Polymerization of Three Bromo-2,6-xylenols in THF Solution

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ABSTRACT: The iodine-initiated polymerization of 4-bromo 2,6-xylenolate (MBX) and its 3,4-dibromo (DBX) and 3,4,5-tribromo (TBX) analogues proceeds exceedingly rapidly in THF solution to give low molecular weight polymers and copolymers. The homopolymer of TBX precipitated as formed, but the other homopolymers and all the copolymers of these monomers remained in solution. The reactivity of DBX and TBX in THF contrasts to their unreactivity under the same conditions in HMPT. Possible radical mechanisms are discussed, as well as some significant conformational factors affecting the NMR of the polymers.

The conversion of 4-bromoxylenolate ion to polymer by overall apparent nucleophilic replacement of aromatic bromine, has been found to proceed with remarkable facility in the presence of one-electron oxidizing agents.[2,3] A free-radical mechanism was proposed but the heterogeneous nature of the conditions (benzene–water) made mechanistic interpretation questionable. In an effort to establish conditions for carrying out the reaction in a homogeneous medium, we[4] have already reported results in hexamethylphosphoric triamide (HMPT). The results, however, suggested that in this medium the reaction proceeded by electrophilic attack of iodine followed by nucleophilic replacement in the resulting 4-bromo-4-iodo-2,6-dimethylhexadienone.[4] In this medium, MBX polymerized readily and rapidly in good yield, DBX gave a mediocre yield (~40%) of low molecular weight oligomer accompanied by a crystalline dimer, and TBX gave no polymer and only a low yield of crystalline dimer.

We wish now to report investigation of the polymerization of mono-, di-, and tribromo 2,6-xylenolate (MBX, DBX, and TBX, respectively) in tetrahydrofuran (THF), since the results in this solvent contrast sharply to those in HMPT, especially for DBX and TBX.

Experimental Section

4-Bromo-2,6-xylenol (MBX), mp 78–78.5 °C, δ (ppm) 2.18 (6), 4.48 (1), 7.05 (2), was prepared by bromination in acetic acid.[5] **3,4-Dibromoxylenol (DBX),** mp 85–86 °C, δ (ppm) 2.18 (3), 2.38 (3), 4.65 (1), 7.22 (1), was similarly prepared[6] as was **3,4,5-tribromoxylenol** (TBX), mp 202–203.5 °C, δ (ppm) 2.96 (6), 4.15 (1).

Polymerization was normally carried out by mixing 8 mmol of monomer and 8 mmol of potassium *tert*-butoxide in dry THF under nitrogen with 0.1 N iodine in THF. There was an immediate precipitation of KBr and, for TBX, its homopolymer. The reaction was quenched by adding 0.5 M HNO_3 in 50% methanol–water. The precipitate was collected and extracted with benzene, and the benzene solution was poured into stirred methanol.

From MBX with 0.2 mequiv of I_2, a 91% yield of polymer, sp 220–230 °C,[7] [η] 0.158 dL/g (C_6H_6, 29.4 °C) (DP ~ 35),[8] δ (ppm, CCl_4) 2.10 (6), 6.48 (2), was obtained in 1 min.

Anal. Calcd for (C_8H_8O): C, 79.97; H, 6.71. Found: C, 78.08; H, 6.89; Br, 0.0.

From DBX and 0.5 mequiv of I_2, a 94% yield of polymer, sp 290–300 °C, [η] 0.120 (DP ~ 22), δ (ppm, CCl_4) 2.05 (3), 2.37 (3), 6.12 (1), was obtained in 5 min.

Anal. Calcd for (C_8H_7BrO); C, 48.27; H, 3.55; Br, 40.15. Found: C, 48.84; H, 3.52; Br, 40.95.

For TBX with 2 mequiv of I_2, polymerization (as indicated by precipitation) required about 5 min. The yellow polymer (77%) was separated from KBr by washing with water and from monomer (mp 199–203 °C, recovered in 15% yield) by methanol wash. The yellow polymer was insoluble in all common solvents at room temperature. It was presumably insoluble due to crystallinity since it melted to a clear brownish liquid at 310–320 °C.

Anal. Calcd for ($C_8H_6Br_2O$): C, 34.56; H, 2.18; Br, 57.50. Found: C, 33.80; H, 2.27; Br, 57.89.

