CSIRO PUBLISHING

Short Communication

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2007**, *60*, 439–443

Effect of Redundant Chain Packing on the Uptake of Calcium Phosphate in Poly(2-Hydroxyethyl Methacrylate) Hydrogels

Traian V. Chirila,[A,B,C,G] *Anita J. Hill*,[D,E] *and David T. Richens*[F]

[A]Queensland Eye Institute, 41 Annerley Road, South Brisbane, QLD 4101, Australia.
[B]School of Physical and Chemical Sciences, Queensland University of Technology, Brisbane, QLD 4001, Australia.
[C]Australian Institute for Bioengineering and Nanotechnology, University of Queensland, St Lucia, Brisbane, QLD 4072, Australia.
[D]CSIRO Manufacturing and Infrastructure Technology, Private Bag 33, Clayton, VIC 3168, Australia.
[E]School of Chemistry, Monash University, Clayton, VIC 3800, Australia.
[F]School of Chemistry, University of St Andrews, Fife, KY16 9ST, Scotland, UK.
[G]Corresponding author. Email: traian.chirila@qei.org.au

A method is described that allows reduction of the amount of calcium phosphate phases deposited spontaneously inside poly(2-hydroxyethyl methacrylate) (PHEMA), a hydrogel of biomedical importance. PHEMA homo-interpenetrating polymer networks (homo-IPNs) were synthesized and then treated in a calcifying solution. A reduction of calcium uptake of 58 to 75% was measured by ICP emission spectroscopy in the IPNs as compared to the PHEMA homopolymer (the parent network). The effect was rationalized in terms of reduction of the free volume available for the penetration and transport of Ca^{2+} and phosphate ions as a result of redundant chain packing through formation of IPNs.

Manuscript received: 12 January 2007.
Final version: 2 May 2007.

Any synthetic polymer may undergo dystrophic calcification when in contact with living tissues. This 'biomaterial-associated calcification' consists of the deposition of calcium phosphate phases (henceforth, CaP), usually apatitic, on the polymer itself and/or on the host tissue. The rigid or elastic polymers that do not have affinity for water are exclusively calcified at the interface unless cracks or other crevice-type defects are present in the material. The situation is different in the case of water-swelling crosslinked polymers (hydrogels), since they usually undergo calcification both at the interface and inside the material. External and/or internal spoliation of hydrogels with deposits is a major cause for their failure as ocular devices (contact lenses, intraocular lenses, and artificial corneas) leading to loss of transparency and possible pathological complications. Substantial clinical evidence has accumulated[1] on the spoliation of these devices with deposits comprised of CaP, lipids, and proteins. By using simulated body fluid formulations or other solutions that contain Ca^{2+} and phosphate ions, spoliation of hydrogels can be easily duplicated in abiogenic conditions, when calcification displays the features of a spontaneous process based on a mechanism yet to be understood. Enhanced supersaturation within the polymer network attributable to local salting-out solute effects[2] and the presence of diffusion gradients[3] have both been suggested as contributive factors. It has also been implied[4] that the abiogenic calcification of synthetic hydrogels and calcification of biogenic substrates (e.g., collagen) may have similar levels of complexity.

In spite of a large variety of hydrogels used in ocular applications, there has been no systematic approach to reduce their propensity for CaP intake. In this study we propose and evaluate a method to reduce the calcification of poly(2-hydroxyethyl methacrylate) (henceforth, PHEMA), a widely used biomedical hydrogel.

Penetration and subsequent transport of a molecule (or ion) through a polymer network must depend on the width and length of the available and accessible subnanometer-sized space between the macromolecular chains. These unoccupied interchain voids (variously designated as holes, cavities, nanopores, or nanovoids) can be qualitatively described by the term 'free volume', a dynamic concept that has been defined in miscellaneous ways.[5] The meaning of free volume is of much greater complexity than that suggested by any static model of the voids, as its size varies in both time and space because of segmental motions of the chains. It should be interpreted as an entropic quantity that measures the probability of the existence of cavities to accommodate penetrant entities, and for the creation of transient gaps or channels to allow their transport, rather than as a distribution of cavities that possess a defined surface energy and light-scattering capacity.[6] Theories based on the free volume concept have been developed to explain the structure of liquids in general, and to rationalize some macroscopic properties of amorphous or semi-crystalline polymers in the liquid or glassy state, such as viscoelastic behaviour, glass transition temperature, and diffusive molecular transport.[5b,5e,6,7]

