Host−Guest Interaction between β-Cyclodextrin and Hydrophobically Modified Poly(isobutene-*alt*-maleic acid) Studied by Affinity Capillary Electrophoresis

Bart Jan Ravoo* and Jean-Christophe Jacquier

Department of Chemistry, National University of Ireland, University College Dublin, Belfield, Dublin 4, Ireland

Received February 19, 2002; Revised Manuscript Received May 8, 2002

ABSTRACT: Poly(isobutene-*alt*-maleic acid)s modified with *p-tert*-butylphenyl or adamantyl groups interact with β-cyclodextrin in water due to inclusion of the hydrophobic substituents in the β-cyclodextrin cavity. The formation of these host−guest complexes was investigated in dilute aqueous solution using affinity capillary electrophoresis. The electrophoretic mobility of the polymers was measured in the presence of increasing concentration of β-cyclodextrin in the capillary. The binding constants *K* (expressed per mole of β-cyclodextrin) were determined from the change of the electrophoretic mobility of the polymers with the increase of β-cyclodextrin concentration. $K = (2.8-3.9) \times 10^4\ M^{-1}$ for *p-tert*-butylphenyl guest polymers and $K = (2.2-3.5) \times 10^3\ M^{-1}$ for adamantyl guest polymers. These findings are consistent with titration microcalorimetry data, demonstrating that capillary electrophoresis is a suitable technique to quantitatively measure interactions with hydrophobically modified polymers. The change in electrophoretic mobility upon complexation can be explained from a transition of the free polymers, which form compact unimer globules, into bound polymers forming extended random coils.

Introduction

Associative thickeners are water-soluble polymers bearing a small number of hydrophobic substituents. The hydrophobic interaction between these substituents can lead to a high increase in viscosity of the solution and gelation. The strength of the hydrophobic interaction depends on the nature of the hydrophobic substituents, concentration, temperature, and shear rate. However, the efficient application of associative thickeners requires a method to prevent interaction during the dissolution of the polymer. In principle, this difficulty can be avoided by mixing two complementary associating polymers or by (temporarily) blocking the self-association during dissolution. Both strategies can benefit from the use of (modified) cyclodextrins. Cyclodextrins (CDs) are readily available water-soluble cyclic oligomers of glucose that bind hydrophobic molecules through inclusion in their internal cavity.

It was shown that complementary associating polymers can be based on a combination of water-soluble polymers of β-cyclodextrin (β-CD) and hydrophobically modified poly(ethylene glycol),[1] poly(isobutene-*alt*-maleic acid) (PiBMA),[2] or poly(maleic acid).[3] Inclusion of the hydrophobic substituents on the *guest polymer* into the β-CD cavities on the *host polymer* leads to large viscosity increases only upon mixing of the two components. Alternatively, the Rohm and Haas Co. has shown that masking of the hydrophobic substituents in a self-associating polymer by β-CD makes this thickener much easier to process, while subsequent removal of the β-CD by surfactant gives the desired high-viscosity product.[4]

Further development of these associative thickeners will require more extensive characterization of host and guest polymers. The interaction of a linear, β-CD-substituted *host polymer* with adamantane guest molecules was studied by titration microcalorimetry,[5] and the interaction of α-CD and β-CD-substituted chitosan *host polymers* with various guests was characterized by NMR.[6] The interaction of β-CD and *guest polymers* of PiBMA substituted with adamantyl and *p-tert*-butylphenyl groups was also studied by titration microcalorimetry,[2] while the interaction with perfluorocarbon-modified poly(ethylene glycol) was studied using ^{19}F NMR.[7] The interaction of β-CD and cholesteryl-bearing pullulan[8a] and poly(L-lysine)[8b] *guest polymers* was studied using static light scattering, gel permeation chromatography, and circular dichroism. Finally, the interaction of β-CD with a *dendritic guest polymer* substituted with adamantyl groups was studied using ^1H NMR.[9]

Capillary electrophoresis is an emerging analytical technique that has proven to be well adapted to the study of binding constants of various molecules to biopolymers in dilute aqueous solution.[10] Furthermore, because of the ability of the CD cavity to form stereoselective complexes with a wide range of enantiomers, this oligosaccharide has become a chiral selector of choice for the electrophoretic enantioseparation of racemic mixtures.[11] Nevertheless, and despite these recent advances, no electrophoretic study of complex formation between hydrophobically modified polymers and CD has been reported to date.

