monomers (each possessing 3 translational degrees of freedom), of which $r \cdot N_r$ are bound into N_r r -mers and N' are free monomers (thus $N = r \cdot N_r + N'$), at temperature T and volume V and in absence of an external potential is given by Eqs. (A.1), (A.2) [122].

$$A(N, V, T) = -k_B T \ln Q(N, V, T) = -k_B T \ln \left\{ \frac{1}{N_r! N'! \Lambda^{3N}} Z_N(V, T) \right\} \quad (\text{A.1})$$

$$Z_N(V, T) = \int_1 \int_2 \dots \int_N e^{-\frac{U_N(\bar{r}_1, \bar{r}_2, \dots, \bar{r}_N)}{k_B T}} d\bar{r}_1, d\bar{r}_2, \dots, d\bar{r}_N \quad (\text{A.2})$$

In Eq. (A.1), N' Represents the number of permutations of the free monomers and $N_r!$ The number of permutations of the r -mers (the N' monomers and the N_r r -mers, respectively, are considered indistinguishable). The position of each monomer $\bar{r}_i$, over which the integration in the configurational integral (Eq. (A.2)) is performed, is given by the three cartesian coordinates in Eq. (A.3).

$$\bar{r}_i = (x_i, y_i, z_i) \quad (\text{A.3})$$

In Eq. (A.2), $d\bar{r}_i$ represents the volume element $dV_i = dx_i dy_i dz_i$ over which the integration is performed. For the derivation of the perturbation term corresponding to the chain formation, it is more convenient to change the variables of integration into spherical coordinates. Furthermore, since the interaction potential U_N only depends on the relative position of the monomers, the position of a monomer j can be expressed from the coordinate of another monomer i . The resulting relative position $\bar{r}_{ij}$ and volume element $d\bar{r}_{ij}$ are given by Eqs. (A.4), (A.5).

$$\bar{r}_{ij} = (r_{ij}, \vartheta_{ij}, \psi_{ij}) \quad (\text{A.4})$$

$$d\bar{r}_{ij} = r_{ij}^2 \sin(\psi_{ij}) d\vartheta_{ij} d\psi_{ij} \quad (\text{A.5})$$

The resulting configuration integral is given by Eq. (A.6).

$$Z_N(V, T) = V \int_{\Theta_{12}} \int_{\Theta_{23}} \dots \int_{\Theta_{N-1,N}} e^{-\frac{U_N(\bar{r}_{12}, \bar{r}_{23}, \dots, \bar{r}_{N-1,N})}{k_B T}} d\bar{r}_{12}, d\bar{r}_{23}, \dots, d\bar{r}_{N-1,N} \quad (\text{A.6})$$

The volume V in the expression of the configuration integral (Eq. (A.6)) comes from the fact that the absolute position of the first monomer can be integrated independently on the remaining $N - 1$ monomers (translational invariancy), since only the relative position of each monomer affects the interaction potential U_N . Θ_{ij} denotes the domain of integration of $\bar{r}_{ij}$. The interaction potential U_N of a mixture of free and joint monomers (into chains of r -mers) can be expressed as a sum of the interaction potential of the system of full disconnected monomers $U_N^{(0)}$ and a term ΔU responsible for the bond into chains. For simplicity, we only consider the formation of r -mers, i.e. chains containing r jointed monomers, in the mixture. The potential U_N is given by Eqs. (A.7), (A.8).

$$U_N = U_N^{(0)} + \Delta U \quad (\text{A.7})$$

$$\Delta U = \sum_{k=1}^{N_r} \sum_{i=1}^{r-1} \Delta u(r_{i,i+1}^{(k)}) \quad (\text{A.8})$$

The perturbation potential Δu is taken to be that of a harmonic oscillator with functional form given by Eq. (A.9).

$$\Delta u(r_{i,i+1}^{(k)}) = \frac{k_H}{2} (r_{i,i+1}^{(k)} - \sigma)^2 \quad (\text{A.9})$$