It is intuitively acceptable that by reducing the size of free volume in a polymer the transport of a penetrant entity (molecule, ion) will be obstructed. Ultimately, if the size of the largest available free-volume holes is smaller than the size of the penetrant

 10.1071/CH07111 0004-9425/07/060439

(diffusant), the latter will be prevented from entering the network. The global consequence of reducing the free volume in a polymer would be the decrease of both permeability and uptake of the penetrant. As a strategy to reduce the size of free-volume holes we propose here to generate interpenetrating polymer networks (IPNs) by the diffusion and subsequent polymerization of monomer #2 into polymer network #1. As the only available space for the creation of network #2 is constituted by the free-volume holes in the parent network #1, the interchain free space that remains after the formation of the IPN, which is available for the diffusion of penetrants, will be considerably smaller than it was in the parent network. This approach is likely to be of general applicability regardless of the nature of penetrants or polymers.

We report the preparation of homo-IPNs, where HEMA is both monomer #1 and #2, and consequently both network #1 and network #2 are PHEMA. The calcification of these IPNs in a metastable calcifying solution is compared to the calcification of the parent network.

Experimental

High-purity HEMA and ethylene glycol dimethacrylate (EDMA) monomers were supplied by Bimax (USA) and used as such. All other chemical reagents were obtained from Sigma–Aldrich (USA) unless otherwise specified. The IPN network #1 was prepared by the free radical polymerization of a solution of 70% HEMA in water. The monomer also contained 0.5% EDMA as a crosslinking agent and 0.1% of an aqueous solution (10%) of ammonium persulfate (APS) as a component of the initiating system. To this homogeneous mixture, 0.1% (to monomer) of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED) was added as the second initiating component and the mixture was rapidly stirred in a vortex. The solution was then poured between two glass plates lined with transparency sheets (3M Co., USA) and spaced at 1.1 ± 0.1 mm by a silicone gasket. The clamp-held plate assembly was kept in an oven for 24 h at 50°C, and then for 24 h at 80°C. Disks of 7 mm in diameter were cut from the PHEMA sheets and subjected to water extraction in a Soxhlet apparatus for 2 days. The disks were then placed on a clean Teflon plate and dried in an oven at 100°C to constant weight. As additional control samples, PHEMA disks were also prepared in the absence of water, by the bulk copolymerization of HEMA and EDMA (0.5%) in the presence of 2,2′-azobis(2,4-dimethyl valeronitrile) (V-65, Wako Industries, Japan) as an initiator, at 50°C for 24 h and 100°C for 3 h, followed by swelling, cutting of disks, extraction, and drying.

As PHEMA does not swell in HEMA, two procedures were designed to generate homo-IPNs, both based on solvent-facilitated diffusion. According to Method A, dried PHEMA disks (produced in 30% water as shown above) were swollen in a solution of HEMA, either in water or in methanol, together with suitable diazo initiators. To obtain the IPN samples '**A1**', the PHEMA disks were immersed in an aqueous solution of HEMA (95%) that also contained 0.35% (to monomer) of EDMA and 0.1% (to monomer) of 2,2′-azobis(2-methylpropionamide) dihydrochloride (V-50, Wako Industries, Japan) as a water-soluble initiator. To obtain the IPN samples '**A2**', the disks were immersed in a solution of 99% HEMA in methanol, which also contained 0.35% (to monomer) of EDMA and 0.1% (to monomer) of V-65. After storing both formulations in a refrigerator for 3 days for complete swelling, the disks were gently blotted with lint-free tissues and kept in an oven for 24 h at 70°C, and then for 3 h at 100°C. According to Method B, the PHEMA disks were first immersed in aqueous solutions of either 0.08% V-50 (samples '**B1**') or 0.16% APS mixed with 0.16% sodium metabisulfite (samples '**B2**'), and kept in a refrigerator for 3 days. The swollen disks were then placed in HEMA that contained 0.35% EDMA and kept for one week in a refrigerator. Afterwards the samples were treated as described for Method A.

