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Some New Frontiers in Chemical Engineering Thermodynamics

J.M. Prausnitz

May 1994



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Some New Frontiers in Chemical Engineering Thermodynamics

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May 1994

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Some New Frontiers in Chemical Engineering Thermodynamics

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Keywords: theory, equation of state, liquid-liquid equilibria, polyelectrolytes, proteins

ABSTRACT

The history of chemical engineering thermodynamics shows that its main concern has been development and extension of concepts and ideas that physicists and physical chemists have proposed in only general terms. For example, van der Waals proposed his theory of fluids in 1873 but its use for chemical engineering came only later, starting in the nineteen twenties, when MIT's Warren K. Lewis (and others) developed the generalized charts that we find today in Perry's Handbook and in undergraduate chemical engineering textbooks. Extension of van der Waals' theory remains a topic of active interest as indicated, for example, in the recent mixing rules of Wong and Sandler which significantly improve calculation of high-pressure phase equilibria for practical process design.

A variety of recent concepts from physics and physical chemistry is now under active development by chemical engineering researchers. Examples include the integral theory of fluids, polymer equilibria, molecular simulation with computers, density functional theory, the theory of electrolytes, fluctuation theory and the properties of fluids under unusual conditions such as the critical region and the metastable state which contains supercooled fluids at negative pressures. Some of these topics are discussed at this symposium. In every case, remarkable progress has been made toward achieving a better understanding of the properties of matter. That understanding, in turn, is useful not only for better design of chemical processes, but also for discovering novel techniques for making new chemical products.

Following a short introduction of these new developments, attention is given to an outline of progress in three areas under active investigation at Berkeley.

The first area concerns phase equilibria in mixtures of polymers with solvents or with other polymers; the main focus is directed at liquid-liquid

equilibria which are more difficult to describe than vapor-liquid equilibria. The basis of this description is a perturbation theory where the reference system is an equation of state for athermal chains based on a Percus-Yevick solution of the Ornstein-Zernike equation coupled with the restraint of chain connectivity. This perturbation theory can describe experimental data for systems with upper or lower consolute temperatures, or both, including closed-loop diagrams.

The second area concerns the properties of polyelectrolyte hydrogels in contact with aqueous solutions. Here emphasis is on experimental studies of swelling properties with semi-quantitative description based on polymer-network elasticity and Donnan equilibria.

The third area concerns selective precipitation of globular proteins from aqueous solution using a salt as the precipitating agent. A theoretical description, similar to that used for colloidal solutions, requires fundamental experimental data (e.g. osmotic virial coefficients) obtained by light-scattering and osmometry. For a given solution of proteins, this theory can identify not only the conditions that are required for precipitation (pH, concentration and nature of salt) but also the expected degree of protein separation.

INTRODUCTION

This conference on molecular thermodynamics comes at an appropriate time in the history of science and its applications. There is much evidence to show that, in molecular thermodynamics, we stand at the entrance of a new age where a variety of novel, powerful concepts and experimental tools are beginning to make a liberating impact on our subject. Measurements and calculations which were nearly impossible five years ago are now becoming routine; new theoretical ideas, previously available only in obscure mathematical form, are now reduced to practice not only because faster computers are available but also because practitioners -- that is, chemical engineers -- are becoming more courageous and sophisticated. Looking back over the history of chemical engineering thermodynamics, I have the impression that the time of childhood and adolescence is now over and the maturity of adulthood has begun. Therefore, participants of this conference are grateful to Professor Nakanishi and his colleagues for sponsoring this timely conference in Kyoto.

The left side of Figure 1 summarizes some of the key concepts that have informed molecular thermodynamics in the past and that continue to do so today. The right side of Figure 1 summarizes some key concepts that are now becoming increasingly important. The list is not complete but a box has been drawn about the last entry because it now appears that molecular simulation provides the most significant and most promising new method for advancing our knowledge of the properties of fluids and fluid mixtures.

The program of this conference contains a wide variety of contributions including some unconventional topics. I cannot mention them all, but here are

some examples: fluctuation theory for liquid solutions of gases or electrolytes; properties of supercooled water; oriented interactions for explaining Van Konijnenburg-Scott type VI mixtures; simulations of complex liquid mixtures, including aqueous solutions of polar organic solutes; fluid mixtures in porous solids; polymer melts and solutions at or near equilibrium or under a stress such as shear.

<u>YESTERDAY AND TODAY</u>	<u>TODAY LEADING TO TOMORROW</u>
• EOS OF v.d. WAALS FORM	• INTEGRAL THEORY OF FLUIDS
• CORRESPONDING STATES	• DENSITY-FUNCTIONAL THEORY
• SEMI-EMPIRICAL MODELS FOR G^E	• FLUCTUATION THEORY
• FLORY-HUGGINS EQ. FOR POLYMER SOLUTIONS	• NONLINEAR SCALING
• EXTENDED DEBYE-HÜCKEL EQUATION FOR ELECTROLYTE SOLUTIONS	• SWELLING THEORY FOR GELS
• CONTINUOUS THERMODYNAMICS	• THEORY OF METASTABLE AND SUPERCOOLED LIQUIDS
• QUASI-CHEMICAL THEORY	• MOLECULAR SIMULATION USING SUPERCOMPUTERS
• "CHEMICAL" THEORY FOR ASSOCIATION	
• GROUP CONTRIBUTIONS	

Fig. 1. Some key concepts and methods in molecular thermodynamics for chemical engineering

Lest we become exclusively occupied with the use of new concepts, let us not forget that the older but still valid concepts can often be used to shed light on important contemporary problems. It is not always necessary to use new tools; for many problems, previously established tools are often more suitable provided that the old tools are sharpened through modification to fit particular needs. The conference program contains a significant number of contributions which address important problems using variations of well-tested classical ideas. Some of these refer to polymer solubility; electrolyte solutions; high-pressure phase equilibria; continuous thermodynamics; group contributions; membranes; supercritical solvents; and alternate refrigerants.

I am much honored by Professor Nakanishi who has allowed me to be the first speaker. I would like to give a brief survey of molecular-thermodynamic research in progress at Berkeley. This research falls into three categories: Polymer Solutions, Hydrogels and Protein Solutions.