In Eq. (A.9), k_H is the Hooks constant giving the stiffness of the spring, which is assumed to be unstrained at $r = \sigma$ (i.e. when the neighbor monomers in the r -mer are at contact) independently on the angles between the monomers in the r -mer. For the sake of simplicity, in the expression of the configuration integral, we consider the first $i = 1, \dots, r, r+1, \dots, 2r, \dots, rN_r$ monomers as belonging to r -mer chains, while the remaining $i = rN_r + 1, \dots, N$ are free (unbound) monomers (we empathize that, to evaluate the configurational integral, we give labels i to each particle in the system, i.e. we make them distinguishable, and in principle this can be done freely). The configuration integral $Z_N(V, T)$ can now be expressed as product of the configuration integral of the reference system $Z_N^{(0)}(V, T)$ and a perturbation term [91] according to Eq. (A.10).

$$Z_N(V, T) = \frac{Z_N^{(0)}(V, T)}{Z_N^{(0)}(V, T)} Z_N(V, T) = Z_N^{(0)}(V, T) \frac{\int_{\Theta_{12}} \int_{\Theta_{23}} \dots \int_{\Theta_{N-1,N}} e^{-\frac{\Delta U(\bar{r}_{12}, \bar{r}_{23}, \dots, \bar{r}_{N-1,N})}{k_B T}} e^{-\frac{U_N^{(0)}(\bar{r}_{12}, \bar{r}_{23}, \dots, \bar{r}_{N-1,N})}{k_B T}} d\bar{r}_{12}, d\bar{r}_{23}, \dots, d\bar{r}_{N-1,N}}{\int_{\Theta_{12}} \int_{\Theta_{23}} \dots \int_{\Theta_{N-1,N}} e^{-\frac{U_N^{(0)}(\bar{r}_{12}, \bar{r}_{23}, \dots, \bar{r}_{N-1,N})}{k_B T}} d\bar{r}_{12}, d\bar{r}_{23}, \dots, d\bar{r}_{N-1,N}}} = Z_N^{(0)}(V, T) \left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0 \quad (\text{A.10})$$

The term $\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0$ denotes the canonical average of the Boltzmann factor $e^{-\frac{\Delta U}{k_B T}}$ in the unperturbed system 0. The perturbation translates exactly into a separation of terms in the Helmholtz energy given by Eqs. (A.11), (A.12).

$$A = A^0 + \Delta A \quad (\text{A.11})$$

$$\Delta A = -k_B T \ln \left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0 \quad (\text{A.12})$$

And the corresponding residual perturbation term ΔA^{res} (the difference between the actual perturbation term ΔA and the perturbation term in the

ideal gas ΔA^{id}) is given by Eq. (A.13).

$$\Delta A^{res} = -k_B T \ln \frac{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0}{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_{id}} \quad (\text{A.13})$$

When moving to the limit of r -mers of spheres at contact (with zero bond length, i.e. $r_{i,i+1}^{(k)} = \sigma$) by letting $k_H \rightarrow \infty$ in Eq. (A.9), the perturbation term ΔA diverges since the argument in the natural logarithm of Eq. (A.12) tends to zero. The same divergence is observed in the TPT1 theory of Wertheim in the limit of complete association [123] and can be eliminated by taking the difference $\Delta A^{res} = \Delta A - \Delta A^{ig}$ between the actual mixture (ΔA) and the ideal gas mixture of N_r r -mers and N' free monomers (ΔA^{ig}), as done in Eq. (A.13). To convert Eq. (A.13) into a more useful expression, we first consider the integral I of the Boltzmann factor of the perturbation potential Δu (Eq. (A.9)) between the limits $r = -\infty$ and $r = +\infty$, which is given by Eq. (A.14).

$$I = \int_{-\infty}^{+\infty} e^{-\frac{k_H}{2k_B T} (r-\sigma)^2} dr = \sqrt{\frac{2\pi k_B T}{k_H}} \quad (\text{A.14})$$

