Noncollapsing Polyelectrolyte Conetwork Gels in Physiologically Relevant Salt Solutions

Gergely Kali[§] and Béla Iván

Polymer Chemistry Research Group, Institute of Materials and Environmental

Chemistry, Research Centre for Natural Sciences, Hungarian Academy of

Sciences

H-1117 Budapest, Magyar tudósok krt. 2, Hungary

[§] Present address: Organic Macromolecular Chemistry, Saarland University,

Campus C 4.2, 66123 Saarbrücken, Germany

E-mail addresses: gergely.kali@uni-saarland.de, ivan.bela@ttk.mta.hu

Abstract

In consequence of some unique properties, such as nanophase separation, biocompatibility and mechanical stability, amphiphilic polymer conetworks (APCNs) have received significant attention in recent years. APCNs are composed of hydrophilic and hydrophobic polymer chains connected with covalent bonds. The unique properties of APCNs make them suitable for many specialized applications. Although APCNs were widely investigated and described in the literature, this is the first study on the swelling behavior of these materials in the solutions of physiologically relevant salts. Homopolymer polyelectrolyte hydrogels are known to suffer phase transition like rapid gel collapse at a certain salt concentration in the solutions of bi- or multivalent metal salts. Systematic swelling investigation of poly(methacrylic acid)-*l*-polyisobutylene (PMAA-*l*-PIB) conetwork series in $CaCl_2$ salt solutions led to unexpected findings. Our results indicate that these polyelectrolyte APCNs do not behave the same way in salt solutions as the homopolymer hydrogels, i.e. APCNs do not suffer gel collapse, the change of the swelling degree remains continuous with increasing salt concentration. The gel contraction was reversible by changing the solute to NaOH solution, i.e. the gels returned to their original volume by reswelling. This non-collapsing swelling means that the presence of hydrophobic polymer segments as cross-linkers in amphiphilic polyelectrolyte gels radically change the swelling behavior of such materials, which become substantially different from that of homopolymer polyelectrolyte gels.

Keywords:

Introduction

Homopolymers and homopolymeric hydrogels[1-4] have gained a keen interest in the biological, especially in the medical field. These polymeric structures are used as carriers of drugs, contact lenses, implants and as scaffolds for tissue engineering.[1] An important class of homopolymers, the polyelectrolytes, has some undesirable properties which are not compatible with the bioapplications mentioned above. One of the unwanted features is the solution and swelling behavior of linear and cross-linked polyelectrolytes in the solution of bi- and multivalent metal ions. In the presence of such ions, polyelectrolytes, such as poly(acrylic acid), poly(methacrylic acid) or polyalginates undergoes various phase transitions.[2-4] Specifically, the linear polyelectrolytes precipitate in the solution of multivalent salts,[2] while homopolymer polyelectrolyte gels collapse at a certain concentration of bi- or multivalent metal salts in the swelling media[3,4]. The precipitation of the linear homopolymers, as well as the contraction of the gels occuring at a critical concentration, mainly depend on the number/concentration of the charged groups of the polyelectrolyte.[3(b),5] Here, it should be noted that, although the volume phase transition of these polyelectrolytes is disadvantageous for bioapplications, but it makes these materials desirable for application in valves and actuators.

Recently, Horkay et al. have investigated the swelling of cross-linked negative polyelectrolytes, namely polyacrylates and polymethacrylates in the solutions of physiologically relevant salts.[4] These hydrogels undergo volume

contracting by increasing the amounts of different cations, and this change in the swelling degree has depended on the valence of the metal ion. In the case of monovalent ions (such as Na^+), this contraction was smooth and continuous, while in the solution of bi- and multi-valent ions (Ca^{2+}, Mg^{2+}, La^{3+}) the swelling behavior, was completely different. At a critical concentration of the multivalent salt, the volume change of the gels became non-continuous, and rapid gel collapse occurred, most probably due to the physical cross-link formation by the bivalent cations and the negatively charged polyelectrolytes. For homopolymer polyelectrolyte hydrogels, this phenomenon excludes these materials from many application possibilities in biological systems which contain bio-relevant multivalent metal salts, for example, Ca(II). Calcium is a biologically significant inorganic material, stored mostly in the bones, but the intra- and extracellular matrices also contain Ca^{2+} around 1 and above 2 mM concentration, respectively.[6]