Copolymerization of 8 mmol each of MBX and DBX and 16 mmol of *t*-BuOK in 25 ml of THF at 5 °C under N_2 was initiated by adding 5 mL of 0.05 N I_2 in THF. The reaction mixture immediately turned turbid with a noticeable increase in viscosity. The copolymer, after reprecipitation from benzene by methanol, was obtained in 91% yield, sp 270–285 °C, [η] 0.146 (DP ~ 28), δ (ppm, CCl_4), 2.09 (9), 2.32 (3), 6.15 (1), 6.4 (2).

Anal. Calcd for (C_8H_8O–C_8H_7BrO): C, 60.18; H, 4.70; Br, 25.05. Found: C, 59.68; H, 4.64; Br, 25.47.

This copolymer was fractionated by dissolving in hot benzene–ethanol (5:1). On cooling, one fraction separated (~50%); it was reprecipitated from benzene by methanol.

Anal. Found: C, 59.83; H, 4.86; Br, 25.19.

The benzene–ethanol filtrate was poured into methanol to give a copolymer sample with an identical 1:1 ratio of units by NMR spectrum.

When the copolymerization of MBX and DBX as above was quenched 5.2 s after addition of iodine, a 48.7% yield of copolymer was obtained, as well as 45% of unreacted DBX, mp 84–86 °C. The copolymer had sp 220–230 °C, [η] 0.127 (DP ~ 24), δ (ppm, $CDCl_3$), 6.42 (a), 6.09 (b), 2.32 (c), 2.08 (d), 2.02 (e), ($a/b \simeq 10$; $c/(d + e) \simeq \frac{1}{6}$).

Anal. Calcd for [$(C_8H_8O)_{3.5}$–C_8H_7BrO]: C, 69.78; H, 5.64; Br, 12.92. Found: C, 69.70; H, 5.73; Br, 12.99.

Copolymerization of 8 mmol of MBX and 12 mmol of TBX with 20 mmol of *t*-BuOK in 25 mL of THF by adding 1 mequiv of I_2 in THF at 25 °C under N_2 caused rapid precipitation of KBr. After 7 min, a 96% yield of copolymer was obtained, sp 240–250 °C. This copolymer was fractionated by dissolving in hot benzene–ethanol as above.

The less-soluble fraction (~50%) had sp 245–260 °C, [η] 0.065 (DP ~ 8), δ (ppm, $CDCl_3$), 2.05 (15), 2.26 (24), 6.33 (3), 6.45 (2).[9]

Anal. Calcd for [(C_8H_8O)–$(C_8H_6Br_2O)_{1.5}$]: C, 44.69; H, 3.16; Br, 44.69. Found: C, 44.30; H, 3.25; Br, 44.73.

The more-soluble fraction had sp 225–234 °C, [η] 0.032 (DP ~ 4), and the same NMR and IR as the less-soluble fraction.

Anal. Found: C, 44.25; H, 3.35; Br, 45.15.

Copolymerization of 8 mmol each of DBX and TBX with 16 mmol of *t*-BuOK in 25 mL of THF was initiated by 5 mL of 0.1 M I_2 in THF. After 5 min, acidification precipitated copolymer which, after reprecipitation from benzene by methanol, represented a 97% conversion, sp 280–300 °C, [η] 0.054 (DP ~ 7), δ (ppm, $CDCl_3$) 1.85 (3), 2.00 (3), 2.24 (9), 2.36 (9), 5.90 (1), 6.10 (1).

Anal. Calcd for (C_8H_7BrO–$C_8H_6Br_2O$): C, 40.25; H, 2.72; Br, 50.31. Found: C, 40.37; H, 2.76; Br, 49.25.

This copolymer was separated into approximately equal fractions from hot benzene–ethanol as above. The less-soluble fraction, sp 290–300 °C, and the more-soluble fraction, sp 265–280 °C, had identical NMR and IR spectra. For the latter, analysis showed: C, 40.16; H, 2.77; Br, 50.97.

When this copolymerization was carried out at 6 °C, 84.8% copolymer was obtained, sp 290–300 °C, and 14% of TBX, mp 190–200 °C, was recovered.

In addition to the preparative polymerizations and copolymerizations described above, a number of experiments were conducted to determine the effect of varying the conditions of the reactions. The results are summarized in Tables I–V.

Many experiments on conversion vs. time at room temperature indicated that whatever polymerization was going to occur had done so within the first 5 s. However, at 5 °C, the rate was measurable in seconds, as indicated in Table IV.

Polymerization of DBX seemed to proceed very much like MBX. The rates were comparable and the amount of I_2 required similar.