Dividing the numerator and denominator in the ratio of the argument of the logarithm of Eq. (A.13) by $I^{N_r(r-1)} = \left(\sqrt{2\pi k_B T / k_H} \right)^{N_r(r-1)}$, the ratio

$$\frac{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0}{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_{id}} = \frac{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0}{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_{id}} \frac{I^{N_r(r-1)}}{I^{N_r(r-1)}} = \frac{\left\langle \prod_{k=1}^{N(r)} \prod_{i=1}^{r-1} \sqrt{\frac{k_H}{2\pi k_B T}} e^{-\frac{k_H}{2k_B T} (r_{i,i+1}^{(k)} - \sigma)^2} \right\rangle_0}{\left\langle \prod_{k=1}^{N(r)} \prod_{i=1}^{r-1} \sqrt{\frac{k_H}{2\pi k_B T}} e^{-\frac{k_H}{2k_B T} (r_{i,i+1}^{(k)} - \sigma)^2} \right\rangle_{id}} \quad (\text{A.15})$$

The normalized Boltzmann factors contained in the double product $\prod_{k=1}^{N(r)} \prod_{i=1}^{r-1} (\dots)$ of Eq. (A.15) strongly resembles the form of a Gaussian distribution which becomes increasingly peaked around σ with increasing k_H and, for $k_H \rightarrow \infty$, becomes a Dirac delta function according to Eq. (A.16).

$$\sqrt{\frac{k_H}{2\pi k_B T}} e^{-\frac{\Delta u(r)}{k_B T}} \rightarrow \delta(r - \sigma) \text{ for } k_H \rightarrow \infty \quad (\text{A.16})$$

Under an integral sign, the Dirac delta function extracts the value of the integrand $f(r)$ at the value $r = \sigma$, according to Eq. (A.17).

$$\int f(r) \delta(r - \sigma) dr = f(\sigma) \quad (\text{A.16})$$

The normalized Boltzmann factor of the perturbation potential ΔU , defined by Eqs. (A.8), (A.9), becomes then a product of Dirac delta functions, according to Eq. (A.17).

$$\left\langle \prod_{k=1}^{N(r)} \prod_{i=1}^{r-1} \sqrt{\frac{k_H}{2\pi k_B T}} e^{-\frac{k_H}{2k_B T} (r_{i,i+1}^{(k)} - \sigma)^2} \right\rangle_0 = \left\langle \prod_{k=1}^{N(r)} \prod_{i=1}^{r-1} \delta(r_{i,i+1}^{(k)} - \sigma) \right\rangle_0 \quad (\text{A.17})$$

At this point, the formulation given by Eqs. (A.15), (A.17) is exact, independently of the employed reference potential (0). The canonical average in Eq. (A.17) is performed by considering all the monomers of the N_r r -mers in the system to be bonded (i.e. with relative distance fixed at $r_{i,i+1}^{(k)} = \sigma$) at the same time, with the integration covering all the remaining angular degrees of freedom within each chain, the distance between all the chains as well as the position of all the remaining non-bound monomers. This is a very involved calculation, and to the best of our knowledge there is no theory, either analytical or solvable with a simple iterative procedure, which fully accounts for all the interactions incorporated in Eq. (A.17). To obtain a mathematical tractable expression for the perturbation term, an assumption common to almost all theories is to integrate the angular degrees of freedom of each chain independently and considering the remaining chains disconnected. This level of approximation is called *single-chain approximation* [123], and results in approximating the whole canonical average in Eq. (A.17) as a product of N_r canonical averages of the Dirac delta function for the terms corresponding to the single chains (which means taking the first product $\prod_{k=1}^{N(r)}$ out of the brackets of Eq. (A.17)), according to Eq. (A.18) (see Fig. 2 for a visualization of this approximation).

