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Viscometric detection of polymer inclusion complexes

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Summary
The reduced viscosity of poly(ethylene glycol) (PEG) is increased in solutions of (2-hydroxypropyl)-α-cyclodextrin (HPACD) significantly more than in the solution of (2-hydroxypropyl)-β-cyclodextrin (HPBCD) in agreement with the fact that a crystalline complex of PEG is formed in solutions of natural α-cyclodextrin but not in solutions of natural β-cyclodextrin. In analogy with that, the viscometry indicates formation of a complex between HPBCD with poly(vinyl alcohol) because the reduced viscosity is markedly increased in solutions of HPBCD but only slightly in solutions of HPACD. On the other hand, the increase in the viscosity of poly(*N*-vinylpyrrolidone) (PVP) was identical in HPACD and HPBCD solutions; therefore, the viscometry did not provide support for the suggested side-chain complexation between PVP and cyclodextrins.

Introduction

The number of papers dealing with axial inclusion complexes of cyclodextrins (cyclic oligosaccharides) (CDs) and synthetic polymers has grown rapidly in recent years. This effort has been mainly due to the group of Wenz and coworkers (1) investigating complexation of polymers with ionogenic groups in the main chain and the group of Harada and coworkers (2) working with non-ionogenic, mostly hydrophilic, polymers. Although the polymers used by Wenz et al. are structurally more complex, their complexation behavior is in fact more straightforward. The bulky hydrated groups in the main chain not only ensure the solubility of the complexes but also prevent the interactions between the neighboring cyclodextrins threaded on the polymer main chain. In the absence of such groups, a significant cooperativity of threading is expected and the complexation results in precipitation. Consequently, Harada et al. concentrated on the preparation of crystalline complexes, their modification and characterization in the solid state. However, concurrent work by others (3-5) revealed that a significant complexation occurs in solution even with non-ionic polymers if the cyclodextrin or the polymer is modified or if sufficiently low concentrations of these substances are used. It became evident that the extent of complexation is determined by three types of interactions - (i) those between polymer and cyclodextrin; (ii) those between adjacent cyclodextrins on the polymer chain; (iii) those between cyclodextrins threaded on different polymer chains.(5) Because the importance of a particular type of interactions depends on concentration, a variety of experimental techniques are required to obtain proper understanding of the phenomenon. In this paper, the use of viscometry is discussed on the basis of the results

obtained with (2-hydroxypropyl)-cyclodextrins (HPCDs) and three synthetic water soluble polymers: poly(ethylene glycol) - (PEG), poly(vinyl alcohol) - (PVA), and poly(*N*-vinylpyrrolidone) - (PVP).

Experimental

Materials. Both polymers and (2-hydroxypropyl)cyclodextrins were of commercial origin and all were dried under vacuum at 40 °C prior to use. Poly(ethylene glycol) (Serva) had nominal molecular weight 40 000; its viscosity-average molecular weight determined from the intrinsic viscosity in benzene at 25 °C was 37 000. Poly(*N*-vinylpyrrolidone) (International Enzymes) had nominal molecular weight 40 000. Two samples of poly(vinyl alcohol) were used: The first one (BDH Chemicals) had a declared degree of hydrolysis higher than 98% and molecular weight 14000; the value 22000 was obtained by light scattering. The second sample (Aldrich) had a degree of hydrolysis 87-89% and label molecular weight 13 000-22 000. Both (2-hydroxypropyl)cyclodextrins were purchased from Aldrich; the average degree of substitution was 0.6 for (2-hydroxypropyl)-α-cyclodextrin and 0.8 for (2-hydroxypropyl)-β-cyclodextrin.

Viscometry. All measurements were done at 25±0.02 °C using an automated Ubbelohde viscometer constructed in the Institute. Values of the reduced viscosity were calculated as $(t/t_s\text{-}1)/c_p$ where t is a flow time of a polymer solution, t_s is a flow time of a solvent (i.e., of a HPCD solution or of pure water), and c_p is the weight concentration of a polymer.