Polymerization of TBX required much more iodine than for MBX

Table I
Effect of Varying I_2 Concentration Polymerization of 2.0 mmol of MBX and *t*-BuOK in 20 mL of THF (25 °C)

I_2, mequiv	% polymer	I_2, mequiv	% polymer
0.03	~0	0.07[a]	57
0.05	2.0	0.10[a]	71
0.05[a]	21	0.20	63
0.07	36	0.20[a]	75

[a] Under air; others under nitrogen.

Table II
Effect of Varying Ratio of MBX to *t*-BuOK, in 20 mL of THF, under N_2

MBX, mmol	*t*-BuOK, mmol	I_2, mmol	% polymer
2	2	0.1	78
2	1	0.1	23
2	3	0.1	9.1
2	5	0.1	0
2	2	0.2	95
2	3	0.2	40

Table III
Polymer Yield, Iodine Consumed, and Bromide Liberated (MBXate, 8 mmol, 50 mL THF, 5 °C, 3 min)

I_2, mequiv	% polymer	I_2 consumed,[b] mequiv	% Br^- lib[c]
0.1	0	0.1	6
0.2	36[a]	0.2	43
0.4	71		93
0.5	72	0.34	94

[a] 37% of MBX recovered. [b] I_2 consumed, by thiosulfate titration. [c] Br^- liberated, by potentiometric titration with 0.1 N $AgNO_3$ corrected for I^- from iodine added.

Table IV
Effect of Time on Conversion at 5 °C (MBX, 8 mmol; *t*-BuOK, 8 mmol; I_2, 0.3 mequiv; THF, 50 mL)

Time, s	% polymer	% MBX rec	I_2 consumed[a]	% Br^- lib[b]
8	18.7	37	0.21	42
11	30	33	0.25	41
20	48		0.24	76
41	73		0.25	91

[a] By titration with 0.1 N thiosulfate. [b] By titration with 0.1 N silver nitrate.

Table V
Polymerization of DBXate (8 mmoles) in 25 mL of THF (0.3 mequiv I_2, 5 °C N_2)

Time, s	% polymer	I_2 consumed	% Br^- lib
20	75	0.22	91
300	91	0.24	91

or DBX. The latter proceeded satisfactorily with about 4% I_2, the TBX required about 25% I_2.

Discussion

The features which characterize the polymerization of MBX, DBX, and TBX in THF can be summarized as follows:

1. The reaction was extremely rapid at room temperature, being complete in a few seconds. This is considerably faster than under comparable conditions in HMPT as solvent.[4]

2. The reaction required only small amounts (less than 5%) of I_2 to go to completion, again in contrast to HMPT solution.

3. Reactions run to 25–50% conversion gave polymers of about the same intrinsic viscosity as at 90–95% conversion, in contrast to oxidative coupling of 2,6-xylenol.[11]

4. There were no blue or green colors developed, nor any ESR signals, as there were in HMPT.[4]

5. The reactivities of DBX and even TBX in copolymerizations are only slightly lower than for MBX.

6. The lower reactivity of TBX in homopolymerization may be related to the insolubility of this polymer.

7. The polymer molecules first formed appear to be reactivated for further polymerization. It is otherwise hard to explain the MBX–TBX data, where interrupted polymerization gives copolymer rich in MBX, but complete polymerization gives copolymer which could not be fractionated into samples with any difference in composition, despite the insolubility which would be expected for copolymer rich in TBX.

8. The polymers have significantly lower molecular weights than those prepared in benzene–water,[3,10] especially the copolymers from TBX. This indicates that, whatever the termination reaction may be, it is favored for TBX units.

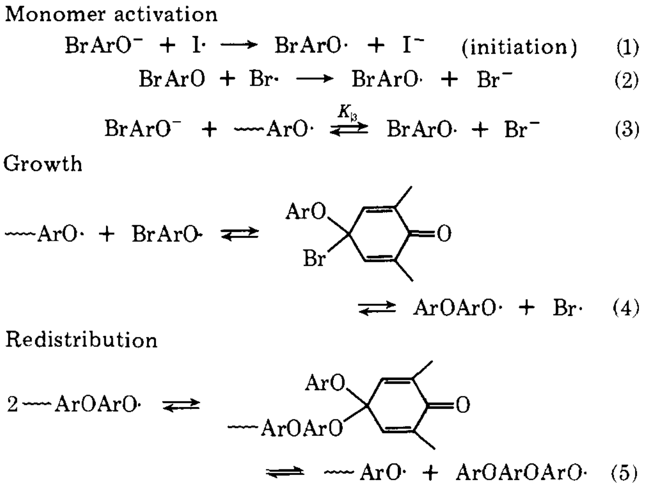
The relative reactivities of MBX, DBX, and TBX appear to be much more divergent in the heterogeneous polymerization system, where White and Klopfer[10] report copolymer for DBX and TBX but not for MBX with either DBX or TBX. In this case, the larger difference in ease of copolymerization could well be due to relative solubility in the benzene–water phases rather than inherent chemical reactivity. These authors did, however, report they could make these copolymers by the oxidative coupling system[10] using 2,6-xylenol with either DBX or TBX.