In this paper we have investigated the interaction of PiBMA substituted with *p-tert*-butylphenyl or adamantyl groups with β-CD in water by means of capillary electrophoresis. These guest polymers were prepared from poly(isobutene-*alt*-maleic anhydride)[2] (PiBM) of $M_w = 60$ kg/mol; i.e., all polymers have the same chain length. Their structural properties are summarized in Figure 1 and Table 1. The binding of β-CD to the guest polymers occurs through inclusion of the hydrophobic substituents into the CD cavity and results in reduction of the electrophoretic mobility of the polymers. The decrease of polymer electrophoretic mobility in the presence of increasing concentration of β-CD was ana-

* Author for correspondence: Tel +353 1 7162449; Fax +353 1 7162127; e-mail bart.ravoo@ucd.ie.

10.1021/ma020270x CCC: $22.00
Published on Web 06/27/2002

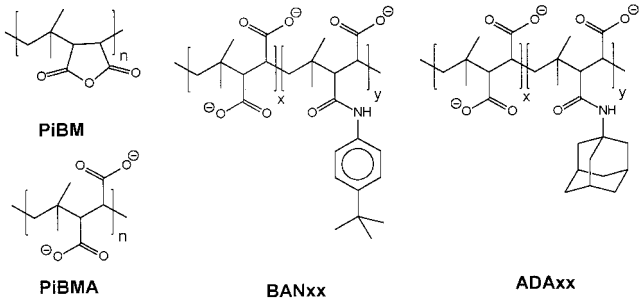

Figure 1. Chemical structures of polymers used in this study. xx refers to the molar percentage of substitution.

Table 1. Structural Properties of Polymers Used in This Study

polymer	substitution $y/(x+y)$,[a] %	MW repeating unit, g mol^{-1}
PiBM		154
PiBMA	0	172
BAN42	42	633
BAN09	9	2437
ADA20	20	1191
ADA10	10	2271

[a] y and x as used in Figure 1.

lyzed in terms of the formation of a 1:1 inclusion complex of guest polymer substituent and β-CD, characterized by the binding constant K. The electrophoretic method was verified by analyzing the inclusion of *p-tert*-butylbenzoate into β-CD. The influence of the nature of the hydrophobic substituent as well as the degree of substitution of the polymers was studied. The change in electrophoretic mobility upon complexation can be explained from different conformations of the free and bound polymers, as confirmed by dynamic light scattering.

Experimental Section

Materials. β-CD was obtained as a gift from Wacker, UK. The guest polymers BANxx and ADAxx were kindly donated by Prof. Gerhard Wenz (Saarbrücken, Germany) and prepared as described by amidation of PiBM of M_w = 60 kg/mol with varying amounts of *p-tert*-butylaniline or adamantylamine, respectively, followed by hydrolysis of the remaining anhydride groups.[2] PiBMA was obtained by hydrolysis of PiBM using aqueous NaOH. *p-tert*-Butylbenzoic acid was obtained from Aldrich and converted to the sodium benzoate by addition of 1 equiv of NaOH. The structure formulas of the polymers are represented in Figure 1, while Table 1 regroups essential chemical characteristics.

Capillary Electrophoresis. Experiments were carried out using a Beckman P/ACE 2100 system using Gold software for operation and data acquisition. Samples were loaded by pressure injection at the anodic end of a fused silica capillary of 57 cm × 75 μm i.d. UV sample detection was performed through the capillary at 50.2 cm from the inlet at a wavelength of 200 nm. To ensure a good dissipation of the Joule effect and to maximize the reproducibility of the measurements, a constant voltage of 15 kV was applied, leading to a dissipated power of about 0.7 W m^{-1}, which is well below the limiting capacity of the instrument. All experiments were carried out at 25 °C. All solutions were prepared in 10 mM phosphate buffer of pH 7.5. To accurately detect the electroosmotic flow, the injection samples were prepared in a twice-dilute buffer (5.0 mM) and injected for 5 s at low pressure (0.5 psi). This injection time resulted in injection plugs of ca. 6 mm, or 1% of the effective column length. The analyte concentration was 0.010 or 0.050 g L^{-1} for the polymers and 0.0020 g L^{-1} for *p-tert*-butylbenzoate, while the β-CD concentration in the capillary was 0.0−10.0 g L^{-1}. All experiments were reproduced at least two times. The error in the reading of the elution times is about 0.02 min, or 0.2%, resulting in a standard deviation of the reported electrophoretic mobilities of less than 1%.