For the calcification experiments, aqueous solutions of $CaCl_2$ (2.57×10^{-3} mol L^{-1}) and Na_3PO_4 (1.54×10^{-3} mol L^{-1}) were individually prepared. After adjusting the latter to pH 8 with HCl, equal volumes of each solution were mixed to provide a metastable calcifying medium with a pH of around 7.3 and a $[Ca^{2+}]/[PO_4^{3-}]$ ratio of 1.67 (as in hydroxyapatite). Three disks each of **A1**, **A2**, **B1**, and **B2** samples, as well as five disks each of the parent PHEMA (network #1) and PHEMA produced by bulk polymerization in the absence of water were stored for 6 weeks at 37°C in vials that each contained 3 mL of calcifying medium. The medium was replaced twice a week with fresh solutions. To determine the amount of Ca uptake, the calcified disks were very gently rinsed in a stream of water, ashed at 600°C in platinum crucibles, and digested with HCl. The resulting solutions were analyzed by inductively coupled plasma emission spectroscopy (ICP-OES) in a Vista PRO CCD Simultaneous ICP-OES (Varian) instrument using Ca emission lines at five different wavelengths and averaging the results.

Results and Discussion

The results summarized in Table 1 indicate that in the homo-IPNs created by packing redundant chains of a second PHEMA network in the available space of PHEMA network #1 there is 58 to 75% less Ca than in the parent network. The results confirm the success of this method for the reduction of spoliation of PHEMA hydrogels; however, elucidation of the underlying mechanism of this reduction is of interest. There are several factors that could result in a diminished calcification. External spoliation of PHEMA depends upon temperature, pH, and surface characteristics (roughness, hydrophilicity, etc.). None of these variables differ between the parent networks and the IPNs, therefore, the reduction of Ca content must occur internally. A physical difference in the chain packing that results in reduced penetrant-accessible free volume is the most likely cause of the differences in Ca uptake shown in Table 1.

In order to test this hypothesis, the Ca uptake in the two PHEMA parent networks can be compared. The results in Table 1 show that bulk polymerization in the absence of water leads to a Ca uptake that is 40% lower than in the network made in the presence of water. This result suggests that the existence of a diluent during polymerization allows the formation of larger interchain spaces, which promotes enhanced penetration of ions and, therefore, higher Ca uptake. The diluent-induced enhancement of the free volume in PHEMA has previously been confirmed by using positron annihilation lifetime spectroscopy (PALS).[8]

The results in Table 1 also suggest that a higher weight gain following the formation of IPNs (like in samples **A1** and **A2**) may be associated with lower calcium uptakes, which indicates that increased redundant packing leads to less space available for the penetration of Ca^{2+} and phosphate ions. However, such a correlation is not convincingly supported in the present study because of the experimental scatter of the values of calcium content in the homo-IPN samples. The redundant chain packing has presumably altered the interchain space by a decrease in size, number, and/or connectivity of the unoccupied cavities available for the penetration of ions. If the number of free volume cavities

Table 1. Calcium content in homopolymers and homo-IPN samples determined by ICP emission spectroscopy

Sample[A]	Weight gain[B,C]	Calcium content[B] [mg calcium (g polymer)$^{-1}$]
PHEMA[D]	–	7.0 ± 1.1 ($N = 5$)
PHEMA (network #1)[E]	–	11.8 ± 0.7 ($N = 5$)
A1	2.31 ± 0.04 ($N = 3$)	3.9 ± 1.7 ($N = 3$)
A2	2.01 ± 0.05 ($N = 3$)	3.0 ± 1.1 ($N = 3$)
B1	1.30 ± 0.02 ($N = 3$)	4.5 ± 1.2 ($N = 3$)
B2	1.31 ± 0.03 ($N = 3$)	4.9 ± 0.3 ($N = 3$)