Amphiphilic polymer conetworks (APCN) are bi-, or multicomponent polymeric materials with both some similarity and differences from homopolymer hydrogels.[7] In contrast to homopolymer hydrogels, the APCNs has not only hydrophilic but hydrophobic component as well, covalently connected to each other. As a result, these materials can swell in both polar and nonpolar solutes. Beyond their amphiphilic nature, APCNs have some other unusual properties, such as their nanophase separated structure[8,9], biocompatibility[10,11], and excellent mechanical strength[9,12,13]. This last property, their improved mechanical stability befalls not only in the dry but the highly swollen state as well, which is a

great advantage, compared to the fragile and mechanically unstable homopolymer hydrogels.[1-4] Due to these advantageous properties, the application of APCNs in biological systems or medical field is well known as matrices for controlled drug delivery[14], scaffolds for tissue engineering[15,16] and implants, materials for soft contact lenses[17-19] and also for other biorelevant application possibilities[20]. It seems to be evident, that APCNs are possible candidates to replace homopolymer hydrogels in many fields. Considering the advantageous properties and the wide range of bioapplication possibilities of APCNs, it is surprising that there is no any report on the swelling behavior of these novel materials in solutions of physiologically relevant salts.

The structure of APCNs can be varied by using various interconnected hydrophobic and hydrophilic polymers. In our case, the lipophilic part was the highly hydrophobic, biocompatible, fully saturated polyisobutylene (PIB). PIB is a rubbery polymer with low glass transition temperature (T_g), which property makes APCNs with PIB as hydrophobic component mechanically and chemically stable.[21] The hydrophilic part of the used conetworks can be neutral polymer or even polyelectrolytes, such as poly(methacrylic acid) (PMAA), even there are only a few examples of anionic APCNs reported in the literature.[9,12,22-24] PMAA is a well-known glassy, hydrophilic polyelectrolyte, which forms mechanically nonstable hydrogel. The synthesis and the intelligent swelling behavior of PMAA based APCNs were investigated and described earlier. The swelling of these conetworks was studied in hydrophobic solvents and in water as well as a

function of pH[9,12,13(b),22-25], but the swelling behavior of polyelectrolyte APCNs in salt solutions has not been described yet.

In this work, we report on the synthesis of a series of poly(methacrylic acid)-*l*-polyisobutylene (PMMA-*l*-PIB) APCNs (*l* stands for *linked by*) and their unexpected swelling behavior in the solutions of the biologically relevant NaCl and $CaCl_2$ salts over a wide range of concentrations.

Experimental

Materials and Methods

Methylmagnesium bromide (3.0 M solution in diethyl ether), 5-*tert*-butylisophthalic acid (98%), ammonium chloride (puriss), titanium tetrachloride (TiCl$_4$, 99.9%), 1,1,4,4-tetramethylethylenediamine (99.5%, TMEDA), 9-borabicyclo[3.3.1]nonane (9-BBN; 0.5 M solution in THF), hydrogen peroxide (35% solution in water), methacryloyl chloride (97%, MACl), trimethylsilyl methacrylate (TMSMA; 98%), calcium hydride (CaH$_2$, 90-95 %) and aluminium oxide (activated, neutral) were all purchased from Aldrich. Hexane (96%) was obtained from Scharlau S. A., Spain. Dichloromethane (DCM, 99.8%), tetrahydrofuran (THF; 99.8%) and methanol (99.8%) were purchased from Chemolab. Isobutylene (IB, 99.8%) and hydrogen chloride (HCl, 99.8 %) were obtained from Messer Griesheim, Germany. Triethylamine (Et$_3$N, 99%) and potassium hydroxide (98%) were purchased from Merck, while calcium chloride (anhydrous), allyltrimethylsilane (ATMS, 97%) and α,α'-azobisisobutyronitrile (AIBN; 98+%) were purchased from Fluka.