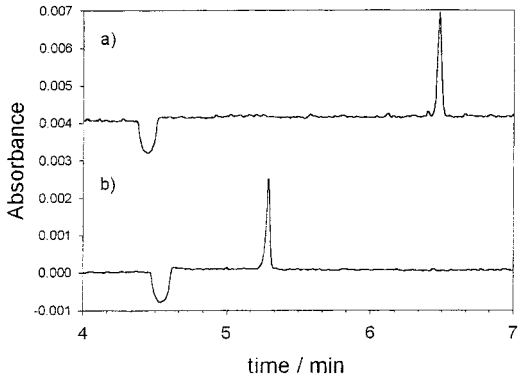

Figure 2. Electrophoregram of *p-tert*-butylbenzoate as a function of β-cyclodextrin concentration: (a) no added β-cyclodextrin; (b) 10^{-2} M β-cyclodextrin.

Dynamic Light Scattering. Experiments were performed using a Malvern PCS-4700 laser light scattering system equipped with a 256-channel correlator. The 488.0 nm line of a Coherent Innova-70 argon ion laser was used for the incident beam. The laser power was maintained at 300 mW, and the scattering angle was fixed at 90°. The temperature was maintained at 25.0 ± 0.02 °C with an external circulator. The polymer samples (0.1−0.2 g/L) were filtered through 0.45 μm Gelman Acrodisk filters prior to use. CONTIN analysis was used to obtain apparent diffusion coefficients from the time correlation function.

Results and Discussion

Validation of Experimental Protocol: Binding of β-CD to *p-tert*-Butylbenzoate. To validate the complexation constants derived for polymer−CD interactions, we evaluated the binding constant of *p-tert*-butylbenzoate to β-CD. The change of electrophoretic mobility of the *p-tert*-butylbenzoate ion was monitored as a function of added β-CD. A typical electrophoregram is reproduced in Figure 2. The first, negative peak corresponds to water and serves as a marker for the electroosmotic flow. The second, positive peak corresponds to the *p-tert*-butylbenzoate ion. Upon complexation with β-CD (Figure 2b), the *p-tert*-butylbenzoate ion will move slower due to its incorporation in the CD cavity, and its peak will get closer to the water peak.

The electrophoretic mobility of the *p-tert*-butylbenzoate ion, μ_{ep}, was calculated from the elution times according to the following classic equation:

$$\mu_{ep} = \frac{lL}{V}\left(\frac{1}{t} - \frac{1}{t_{eof}}\right) \quad (1)$$

where l and L denote the length of the capillary from injector to detector and total length respectively, V is the applied voltage, and t_{eof} and t are the elution times of the electroosmotic flow and the *p-tert*-butylbenzoate, respectively.

The electrophoretic mobility of *p-tert*-butylbenzoate as a function of added β-CD in the extended range of concentration between 10^{-6} and 10^{-2} M is presented in Figure 3.

This semilogarithmic plot displays a typical sigmoidal curve characteristic of 1:1 inclusion of *p-tert*-butylbenzoate into β-CD. The results of the nonlinear regression are summarized in Table 2. From this curve a binding constant is derived. $K = (12.7 \pm 0.3) \times 10^3$ L mol^{-1}, in

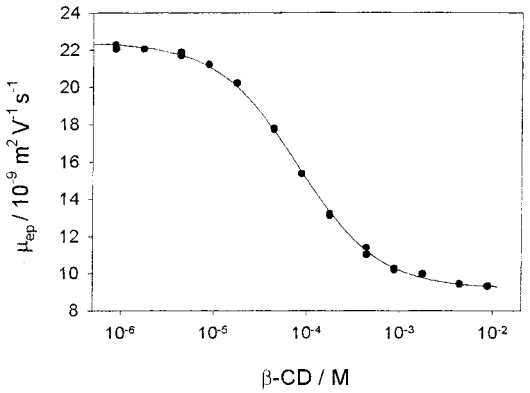

Figure 3. Electrophoretic mobility μ_{ep} of *p-tert*-butylbenzoate as a function of β-cyclodextrin concentration.