[A] See text for the meaning of **A1**, **A2**, **B1**, and **B2**.
[B] Given as mean values ± standard deviation, rounded to two decimal places (in the case of weight gain) or one decimal place (in the case of calcium content).
[C] Expressed as the ratio of the dry weight acquired by a sample after formation of IPN (i.e., sum of network #1 and #2) to the initial dry weight of the same sample as a homopolymer (before the formation of IPN, i.e., network #1 only).
[D] Synthesized by bulk polymerization (in the absence of water).
[E] Synthesized in the presence of 30% water.

were reduced, then the amount of deposited Ca would be reduced. If the mean size of the cavities were reduced then it is likely that a cavity of a minimum size able to accommodate the ions would be available. If the connectivity of the free volume cavities were reduced then the penetrant diffusion would be reduced. Explicitly, these results suggest that the homo-IPN approach can be used to alter the free volume and hence the transport properties of these polymers.

The manipulation of free volume is not a new strategy to tailor the transport properties of polymers, albeit not many studies are available to date. The dual nature of the free volume concept, i.e., static (pertaining to chain packing and its topology) and dynamic (pertaining to chain interactions and cooperative segmental motion) has been recognized in early landmark studies.[6,9] However, there were few attempts to use this knowledge in order to alter the free volume in polymers,[10] and it was only recently that specific approaches to the manipulation of free volume have been tentatively defined and successfully applied. Disruption of normal chain packing through changes in the backbone structure, or caused by thermal treatment, or induced by the addition of nanoparticles led to enhanced permeability in certain polymers because of an inefficient chain packing.[11] Similarly, the incorporation in polymers of large organic molecules that have their own internal free volume significantly affected the free-volume related properties in specific classes of polymers and liquid crystals.[12]

The transport of penetrants through a polymer network is believed to occur in the accessible unoccupied free-volume cavities by way of subnanometer- and nanosecond-scale diffusive events. The cavities, which according to widely accepted theoretical models[5h,13] are distributed in clusters, fluctuate in size and shape because of the segmental motion of the polymer chains, and channels may form for a very short time between two neighboring clusters. A penetrant cannot participate in a diffusive event until such a temporary channel opens, when, if present in the vicinity, the penetrant can jump into the next cluster before the channel closes. In a purely static approach, a percolation pathway must exist to enable the penetrant to find clusters of a size greater than its own size, without having to wait for a transient channel to open. However, the penetrant is unable to trespass if the size of available clusters is smaller than its own size, regardless of transient channel formation. Although the method reported here may be described in principle as static, purely static approaches are ultimately implausible because of the dynamic nature of the polymer chain segments and the fact that any alteration of chain packing should also affect the chain mobility.

In the case of the diffusion of small solutes in water-swollen polymer networks (hydrogels) there is an additional complication to the model, as these systems involve two penetrants. Water is the first penetrant, and already occupies all accessible free-volume cavities (but not those delineated by the hydrophobic regions in the network), while the second penetrant is the solute, in our case Ca^{2+} and phosphate ions. As most of the practical applications of hydrogels rely upon their capacity to restrict the penetration of solutes, the topic has been extensively investigated and several theoretical models have been developed to explain how the hydrogel networks can restrict the diffusion of solutes.[14] The hydrogel system can be imagined as a permeable continuum (water) in which large impenetrable obstacles (polymer), variable in shape and size within ranges specific to each polymer, are embedded and stand in the diffusion pathway of the second penetrant (solute), which can be imagined as small spheres. This model is particularly useful for the treatment of retardation of solute movement in hydrogels by obstruction effects or by hydrodynamic drag. Retardation can be caused concurrently by the reduction of the average free volume available to the solute. When a significant number of accessible cavities between obstacles are too small to allow the passage of a solute, its diffusion is restricted. Inside a hydrogel, the second penetrant must not only find sufficient free volume within the first penetrant (water), which arises from the random redistribution of water molecules and segmental motion of polymer chains, but must also find cavities within the polymer network large enough to allow its passage.