I - Polymer-Solvent and Polymer-Polymer Mixtures

Experimental data for binary systems containing polymers indicate a variety of phase diagrams. At low temperatures, such systems tend to exhibit

partial miscibility leading to an upper critical solution temperature (UCST) where the two components become completely miscible. At high temperatures, however, these systems often again show limited solubility characterized by a lower critical solution temperature (LCST) such that the LCST lies above the UCST. In a typical case, the UCST depends weakly on pressure while the LCST often depends strongly on pressure. In a typical system, an increase in pressure lowers the UCST and raises the LCST such that when a system has an hour-glass shape at low pressures, an increase in pressure creates a window (a small temperature range) where both components are completely miscible.

In a binary system, if there is a specific interaction between the two components (e.g. hydrogen bonding), a LCST may exist below the UCST. In that event, the phase diagram (temperature versus composition) exhibits a closed loop.

To describe these phase diagrams quantitatively, we require an equation of state (EOS) for the polymer-containing binary system. We first establish an EOS for a pure fluid and then generalize it to mixtures. We confine attention to fluids which are above their glass-transition temperatures and have zero crystallinity.

The EOS has the form

$$\frac{P}{\rho kT} = \left(\frac{P}{\rho kT} \right)_{\text{reference}} + \left(\frac{P}{\rho kT} \right)_{\text{perturbation}} \quad (\text{I-1})$$

where ρ is the number density. For the reference part, we use the hard-sphere-chain EOS proposed by Chiew (1990) as modified by Song et al. (1994a):

$$\left(\frac{P}{\rho kT} \right)_{\text{ref}} = 1 + r^2 b \rho g(d^+) - (r-1) [g(d^+) - 1] \quad (\text{I-2})$$

where $b = 2/3 \pi d^3$ and $g(d^+)$, the radial distribution function at sphere-sphere contact, is obtained from the Carnahan-Starling equation. The number of spheres in the chain is designated by r .

For the perturbation term, we use a simple van der Waals form

$$\left(\frac{P}{\rho kT} \right)_{\text{pert}} = -\frac{r^2 a \rho}{kT} \quad (\text{I-3})$$

where a is a temperature-dependent constant reflecting attractions between non-bonded spheres. Both a and b are functions of temperature according to

$$a(T) = 2/3 \pi \sigma^3 \epsilon \mathfrak{S}_a(kT/\epsilon s) \quad (\text{I-4})$$

$$b(T) = 2/3 \pi \sigma^3 \mathfrak{S}_b(kT/\epsilon s) \quad (\text{I-5})$$

where ϵ and σ are the coordinates of the minimum in the sphere-sphere potential function and s is a known function of r only, determined from the calculated vapor-liquid critical point. Universal functions \mathfrak{S}_a and \mathfrak{S}_b have been established from experimental vapor-pressure and liquid-density data for pure methane and pure argon where $s = 1$.

For a mixture containing m components, Eq. (2) becomes

$$\left(\frac{P}{\rho kT} \right)_{\text{ref}} = 1 + \rho \sum_{i,j=1}^m x_i x_j r_i r_j b_{ij} g_{ij}(d_{ij}^+) - \sum_{i=1}^m x_i (r_i - 1) [g_{ii}(d_{ii}^+) - 1] \quad (\text{I-2a})$$

where x is the mole fraction; $g_{ij}(d_{ij}^+)$ is given by the Boublik-Mansoori extension of the Carnahan-Starling equation to mixtures.

Equation (2a) follows from Eq. (2) without any additional assumptions. Equation (2a) does not contain any mixing rules.

For the perturbation, we use the one-fluid theory giving

$$\left(\frac{P}{\rho kT} \right)_{\text{pert}} = -\frac{\rho}{kT} \sum_{i,j=1}^m x_i x_j r_i r_j a_{ij} \quad (\text{I-3a})$$

For a_{ij} and b_{ij} we use the combining rules

$$a_{ij}(T) = 2/3 \pi \sigma_{ij}^3 \epsilon_{ij} \mathfrak{S}_{a,ij}(T) \quad (\text{I-4a})$$

$$b_{ij}(T) = 2/3 \pi \sigma_{ij}^3 \mathfrak{S}_{b,ij}(T) \quad (\text{I-5a})$$

For the ij interaction, generalized functions $\mathfrak{S}_{a,ij}$ and $\mathfrak{S}_{b,ij}$ are given by the geometric means of the corresponding generalized functions for the ii and jj interactions.

For a binary system, there are two adjustable binary parameters: ϵ_{ij} and σ_{ij} .

Pure-component parameters (r , ϵ , σ) have been obtained from vapor-pressure and liquid-density data for 70 solvents and from $P\rho T$ data for 23 polymers (Song et al., 1994b).

From the equation of state, standard thermodynamics provides expression for the chemical potentials. From these, phase diagrams can be calculated (Song et al., 1994c).

Figure 2 shows calculated and observed results for the system *t*-butyl acetate/polystyrene. The polystyrene is essentially monodisperse with a molecular weight of 10^5 . This system shows a LCST which lies above an UCST. Using two adjustable binary parameters, the theory described here can fit the experimental data of Bae et al. (1991).

Figure 3 shows calculated and observed results for the polymer blend polybutadiene/polystyrene for two molecular weights of polystyrene. Using the same binary parameters, theoretical calculations can reproduce both phase boundaries observed by Bungert (1992).