Preparation of the bifunctional cationic initiator and the macromonomer

The *tert*-butyldicumyl chloride bifunctional carbocationic initiator was obtained by the esterification of 5-*tert*-butylisophthalic acid, followed by a Grignard reaction, and a hydrochlorination step as reported before.[26]

The methacrylate-telechelic PIB macromonomer (MA−PIB−MA) was synthesized by quasiliving carbocationic polymerization[21,26] of isobutylene. The

quasiliving carbocationic initiator system was $TiCl_4$/*tert*-butyldicumyl chloride, and the nucleophilic additive was 1,1,4,4-tetramethylethylenediamine. The polymerization reaction was terminated by allyltrimethylsilane, yielded quantitative end group functionalized allylic telechelic PIB. After the allylation, three end-group modification steps were carried out. First, the allylic chain ends were modified by hydroboration, and the second step was an oxidation by H_2O_2 and KOH. Finally, methacrylation with methacryloyl chloride in the presence of Et_3N yielded MA−PIB−MA macromonomer. The macromonomer was characterized regarding the functionality, molecular weight and polydispersity by ^1H NMR and GPC.

Network Synthesis

The amphiphilic conetworks were prepared using macromonomer method via free radical copolymerization, as described previously.[25] The bifunctional macromonomer (MA-PIB-MA) was copolymerized with a precursor comonomer, trimethylsilyl methacrylate (TMSMA). The copolymerization was carried out in THF, as a common solvent, via free radical copolymerization utilizing AIBN thermal radical initiator at 65 °C for 72 hours. After the reaction, the gels were placed in THF to extract the non-reacted materials, and the protecting groups were removed by acidic hydrolysis.[25] The composition of the conetworks was determined by elemental analyses.

Characterization

The molar mass and dispersity of the macromonomer were measured by gel permeation chromatography (GPC) with Polymer Laboratories Mixed C type column set, equipped with a viscometer (Viscotec) and laser light scattering (Wyatt Co.) detectors. THF was used as mobile phase with a flow rate of 1.5 mL/min. The average molar mass, as well as the dispersity, was calculated by the use of universal calibration made with narrow MWD polystyrene standards in the range of 104 to 3×10^6 g mol^{-1}. ^{1}H NMR measurements were performed by Varian 400 (in 30 ^{0}C, in CDCl$_3$) to determine the functionality after the polymerization and every end group modification. The compositions of the deprotected conetworks were investigated by elemental analyses using Hereaus CHN-O-Rapid apparatus with CuO catalyst. We calculated the equilibrium swelling degree (R%) as the mass of solvent uptakes ($m_{swollen}$-$m_{dry)}$ divided by the mass of the dry sample (m_{dry}). The R% was determined using the following procedure. The deprotected conetwork samples were dried in vacuum and were cut into small cubes (1-2 cm^3). The mass of the dry samples was weighted. First, the dry gels were let to swell in 1 M NaOH solution for the neutralization of the polyacid. Then the conetwork samples transferred into a 40 mM NaCl containing solution and finally the CaCl$_2$ was added. The mass of the samples was measured from time to time until the equilibrium swelling reached.

$$R = (m_{swollen}\text{-}m_{dry})/m_{dry}$$

Results and Discussion

Linear polyisobutylene-dimethacrylate (PIB) macro cross-linker was synthesized by quasiliving carbocationic polymerization of isobutylene, followed by end group modification steps. The results of the GPC measurements on the PIB macromonomer indicated number average molar mass close to the theoretical (M_n=5700 g/mol) and also confirmed the low dispersity (M_w/M_n=1.02) (Supporting Information, Figure S1). The nearly quantitative bifunctionality of the resulting methacrylate-telechelic PIB was proven by[1]H NMR measurements. This macromonomer was radically copolymerized with a protected methacrylic acid derivative, namely trimethylsilyl methacrylate, to form covalent amphiphilic conetwork. After three days of AIBN initiated radical copolymerization/cross-linking at 60 °C, the samples were extracted with THF to remove the nonreacted monomers, initiator, and homopolymeric contaminants. Trimethylsilyl protecting group was removed from the poly(methacrylic acid) chains by acidic hydrolysis using HCl. The results of the elemental analyses, after conetwork formation, extraction and deprotection indicated that the formation of a series of PMAA-*l*-PIB conetworks was successful in a wide composition range, where the PIB content of the conetworks was between 15-55 w/w% (Supporting Information, Table S1).