$$\left\langle \prod_{k=1}^{N(r)} \prod_{i=1}^{r-1} \delta(r_{i,i+1}^{(k)} - \sigma) \right\rangle_0 \approx \prod_{k=1}^{N(r)} \left\langle \prod_{i=1}^{r-1} \delta(\|r_{i,i+1}^{(k)} - \sigma\|) \right\rangle = \left\langle \prod_{i=1}^{r-1} \delta(\|r_{i,i+1} - \sigma\|) \right\rangle^{N(r)} \quad (\text{A.18})$$

In Eq. (A.18), the index (k) in $r_{i,i+1}^{(k)}$ was dropped to indicate that only one chain is now considered in the canonical ensemble average. It should be noted that the single-chain approximation is exact for the ideal gas, in which each chain does not interact with any of the surrounding particles, either free monomer or r -mers.

The canonical average of the Dirac delta function in Eq. (A.18), $\left\langle \prod_{i=1}^{r-1} \delta(\|r_{i,i+1} - \sigma\|) \right\rangle_0$, corresponds to a r -body probability distribution function

$P^{(r)}$ at the value of the radial coordinate $r_{i,i+1}$ fixed at σ (for $i = 1, \dots, r-1$) [124]. It is important to note that $P^{(r)}(r_{i,i+1} = \sigma)$ is NOT function of the particle coordinates, as it is $P^{(r)}(r_{i,i+1})$, but is a thermodynamic quantity dependent only on the volume V , the total number of particles N_r and N and the temperature T . $P^{(r)}(r_{i,i+1} = \sigma) dr_{12} dr_{23} \dots dr_{r-1,r}$ has the meaning of the probability of finding (pairwise) r monomers, in a system interacting only through the reference potential $U_N^{(0)}$, in the distance range between $r_{i,i+1} = \sigma$ and $r'_{i,i+1} = \sigma + dr_{i,i+1}$ of monomer i and $i+1$ (for $i = 1, \dots, r-1$), irrespective of their angular configuration and the configuration of all the other monomers. $P^{(r)}(r_{i,i+1} = \sigma)$ is given by Eq. (A.19).

$$P^{(r)}(r_{i,i+1} = \sigma) = \frac{\sigma^{2(r-1)} \int_{\Psi_{12}} \dots \int_{\Psi_{r-1,r}} \int_{\Theta_{r,r+1}} \dots \int_{\Theta_{N-1,N}} e^{-\frac{U_N^{(0)}(r_{i,i+1}=\sigma)}{k_B T}} \sin(\psi_{12}) d\psi_{12} d\vartheta_{12}, \dots, d\bar{\mathbf{r}}_{N-1,N}}{\int_{\Theta_{12}} \int_{\Theta_{23}} \dots \int_{\Theta_{N-1,N}} e^{-\frac{U_N^{(0)}}{k_B T}} d\bar{\mathbf{r}}_{12}, d\bar{\mathbf{r}}_{23}, \dots, d\bar{\mathbf{r}}_{N-1,N}} \quad (\text{A.19})$$

In Eq. (A.19), $\Psi_{i,i+1}$ denotes the domain of integration comprising only the angular coordinates $\psi_{i,i+1}$ and $\vartheta_{i,i+1}$ ($\Psi_{i,i+1} = \{0, \pi\}; \{0, 2\pi\}$) between (pairwise) the first r monomers, whose relative distance $r_{i,i+1}$ is kept fix at σ (thus forming a r -mer). For an ideal gas, $P^{(r),id}(r_{i,i+1} = \sigma)$ is given by Eq. (A.20).

$$P^{(r),id}(r_{i,i+1} = \sigma) = \frac{\sigma^{2(r-1)} \int_{\Psi_{12}} \dots \int_{\Psi_{r-1,r}} e^{-\frac{U_N^{(0)}(r_{i,i+1}=\sigma)}{k_B T}} \sin(\psi_{12}) d\psi_{12} d\vartheta_{12}, \dots, \sin(\psi_{r-1,r}) d\psi_{r-1,r} d\vartheta_{r-1,r}}{V^{r-1}} \quad (\text{A.20})$$