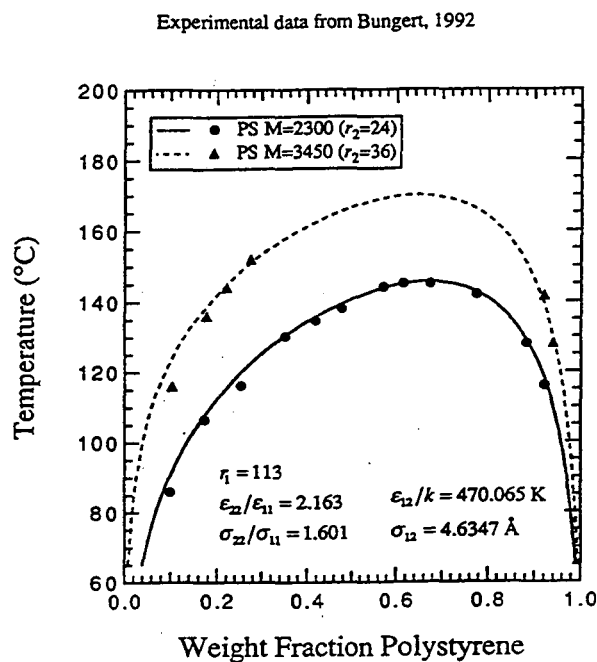
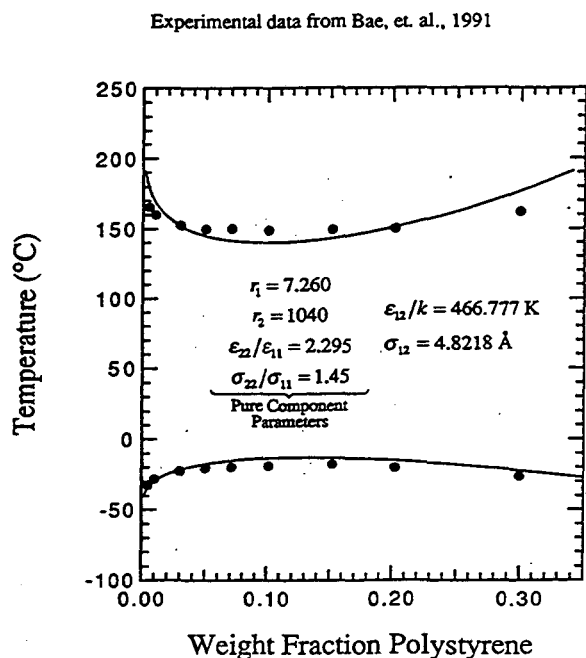


Fig. 2. Calculated and observed results for *tert*-Butyl Acetate(1)/Polystyrene(2)($M = 100,000$)

Fig. 3. Calculated and observed results for Polybutadiene(1) ($M=2620$)/Polystyrene(2)

The calculated effect of pressure is shown in Figure 4 where the temperature (divided by the calculated critical temperature of the solvent) is

plotted against composition. The pressure range covered in this calculation is from zero to twice the calculated critical pressure of the solvent. At low pressure, we obtain an hour-glass figure while at high pressure we obtain a LCST which lies above the UCST. At ordinary pressures, the two components show limited solubility at all temperatures. But as pressure rises, there exists a range of temperatures where the system is completely miscible.

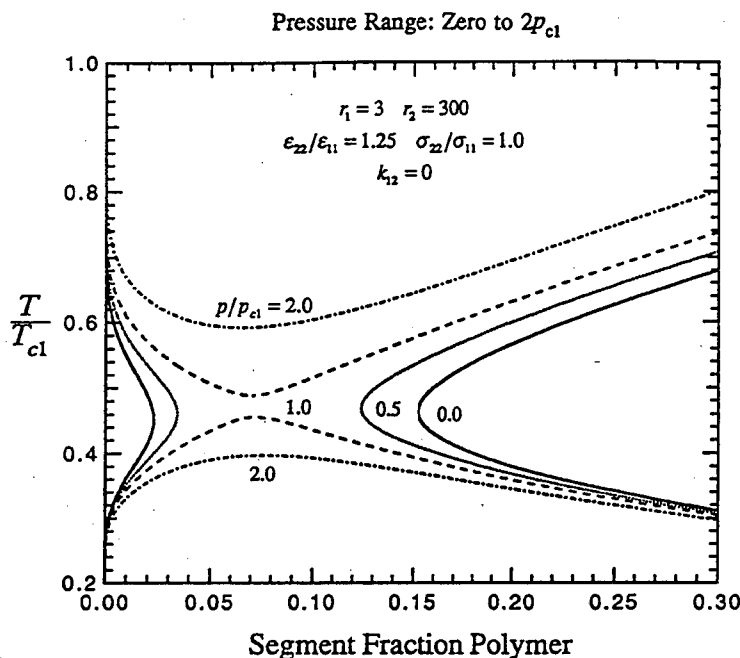


Fig. 4. Calculated effect of pressure on phase behavior

The theory briefly described here can be used to calculate the theta temperature of a polymer-solvent system, here defined as the limit of the liquid-liquid critical temperature as the molecular weight of the polymer becomes infinite. As suggested by Flory (1953), the theta temperature can be found as the intercept of the line where the inverse of the theta temperature is plotted against a suitable function of the reciprocal of the chain length.

Figure 5 shows calculations leading to the theta temperature of a particular binary system. (The theta temperature is T_c in the limit where $1/r$ goes to zero.) Flory's original definition applied only to the high-molecular-weight limit of UCST; however, for the system shown in Figure 5, we obtain two theta temperatures, an upper and a lower theta temperature. In practice, it has become conventional knowledge that, to prevent flocculation of a colloidal polymer solution, it is necessary to operate at a temperature exceeding the (UCST) theta temperature. The results shown in Figure 5 suggest that, to prevent flocculation, it is necessary to operate above the lower theta temperature but also, perhaps, below the upper theta temperature. It may happen that the

upper theta temperature lies below the lower theta temperature; in that event, perhaps, it may be impossible to stabilize the colloidal polymer solution by ordinary methods.

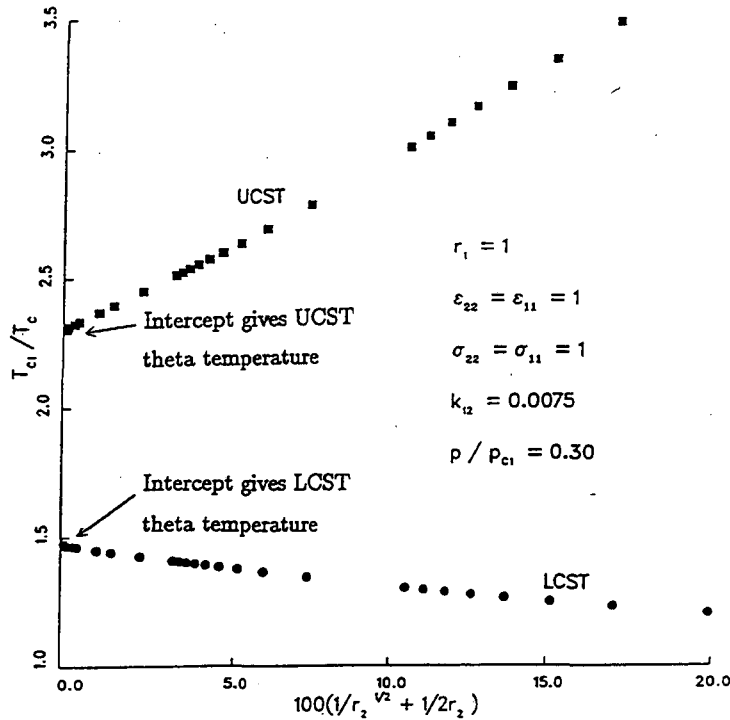


Fig. 5. Calculation of theta temperature

To allow for specific ij interactions such as hydrogen bonding, we have introduced into the theory the method of ten Brinke and Karasz (1984).