The size of the penetrants is crucial for their transport through networks. As hydration is required for ions to be stable, the primary hydration shell should be considered when assessing their size as penetrants. The primary hydration shells contain water molecules that interact directly with the ions and, consequently, this water is more tightly bound to the ions than that in the secondary hydration shells and beyond.[15] The latter are presumably too mobile to contribute to the ion size. Theoretical approaches[16] and experimental investigations[17] have indicated that the hydrated radius of the Ca^{2+} ion is around 3 Å and the average number of water molecules in the primary shell is between 6 and 10, depending on the concentration. The orthophosphate ion is assumed to have a rigid tetrahedral structure. There are only a few theoretical and experimental studies on the hydration of this ion,[18] which all indicate a hydrated radius between 3.4 and 3.9 Å and 12 to 18 water molecules in the primary hydration shell. At a neutral pH, the phosphate ions are likely hydrogen- and dihydrogenphosphates, but essentially this does not affect the estimated ion size in the context of our approach, and it should be understood that by 'phosphate' we designate $H_nPO_4^{(3-n)-}$, where n is 1 or 2, rather than 0. The hydration shells on both ions have a highly dynamic nature.[19] Water molecules are held together in clusters through hydrogen bonds that are permanently broken and reformed in very fast processes. A molecule can be in one instance in a cluster and in another moment in a different cluster or free. The residence time of a water molecule hydrating the Ca^{2+} ion will be of the order of 100 ns while on the phosphate ions it is estimated to be around 100 ps. In spite of this extreme mobility of primary hydration shells, they should be included in the estimation of ion

size, at least for the reason that ions are not stable in their naked state. In addition, it was demonstrated by neutron diffraction[20] that Ca^{2+} confined in very small spaces (8.5 Å pores in vermiculite clay) maintained a primary hydration shell of six water molecules. Also, it was determined by elution on Sephadex G-10 size exclusion columns[21] that at least a fraction of the water in the primary hydration shell is bound to the ions tightly enough to move with them when they diffuse. It is assumed that as hydrated ions enter the free-space cavities in the polymer network, the water molecules of their primary hydration shell are replaced in a concerted process by other water molecules that are present in the network.

The above considerations suggest that the free-volume cavities in the polymer that are smaller than 6 Å will not allow the penetration and transport of hydrated Ca^{2+} and phosphate ions, provided that the ions do not pair up before entering the network. If they pair up (as was found in a study that measured the apparent molecular weights of a series of ions by size exclusion chromatography[21]), then any cavity smaller than 13 Å will prevent the transport of nascent CaP phases. This is significantly smaller than the 'critical space' for the initial hydroxyapatite crystallites generated in biogenic conditions (on collagen, elastin, etc.), which was postulated[22] at 50–60 Å (including a 15 Å thick hydration shell). However, it is likely that amorphous CaP phases are formed in abiogenic conditions,[4] rather than hydroxyapatite.

In conclusion, the redundant chain packing in hydrogels through the formation of IPNs can lead to a size reduction of the free-volume cavities available for the transport of Ca^{2+} and phosphate ions, which is able to significantly diminish the amount of CaP phases precipitated inside the hydrogel materials.

Acknowledgments

This study was supported in part by the Australian Research Council (grant DP0208223) and by the Sylvia & Charles Viertel Charitable Foundation (Queensland).

References

[1] (a) M. Ruben, R. C. Tripathi, A. F. Winder, *Br. J. Ophthalmol.* **1975**, *59*, 141.
(b) J. M. Abbott, R. W. J. Bowers, V. Franklin, B. J. Tighe, *J. Br. Contact Lens Assoc.* **1991**, *14*, 21. doi:10.1016/0141-7037(91)80058-T
(c) B. Tighe, V. Franklin, in *The Eye in Contact Lens Wear, 2nd edn* (Ed. J. R. Larke) **1997**, Ch. 4, pp. 49–100 (Butterworth–Heinemann: Boston, MA).
(d) P. J. M. Bucher, E. R. Buchi, B. C. Daicker, *Arch. Ophthalmol.* **1995**, *113*, 1431.
(e) M. W. Dorey, S. Brownstein, V. E. Hill, B. Mathew, G. Botton, P. J. Kertes, S. El-Defrawy, *Am. J. Ophthalmol.* **2003**, *135*, 591. doi:10.1016/S0002-9394(02)02154-2
(f) C. R. Hicks, T. V. Chirila, L. Werner, G. J. Crawford, D. J. Apple, I. J. Constable, *Clin. Exper. Ophthalmol.* **2004**, *32*, 185. doi:10.1111/J.1442-9071.2004.00781.X