It is well known from the literature that the fully neutralized homopolymer polyelectrolytes, for example, poly(acrylic acid) hydrogels, collapses at around 1.0 mM of $CaCl_2$.[4] We have been measured the equilibrium swelling degrees of

poly(methacrylic acid)-*l*-polyisobutylene amphiphilic polyelectrolyte conetworks under the same conditions as Horkay et al. used.[4] Namely, the conetwork samples were let to swell in a NaOH solution to form poly(sodium methacrylate) salt, and then the neutralized APCNs were transferred to a NaCl solution. After the equilibrium swelling degree had reached in the aqueous solution of this monovalent salt, $CaCl_2$ was added in small portions. The concentration of the $CaCl_2$ salt was varied between 0.5 – 2.5 mM, which covered the physiological concentration range. The equilibrium swelling degree was determined for these conetworks by gravimetry, at the given bivalent salt concentration.

The dependence of the equilibrium swelling degree of the PMAA-*l*-PIB series on the $CaCl_2$ concentration of the solution is presented in **Figure 1**. The numbers for sample identification denote the PIB contents of the PMAA-*l*-PIB samples in m/m%. The swelling degrees versus PIB content are also shown in **Figure 2**.
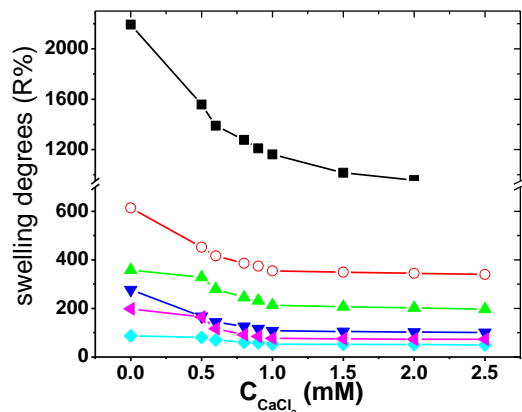
Figure 1. The equilibrium swelling degree as a function of $CaCl_2$ salt concentration for APCNs with (■) 15 wt.% (○) 22 wt.% (▲) 29 wt.% (▼) 39 wt.% (◄) 47 wt.% and (◊) 55 wt.% PIB content (single column)
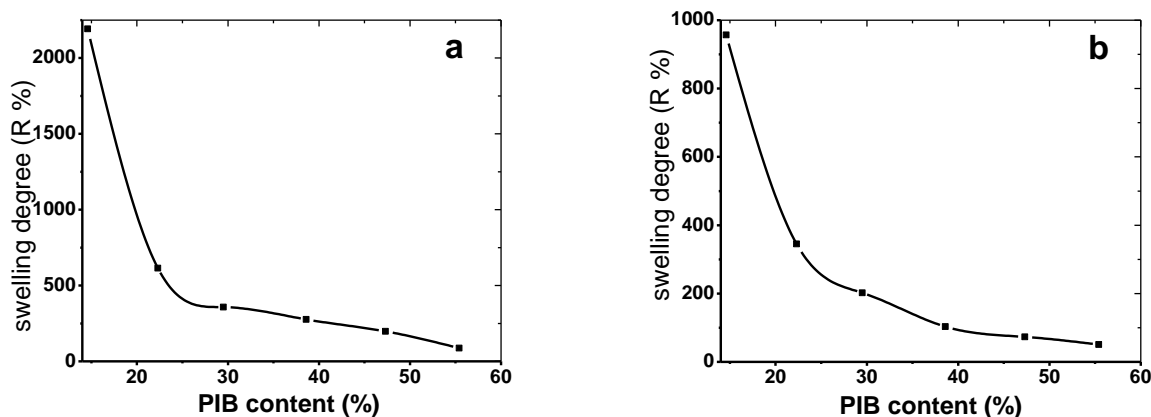
Figure 2: The dependence of equilibrium swelling degree on PIB content in the case of (a) 0 mM CaCl$_2$ + 40 mM NaCl and (b) 2.0 mM CaCl$_2$ + 40 mM NaCl. (2 column)