The most obvious difference between the oxidative coupling polymerization of xylenol and the bromodisplacement polymerization of MBX (or DBX or TBX) is that the former involves slow, stepwise buildup of polymer. Mostly low molecular weight oligomer is formed at 50% conversion. In contrast, the very rapid MBXate polymerization, either in the heterogeneous system[2,3] or the homogeneous THF system reported here, gives recovered monomer and high molecular weight polymer. We had earlier assumed a rapidly propagating radical attack on monomer ion to explain these facts.[2]

There is, however, no reason to rule out a radical–radical coupling mechanism[12] if one can assume that a 4-aryloxyphenoxy radical is formed very much in favor of a 4-bromophenoxy radical. One could then write Scheme I for the polymerization.

If the main factor affecting the equilibrium constant K_3 is the relative stability of anions involved, then one would expect the equilibrium to favor the aryloxyphenoxy radical for 4-bromoxylenol. With the equilibrium favoring oligomer radicals, any monomer radical formed would be rapidly attacked by the prevalent oligomer radicals (4), giving the features of preferred growth of oligomer. In the case of oxidative coupling of xylenol, the stepwise buildup of molecular weight, involving preferred reaction of monomer, may be related to the coordination of both monomer and nascent radicals to the copper–amine catalyst complex.[11] In this case, the monomer molecules may indeed be preferentially adsorbed on the polar catalyst and thus preferentially converted to nascent radicals.[13]

Scheme I



$$\mathrm{BrArO^- + I\cdot \longrightarrow BrArO\cdot + I^-} \quad \text{(initiation)} \qquad (1)$$

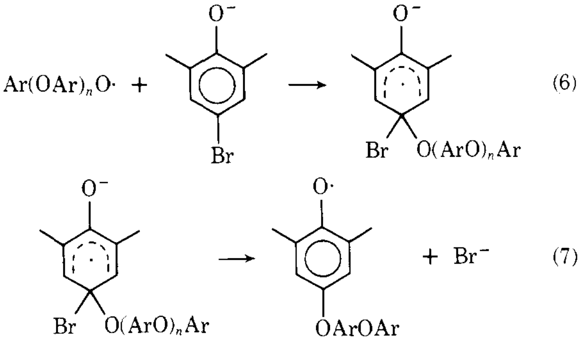
$$\mathrm{BrArO + Br\cdot \longrightarrow BrArO\cdot + Br^-} \qquad (2)$$

$$\mathrm{BrArO^- + {\sim}ArO\cdot \overset{K_3}{\rightleftharpoons} BrArO\cdot + Br^-} \qquad (3)$$

$$\mathrm{{\sim}ArO\cdot + BrArO\cdot \rightleftharpoons \ldots \rightleftharpoons ArOArO\cdot + Br\cdot} \qquad (4)$$

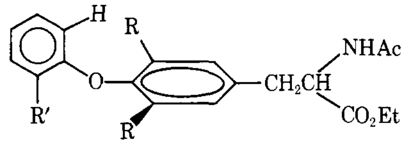
$$\mathrm{2{\sim}ArOArO\cdot \rightleftharpoons \ldots \rightleftharpoons {\sim}ArO\cdot + ArOArOArO\cdot} \qquad (5)$$

The direct radical–MBXate coupling (eq 6) we originally proposed remains a reasonable alternate mechanism. The rate constants estimated by Detar[14] for coupling of Ph· and $PhCO_2$· with benzene (2×10^3 and 35 $L/mol^{-1}\ s^{-1}$, respectively) are large and only four or five orders of magnitude less than the radical–radical coupling of the diene radicals (10^7). Since the MBXate concentration could well be at least five orders of magnitude greater than the phenoxy radical concentration, and since the radical–radical coupling rate for 2,4,6-trisubstituted phenoxy radicals would be expected to be much slower than the phenylhexadiene radicals of Detar, the rate of radical–MBXate reaction (eq 6) should be highly competitive with radical–radical coupling (eq 4). This course has the added advantage of a much easier loss of bromine, as Br^- (eq 7), rather than as the atom (eq 4). The intervention of radical anions as reactive intermediates in apparently simple nucleophilic displacements has been proposed for a number of reactions.[15]