[2] T. V. Chirila, Z. Gridneva, D. A. Morrison, C. J. Barry, C. R. Hicks, D. J. T. Hill, A. K. Whittaker, Zainuddin, *J. Mater. Sci.* **2004**, *39*, 1861. doi:10.1023/B:JMSC.0000016204.30023.69

[3] Zainuddin, T. V. Chirila, D. J. T. Hill, A. K. Whittaker, *J. Mol. Struct.* **2005**, *739*, 199. doi:10.1016/J.MOLSTRUC.2004.06.038

[4] T. V. Chirila, D. A. Morrison, Z. Gridneva, A. J. A. Garcia, S. T. Platten, B. J. Griffin, Zainuddin, A. K. Whittaker, D. J. T. Hill, *J. Mater. Sci.* **2005**, *40*, 4987. doi:10.1007/S10853-005-1423-Z

[5] (a) J. Hirschfelder, D. Stevenson, H. Eyring, *J. Chem. Phys.* **1937**, *5*, 896. doi:10.1063/1.1749960
(b) A. K. Doolittle, *J. Appl. Phys.* **1951**, *22*, 1471. doi:10.1063/1.1699894
(c) A. Bondi, *J. Phys. Chem.* **1954**, *58*, 929. doi:10.1021/J150521A001
(d) H. Fujita, A. Kishimoto, *J. Colloid Sci.* **1958**, *13*, 418. doi:10.1016/0095-8522(58)90051-5
(e) M. H. Cohen, D. Turnbull, *J. Chem. Phys.* **1959**, *31*, 1164. doi:10.1063/1.1730566
(f) J. H. Hildebrand, R. L. Scott, *Regular Solutions* **1962**, Ch. 5, pp. 60–65 (Prentice–Hall: Englewood-Cliffs, NJ).
(g) J. S. Vrentas, J. L. Duda, *J. Polym. Sci., Polym. Phys. Edn* **1977**, *15*, 403.
(h) M. L. Greenfield, D. N. Theodorou, *Macromolecules* **1993**, *26*, 5461. doi:10.1021/MA00072A026

[6] A. Peterlin, *J. Macromol. Sci.-Phys. B* **1975**, *11*, 57.

[7] (a) H. Fujita, *Forpschr. Hochpolym. Forsch.* **1961**, *3*, 1.
(b) C. A. Kumins, T. K. Kwei, in *Diffusion in Polymers* (Eds J. Crank, G. S. Park) **1968**, Ch. 4, pp. 107–140 (Academic Press: London).
(c) D. H. Kaelble, in *Rheology, Theory and Applications* (Ed. F. R. Eirich) **1969**, Vol. 5, Ch. 5, pp. 223–296 (Academic Press: New York, NY).
(d) M. H. Cohen, G. S. Grest, *Phys. Rev. B* **1979**, *20*, 1077. doi:10.1103/PHYSREVB.20.1077
(e) K. Ghosal, B. D. Freeman, *Polym. Adv. Technol.* **1994**, *5*, 673. doi:10.1002/PAT.1994.220051102

[8] K. M. Varcoe, I. Blakey, T. V. Chirila, A. J. Hill, A. K. Whittaker, in *New Approaches in Biomedical Spectroscopy* (Eds K. Kneipp, R. Aroca, H. Kneipp, E. Wentrup-Byrne) **2007**, *ACS Symp. Ser. 963* in press (American Chemical Society: Washington, DC).

[9] G. Adam, J. H. Gibbs, *J. Chem. Phys.* **1965**, *43*, 139. doi:10.1063/1.1696442

[10] A. Garton, G. S. Haldankar, P. D. McLean, *J. Adhes.* **1989**, *29*, 13.