Results

Two types of measurements were done: (i) at a fixed HPCD concentration and at (ii) a fixed polymer concentration. The effect of time was not observed in any of these experiments.

The dependences of the reduced viscosity on polymer concentration were linear for all polymers both in water and 10% HPCD solutions. Therefore it was possible to determine the intrinsic viscosities by linear regression as the intercepts of the Huggins plots (the reduced viscosity vs. polymer concentration). The results are collected in Table 1. It can be seen that for all polymers the intrinsic viscosity was higher in 10% HPCD solutions but the observed pattern was not identical. While with PVP the increase was almost identical in both types of HPCD used, a higher value of the intrinsic viscosity was obtained in (2-hydroxypropyl)-α-cyclodextrin (HPACD) than in (2-hydroxypropyl)-β-cyclodextrin (HPACD) with PEG whereas the reverse was found with both samples of PVA. This finding was also confirmed by measuring the dependences of the reduced viscosity on a HPCD concentration at a fixed polymer concentration. The results shown in Figures 1 and 2 indicate a saturation effect although the saturation has not been achieved, possibly with the exception of PVA samples in HPACD.

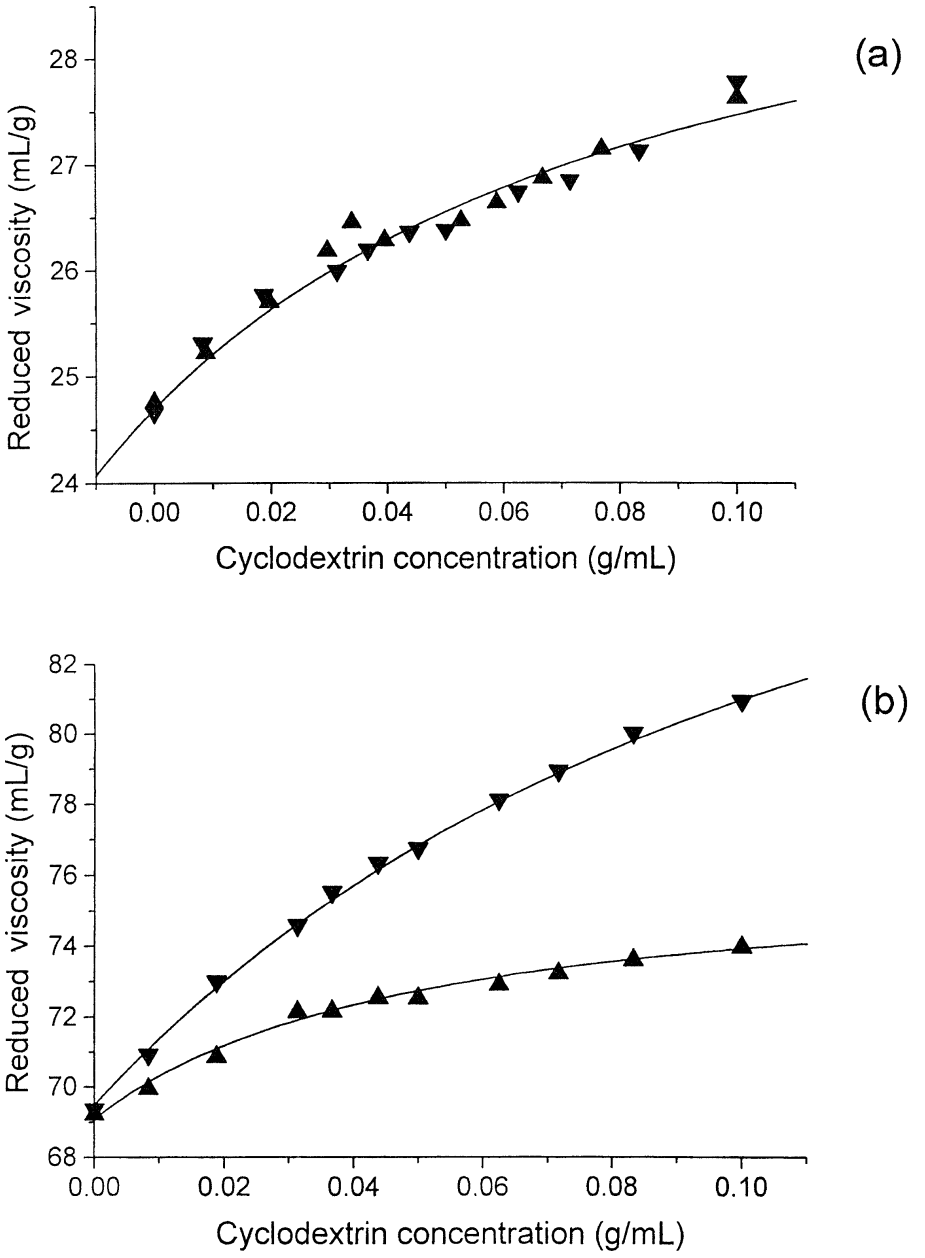

Figure 1. The dependence of the reduced viscosity on the concentration of cosolute at 25 °C. Cosolutes: ▼ (2-hydroxypropyl)-α-cyclodextrin; ▲ (2-hydroxypropyl)-β-cyclodextrin. Polymers: (a) poly(*N*-vinyl pyrrolidone) at concentration 20 mg/mL; (b) poly(ethylene glycol) at concentration 15 mg/mL.