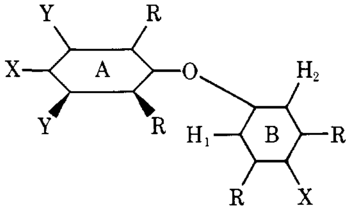


The NMR spectra of the polymers and copolymers reported here suggest that there may be considerable restraint on free rotation at the aryl ether bonds, especially in the case of copolymers formed from TBX. The resulting dibromoxylenol units are completely substituted with bulky substituents and models indicate a great deal of hindrance to free rotation of one ring with respect to the next. Such hindrnce may offer an explanation for the appearance of two peaks for the aromatic H in MBX–TBX copolymer and for aromatic H and the adjacent CH_3 in DBX–TBX copolymer and for the strong upfield shift for the aromatic H in the brominated unit in MBX–DBX copolymer.

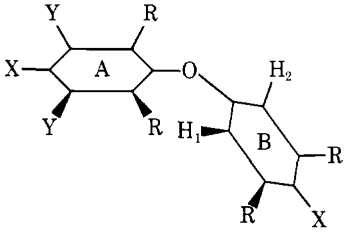
The latter case is analogous to the substituted thyroxine analogues which showed a strong upfield shift. In this case, Lehman and Jorgensen[16] found that for R = NO_2 or I and R′ = alkyl, the remaining hydrogen ortho to the ether link was shifted upfield to δ = ~6 ppm. They suggested the skewed conformation above, placing the hydrogen over the π-electron cloud of the adjacent ring. When R′ was hydrogen, the NMR resonance occurred near δ = 7 ppm, indicating either no preference or a rapid rotational exchange.



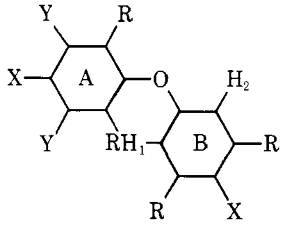
In comparing the ortho hydrogens in diphenyl ether (δ = 6.92 ppm) to those in anisole (δ = 7.77 ppm), one possible explanation is that diphenyl ether prefers a conformation limiting resonance with the ether group. Of the three extreme conformers represented below, anisole may prefer III, (A = CH_3) enhancing resonance, whereas diphenyl ether may prefer either II or a rapidly rotating I, exchanging H_1 and H_2.



I



II



III

The upfield shift in polyxylenol (R = CH_3) compared to diphenyl ether may be ascribed to an increased population of I due to the hindrance of the methyl groups. The spectra for the copolymers of TBX may be explained by assuming that the buttressing effect of bromines in ring A (R = CH_3, Y = Br) so enhances the steric effect of methyl that the preference for I over II is still further enhanced, leading to a shift of aromatic H from δ = 6.45 ± 0.05 ppm (ring A, no or one bromine) to δ = 6.33 ppm (ring A, two bromines).

In MBX–DBX, the bromine in place of H_2 causes the same shift as observed by Lehman and Jorgensen, with H_1 now appearing at δ = 6.15 ppm, rather than at 6.48 ppm as in polyxylenol.

In the DBX–TBX polymer, the hydrogen H_1 appears at δ = 6.10 ppm if ring A contains one bromine, at δ = 5.90 ppm if ring A contains two bromines.

These explanations for the effect of TBX in the copolymers fit quantitatively with integrated peak heights if one assumes a random distribution of the two monomer units in copolymer, due either to equal rates of incorporation or to effective redistribution reactions.