In Eq. (A.20), the expression on the numerator is the internal configuration integral of an r -mer in the ideal gas (with the intrachain monomer-monomer as the only interactions occurring in the system). The factor $\sigma^{2(r-1)}$ comes from the fact that the term $r_{ij}^2 \sin(\psi_{ij})$ appears in the configurational integral when moving from cartesian into spherical coordinates and that the Dirac delta function extracts the value $r_{ij}^2 = \sigma^2$ ($r-1$) times in Eq. (A.18). The r -body correlation function $g^{(r)}$ is related to the probability distribution $P^{(r)}$ through the density distribution $\rho^{(r)}$ and the bulk particle density ρ via Eq. (A.21) [122].

$$g^{(r)} = \frac{\rho^{(r)}}{\rho^r} = \left(\frac{V}{N}\right)^r \frac{N!}{(N-r)!} P^{(r)} \approx V^r (1 + O(N^{-1})) P^{(r)} \quad (\text{A.21})$$

Since $g^{(r)}$ and $P^{(r)}$ differ by a constant value which is independent on whether the system is considered as ideal gas or not, Eq. (A.13) can be rewritten into Eq. (A.22) using $g^{(r)}$ and Eqs. (A.18)–(A.21).

$$\Delta A^{res} = -k_B T \ln \frac{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle_0}{\left\langle e^{-\frac{\Delta U}{k_B T}} \right\rangle} = -k_B T N^{(r)} \ln \frac{P^{(r)}(r_{i,i+1} = \sigma)}{P^{(r),id}(r_{i,i+1} = \sigma)} = -k_B T N^{(r)} \ln \frac{g^{(r)}(r_{i,i+1} = \sigma)}{g^{(r),id}(r_{i,i+1} = \sigma)} = -k_B T N^{(r)} \ln y^{(r)}(r_{i,i+1} = \sigma) \quad (\text{A.22})$$

With $y^{(r)}$ in Eq. (A.22) being the r -body cavity correlation function. The single-chain approximation strongly simplifies the mathematical treatment of the chain formation by reducing the estimation of the perturbation term to the calculation of an r -body correlation function $g^{(r)}$. The r -body correlation function can, in principle, be estimated by molecular simulation or by an integral equation theory. However, the correlation function for a given molecular model is only seldom reported for $r > 2$ and is almost inexistent for $r > 3$.

A further approximation, which allows estimating the chain contribution term based on the often available two-body pair correlation function, is the *nearest-neighbor correlation*, which consists of approximating the canonical average of the Dirac delta function of r monomers, at the fixed pairwise distance of σ (Eq. (A.18)), into a product of $(r-1)$ canonical averages of the Dirac delta function corresponding to only two monomers at the distance σ , each of them considered alone in the mixture of fully disconnected monomers, according to Eq. (A.23).

$$\left\langle \prod_{i=1}^{r-1} \delta(\|r_{i,i+1} - \sigma\|) \right\rangle^{N^{(r)}} \approx \prod_{i=1}^{r-1} \langle \delta(\|r_{i,i+1} - \sigma\|) \rangle = \langle \delta(\|r_{1,2} - \sigma\|) \rangle^{r-1} \quad (\text{A.23})$$

The consequence of this approximation is that the probability of finding two monomers at a distance σ is independent on whether one, none or a chain of monomers is already bound to one or both dimerizing monomers. The r -body correlation function $g^{(r)}$ becomes then a product of $(r-1)$ identical pair correlation functions g at $r_{12} = \sigma$ (and so the cavity correlation function), according to Eq. (A.24).

