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Evidence for the Amphiphilic Structure of Partially Hydrogenolyzed Poly(β-Malic Acid Benzyl Ester)

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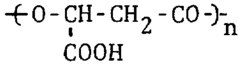
Summary

Acidic copolymers of the poly(β-hydroxy-acid) type containing β-malic acid (hydrophilic) and β-malic acid benzyl ester (hydrophobic) repeating units in various proportions are prepared by two differentes routes : - catalytic hydrogenolysis of the benzyl ester bonds of homopoly(β-malic acid benzyl ester) and - chemical coupling of benzyl alcohol to poly(β-malic acid). In attempts to account for the route-dependence of the physico-chemical properties of resulting copolymers, GPC in aqueous medium and measurements of the solubility of Yellow OB, a lipophilic dye, in aqueous solutions have been carried out. The results are discussed in regard to the sequence distributions of hydrophilic and hydrophobic repeating units.

Introduction

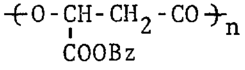
In aqueous solutions, the physico-chemical properties of polyelectrolytes of the carboxylic type bearing hydrophobic groups either in the main chain or in the side chain depend on the balance between cohesive forces due to hydrophobic groups and repulsive coulombic interactions due to carboxylate anions (CRESCENZI 1968, MULLER et al. 1975).

Recently, the synthesis has been reported of a new water-soluble polycarboxylic acid, poly(β-malic acid) (PMLA 100), selected for its potentiality as drug-polymeric carrier (VERT and LENZ 1979). Basically, the attachment of hydrophobic drugs to PMLA 100, in the tailoring procedure, should give rise, under certain conditions, to perturbations of the physico-chemical properties of the initial polycarboxylic acid, e.g. conformational and ionization behaviors and solubility. In order to figure out the possible perturbations, we have undertaken the study of PMLA X copolymers composed of β-malic acid and β-malic acid benzyl ester units (X = percentage of acidic repeating units) where the benzyl substituents play the role of a hydrophobic drug.



$$-\!\!\left(O-\underset{\displaystyle COOH}{CH}-CH_2-CO\right)\!\!-_n$$

PMLA 100



$$-\!\!\left(O-\underset{\displaystyle COOBz}{CH}-CH_2-CO\right)\!\!-_n$$

PMLABE

Such copolymers have been firstly obtained by partial catalytic hydrogenolysis of the homopoly(β-malic acid benzyl ester)(PMLABE), and will be referred to as PMLA X_h in the following (VERT and LENZ 1979). The characterization and some physico-chemical properties of PMLA X_h have been preliminarily described (BRAUD et al. 1981). Unusual solubility characteristics have been found, regarding the usual behavior of hydrophobic-hydrophilic polycarboxylic acids. Furthermore, no effect of the hydrophobic moieties on potentiometric titration curves was detected. Because of these unexpected features, it was suspected that PMLA X_h have a bi-block structure of the amphiphilic type in water. In order to check this working hypothesis, we have considered the physico-chemical properties of PMLA X obtained by other routes with the aim of getting various repeating unit distributions.

In this paper, we wish to report the synthesis of a PMLA X copolymer with 78 % of carboxylic acid units (PMLA 78_c) according to a route based on chemical coupling of benzyl alcohol to PMLA 100. Comparison is made between PMLA 78_c and PMLA 80_h, two compounds of similar gross chemical composition, regarding GPC chromatograms in aqueous medium and solubilization of a water-insoluble dye, Yellow OB (Y_{OB}).