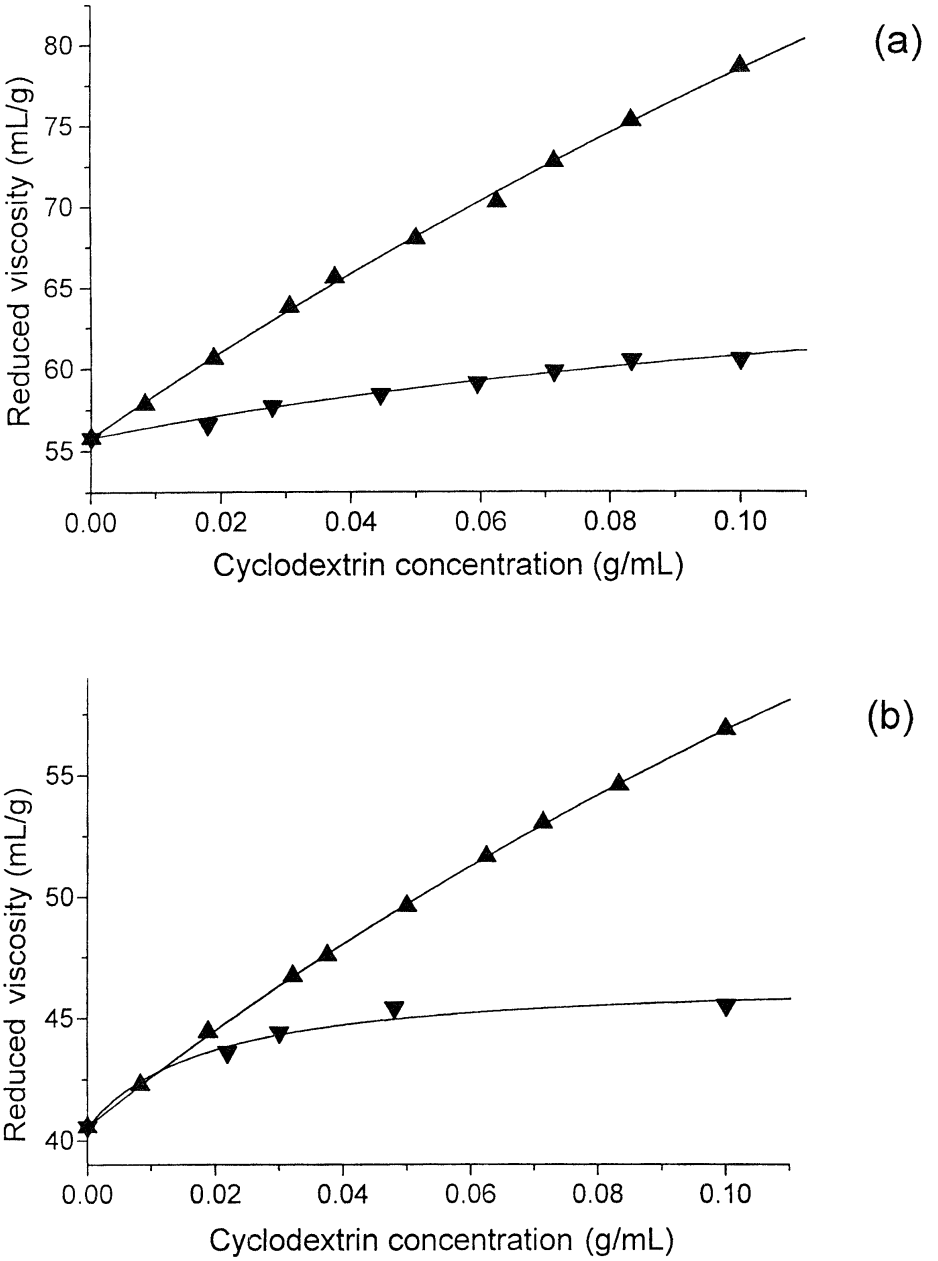

Figure 2. The dependence of the reduced viscosity on the concentration of cosolute at 25 °C. Cosolutes: ▼ (2-hydroxypropyl)-α-cyclodextrin; ▲ (2-hydroxypropyl)-β-cyclodextrin. Polymers: (a) poly(vinyl alcohol) (degree of hydrolysis >98%) at concentration 15 mg/mL; (b) poly(vinyl alcohol) (degree of hydrolysis 87-89%) at concentration 15 mg/mL.

Table 1. Intrinsic viscosities (mL/g) of polymers in water and in 10% (2-hydroxypropyl)-cyclodextrins at 25 °C.

	Water	HPACD	HPBCD
PEG	54.9	62.3	56.7
PVA (87-89%[1])	31.1	35.5	44.5
PVA (>98%[1])	40.6	46.9	53.3
PVP	20.4	23.3	23.5

[1] Degree of hydrolysis

Discussion

The viscosity of a polymer solution, η, is given as

$$\eta = \eta_0(1 + [\eta]c_p + k_H[\eta]^2 c_p^{\ 2} + ...)$$

where η_0 is the viscosity of the solvent, c_p is the concentration of the polymer, $[\eta]$ is the intrinsic viscosity, and k_H is the Huggins coefficient. Accordingly, the intrinsic viscosity may be defined as

$$[\eta] \equiv \frac{1}{\eta_0} \lim_{c_p \to 0} \frac{d\eta}{dc_p}$$

However, if the solvent is a mixed solvent and one of its components (cosolute or cosolvent) binds to a macromolecular component, then η_0 is a function of c_p. If this fact is ignored and the initial viscosity of the solvent η_s is used in calculations erroneous value $[\eta]'$ is obtained (6), given by the relation

$$[\eta]' = [\eta] + \frac{1}{\eta_s}\left(\frac{d\eta_0}{dc_p}\right)_{c_p=0}$$

If the change in the mixed solvent viscosity is the only reason for the change in overall solution viscosity - in other words, if $[\eta]$ and k_H are not affected by complexation - then viscometry may be used for determining the binding isotherm. Unfortunately, $[\eta]$ and/or k_H of polymers investigated are affected by complexation with cyclodextrins as can be inferred from the fact that higher viscosities were found in HPCD solutions than in water. The relation $[\eta]' < [\eta]$ holds for a solvent the viscosity of which decreases with the concentration of the principal component (water), as is the case of HPCD solutions, because then η_0 is a decreasing function of polymer concentration. Consequently, another factor than the change in solvent viscosity must be involved, namely the change in polymer hydrodynamic and conformational properties.