$$\Delta A^{res} = -k_B T N^{(r)} \ln \frac{g^{(r)}(r_{i,i+1} = \sigma)}{g^{(r),id}(r_{i,i+1} = \sigma)} \approx -k_B T N^{(r)} (r-1) \ln \frac{g(\sigma)}{g^{id}(\sigma)} = -k_B T N^{(r)} (r-1) \ln y(\sigma) \quad (\text{A.24})$$

Dividing Eq. (A.24) by $Nk_B T$, Eq. (4) is recovered. The pair correlation function $g(r)$ is related to the potential of mean force $w(r)$ by Eq. (A.25) (see [122] for a derivation).

$$g(r) = e^{-\frac{w(r)}{k_B T}} \quad (\text{A.25})$$

At the limit of vanishing density, interactions with the surrounding particles vanish and the system approaches ideal gas behavior. The potential of mean forces between two particles at distance r becomes then the bare interaction potential at r , $u(r)$. The cavity correlation function can therefore be rewritten into Eq. (A.26).

$$y(\sigma) = g(\sigma) e^{\frac{u(\sigma)}{k_B T}} \quad (\text{A.26})$$

By inserting the coulombic potential in Eqs. (A.26), (7) is recovered. If instead the hard-sphere interaction potential is used, $u(\sigma)$ (which has the meaning of the limiting value that $u(r)$ takes when the radial distance r between two hard-spheres approaches σ from outside the hard-core, $r \rightarrow \sigma^+$)

vanishes and the cavity correlation function becomes equal to the pair correlation function. Eq. (A.24) can then be rewritten into Eq. (A.27), which is the chain formation term employed in classical PC-SAFT.

$$\Delta A^{\text{res}} = -k_B T N_r (r - 1) \ln(\sigma) \quad (\text{A.27})$$

Attempts to go beyond the nearest-neighbor correlation approximation in the description of chain formation were pursued, for example, by Chang et al. [125] and Tavares et al. [126], who for two different models considered the dimer as reference fluid (which, moreover, represents an improvement of the single-chain approximation as well), and by Wertheim [127] Honnel et al. [128] and Zimptas et al. [129], who improved the approximation of Eq. (A.20) by considering next-to-nearest neighbor correlations via the second order TPT2 perturbation theory, with both approaches leading to an improvement of the equation of state for chains in the low-density limit. The dual chain perturbation theory of Marshall [130] represents an attempt to include chain-chain interactions into the perturbation term and thus to go beyond the single-chain approximation.

Appendix B. Calculation framework of LLE

The strategy to for the calculation of LLE is explained in detail in our previous work [119] and will be only shortly elucidated here to the specific case of a complex coacervate mixture, which in general consists of 5 components: 2 polyions (polycation and polyanion) 2 counterions (countercation and counteranion) and water. De-mixing of a liquid system of N components at overall concentration $\bar{z} = (z_1, \dots, z_N)$ at constant temperature T and pressure p is predicted when, according to the specific model used to describe the system, there are at least two compositions $\bar{x}^I$ and $\bar{x}^{II}$ satisfying the mass balance $\bar{z} = \alpha \bar{x}^I + (1 - \alpha) \bar{x}^{II}$ for which the Gibbs energy of the two-phase system, $G'' = \alpha G(\bar{x}^I) + (1 - \alpha) G(\bar{x}^{II})$, is lower than that of the hypothetical homogeneous system $G' = G(\bar{z})$. We only consider systems that split into only two liquid phases (which is the only relevant phase separation for this work). The values of the concentrations $\bar{x}^I$ and $\bar{x}^{II}$ (and of the resulting phase amount α) at which the Gibbs energy G'' is minimized represent the equilibrium concentration that we search. As discussed in our previous work [119], at equilibrium the equality of the chemical potential of all neutral components, the equality of $N^{ch} - 1$ mean ionic chemical potentials (defined over $N^{ch} - 1$ linear independent pairs of positively and negatively charged ionic components, with N^{ch} as the number total charged components), the mass balance and the electroneutrality condition must be satisfied.