Experimental

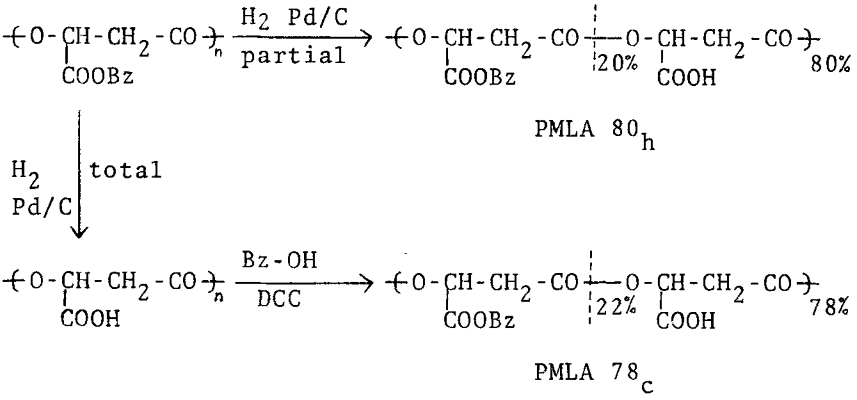
PMLA 78_c was prepared by adding 107 mg of PMLA 100, 96 mg of dicyclohexylcarbodiimide (DCC) and 91 mg of benzyl alcohol to 20 cm^3 of dry acetone. The mixture was allowed to stirring for 3 days at room temperature. PMLA 80_h was prepared by using a procedure already described (BRAUD et al. 1981). In the two cases, values of X where determined from ^1H NMR and potentiometric titration with good agreement.

GPC chromatograms were obtained with a Waters apparatus equipped with µ-styragel columns calibrated with polystyrene standards for measurements in dioxane, and equipped with TSK 125 + 250 Biorad columns calibrated with dextran standards from Pharmacia Fine Chemicals for measurements in aqueous solutions. All the MW data are referred to the maximum of the refractive index deviation.

The solubility of Y_{OB} (o-tosylazo-β-naphthylamine) was measured by colorimetry according to a method already described for other hydrophobic-hydrophilic polyacids (VILLIERS and BRAUD 1978).

Results and discussion

PMLA 78_c has been synthesized by coupling benzyl alcohol to PMLA 100, using DCC as the coupling reagent. PMLA 100 and PMLA 80_h have been obtained respectively by total and partial catalytic hydrogenolysis of a PMLABE sample. The three compounds give similar GPC chromatograms with peaks in the 15,000 to 20,000 range when they are dissolved in dioxane (acidic form for PMLA 100, PMLA 80_h and 78_c). These results well agree with the absence of basic difference between the two copolymers insofar as MW is concerned. Indeed, both compounds derive from the same parent PMLABE.



GPC measurements were also performed in aqueous medium (1M NaNO$_3$) for the sodium salt forms of PMLA 100, PMLA 78_c and PMLA 80_h (fig. 1). The presence of NaNO$_3$ was necessary to supress the polyelectrolytic effect which occurs in pure water (SUGISAKA and PETRACEK 1977). Under these conditions, PMLA 100 and PMLA 78_c are eluted in the low MW range (∼ 10,000) in agreement with the MW found in dioxane. Therefore, it is concluded that both polyelectrolytes have similar hydrodynamic volumes in salted water.

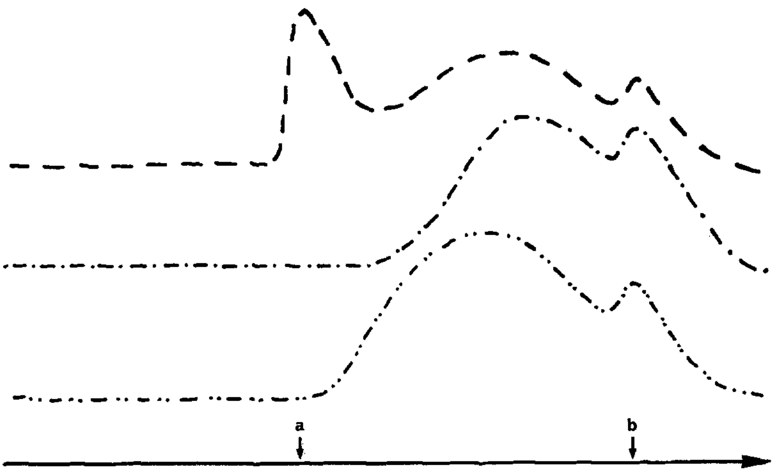


Fig. 1 Molecular size profiles of PMLA 100 (—··—··—), PMLA 78$_c$ (—·—·—·) and PMLA 80$_h$ (————). Elution was carried out with 1M NaNO$_3$ at a flow rate of 1.0 cm^3/min. The total exclusion corresponds to arrow a and the total permeation to arrow b. At the level of the total permeation, a peak due to the solvent is observed.

