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How To Separate Polydisperse Polyelectrolytes by Thermal Field Flow Fractionation Techniques

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Thermal field flow fractionation (TFFF)[1] allows for the separation of macromolecules over a broad range of molecular weights—from 4000 to several millions. A macromolecular solution is placed between two plates and heated from above. A laminar flow between the two plates $V_X(Z)$ is superimposed at right angles to the thermal gradient $\partial T/\partial Z$. Coils of different molecular weight have different concentration profiles $c(Z)$ in steady state under the thermal gradient. They are transported by the fluid at different velocities $V_X(Z)$ and separated. The analysis of TFFF data[1,2] is based on the distribution in the channel for one single species. Let us start with a monodisperse solution of macromolecules (degree of polymerization N). In the thermal gradient, the macromolecules migrate toward one plate (the cold plate in most cases). The steady-state concentration profile is given by the balance of this thermal flow (diffusion coefficient D_T) with the mass diffusion flow (cooperative diffusion coefficient D_M):

$$J = -cD_T\nabla T - D_M\nabla c = 0 \qquad (1)$$

where c is the monomer concentration and J the monomer current. The profile deduced from eq 1 is controlled by the ratio $s = D_T/D_M$, called the Soret coefficient. If s is strongly dependent upon N, we expect a good separation of macromolecules of different molecular weight. If s is independent of N, no separation will occur.

Our aim here is to review the case for different types of macromolecules (coils, rods, and compact chains) and to discuss what happens if they become *charged*.

(1) Neutral Flexible Polymer in Dilute Solutions. The mass diffusion coefficient D_M is well-known, both experimentally and theoretically.[3,4,7] Quite generally, D_M is related to the mobility coefficient μ and to the osmotic pressure Π by the relation

$$D_M = \mu(\partial\Pi/\partial c) \qquad (2)$$

[μ is the transport coefficient relating the velocity of a monomer to an applied external force ($v = \mu F$).]

In the dilute regime, $\Pi = (c/N)kT$. Kirkwood showed that backflow interactions control the sedimentation coefficient.[3] A polymer coil behaves hydrodynamically as a rigid sphere of radius R comparable (within a coefficient) to the radius of gyration. Then, $\mu = N/6\pi\eta R$, where η is the solvent viscosity. This leads to

$$D_M = kT/6\pi\eta R \qquad (3)$$

In good solvents, $R \sim N^{0.58}$ and $D_M \sim N^{-0.58}$ in one typical experiment on polystyrene.[4]

For the thermal diffusion coefficient, de Gennes and Brochard have argued recently[5] that backflow does *not* lead to a long-range coupling between monomers. Thermally, the chain behaves as a Rouse chain and in a thermal gradient, a coil moves with the same velocity that would be seen with separated monomers. D_T is independent of N, as observed experimentally,[1,2,6] and of the order of 10^{-7} cm^2 s^{-1} K^{-1}:

$$D_T = D_{T_0}N^0 \qquad (4)$$

From the results (3) and (4), we expect

$$s = D_T/D_M \sim N^{0.58} \qquad (5)$$

This prediction is remarkably verified on polystyrene.[1] With these coils, the N dependence of D_M is entirely responsible for the separation of polymer chains. The solution of eq 1 is

$$c = C_0e^{-Z/l_s} \qquad (6a)$$

$$l_s = s/\nabla T \qquad (6b)$$

For a channel of thickness $d = 0.1$ mm and a temperature difference $T_2 - T_1 = 30$ °C, one can separate chains if $l_s < d$, i.e., for $N > 6000$. Note that one must constantly work with *dilute* solutions. In the semidilute regime, the cooperative diffusion coefficient becomes independent of N[7] and no separation occurs.

(2) Charged, Flexible Polymers. The discussion of D_T is unchanged and result (4) is valid. From experiment,[7] one knows that D_M is (1) very large and (2) independent of both N and concentration. Theoretically, D_M was first calculated by a RPA or Debye–Hückel theory[11] in the dilute regime. However, for ions of large charge, the RPA approach extended to semidilute solutions[12] does not explain the neutron scattering data[9,13] because the high electrostatic repulsions cannot be treated as a perturbation. By a more powerful scaling approach,[9] we have shown that in both dilute and semidilute regimes, one expects

$$D_M = kT/6\pi\eta a = D_{M_0}N^0 \qquad (7)$$

where a is monomer size. The result (7) can be understood easily: in the dilute regime, the chain forms a rod of length $2R \sim Na$. The sedimentation coefficient per monomer is then roughly $\mu = N/6\pi\eta R$. The osmotic pressure is very large ($\Pi = ckT$). By using eq 2, we find result (7). The resulting Soret coefficient is then independent of N:

$$s = D_{T_0}/D_{M_0} \qquad (8)$$

We conclude that (a) the concentration profile is completely independent of N and no separation is expected, (b) $s = s_0$ is very small (the concentration profile given by eq 7 is completely flat (l_s is larger than d) and the polyelectrolyte moves with the mean solvent velocity (zero retention)), and (c) in semidilute solutions, the equations for Π and for D_M are not qualitatively modified and the value of l_s (eq 6) is not changed: again we expect zero retention.