We distinguish between two types of ij interactions. One type is the "ordinary" nonspecific (dispersion-force) interaction characterized by parameter ϵ_{ij} . The other type is a specific interaction characterized by parameter $\epsilon_{ij} + \delta\epsilon_{ij}$. The probability that an ij interaction is specific is f_{ij} ; the probability that it is nonspecific is $(1 - f_{ij})$. The average energy parameter is then given by

$$\bar{\epsilon}_{ij} = \epsilon_{ij} + f_{ij} \delta\epsilon_{ij} \quad (I-6)$$

Probability f_{ij} is given by Boltzmann statistics

$$f_{ij} = \left[1 + \omega_{ij} \exp(-\delta\epsilon_{ij}/kT) \right]^{-1} \quad (I-7)$$

where ω_{ij} is the ratio of degeneracy of nonspecific to specific ij interactions.

This simple method allows us to use the previously derived expressions for chemical potentials provided that we replace temperature-independent ϵ_{ij} by temperature-dependent $\bar{\epsilon}_{ij}$. The temperature dependence of ϵ_{ij} is fixed through Equations (6) and (7) which introduce two additional binary parameters $\delta\epsilon_{ij}$ and ω_{ij} .

Figure 6 shows calculated and observed spinodal curves for the polymer blend polyvinylmethylether and polystyrene. Results are given for two sets of molecular weights. Using physically reasonable parameters, calculations with the same binary parameters can fit the experimental measurements of Han et al. (1988).

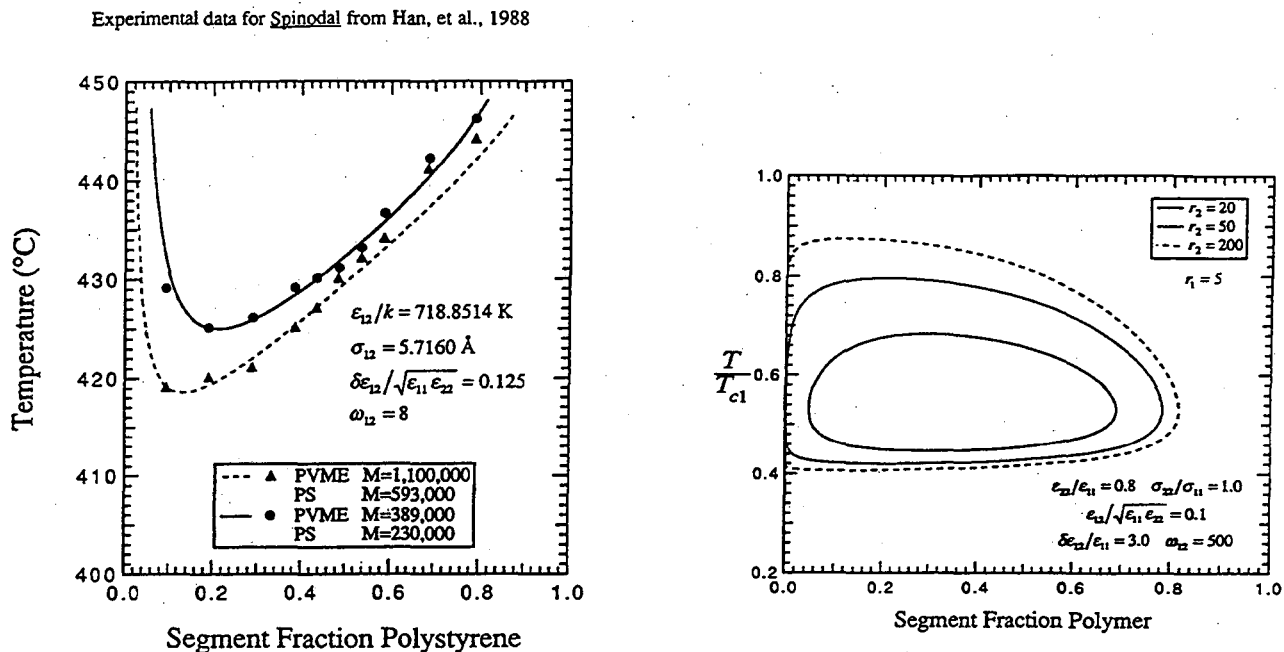


Fig. 6. Calculated and observed results for Poly(vinyl methyl ether)(1)/ Polystyrene (2)

Fig. 7. Calculated closed-loop phase diagram for a solvent(1)-polymer(2) system at low pressure

Finally, Figure 7 shows calculated closed-loop phase diagrams for three systems with (solvent) $r_1 = 5$ and polymer $r_2 = 20, 50, \text{ or } 200$. Because of large size asymmetry, the ratio of degeneracy (ω_{12}) is now much larger than that in Figure 8 where the two components, both polymers, do not differ excessively in molecular size. In binary systems where one component is a polymer and the other is a monomer ($r_1 = 1$), the typical ratio of degeneracies is in the region $2\text{-}6 \times 10^3$.

Research in polymer-solution thermodynamics at Berkeley is now directed at multicomponent systems and at mixtures containing random copolymers.

II - Hydrogels

A gel is a three-dimensional, cross-linked polymer. When the gel is hydrophilic, it can swell, that is, it can absorb a large quantity of water, depending on the physical and chemical properties of the gel and on external conditions like temperature. When the polymer comprising the gel has fixed electric charges, we have a polyelectrolyte gel; in that event, swelling is sensitive to the ionic strength of the surrounding aqueous medium. If the fixed charges are weak electrolytes (e.g. amino or carboxyl groups), swelling depends on the pH of the medium. It is common practice to refer to the external medium as the bath.