Suppose that, in the hypothetical complex coacervate mixture, both polycation and polyanion have an equal number of 20 charges, $|z_{p+}| = |z_{p-}| = 20$, and that both small ions are monovalent, $|z_{cat}| = |z_{an}| = 1$. In this case, one set of linear independent pairs of oppositely charged components is, for example, (cation-anion), (cation-polyanion) and (polycation-polyanion), which defines 3 mean ionic chemical potentials. The transfer matrix $\bar{E}$ for this set of pairs is then given by Eq. (B.1).

$$\bar{E} = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1/20 \\ 0 & 0 & 1/20 & 1/20 \end{bmatrix} \quad (\text{B.1})$$

And from Eq. (B.1), the 3 mean ionic chemical potential are defined, from the 4 single-ion chemical potentials, by Eq. (B.2).

$$\begin{bmatrix} \mu_{\pm,1} \\ \mu_{\pm,2} \\ \mu_{\pm,3} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1/20 \\ 0 & 0 & 1/20 & 1/20 \end{bmatrix} \cdot \begin{bmatrix} \mu_{cat} \\ \mu_{an} \\ \mu_{p+} \\ \mu_{p-} \end{bmatrix} = \bar{E} \cdot \bar{\mu} \quad (\text{B.2})$$

The equilibrium conditions between phase I and II are thus defined, for the ionic components and water (w), by Eq. (B.3).

$$\begin{aligned} \mu_w^I &= \mu_w^{II} \\ \mu_{\pm,1}^I &= \mu_{\pm,1}^{II} \\ \mu_{\pm,2}^I &= \mu_{\pm,2}^{II} \\ \mu_{\pm,3}^I &= \mu_{\pm,3}^{II} \end{aligned} \quad (\text{B.3})$$

For the calculation, a unimolar feed amount is defined, $n_f = 1$. Thus, the total number of moles of each component is equal to the composition, $n_i^f = z_i$. The algorithm varies the number of moles of water subject to the mass balance condition, $z_w = n_w^I + n_w^{II}$. The number of moles of the charged components are not directly varied. As described in [119], 3 transformed variables $\bar{\xi} = (\xi_1, \xi_2, \xi_3)$ are used to vary the number of moles of charged components according to Eq. (B.4).

$$\begin{bmatrix} n_{cat} \\ n_{an} \\ n_{p+} \\ n_{p-} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1/20 \\ 0 & 1/20 & 1/20 \end{bmatrix} \cdot \begin{bmatrix} \xi_1 \\ \xi_2 \\ \xi_3 \end{bmatrix} = \bar{E}^T \cdot \bar{\xi} \quad (\text{B.4})$$

The advantage of calculating, for each of the 2 phases, 4 mole numbers from 3 variables according to Eq. (B.4) is that the resulting composition of the phase is always electroneutral, since changing each of the transformed variable ξ_i changes, at the same time, the number of moles of a pair of oppositely charged component according to their charge ratio.

For a given feed composition, stability of the mixture is inferred using the Tangent-Plane Distance Function (TPDF) of Michelsen [131], modified for mixtures of electrolytes using Eq. (B.4) as described in our previous work [119]. However, it was found that the TPDF gives, for a number of ionic species greater than 3, very poor initial values for both phases which resulted in poor convergence of the subsequent algorithm for solving Eq. (B.3). Therefore, once instability was detected, the amount of both cations and anions in the feed was simultaneously reduced (to maintain electroneutrality) until one or both ions completely disappeared from the homogeneous mixture. This is equivalent of removing a stoichiometric ratio of the counterions until the feed composition lies in the surface of minimal counterion concentration in Fig. 7a. Then a complete flash calculation was performed to this reduced system, for which the TPDF always provided excellent initial values. The amount of cations and anions is then stepwise increased (adding

amounts at stoichiometric ratio), and the LLE calculation (Eq. (B.3)) is performed again, until the initial composition of the system is recovered.

Data availability

Experimental data from literature was cited in the paper.

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