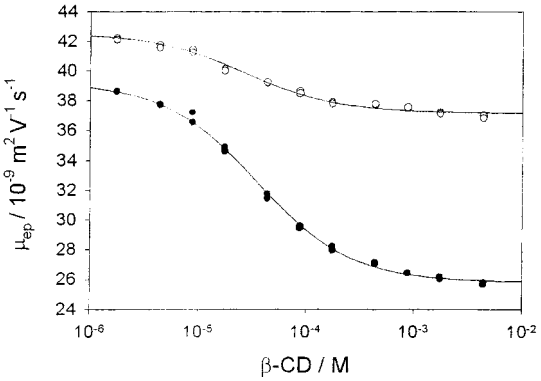

Figure 4. Electrophoretic mobility μ_{ep} of polymers BANxx as a function of β-cyclodextrin concentration: (○) BAN09; (●) BAN42.

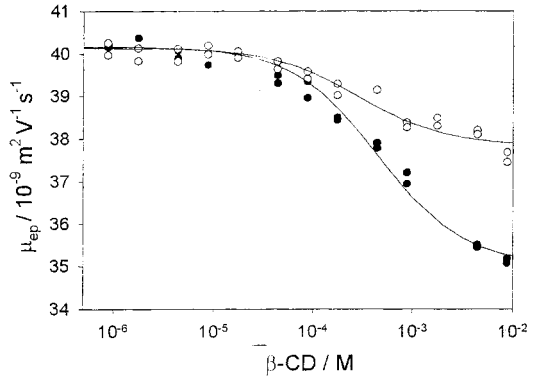

Figure 5. Electrophoretic mobility μ_{ep} of polymers ADAxx as a function of β-cyclodextrin concentration: (○) ADA10; (●) ADA20.

good agreement with the microcalorimetry data that yield $K = (17.9 \pm 0.7) \times 10^3$ L mol^{-1}.[2,12] The difference can be attributed to the higher ionic strength used in the microcalorimetry study (100 mM phosphate vs 10 mM phosphate here) which will increase the "salting out" of *p-tert*-butylbenzoate and raise its affinity for the CD cavity. At this point, it is important to note that the concentration of complex was neglected compared to that of β-CD, so that the concentration of free β-CD was approximated to that in the background electrolyte. This assumption is validated by the fact that the concentration of *p-tert*-butylbenzoate is small compared to that of β-CD at midpoint (approximately 10%) and that the concentration of *p-tert*-butylbenzoate at the peak height is even lower than in the injection plug due to various contributions in the spreading of the sample zone during the course of the analysis.

No binding constant has been obtained for the complexation of adamantylcarboxylate to β-CD. It is known from microcalorimetry[2b] that $K = (32.6 \pm 0.1) \times 10^3$ L mol^{-1}, and because of the absence of a chromophore on the adamantyl group, accurate determination of this binding constant by capillary electrophoresis would have imposed a too low concentration of sample in the injection plug for direct UV detection. Nonetheless, it is important to note here the similar order of magnitude of binding between these two hydrophobic anions and β-CD.

Binding of β-CD to Polymers. Having validated the electrophoretic protocol for small hydrophobic ions, we then turned our attention to the binding of β-CD to the poly(isobutene-*alt*-maleic acid)s. In the case of the underivatized polymer PiBMA, no significant change of mobility was observed upon addition of excess β-CD (10^{-2} M): $\mu_{free} = 44.6 \times 10^{-9}$ m^2 V^{-1} s^{-1} and $\mu_{complex} = 43.9 \times 10^{-9}$ m^2 V^{-1} s^{-1}. This polymer has no hydrophobic substituents and cannot form stable inclusion complexes. The slight reduction of the electrophoretic mobility of PiBMA in the presence of β-CD could result from the formation of a pseudo-poly(rotaxane) through inclusion of the polymer backbone in the β-CD cavity.[13] However, such a complex will be unstable due to the strongly hydrophilic nature of the maleic acid polymer backbone. Moreover, as no significant shift in the electroosmotic flow was observed within this extensive range of β-CD concentration, no adjustment of electrophoretic mobility was made to take into account a variation in the viscosity of the background electrolyte.[14]

In the case of the four hydrophobically modified polymers, a noticeable reduction of electrophoretic mobility was observed upon addition of β-CD to the background electrolyte. The change of electrophoretic mobility with β-CD concentration for the *p-tert*-butylphenyl and adamantyl derived polymers are reported in Figures 4 and 5, respectively. The extrapolated values of the electrophoretic mobility of free and complexed polymers are summarized in Table 2, along with the values of binding constants deduced from nonlinear regressions. For ease of comparison, microcalorimetry data from Wenz et al.[2b,12] are also included. As before, the concentration of complex formed was neglected, and the free concentration of β-CD was taken as its total concentration in the background electrolyte. This as-