Because of their swelling properties, gels have a variety of applications; the most important, perhaps, is for controlled-release devices where the gel contains a solute (e.g. a pharmaceutical for medical use or a spice for foods) that is released to the surrounding medium at a desired rate; that rate is determined in large part by the gel's swelling properties. The literature is rich with articles that report experimental studies and possible applications. However, fundamental studies are as yet not plentiful and many questions remain unanswered. An introduction to the vast gel literature is given in a survey by Tanaka (1992).

For chemical engineering purposes, the most useful molecular-thermodynamic framework is that outlined by Flory many years ago. As a hydrogel swells, its pressure rises but as pressure rises, so does the elastic restraining force of the polymer strands that form the gel. Swelling continues until the forces that increase pressure (due to the influx of water) are matched by the forces that restrain further stretching of the polymer strands:

$$\Delta \pi_{\text{swelling}} = - \frac{\mu_{\text{H}_2\text{O}}^{\text{gel}} - \mu_{\text{H}_2\text{O}}^{\text{bath}}}{V_{\text{H}_2\text{O}}} = 0 \quad (\text{II-1})$$

where μ is the chemical potential, V is the molar volume and π is the pressure inside the gel.

Following Flory, we can consider several contributions to $\Delta \pi_{\text{swelling}}$. For gels with or without fixed charges

$$\Delta \pi_{\text{swelling}} = \Delta \pi_{\text{mixing}} + \Delta \pi_{\text{elastic}} + \Delta \pi_{\text{ion}} \quad (\text{II-2})$$

The first contribution follows from mixing water with the polymer strands. For lightly crosslinked polymers, $\Delta \pi_{\text{mixing}}$ can be estimated using the Flory-Huggins equation for polymer solutions with a Flory χ parameter obtained from

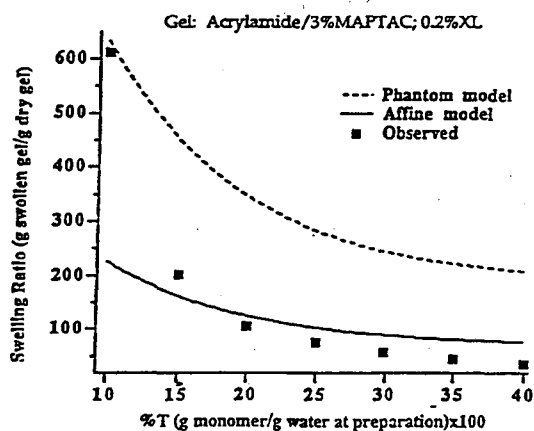
experimental equilibrium data where the non-crosslinked polymer is dissolved in water. Parameter χ varies with temperature and may be composition-dependent. In typical cases, $\Delta\pi_{\text{mixing}}$ makes only a small contribution to $\Delta\pi_{\text{swelling}}$.

More important are the last two terms in Eq. (II-2). Fundamental models for $\Delta\pi_{\text{elastic}}$ have been suggested; the most common ones are the Affine and Phantom models discussed elsewhere (Mark and Erman, 1988). These two models are similar, differing only by a factor of 2. In some typical cases, $\Delta\pi_{\text{elastic}}$ is observed to fall in between, depending on gel-preparation conditions, as shown in Figure 8 (Baker et al., 1994a). The Phantom and Affine models are derived using a theory of mechanics where the stress imposed is a mechanical stress. However, in hydrogel thermodynamics, the imposed stress is due to an internal pressure generated by water. For further progress, we need a more directly applicable theory of elastic deformation.

Affine model: chains deform linearly; crosslinks do not fluctuate
Phantom model: crosslinks fluctuate

$$\Delta\pi_{\text{elastic}} = -\theta_c RTN \left(\frac{\phi_2}{\phi_{2c}} \right)^N$$

θ_c : concentration of crosslinks at synthesis
 ϕ_2, ϕ_{2c} : volume fraction of polymer in hydrogel at equilibrium and at synthesis
N: semi-empirical interpolation parameter (N=1 for affine model; N=2 for phantom model)



%XL: mole percent crosslinker (methylene bisacrylamide)
MAFTAC: methacrylamidopropyl trimethylammonium chloride (has a positive charge)

Fig. 8. Affine and Phantom models for elastic contribution to $\Delta\pi_{\text{swelling}}$

For uncharged gels, $\Delta\pi_{\text{ion}}$ is zero but for charged gels, to obtain $\Delta\pi_{\text{ion}}$, we must solve a Donnan-equilibrium problem; we have mobile ions that can go back and forth between gel and bath and we have fixed charges that are restricted to the gel phase. The key equation is

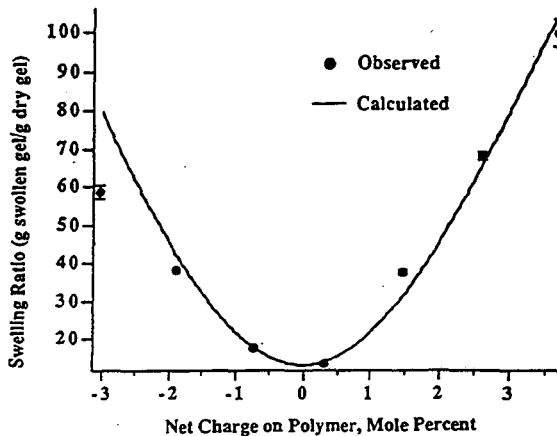
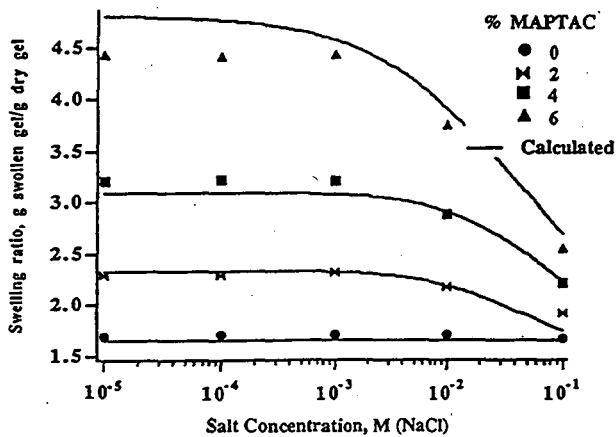
$$\Delta \pi_{\text{ion}} = \pi_{\text{ion}}^{\text{gel}} - \pi_{\text{ion}}^{\text{bath}} = RT \sum_i (c_i^{\text{gel}} - c_i^{\text{bath}}) + \text{electrostatic contributions for charge shielding} \quad (\text{II-3})$$

where c_i = concentration of mobile ion i . To obtain c_i^{gel} and c_i^{bath} , we satisfy two conditions: electroneutrality in each phase; phase equilibrium for each mobile ion.