The results in **Figure 1** clearly indicates that the PMAA-*l*-PIB amphiphilic polyelectrolyte conetworks do not behave as it was expected from the results known from the literature for homopolymer polyelectrolytes. In the case of this amphiphilic-polyelectrolytes, sharp gel collapse does not occur at around, and even not above 1 mM CaCl$_2$ concentration. In details, the polyelectrolyte APCNs are shrinking by increasing the amount of CaCl$_2$ as expected. In the concentration range of 0.5 – 0.9 mM, the tendencies in the swelling degrees are similar to that for homopolymer hydrogels, found in the literature, i.e. only slight and continuous deswelling occurs. After this concentration limit or even at much higher salt contents, the APCNs do not undergo a discontinuous gel collapse like the cross-linked homopolymer polyelectrolytes, but the change in the swelling degree remains smooth and continuous. The range of the investigated CaCl$_2$ concentrations expanded to 0.0 - 2.5 mM, but above the indicated limit for homopolymeric polyelectrolyte gels (1.0 mM) no further significant deswelling

was observed. Here should be noted that the first data points at 0.0 mM $CaCl_2$ concentration belong to 40 mM NaCl solution, and this monovalent salt content was kept during the whole measurement, to provide constant ionic strength. The increasing PIB content cause decrease in the swelling degree, as shown in **Figure 2** and as it was expected based on the previous results with this kind of conetworks. [7,8,20-23] The gel that had the highest volume shrinkage was the one that had the lowest PIB content since this gel composition is the closest to the homopolymer composition. Gel collapse did not occur even in this case, so only 15 wt.% PIB can inhibit the phase transition like shrinkage. Due of the hydrophobicity, mechanical strength and their strong, covalently connected presence, even a tiny amount of PIB cross-linker can stabilize the conformation of the solvated PMAA chains, and change the thermodynamic environment of these hydrophilic polymers. The physical cross-linking of the polyelectrolyte phase of the conetwork is also limited due to the hydrophobic environment. Thus, it can be concluded that the presence of PIB, these elastic, hydrophobic polymer chains in the conetworks significantly influence the swelling behavior of PMAA as one of the components of APCNs in aqueous media.

As another interesting aspect, we investigated, the effect of the excess of Ca^{2+} compared to the ionized carboxylic groups in the conetwork. Surprisingly there is no any information about the effect of the ion excess in the literature for polyelectrolyte gels; even this could also be interesting information which helps us to understand the nature of this phenomenon.
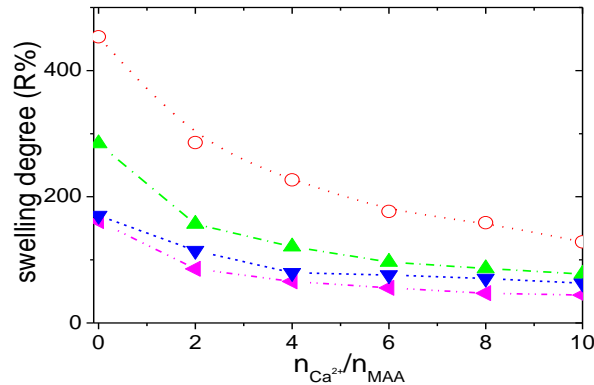
Figure 3: The effect of the excess of the bivalent cation to polyacid on the swelling of APCNs with (○) 22 wt.% (▲) 29 wt.% (▼) 39 wt.% and (◄) 47 wt.% PIB content. (1.5 column)

As it can be seen in **Figure 3,** Ca^{2+} was highly overdosed compared to the anionic groups for these experiments. Even ten times more salt than acidic groups cannot cause drastic, phase transition like gel collapse on the investigated PMAA-*l*-PIB conetworks, the deswelling process remained continuous.

The reversibility of the gel contraction was also studied and found that the reswelling of the conetworks depends on the conditions of the surrounding media. The contracted gels were placed into aq. 40 mM NaCl solution and the equilibrium swelling degrees were determined gravimetrically. In this solution, i.e. pure aqueous NaCl, the swelling degree of the gels increased only until the two third of the original. For further investigations, a strong base, NaOH was also added to the solution of the monovalent salt, to study the effect of pH on