On its own, the fact that hydrodynamic and conformational properties of a polymer changed upon addition of a cosolute is not a definite proof of complexation because the change may be caused by less specific and less localized interactions which are usually collected under the term “quality” of a solvent. Two macroscopic criteria are used to distinguish between specific (including complexation) and generic effects although the division is rather vague and arbitrary. The first criterion is the concentration at which the effects are observed, the generic ones requiring higher concentrations of cosolute. The use of this criterion is, however, dubious in the present case because concentrations used are below the demarcation value on the molar scale (0.1 M) but not so low on the weight scale (tip to 10%). The second criterion is the sensitivity to changes in the structure of a cosolute or a polymer, which is rather high for specific effects (7). In the case of inclusion (guest-host) complexation, the size of host’s cavity is important and the differences between the effect of various CDs may be expected as α-CD and its derivatives have six glucose units in the molecule whereas β-CD and its derivatives have seven units.

Accordingly, viscometry indicates only a generic effect of cyclodextrins on poly(*N*-vinyl pyrrolidone) (PVP) solutions because the same values of viscosity were found in HPACD and HPBCD (Table 1 and Figure 1a). However that can not be taken as a proof that the suggested (4) side-chain complexation between PVP and CD does not occur. Generic effects may overshadow the effect of complexation or the effects of complexation are identical for HPACD and HPBCD; the latter possibility is rather hypothetical since binding of low-molecular-weight compounds usually significantly differs between CDs (8).

The results for poly(ethylene glycol) (PEG) are more informative; not only the viscosities differ in HPACD and HPBCD solutions (Table 1 and Figure 1b) but this difference is consistent with the results obtained by solubility methods. PEG forms crystalline complexes with natural (unmodified) α-cyclodextrin (α-CD) but not with natural β-cyclodextrin (β-CD), and the explanation is that the PEG chain, being without side groups, better fits into a smaller cavity of α-CD (2).

The origin of a small viscosity change observed with PEG in HPBCD cannot be determined from viscosity data only. Although it may be of generic character there is some evidence that β-CD threads on PEG chains. (3) While an oversized cavity effectively prevents the inclusion of a low-molecular-weight compound the situation may be different with chain molecules simply because the newly threaded cycle has to move in a right direction to unravel, otherwise it remains trapped on the chain.

Reviewing the results for PEG, it is possible to interpret the difference in the viscosity behavior of PVA in HPACD and HPBCD as an indication of the complexation between PVA and HPBCD although PVA forms no crystalline complex with any CD. On the other hand, the support for such interpretation is provided by another hydrophilic polymer with small side groups, namely poly(propylene glycol), which forms crystalline complexes with β-CD but not with α-CD (2). The size exclusion is more restrictive for an axial inclusion of chain molecules (i.e., for an inclusion of the main chain) than for other modes of inclusion complexation where inclusion of some part of a molecule is frequently sufficient (8). However, even bearing this in mind it is not possible to interpret the small increase in viscosity observed with PVA and HPACD

strictly as a generic effect because the size exclusion restriction may be somewhat relaxed by the conformational flexibility of a HPACD ring.

An interesting finding is the absence of any time effects, which means that the complexation is completed within a few minutes. Contrary to that it may require up to several hours according to the turbidimetry (2). The obvious explanation of this contradiction is that the precipitation is a slow process but this explanation is not the only one. The formation of a polymer inclusion complex consists of several steps and the difference between viscometric and turbidimetric results merely shows that the rate-limited step occurs beyond the scope of "viscometric visibility". Thus, the regular head/head, tail/tail arrangement is supposed in crystalline complexes (2) but the CDs are threaded with random orientation. Therefore, there is some delay between the initial formation of a fully covered chain (as would be detected by the viscometry) and the time when the complex is rearranged and ready to participate in crystallization. However, the probable explanation is that the viscometry detects the threading of CDs before the polymer chain is fully covered and two arguments indicate that the chain coverage was incomplete in the present experiments. (i) It is assumed that the high degree of threading, found for example with PEG and α-CD, is due to cooperativity of the process (2) but it also is assumed (1) that such cooperativity is hindered by derivatization of CD, which is the case of HPCDs. (ii) HPBCD affected also the viscosity behavior of the less hydrolyzed PVA, in which substantial portion of the main chain is excluded from complexation by acetate side groups.

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