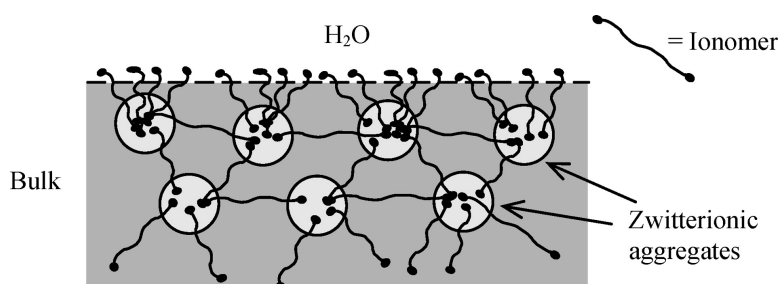


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J. Am. Chem. Soc., **2004**, 126 (47), 15350-15351 • DOI: 10.1021/ja0457314 • Publication Date (Web): 04 November 2004

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Phosphoryl Choline Introduces Dual Activity in Biomimetic Ionomers

Fredrik Nederberg,[†] Tim Bowden,[†] Bo Nilsson,[‡] Jaan Hong,[‡] and Jöns Hilborn^{*†}

Department of Materials Chemistry, Polymer Chemistry, Box 538, Uppsala University, S-751 21 Uppsala, Sweden,
and Department of Oncology, Radiology and Immunology, University Hospital, Uppsala University,
S-751 21 Uppsala, Sweden

Received July 16, 2004; E-mail: hilborn@polymer.uu.se

This communication reports a new feature of phosphoryl choline (PC)-functionalized poly(trimethylene carbonate) (PTMC) to provide biomimetic, hemocompatible, and fully biodegradable ionomers.

PC is an essential part of cell membrane bound phospholipids. In combination with lipophilic carbon chains, PC contributes to the hydrophilicity of such amphiphiles. In addition, PC is a key in vivo functionality as it is one of the major components of the cell membrane, in which a multitude of cellular activities take place.¹

Recent reports about the development of bioactive polymers have taken advantage of the properties conferred to the resulting polymer by the addition of PC. For instance, Ishihara et al. have in many reports used a PC containing acrylate monomer (MPC) to obtain homo- and block copolymers.^{2,3} The resulting polymers show a significant reduction of protein adsorption that has been related to the interaction of the polymer with phospholipids as well as to the hydrating ability of the PC group.³ Others used a similar approach for the formation of fully biodegradable and biomimetic polymers by using PC-functionalized poly(ϵ -caprolactone) (PCL).⁴ In vitro studies have shown that the PC group can be enriched at the surface of films from such polymers and that they are hemocompatible.⁵

This communication describes a new feature of PC for tuning specific material properties, specifically the elastic modulus, in addition to being bioactive. Modulus matching of biomaterials is believed to be vital for its in vivo performance, and the present strategy might be a useful method to address some of these issues.⁶ Yoo et al. previously reported ionomeric behavior for the biodegradable poly(butylene adipate); however, they used a sulfonate salt as ionic part.⁷

In this work, the material is prepared by using multifunctional polymers with an added PC functionality. The polar PC zwitterion was shown to aggregate in bulk to provide physical cross-links. To achieve this, a low molecular weight bifunctional PTMC (PTMC_{diol}) was synthesized. Polymerization was initiated from 1,4-butanediol, and ¹H NMR end group analysis revealed a molecular weight (M_n) of \sim 3900 g/mol. The one-pot end capping reaction first included phosphorylation of the polymer hydroxyl using ethylene chlorophosphate. Subsequently, trimethylamine was introduced to ring open the cyclic phosphate, providing full conversion to the targeted functionality, which resulted in a final PC content of about 8 wt %.⁸ Typically the yield was more than 90%. In Figure 1, the structure of the bifunctional PC containing PTMC is shown.

The resulting material showed completely new properties as compared to PTMC_{diol}. While the starting material was tacky and with poor film forming capabilities, the functionalized material was firm and showed more elastic properties, and in addition it could be cast into solid films. We believe that the anticipated ionomeric behavior explained by microscopic phase separation into zwitter-

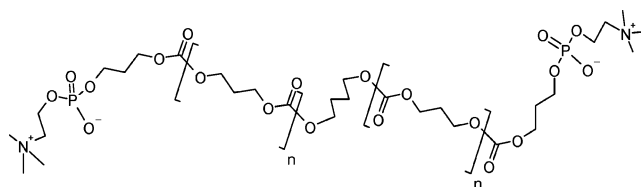


Figure 1. Structure of PC-PTMC-PC (ionomer), $n = 19$.

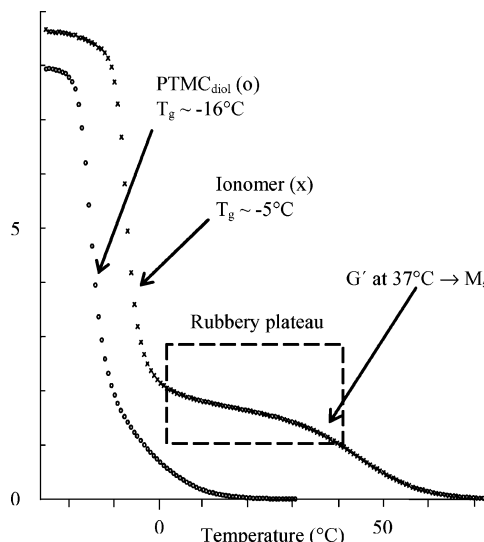


Figure 2. Results of oscillating rheology measurement of PTMC_{diol} and ionomer. (Insets: T_g , G' at 37 °C, and rubbery plateau of ionomer).

ionic aggregates results in the drastic change of the material characteristics.