We need a polyelectrolyte model for calculating the electrostatic contributions for charge shielding. We use the cell model of Katchalsky (1971). For low ionic strength in the bath and for low or moderate charge density in the polyelectrolyte, the electrostatic contributions for charge shielding are small, often negligible (Baker et al., 1994a).

To illustrate, Figure 9 shows calculated and observed swelling ratios for a lightly (1%) crosslinked HEMA hydrogel, copolymerized with small amounts of positively charged MAPTAC. Results are shown as a function of salt concentration. These gels are characterized by 65% T (as defined on the horizontal axis of Figure 8).

Gels: 2-hydroxyethylmethacrylate(HEMA)/MAPTAC,
65%T,1%XL



Gels: Acrylamide/MAPTAC/Sodium Styrene Sulfonate (SSS),
16%T, 0.2%XL

Fig. 9. Swelling equilibria for polyelectrolyte hydrogels. Swelling increases with rising amount of positively-charged monomer and decreases with ionic strength.

Fig. 10. Swelling of polyampholyte hydrogels: effects of gel charge density. Lowest swelling is expected for gels with no net charge (equal amounts of positive and negative charge). Swelling ratios are not symmetric with respect to the gel isoelectric point because of physico-chemical differences between the two charged monomers.

For these gels, swelling is not large but when the percent MAPTAC exceeds zero, swelling depends on the salt concentration of the bath. HEMA gels are of

particular interest in medicine where they are used to make contact lenses and inserts following surgery as, for example, removal of cataracts.

A possibly interesting material is an ampholyte gel, i.e. a polyelectrolyte gel where the net charge is zero or close to zero. Figure 10 (Baker et al., 1992 and 1994b) shows swelling properties of an ampholyte acrylamide gel copolymerized with positively charged MAPTAC and negatively charged SSS. The extent of crosslinking (0.2%) is very small. Swelling is a minimum when the net charge is zero but rises swiftly as the net charge increases, either way.

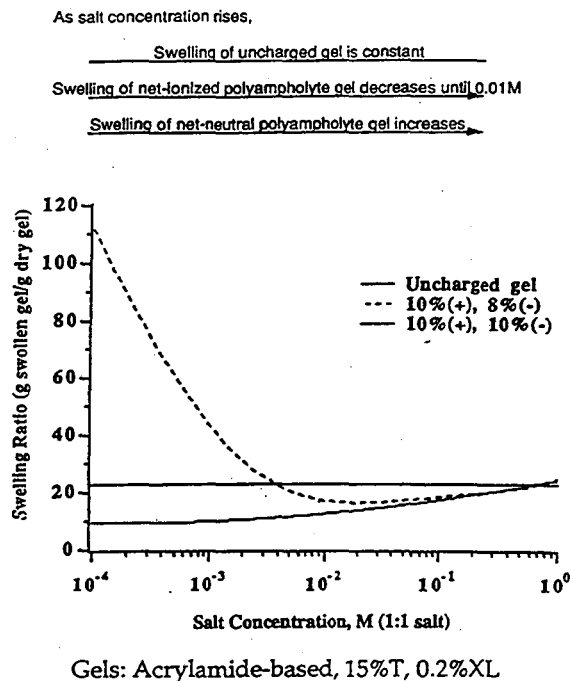


Fig. 11. Calculated swelling equilibria for uncharged and polyampholyte hydrogels. Activity coefficients based on screened Debye-Hückel model are incorporated into calculations.

The results in Figure 10 are for a salt-free bath. For practical application, it is of interest to compare swelling properties of the uncharged gel with those of the net-zero-charge ampholytic gel and with those of a slightly positively charged ampholytic gel, as shown in Figure 11. As expected, the salt concentration of the bath has no effect on the swelling properties of the uncharged gel but it does have a small effect on the net-zero-charge ampholyte gel, because as salt concentration rises, the attractive charge-charge forces in the gel decline due to charge shielding. Salt concentration has a large effect on the positively charged ampholytic gel because dissolved salt shields the repulsive charge-charge forces. There is a surprising minimum in the curve, lying below the horizontal line for the uncharged gel; this minimum would not be observed if the gel were not a polyampholyte but had only a positive charge. The minimum occurs because while there are plus-plus repulsions, at the same time there are also plus-minus attractions that are diminished with rising salt

concentration. In the vicinity of the minimum the plus-plus repulsions are essentially shielded out but the more plentiful plus-minus attractions retain some influence on swelling properties. At sodium chloride concentrations exceeding 1 molal, all electrostatic influences have disappeared.

Gels are of increasing interest in high-tech industry, especially in medicine, pharmaceuticals, packaging, biotechnological separations, and personal-care products (e.g. hair lotions, lipsticks, moisturizers). Many experimental studies have been reported. It is an area where molecular thermodynamics can make a useful contribution.

III - Precipitation of Globular Proteins With Salts

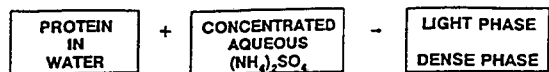
When a protein is dissolved in water, addition of salt precipitates most of the dissolved protein, provided that the salt concentration is large, typically five or six molar. Experimental data indicate that addition of a concentrated salt solution to a homogeneous protein solution typically causes phase splitting where two liquid phases coexist. One of these phases is very dilute in protein while the other is highly concentrated. The salt concentration in one phase is nearly the same as that in the other.

Solubilities of proteins in salt solutions have received attention from various authors (Cohn and Edsall, 1943; Shih et al., 1992) but many questions remain. A possible method for developing an appropriate theory is provided by the Random-Phase Approximation as discussed, for example, by Vlachy et al. (1993), following similar efforts for aqueous protein-polymer mixtures by Mahadevan and Hall (1990, 1992). The immediate purpose for developing a suitable theory is to identify the variety of forces that contribute to the distribution coefficient of the protein between the two phases. The ultimate purpose is to extend such theory to a solution containing several proteins and to calculate separation factors.