14

reswelling (**Figure 4**). At higher pH region, the gels swelled back around the original volume, namely, reached the same swelling degree as before Ca(II) addition. In this case, the amount of NaOH was equivalent to the acidic units at the hydrophilic polymer chains in the conetwork. The appearing high swelling degree, in the case of high pH, is more likely due the strong electrostatic repulsion between the polyacidic units since their ionization by the used alkaline solution. In contrast, if no NaOH is added the replacement of the bivalent calcium ions by monovalent sodium from the NaCl induces only neutral hydrogel reswelling.
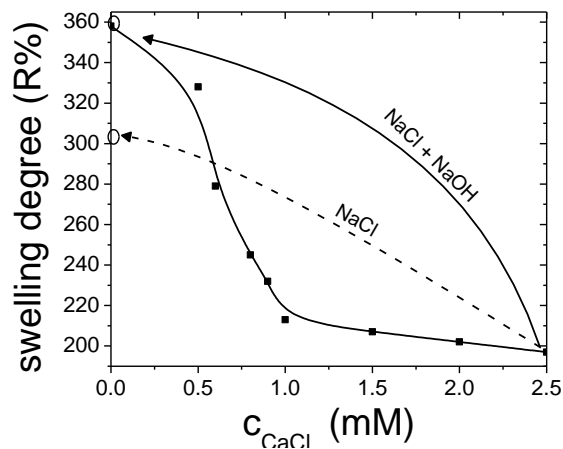
Figure 4: Reversibility of gel contraction by different aqueous solutions for the APCN gel with 29 wt% PIB content. Empty circles indicate the swelling degrees of the conetworks reswollen in the various swelling media.

Conclusion

The swelling behavior of poly(methacrylic acid)-*l*-polyisobutylene (PMAA-*l*-PIB) amphiphilic conetworks was investigated in the solution of NaCl and CaCl$_2$ as a function of bivalent salt concentration, and the hydrophobic content of the

conetwork. The swelling behavior of APCN polyelectrolytes in Ca^{2+} solution substantially differs from the corresponding cross-linked homopolymer polyelectrolytes in the range of physiological concentration. We found that these APCNs, in contrast to homopolymer hydrogels, do not undergo rapid gel collapse, even at very high salt concentration and low PIB content. The covalently bonded hydrophobic PIB macromolecular cross-linkers can prevent the phase transition like shrinkage of the conetwork. Many natural, biological systems also have amphiphilic character, and these novel conetworks can mimic those biomaterials and could help to understand their behavior in such aqueous solvents. Thus, the application of polyelectrolyte gels can be expanded to the biological solutions with high ion content, simply by using the synthetic conetworks with not only hydrophilic but also hydrophobic components.

References

1. (a) A.S. Hoffman *Adv. Drug Deliver. Rev.*, **2002**, *54*, 3. (b) N.A. Peppas, Y. Huang, M. Torres-Lugo, J. H. Ward, J. Zhang *Annu. Rev. Biomed. Eng.* **2000**, *2*, 9.

2. (a) Flory, P. J.; Osterheld, J. E. *J. Phys. Chem.* **1954**, *58,* 653, (b) Michaeli, I. *J. Polym. Sci.* **1960**, *48*, 291, (c) Ikeda, Y.; Beer, M.; Schmidt, M.; Huber,

K. *Macromolecules* **1998,** *31,* 728, (d) Lee, K.Y.; Mooney, D.J. *Prog. Polym. Sci.* **2012**, *37*, 106.

3.   (a) Katchalsky, A.; Zwick, M. *J. Polym. Sci.* **1955**, *16*, 221, (b) Katchalsky, A. *Pure Appl. Chem.* **1971**, *26*, 327-373. (c) J. Ricka, J. Tanaka, T. Macromolecules 1984, 17, 2916. (d) Tasaki, I.; Byrne, P. M. *Biopolymers*, **1994**, *34*, 209. (e) Eichenbaum, G.M.; Kiser, P.F.; Shah, D.; Meuer, W.P.; Needham, D.; Simon, S.A. *Macromolecules*, **2000**, *33*, 4087.

4.   (a) Horkay F.; Tasaki, I.; Basser, P. J. *Biomacromolecules* **2000,** *1*, 84, (b) Horkay, F.; Burchard, W.; Geissler, E.; Hecht, A. M. *Macromolecules* **1993**, *26*, 1296, (c) Horkay, F.; Basser, P. J.; Hecht, A. M.; Geissler, E. *Macromolecules* **2000,** *33,* 8329, (d) Horkay, F.; Tasaki, I.; Basser, P. J. *Biomacromolecules* **2001,** *2*, 195.