To obtain more data regarding the mechanical performance of the material and thus support the presence of ionomers, rheology measurements were performed. An oscillating torque experiment was used in which PC-PTMC-PC (ionomer) was compared with PTMC_{diol} at a frequency of 1 Hz. Figure 2 shows the storage shear modulus (G') as function of temperature of the two materials. At ambient conditions, PTMC_{diol} behaves as an amorphous melt with no mechanical integrity, whereas the ionomer, as anticipated, behaves like a rubber and with a G' value of \sim 2 MPa.

In addition, Figure 2 reveals a rubbery plateau of the ionomer, stretching from 5 °C to about 40 °C, and the viscous region is not reached until 70 °C. This demonstrates that one could benefit from the rubbery behavior at physiological conditions, that is, \sim 37 °C.

Moreover, one can observe an interesting shift in the glass transition temperature (T_g) of the two materials. For PTMC_{diol}, the T_g is located at -16 °C since the contribution of flexible end groups is significant. For the ionomer, however, a large difference was observed as the T_g shifted to -5 °C. Most likely the end groups are captured in zwitterionic aggregates, forming physical cross-

[†] Department of Materials Chemistry, Uppsala University.

[‡] University Hospital, Uppsala University.

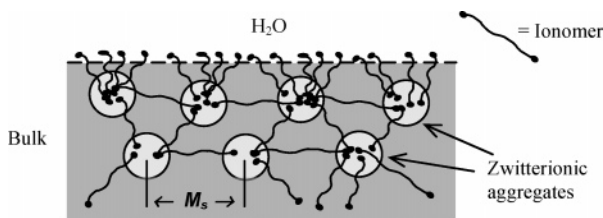


Figure 3. Dual ionomer activity showing surface enrichment and network formation. (Inset: Ionomer representation).

links that restrain molecular mobility that raise T_g instead of lowering it. The higher temperature, needed for the onset of translational mobility, agrees well with the behavior of ionomers reviewed by Eisenberg as early as 1971.⁹ Below the glass transition, the G' value of the ionomer is about 10% higher than PTMC_{diol}.

Interestingly, using the G' value at 37 °C and $M_s = \rho RT/G'$ when calculating the average segment molecular weight (M_s) between physical cross-links of the ionomer (see Figure 3), one obtains a value of ~ 2900 g/mol.^{10,11} Despite the noncovalent nature and the low molecular weight of the material, this is in qualitative agreement with the molecular weight of the starting material that was ~ 3900 g/mol from NMR end group analysis.

Since it now was known that polar PC groups provide physical cross-links by zwitterionic ionomers in bulk,¹² we assume that the hemocompatibility of cast films could be improved by enriching the PC group at the surface. Thus, a dual activity of the PC group organized both in bulk and at the surface could be achieved, as schematically shown in Figure 3.

To enrich the PC group at the surface, cast films were dipped into water, which upon insertion for 60 s, result in full wetting. The dynamic behavior was confirmed by contact angle measurements, in which the advancing angle of a dry film was $73 \pm 2^\circ$ and the following receding angle, of the wetted surface, was $< 5^\circ$. ESCA was used to support the surface depletion at dry conditions. Nitrogen and phosphorus were evenly distributed in the bulk following a sputtering experiment, but not observed at the utmost surface layer.¹³

The films were then tested in contact with whole blood to study the hemocompatibility of the material. More specifically, the decrease of platelets in whole blood as well as the formation of thrombin–anti-thrombin (TAT) complexes were investigated by using an in vitro model recently developed by Hong et al.¹⁴ All the surfaces were kept in contact with whole blood for 30 min at physiological conditions.

The result from the whole blood model indicates that the ionomer system holds nonthrombogenic properties and that the formation of TAT, compared to PTMC, is reduced. For the ionomer, the value of TAT was $55 \mu\text{g/L}$. Moreover, it was found that 98% of all platelets were maintained following the contact with whole blood with the ionomer surface. The same count for PTMC and PVC, a well-known low activating biomaterial, were 94 and 91%, respec-

tively. The overall results indicate a low coagulation activation, which clearly demonstrates the feasibility of the polymer as a blood-contacting biomaterial with enhanced hemocompatibility.

In summary, the synthesis of phosphoryl choline functional poly(trimethylene carbonate) leads to dual activity since the zwitterionic biomimetic PC group induces physical cross-links with ionomers in the bulk and at the same time in water enriches at the surface of cast films. The formation of zwitterionic domains from a bifunctional PC–PTMC–PC provided firm films with a low elastic modulus quite different from the tacky starting material ($M_n \approx 3900$ g/mol) that lacked any mechanical integrity as observed in rheology measurements. Additionally, the material possessed improved hemocompatible properties that can be explained by the enrichment of PC at the surface. Thus, it suggests that one could tailor the mechanical performance of biodegradable PTMC-based ionomers while providing its bioactivity. Tailored elasticity while maintaining hemocompatibility should be of particular interest for a variety of in vivo applications.

Acknowledgment. Uppsala University is acknowledged for the financial support of this work.

Supporting Information Available: Experimental information, including synthetic procedures, NMR and ESCA data, complete rheological data, and procedures for the slide chamber model. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0457314