The random-phase approximation provides an equation of state for a one-component system. That component is the protein in a medium of salt water. From this equation of state, we calculate the pressure as a function of protein concentration and the chemical potential of the protein as a function of pressure, all at constant temperature and constant salt concentration and at some fixed pH where we can independently determine the electric charge on the protein. These ideas are illustrated in Figure 12. The ratio of the two equilibrium protein concentrations (indicated by arrows) gives the desired distribution coefficient K_e .

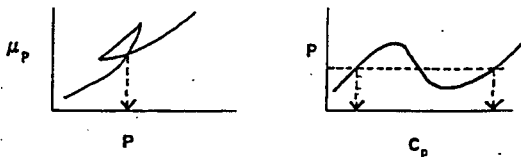
Figure 13 gives essentials of the Random-Phase Approximation for a solute in a liquid; this approximation, in form and in concept, is similar to the van der Waals equation of state for a gas, i.e. a solute in free space. Near the top of Figure 13, the first term is the compressibility factor of a hard-sphere system; here globular proteins are considered to be hard spheres in a medium of salt

water. The second term reflects the forces of attraction (or repulsion) between hard spheres; these forces come from potentials of mean force designated by W .



- LIGHT PHASE HAS VERY LOW PROTEIN CONCENTRATION.
- HEAVY PHASE HAS HIGH PROTEIN CONCENTRATION.
- CONCENTRATION OF $(\text{NH}_4)_2\text{SO}_4$ IS NEARLY THE SAME IN BOTH PHASES.

THERMODYNAMICS OF PHASE SEPARATION AT CONSTANT T



- μ_p = CHEMICAL POTENTIAL OF PROTEIN
- C_p = CONCENTRATION OF PROTEIN

PROTEINS ARE ELECTRICALLY CHARGED, DEPENDING ON pH

$$z = \frac{P}{\rho kT} = \frac{P_{HS}}{\rho kT} + \frac{\rho U}{2kT} \quad \rho = \text{PROTEIN DENSITY}$$

P_{HS} = PRESSURE FOR A HARD-SPHERE SYSTEM
GIVEN BY CARNAHAN - STARLING EQUATION

GLOBULAR PROTEINS ARE MODELED AS CHARGED HARD SPHERES WITH A VARIETY OF ATTRACTIVE FORCES REPRESENTED BY AN ENERGY INTEGRAL

$$U = 4\pi \int_{d_p}^{\infty} \left[\frac{W(r)}{d_p} + \frac{W(r)}{d_p} + \frac{W(r)}{d_p} \right] r^2 dr$$

d_p = PROTEIN DIAMETER r = CENTER-TO-CENTER DISTANCE

$W(r)$ IS A POTENTIAL OF MEAN FORCE.

$W(r)$ electric GIVEN BY SHIELDED COULOMB POTENTIAL

$W(r)$ dispersion GIVEN BY HAMAKER POTENTIAL

Fig. 12. Salting out proteins from aqueous solution

Fig. 13. Random-Phase Approximation

Consideration is given to three potentials of mean force: one due to electric charges on the protein, one due to dispersion (London) forces between protein spheres and one due to an osmotic effect as indicated in Figure 13. It is this osmotic effect which is crucial; the corresponding potential of mean force was obtained very recently by Y. Chiew et al. (1994) using Percus-Yevick theory with the Ornstein-Zernike equation. Chiew's result goes beyond those derived earlier by others because he allows the salt ions to form clusters with an average cluster size equal to N_{12} such that $N_{12} = 1$ for a dimer. Previous authors did not consider clusters because they were concerned only with dilute salt solutions. However, independent evidence indicates that at molalities exceeding about 2 or 3, salts form pairs and higher aggregates. Formation of these aggregates raises the average diameter of the salt ions; an increase in that diameter makes the potential of mean force more attractive.

Figure 14 shows the effect of salt concentration on the distribution coefficient K_c . When that concentration is 0.5 or 1.0 moles/liter, no precipitation occurs. Precipitation (i.e. phase splitting) begins only when the salt concentration reaches a critical value of 1.6 moles/liter.

In addition to the potentials of mean force, we consider a "chemical" effect: association due to hydrophobic bonding at one or more bonding sites. Using the theory of Wertheim as developed by Jackson et al. (1988), the effect of association on the distribution coefficient was calculated, using an equilibrium constant which requires a dimensionless energy ϵ/kT and a dimensionless volume V_0 . As shown in Figure 15, the number of bonding sites M is the most crucial parameter.