In contrast, significant differences are observed for PMLA 80$_h$ in the same aqueous medium. Indeed the GPC curve is bimodal with a thin peak corresponding to the exclusion volume of the column (MW > 200,000) and a broad one in the low MW range. The peak observed at the exclusion volume reflects the presence of high molecular weight species which have to be aggregates of many macromolecules. The presence of these aggregates agrees with the assumed hydrophobic-hydrophilic block structure. Indeed, such aggregates have been observed for amphiphilic bi-block copolymers synthesized as such and composed of a hydrophilic block of the polyvinylpyridinium type and of a hydrophobic block of the polystyrene type (SELB and GALLOT 1980). For these compounds in water, the hydrophobic blocks stick together to form organic microdomains which are solubilized by the hydrophilic blocks floating in the aqueous medium. The similarities between the aqueous behaviors of these micelle-forming bi-block copolymers and of PMLA 80$_h$ led us to the search for hydrophobic microdomains in PMLA 80$_h$ aqueous solutions.

Evidence for the presence of such microdomains has been obtained by measuring the solubility of Y_{OB} in salt-free solutions of PMLA 80$_h$ and PMLA 78$_c$. Y_{OB} was selected because it is known to dissolve specifically in organic microdomains formed by compactly coiled polycarboxylic acids (DUBIN and STRAUSS 1975, VILLIERS and BRAUD 1978). Data are given in Figure 2. The total insolubility of Y_{OB} in PMLA 78_c salt-free aqueous solutions, regardless of the degree of ionization of -COOH groups, shows the absence of hydrophobic microdomain and thus agrees with an open-coil conformational structure for this copolymer.

In contrast, the solubility of Y_{OB} in PMLA 80_h salt-free aqueous solutions demonstrates the presence of hydrophobic microdomains. Furthermore, it is noteworthy that the solubility of Y_{OB} does not depend very much of the degree of ionization. This feature contrats with the dramatic decrease of solubility usually observed for compact-coil conformations of polycarboxylic acids, even when these compounds take on polysoap-like structures (VILLIERS and BRAUD 1978). Only the presence of hydrophobic microdomains solubilized by the hydrophilic blocks of β-malic acid units can account for the high solubilizing effect for Y_{OB} whatever the degree of ionization of these units.

Finally, both GPC and solubility of Y_{OB} data agree to show that PMLA 80_h does not behave as PMLA 78_c in spite of the fact that both compounds have similar gross compositions. These findings support our hypothe-

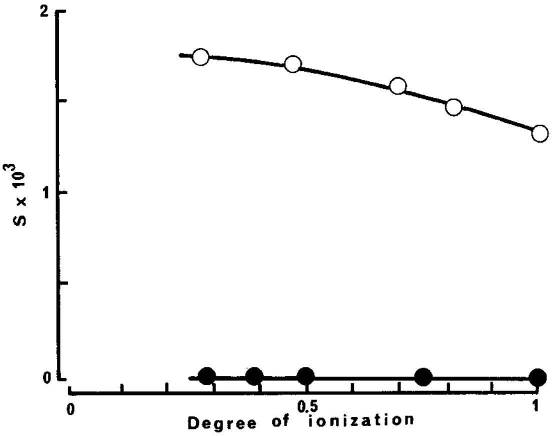


Fig. 2 Solubility S of Y_{OB} (mole/T_N) in salt-free solutions of PMLA 78_c (●) and PMLA 80_h (o) as a function of the degree of ionization of -COOH (T_N = 9.10^{-4}equiv/l).

sis for a difference in repeating unit distributions and are strongly in favor of the presence of two blocks in PMLA 80_h i.e. one hydrophobic PMLABE block and one hydrophilic PMLA 100 block weighing 20 and 80 % respectively, in regard to the number of units. This unusual structure for polyelectrolytes obtained from chemical modification is certainly due to the particular method of cleavage of the benzyl ester bonds consisting in a catalytic hydrogenolysis in heterogeneous medium. As a matter of fact, a controlled hydrolysis of PMLABE is precluded because of the presence of ester bonds in the main chain.

Further investigations are under way in order to prove the bi-block structure on the basis of solid state properties. Anyhow, the route dependence of the physico-chemical properties of PMLA X copolymers reported herein is of primary importance for the further tailoring of drug-polymeric carrier systems from poly (β-malic acid).

Acknowlegments

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