References and Notes

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(8) The approximate degree of polymerization (DP) for polymers and copolymers was estimated using the Hay relationship, $[\eta] = 3.8 \times 10^{-4} M^{0.73}$ (A. S. Hay, General Electric Co., Schenectady, N.Y.), assuming that the bromo and dibromo units in the polymer make the same molar contribution to viscosity as the unbrominated unit. Dr. White[10] used a similar assumption and equation ($[\eta] = 4.66 \times 10^{-4} M_n^{0.70}$; Dwain M. White, General Electric Co., private communication).
(9) Dr. D. M. White (private communication) has indicated that in Table II, p 174 of ref 10, the methyl H data for his compounds XII and VI were inadvertently exchanged. His data and ours are therefore in agreement.
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Preferential and Absolute Adsorption to Poly[N^5-(3-hydroxypropyl)-L-glutamine] in Water/2-Chloroethanol Solvent Mixtures

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ABSTRACT: Preferential adsorption to poly[N^5-(3-hydroxypropyl)-L-glutamine] (PHPG) in water/2-chloroethanol solvent mixtures has been determined by measuring density increments at constant concentration and at constant chemical potential. At low alcohol concentrations, decreasing preferential adsorption of 2-chloroethanol is observed. When the organic solvent content is increased, an inversion of preferential adsorption occurs, water being preferentially adsorbed. The inversion zone parallels the conformational transition curve. As an explanation it is proposed that a competition occurs between noninteracting helicogenic 2-chloroethanol, which stabilizes hydrophobic interactions, and the hydrophilic interactions of water with PHPG. The former retains a helical structure, whereas the latter induces a helix-to-coil transition.

It is well known[1-4] that the conformational transition in proteins and synthetic polypeptides is accompanied by changes in preferential and absolute adsorption onto the polymer in water/organic solvent mixtures. To elucidate the mechanisms responsible for the stabilization of protein conformation, it is common to study model synthetic polypeptides. The aim of this work is to study the conformational transition and the interactions of a nonionizable water soluble polypeptide, poly[N^5-(3-hydroxypropyl)-L-glutamine] (PHPG), in the water/2-chloroethanol mixed solvent system. The interactions of proteins with solvent components of mixed water/2-chloroethanol have been extensively studied:[1-6] 2-chloroethanol was shown to be a structure-forming denaturant solvent and was capable of interacting with proteins, probably by way of hydrophobic interactions with the aliphatic side chains. Thus, it seemed to us interesting to study preferential adsorption in the PHPG/water/2-chloroethanol system.

Such a study has been reported for the PHPG/water/dioxane system.[7] The authors indicated that an increasing hydration took place with increasing helicity of the polymer. Very high values of the helical content were not obtained and no preferential solvation of dioxane to the polymer was observed. In a study of the poly(L-glutamic acid)/water/dioxane system, it was noticed[8] that the structural transformation of the polypeptide was preceded by preferential solvation of dioxane and followed by increasing preferential hydration. In counterpart, 2-chloroethanol was shown to be a better helicogenic agent for poly(L-glutamic acid)[9] than dioxane.

Furthermore, we obtained higher values of the helical content of PHPG in water/2-chloroethanol mixtures. Therefore, 2-chloroethanol seems to be of much interest. Knowing that the side chain methylene groups of PHPG are responsible for stabilization of an α-helical secondary structure,[10-12] we expected important hydrophobic interactions enhancing the helical structure of PHPG.

Preferential interactions can be detected by a variety of methods: light-scattering measurements,[5] equilibrium sedimentation measurements,[6,13] isopiestic measurements of vapor pressure,[14] differential refractometry,[1,7,8,13] and density measurements.[13,15] For the water/2-chloroethanol system it is very convenient to use the latter method, and instruments now available allow easy and accurate measurements.

Theoretical

We use the Scatchard-Stockmayer[16,17] notation, in which the polymer is refered to as component 2, water as component 1 (which is considered as the principal solvent), and the organic solvent as component 3. At constant P and T, the preferential adsorption coefficient is related to the density increments $(\partial\rho/\partial c_2)_m{}^0$ and $(\partial\rho/\partial c_2)_\mu{}^0$, respectively at constant molality of component 3 and constant chemical potential of components 1 and 3, at vanishing polymer concentration, by the relation:[13,15,18,19]

$$\left(\frac{\partial g_3}{\partial g_2}\right)_\mu = \frac{(\partial\rho/\partial c_2)_\mu{}^0 - (\partial\rho/\partial c_2)_m{}^0}{1 - \bar{V}_3\rho_0} \qquad (1)$$

where $\bar{v}_3$ represents the partial specific volume of the organic solvent and ρ_0 is the density of the mixed solvents. The preferential adsorption coefficient $(\partial g_3/\partial g_2)_\mu$ represents the preferential binding of component 3 to the polymer, given in grams of component 3 to be added to the solution per gram of component 2, in order to maintain the constancy of the chemical potential of components 1 and 3. Thus, a negative value of $(\partial g_3/\partial g_2)_\mu$ signifies a deficiency of component 3 in the vicinity of the macromolecule, i.e., preferential hydration takes place.