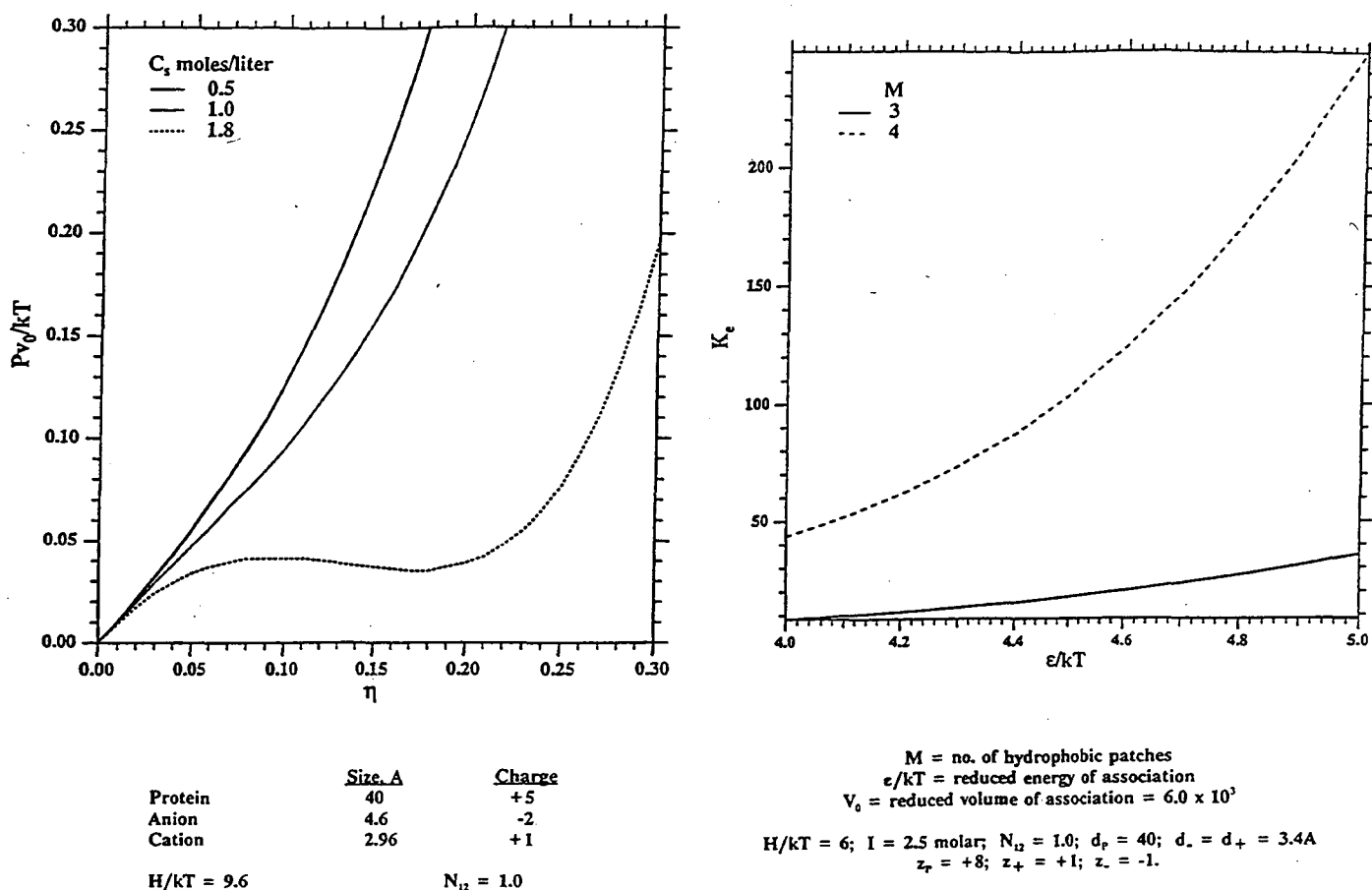


Fig. 14. Reduced pressure as a function of protein-packing fraction for different salt concentrations

Fig. 15. Distribution coefficient K_c calculated with hydrophobic association in addition to the potentials of mean force

The large number of parameters is frightening; some, indeed most of them, must be obtained from independent experimental data, i.e. from data other than the phase-equilibrium (precipitation) data themselves. Experimental studies which can provide some of these parameters are now in progress at Berkeley; they include low-angle laser-light scattering, membrane osmometry and dynamic

light scattering; measurements are obtained for a fixed temperature and pH, as a function of protein concentration and salt concentration. The ultimate goal is to understand (and perhaps predict) selective precipitation data like those shown in Figure 16 for aqueous solutions containing two proteins, lysozyme and hemoglobin, at pH = 7 using ammonium sulfate (Coen et al., 1993). The experimental data show that when the ionic strength of ammonium sulfate exceeds about 7.5 molal, excellent separation of the proteins can be obtained.

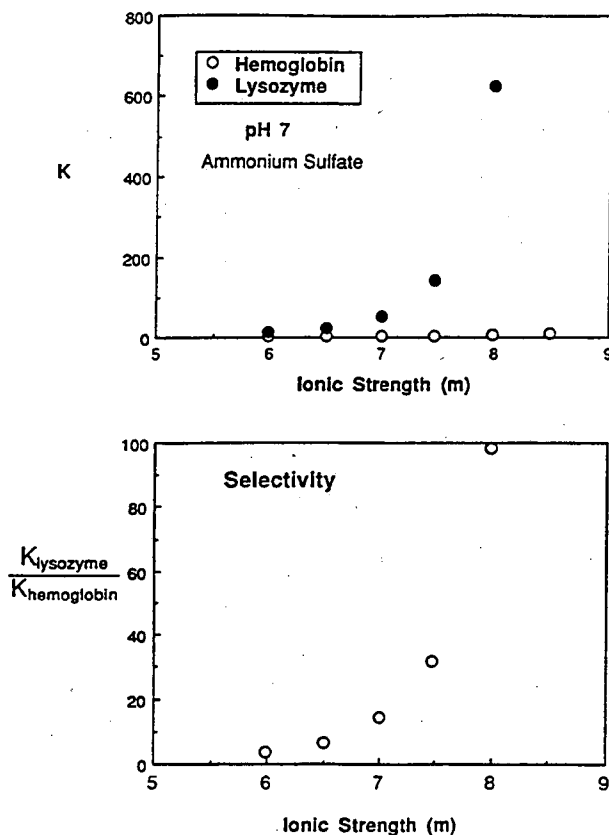


Fig. 16. Selective separation

CONCLUSION

The program of this conference in Kyoto indicates a broad variety; many contrasting points of view are represented. It is precisely their contrast which is so illuminating because progress in one area becomes more significant when it is compared with progress in another, just as different shades of color bring out the essence of a painting.

At Kyoto, we should contemplate a haiku by one of the great Japanese literary masters, Basho (1644-1694):

Yes, spring has come;
This morning a nameless hill
is shrouded in mist.

It is easy to misinterpret Basho's last line to imply that the research reported at this conference is obscure and difficult to see. No, that is not the intent; the key word is "nameless". The ordinary, previously disregarded hill becomes visible only because it is partly covered by clouds. The beauty of the hill becomes apparent only because a cloud has called it to our attention.

May Basho's haiku characterize this conference. We come to Kyoto to teach and to learn, together.

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LIST OF SYMBOLS

a	attraction parameter defined in Eq. (I-4)
b	size parameter defined in Eq. (I-5)
c	concentration
f	probability that an interaction is specific
\mathcal{S}	universal function
$g(d^+)$	radial distribution function at sphere-sphere contact
k	Boltzmann's constant
K_e	distribution coefficient
m	number of components in mixture
M	number of bonding sites
N	average cluster size
P	pressure
r	number of spheres in the chain
T	temperature
x	mole fraction
V	molar volume
W	potential of mean force
$\delta \epsilon_{ij}$	binary parameter
ϵ	coordinate of the minimum in the sphere-sphere potential function
ϵ_{ij}	adjustable binary parameter
μ	chemical potential
π	pressure inside the gel
ρ	number density
σ	coordinate of the minimum in the sphere-sphere potential function
σ_{ij}	adjustable binary parameter

χ	Flory parameter
ω	ratio of degeneracy of nonspecific to specific interactions

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