Table 2. Electrophoretic Mobility of BAN and ADA Polymers and *p-tert*-Butylbenzoate in the Absence of β-Cyclodextrin (μ_{free}) and in the Presence of Excess β-Cyclodextrin ($\mu_{complex}$); Binding Constants for Complexation of Polymers and *p-tert*-Butylbenzoate to β-Cyclodextrin Derived from Capillary Electrophoresis (K^{ce}) and from Microcalorimetry (K^{mcal})[2b,12]

sample	μ_{free}, 10^{-9} m^2 V^{-1} s^{-1}	$\mu_{complex}$, 10^{-9} m^2 V^{-1} s^{-1}	K^{ce}, 10^3 L mol^{-1}	K^{mcal}, 10^3 L mol^{-1}
BAN42	39.25 ± 0.08	25.82 ± 0.09	28 ± 1	26.0 ± 0.2
BAN09	42.50 ± 0.07	37.18 ± 0.07	39 ± 3	21.0 ± 0.9
ADA20	40.17 ± 0.07	35.0 ± 0.2	2.0 ± 0.3	4.9 ± 0.3
ADA10	40.14 ± 0.07	37.8 ± 0.1	3.5 ± 0.9	6.5 ± 0.4
p-tert-butylbenzoate	22.42 ± 0.04	9.21 ± 0.05	12.7 ± 0.3	17.9 ± 0.7

sumption is even more justified than in the case of *p-tert*-butylbenzoate due to the peak spreading that occurs as a result of complex formation. This peak spreading, only noticeable at intermediary concentration of β-CD, can be attributed to polydispersity in molecular weight of the polymers as well as some heterogeneity in the extent of derivation.

It is clear from Table 2 that the binding constants derived from our electrophoretic experiments are in good agreement with the microcalorimetry data for both sets of polymers. Both BAN09 and BAN42 display high affinity to bind β-CD, with binding constants similar to that of *p-tert*-butylbenzoate. On the other hand, both ADA10 and ADA20 display a much lower affinity for β-CD, with binding constants 1 order of magnitude *lower* than that of adamantylcarboxylate. This remarkable difference was previously attributed to the more compact nature of the adamantyl substituent compared to that of the *p-tert*-butylphenyl substituent, which would make it less accessible for inclusion in β-CD when it is attached to the hydrophilic PiBMA backbone.[2b] However, our electrophoretic data offer an alternative explanation.

For both sets of polymers the decrease in electrophoretic mobility upon complex formation is larger when the degree of substitution is higher (Figures 4 and 5). This difference cannot be solely attributed to a reduction of structural charge of the polyelectrolytes upon hydrophobic modification, and some explanation has to be looked for in terms of hydrodynamic friction increase. In fact, these modified polymers are known as *polysoaps* due to their ability to form unimolecular micelle-like microstructures where the hydrophobic units form interior domains and the charged backbone form an outer layer.[15] As the concentrations of polymer used in the injection plug are well below their critical aggregation concentration (data not shown), it is most probable that both BANxx and ADAxx polysoaps are indeed in unimer conformation, and intermolecular interactions between the polymers can be neglected. Complex formation between the hydrophobic units and β-CD will therefore be in competition with *intramolecular* association.[16] The significant (one degree of magnitude) difference between ADAxx and BANxx polymer binding constants with CD would suggest that the intramolecular association between adamantyl units is 1 order of magnitude higher than is the case with *p-tert*-butylphenyl units.[17] This interpretation is based on the fact that *p-tert*-butylbenzoate and adamantylcarboxylate ions form β-CD inclusion complexes characterized by a similar binding constant.[2b,12] The slight decrease in apparent binding constant with the degree of substitution, observed for both polymers, would corroborate such an interpretation since the more substituted polymer will be more prone to unimer formation, tilting the balance toward intramolecular association to the detriment of binding to β-CD. A decrease of K with increasing substitution was found for the ADA polymers but not for the BAN polymers in the microcalorimetry study.[2b,12]

In fact, when the electrophoretic mobility of the polymers saturated with β-CD is plotted against the degree of hydrophobic substitution (Figure 6), it can be seen that the mobility of the complex correlates linearly with the degree of substitution, indicating that both polymer types adopt a similar conformation in the background electrolyte upon complexation with β-CD. At full complexation, both polymer types will have all