5.   Michaeli, J. *J. Polymer Sci.* **1960**, *48*, 291.

6.   (a) *Calcium in Human Biology*, ed. Nordin, B., Springer-London, 1988 (b) *Diem K, Lenter C., Scientific Tables, Ciba-Geigy–Basel, 1981*

7.   (a) Patrickios, C.S.; Georgiou, T.K. *Curr. Opin. Colloid Interface Sci.*, **2003**, *8*, 76, (b) Erdodi, G.; Kennedy, J.P. *Prog. Polym Sci.* **2006**, *31*, 1, (c) Mespouille, L.; Hedrick, J. L.; Dubois, P. *Soft Matter* **2009**, *5*, 4892.

8.   (a) Domján, A.; Erdődi, G.; Wilhelm, M.; Neidhöfer, M.; Landfester, K.; Iván, B.; Speiss, H. W. *Macromolecules* **2003,** *36,* 9107, (b) Bruns, N.; Scherble, J.; Hartmann L.; Thomann, R.; Iván, B.; Mülhaupt, R.; Tiller, J. C. *Macromolecules* **2005,** *38,* 2431, (c) Tobis, J.; Thomann, Y.; Tiller, J. C. *Polymer* **2010**, *51*, 35, (d) Lequieu, W.; Van De Velde, P.; Du Prez, F.; Adriaensens, P.; Strome, L.; Gelan, J. *Polymer* **2004,** *45,* 7943. (e) Dech, S.; Wruk, V.; Fik, C.P.; Tiller, J.C. *Polymer*, **2012**, *53*, 701. (f) Domjan, A.; Mezey, P.; Varga, J. *Macromolecules*, **2012**, *45*, 1037, (g) Zhang, X.; Kyriakos, K.; Rikkou-Kalourkoti, M.; Kitiri, E.N.; Patrickios, C.S.; Papadakis, C.M. *Colloid. Polym. Sci.*, **2016**, *294*, 1027, (h) Nardi Tironi, C.; Graf, R.; Lieberwirth, I.; Klapper, M.; Müllen, K. *ACS Macro Lett.* **2015**, *4*, 1302

9.   (a) Kali, G.; Georgiou, T. K.; Iván, B.; Patrickios, C. S.; Loizou, E.; Thomann, Y.; Tiller, J. C. *Macromolecules*, **2007**, *40,* 2192. (b) Kali, G.;

Georgiou, T. K.; Iván, B.; Patrickios, C. S.; Loizou, E.; Thomann, Y.; Tiller, J. C. *Langmuir*, **2007**, *23*, 10746. (c) Kali, G.; Georgiou, T. K.; Iván, B.; Patrickios, C. S.; Loizou, E.; Thomann, Y.; Tiller, J. *ACS Symp. Ser.* **2008**, *996*, 286, (d) Kepola, E.J.; Loizou, E.; Patrickios, C.S.; Leontidis, E.; Voutouri, C.; Stylianopoulos, T.; Schweins, R.; Gradzielski, M.; Krumm, C.; Tiller, J.C.; Kushnir, M.; Wesdemiotis, C. ACS Macro Lett. 2015, 4, 1163.

10.   (a) Kennedy, J. P. *Macromol. Symp.* **1994**, *85*, 76, (b) Isayeva, I. S.; Gent, A. N.; Kennedy, J. P. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2075.

11.   (a) Haigh, R.; Fullwood, N.; Rimmer, S. *Biomaterials* **2002**, *23*, 3509. (b) Rimmer, S.; German, M. J.; Maughan, J.; Sun, Y.; Fullwood, N.; Ebdon, J.; MacNeil, S. *Biomaterials* **2005**, *26*, 2219.

12.   Kali, G.; Georgiou, T. K.; Iván, B.; Patrickios, C. S. *J. Polym. Sci., Part A: Polym. Chem.*, **2009**, *47*, 4289.

13.   (a) Rikkou-Kalourkoti, M.; Kitiri, E.N.; Patrickios, C.S.; Leontidis, E.; Constantinou, M.; Constantinides, G.; Zhang, X.; Papadakis, C.M. *Macromolecules*, **2016**, *49*, 1731, (b) Kafouris, D.; Kossivas, F.; Constantinides, C.; Nguyen, N.Q. ; Wesdemiotis, C. ; Patrickios, C.S. *Macromolecules*, **2013**, *46*, 622, (c) C.S. Cui, J.; Lackey, M.A.; Tew, G.N. ; Crosby, A.J. *Macromolecules*, **2012**, *45*, 6104, (d) Guzman, G.; Turgut Nugay, T.; Isil Nugay, I.; Nugay, N.; Kennedy, J.P.; Cakmak, M. *Macromolecules*, **2015**, *48*, 6251.