(3) Neutral Rods. The only difference with case 1 is the value of D_M. If L is the length of the rod, we have (ignoring weak logarithmic corrections)

$$D_M \simeq kT/6\pi\eta L \sim N^{-1} \qquad (9)$$

This leads to a very large Soret coefficient

$$s = s_0N \qquad (10)$$

and TFFF is expected to be very efficient for separating rigid polymers.

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(4) Charged Rods. This case is identical with case 2 in the dilute regime. TFFF is not useful.

(5) Neutral Globular Chains. For collapsed chains, $R \sim N^{1/3}a$ and D_M is given by

$$D_M = kT/6\pi\eta R \sim N^{-1/3}$$

Our analysis of ref 5 is not applicable to this situation. A recent (unpublished) calculation of Mazur shows that for a rigid sphere, D_T is small and independent of R. Then the result (4) remains valid, leading to $s \sim N^{1/3}$. TFFF is thus applicable to globular chains but is less efficient than for swollen coils.

(6) Charged Globular Chains. Assume Z charges per chain. The main effect of the charges is to increase the osmotic pressure, leading to a higher cooperative diffusion coefficient D_M. We may roughly put (in analogy with eq 7)

$$D_{M_{\text{charged}}} \simeq Z D_{M_{\text{neutral}}}$$

The Soret coefficient is then reduced by a factor of the order of the number of charges. This strong decrease of s will lead rapidly to flat concentration profiles and to zero retention. We do have experiments in that case: No retention is observed with many proteins.[10]

Conclusion

For strongly charged macromolecules, the TFFF technique is expected to break down. This result was frequently reported in the literature without explanations. Our explanation is simple: as soon as macromolecules are charged, the electrostatic repulsions increase strongly the osmotic pressure, and a thermal gradient cannot establish a concentration gradient. The TFFF technique can be used only if the charges are screened by adding enough salt.

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Communications to the Editor

Ring-Opening Polymerization of 2,6-Dialkoxy-5-cyano-3,4-dihydro-2*H*-pyrans:[1] A Novel Monomer-to-Polymer Route to Head-to-Head Alternating Copolymers

Vinyl polymers of head-to-head (H–H) structure have long been the subject of curiosity and have caused recent interest.[2] Long sought after, however, have been synthetic routes that lead to unequivocal and pure H–H structures. Reactions on the polymers are often useful, but clean quantitative conversions are always difficult.[3] Certain, 1,2-disubstituted cyclobutanes, which are accessible by [2 + 2] H–H cycloaddition reactions, would give H–H alternating copolymers upon ring-opening polymerizations. Stille and Chung[4] have prepared several 1,2-disubstituted cyclobutanes and attempted their ring-opening polymerizations. However, all the substituted cyclobutanes failed to polymerize.

In the course of our study of the ring-opening polymerizations of substituted small carbocyclic compounds,[5] we have prepared a series of substituted cyclobutanes and attempted their polymerizations. Most of the substituted cyclobutanes were reluctant to polymerize, confirming the results reported previously.[4] However, we found that the particular adducts between ethyl α-cyanoacrylate and alkyl vinyl ethers were not only found readily but also polymerized well by anionic or cationic catalysts. Interestingly, these adducts were not cyclobutanes but 2,6-dialkoxy-5-cyano-3,4-dihydro-2*H*-pyrans[6] (**1** and **2**), as reported recently by Hall and co-workers.[7] These substituted dihydro-2*H*-pyrans possess the structural moiety in such a way that they are vulnerable to attack by nucleophiles as well as electrophile, resulting in the generation of stable propagating anions and cations for the polymerizations. Thus we have found a new class of unsaturated cyclic ethers that undergo facile ring-opening polymerization. Furthermore, the striking feature of this particular polymerization is that it provides an unprecedented, unique monomer-to-polymer route for H–H alternating copolymer systems. We now report the results of the initial phase of the work.

Dihydro-2*H*-pyrans **1** (mp 16 °C) and **2** (liquid) were prepared according to a procedure[6] similar to that reported already,[7] and they were polymerized[8] with NaCN in Me_2SO at room temperature or with BF_3 in $CHCl_3$ at −30 °C (Scheme I). The results are summarized in Table I. For purposes of comparison, the samples of head-to-tail (H–T) alternating copolymers (**5** and **6**) were prepared by radical copolymerization[9] of ethyl α-cyanoacrylate with alkyl vinyl ethers in benzene with AIBN at 60 °C. Copolymers **3** and **4** were soluble in common solvents such as $CHCl_3$, Me_2CO, and MeC_6H_5 as were copolymers **5** and **6**. The chemical structures of these copolymers were confirmed by their ^1H NMR and IR spectra. However, those spectra exhibited only minor differences, failing to differentiate H–H from H–T microstructures.

The conclusive spectral evidence identifying H–H microstructures of **1** and **2** was secured from their ^{13}C NMR spectra. ^{13}C NMR spectra of **3** and **5** are shown in Figure 1. The most notable structural characteristic of the H–H

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