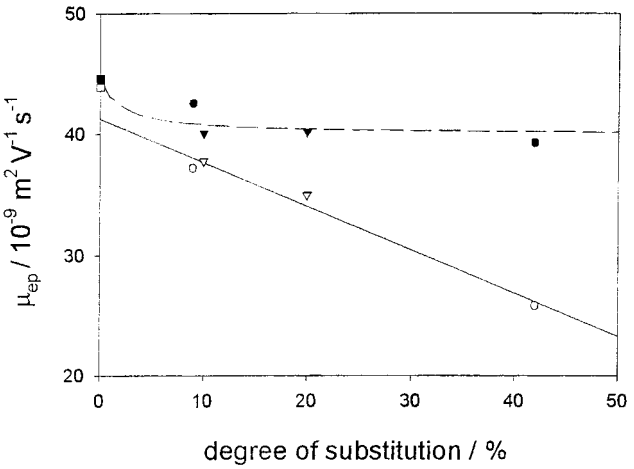

Figure 6. Electrophoretic mobility μ_{ep} of polymers PiBMA, ADAxx, and BANxx as a function of percentage substitution. Closed symbols: free polymers (μ_{free}). Open symbols: fully complexed polymers ($\mu_{complex}$). (●, ○) BANxx; (▲, △) ADAxx; (■, □) PiBMA.

Table 3. Diffusion Coefficients of PiBMA, BAN42 and ADA20 in the Absence of β-Cyclodextrin ($D_{app,free}$) and in the Presence of Excess β-Cyclodextrin ($D_{app,complex}$). Relative Changes in Diffusion Coefficients and in Electrophoretic Mobility

sample	$D_{app,free}$, 10^{-12} m^2 s^{-1}	$D_{app,complex}$, 10^{-12} m^2 s^{-1}	$\Delta D_{app}/D_{app,free}$, %	$\Delta\mu/\mu_{free}$, %
PiBMA	20.4	21.5	−5.0	1.6
BAN42	25.8	17.6	32	34
ADA20	19.4	15.2	22	12

hydrophobic units included in the CD cavities and, due to the hydrophilic characteristics of the CD exterior, resemble a CD-derived polymer with little or no intramolecular association.

In the case of the free polymers, the picture is somewhat different (Figure 6). Depending on the hydrophobic unit, there is a tendency to reach a plateau in mobility despite increasing degree of substitution, indicating compensation of the net loss in structural charge upon derivation with a decrease in hydrodynamic friction. This tendency could be well understood within the framework of unimer formation, a more substituted polymer giving a more compact unimer globule with higher charge density. Upon complex formation, this unimer globule—with hydrophobic units packed tightly in its core and ionic backbone exposed at the surface—undergoes a conformational transition to form an extended coil that closely resembles a CD-derived polymer, with no intramolecular interaction.

The hypothesis that the changes in electrophoretic mobility of the polymers upon complexation with β-CD are primarily due to changes in hydrodynamics was confirmed in a dynamic light scattering analysis of dilute polymer solutions in the presence of excess β-CD (5.0 g/L) and in the absence of β-CD. The results are summarized in Table 3. These results are consistent with the capillary electrophoresis experiments in that a significant decrease in apparent diffusion coefficient (i.e., an increase in hydrodynamic radius) is observed for both hydrophobically modified polymers upon complexation with β-CD but not for the unmodified polymer PiBMA. Moreover, the relative change in apparent diffusion coefficient is in fair agreement with the relative decrease in electrophoretic mobility. We conclude that the hydrodynamic radius of the polymers

increases dramatically upon complex formation from a compact globule to an extended random coil and that this expansion is most pronounced for the most highly substituted polymer.

Conclusions

The inclusion of hydrophobic substituents on poly(isobutene-*alt*-maleic acid) by β-cyclodextrin in dilute aqueous solution was investigated by affinity capillary electrophoresis. The change in electrophoretic mobility of the polymers upon complexation with β-cyclodextrin allowed accurate measurement of the binding constants. The change in electrophoretic mobility upon complexation can be explained from a transition of the free polymers, which form compact unimer globules, into bound polymers forming extended random coils.

Acknowledgment. We gratefully acknowledge Professor Gerhard Wenz (Saarland University at Saarbrücken, Germany) for his generous gift of guest polymers. B.J.R. is a Schering-Plough Co. Newman Scholar in Organic Chemistry at UCD.

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