14.   (a) Bromberg, L.; Temchenko, M.; Hatton, T. A. *Langmuir* **2002,** *18,* 4944, (b) Lin, C.; Gitsov, I. *Macromolecules* **2010,** *43,* 10017, (c) Kennedy, J. P. *Macromol. Symp.* **2001,** *175,* 127.

15.   (a) Rimmer, S.; German, M.J.; Maughan, J.; Sun, Y.; Fullwood, N.; Ebdon, J.; MacNeil, S. *Biomaterials* **2005,** *26*, 2219, (b) Sun. Y.; Collett, J.; Fullwood, N. J.; Mac Neil, S.; Rimmer, S. *Biomaterials* **2007**, *28*, 661.

16.   Behraves, E.; Jo, S.; Zygourakis, K.; Mikos, A. G. *Biomacromolecules* **2002,** *3,* 374.

17.   Künzler, J. F. *Trends Polym. Sci.* **1996**, *4*, 52.

18.   Xu, J. K.; Li, X. S.; Sun, F. Q. *Drug Delivery* **2011**, *18*, 150.

19. Nicolson, P. C.; Vogt, J. *Biomaterials* **2001,** *22,* 3273.

20. (a) Haigh, R.; Fullwood, N.; Rimmer, S. *Biomaterials* **2002,** *23*, 3509, (b) Bruns, N.; Tiller, J. C. *Nano Lett.* **2005,** *5,* 45, (c) Jewrajka, S. K.; Erdődi, G.; Kennedy, J. P.; Ely, D.; Dunphy, G.; Boehme, S.; Popescu, F. *J. Biomed. Mater. Res., Part A* **2008**, *87A*, 69, (d) Bruns, N.; Hanko, M.; Dech, S.; Ladisch, R.; Tobis, J.; Tiller, J. C. *Macromol. Symp.* **2010**, *291-292*, 293; (e) S. Dech, T. Cramer, R. Ladisch, N. Bruns, J. C. Tiller *Biomacromolecules* **2011**, *12*, 1594. (f) Schöller, K.; Küpfer, S.; Baumann, L.; Hoyer, P.M.; de Courten, D.; Rossi, R.M.; Vetushka, A.; Wolf, M.; Bruns, N.; Scherer, L.J. *Adv. Funct. Mater.,* **2014**, *24*, 5194.

21. Rother, M.; Barmettler, J.; Reichmuth, A.; Araujo, J.V.; Rytka, C.; Glaied, O.; Pieles, U.; Bruns, N. *Adv. Mater.*, **2015**, *27*, 6620.

22. *Kennedy, J. P.; Iván, B. Designed Polymers by Carbocationic Macromolecular Engineering: Theory and Practice; Hanser Publishers: New York, 1992.*

23. (a) Guan, Y.; Jiang, W. W.; Zhang, W. C.; Wan, G. X.; Peng, Y. X. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1784, (b) Guan, Y.; Jiang, W. W.; Zhang, W. C.; Wan, G. X.; Peng, Y. X. *J. Appl. Polym. Sci.* **2002**, *85*, 351.

24. (a) Tiller, J. C.; Sprich, C.; Hartmann, L. *J. Controlled Release* **2005**, *103*, 355, (b) Tiller, J. C.; Hartmann, L.; Scherble, J. *Surf. Coat. Int.: Part B: Coatings Trans.* **2005**, *88*, 49.

25. (a) Haraszti, M.; Tóth, E.; Iván, B. *Chem. Mater.* **2006**, *18*, 4952. (b) Kali, G.; Iván, B. *Macromol. Chem. Phys.*, **2015**, *216*, 605

26. (a) C. Fodor, G. Kali, B. Ivan *Macromolecules* **2011**, *44*, 4496 (b) Cs. Fodor, B. Ivan *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 4729.

27. Iván, B.; Kennedy, J. P. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 89.