[11] (a) B. D. Freeman, A. J. Hill, in *Structure and Properties of Glassy Polymers* (Eds M. R. Tant, A. J. Hill) **1998**, *ACS Symp. Ser.* 710, Ch. 21, pp. 306–325 (ACS: Washington, DC).
(b) A. J. Hill, P. Meakin, *Desalination* **2002**, *146*, 1. doi:10.1016/S0011-9164(02)00461-7
(c) T. C. Merkel, B. D. Freeman, R. J. Spontak, Z. He, I. Pinnau, P. Meakin, A. J. Hill, *Science* **2002**, *296*, 519. doi:10.1126/SCIENCE.1069580
(d) A. J. Hill, B. D. Freeman, M. Jaffe, T. C. Merkel, I. Pinnau, *J. Mol. Struct.* **2005**, *739*, 173. doi:10.1016/J.MOLSTRUC.2004.05.041

[12] (a) J. Yang, T. M. Swager, *J. Am. Chem. Soc.* **1998**, *120*, 11864. doi:10.1021/JA982293Q
(b) T. M. Long, T. M. Swager, *Adv. Mater.* **2001**, *13*, 601. doi:10.1002/1521-4095(200104)13:8<601::AID-ADMA601>3.0.CO;2-V
(c) T. M. Long, T. M. Swager, *J. Am. Chem. Soc.* **2002**, *124*, 3826. doi:10.1021/JA017499X
(d) J. P. Amara, T. M. Swager, *Macromolecules* **2004**, *37*, 3068. doi:10.1021/MA0354694

[13] S. Arizzi, P. H. Mott, U. W. Suter, *J. Polym. Sci., Part B: Polym. Phys.* **1992**, *30*, 415. doi:10.1002/POLB.1992.090300501

[14] (a) A. H. Muhr, J. M. V. Blanshard, *Polymer* **1982**, *23*, 1012. doi:10.1016/0032-3861(82)90402-5
(b) B. Amsden, *Macromolecules* **1998**, *31*, 8382. doi:10.1021/MA980765F
(c) B. Amsden, *Polym. Gels Network* **1998**, *6*, 13. doi:10.1016/S0966-7822(97)00012-9

[15] J. Burgess, *Ions in Solutions: Principles of Chemical Interactions* **1988**, Ch. 1, pp. 25–27 (Ellis Horwood Ltd: Chichester).

[16] (a) E. Kochanski, E. Constantin, *J. Chem. Phys.* **1987**, *87*, 1661. doi:10.1063/1.453229
(b) I. Bakó, J. Hutter, G. Pálinkás, *J. Chem. Phys.* **2002**, *117*, 9838. doi:10.1063/1.1517039
(c) J. L. Fulton, S. M. Heald, Y. S. Badyal, J. M. Simonson, *J. Phys. Chem.* **2003**, *107*, 4688.
(d) M. M. Naor, K. Van Nostrand, C. Dellago, *Chem. Phys. Lett.* **2003**, *369*, 159. doi:10.1016/S0009-2614(02)01998-X

[17] (a) L. Mazzarella, A. L. Kovács, P. De Santis, A. M. Liquori, *Acta Crystallogr.* **1967**, *22*, 65. doi:10.1107/S0365110X6700012X
(b) N. A. Hewish, G. W. Neilson, J. E. Enderby, *Nature* **1982**, *297*, 138. doi:10.1038/297138A0

(c) H. Ohtaki, T. Radnai, *Chem. Rev.* **1993**, *93*, 1157. doi:10.1021/CR00019A014

[18] (a) L. W. Schroeder, M. Mathew, W. E. Brown, *J. Phys. Chem.* **1978**, *82*, 2335. doi:10.1021/J100510A018
(b) W. K. Lee, E. W. Prohofsky, *J. Chem. Phys.* **1981**, *75*, 3040. doi:10.1063/1.442399
(c) C. C. Pye, W. W. Rudolph, *J. Phys. Chem.* **2003**, *107*, 8746.
(d) P. E. Mason, J. M. Cruickshank, G. W. Neilson, P. Buchanan, *Phys. Chem. Chem. Phys.* **2003**, *5*, 4686. doi:10.1039/B306344E
(e) C. Ebner, U. Onthong, M. Probst, *J. Mol. Liq.* **2005**, *118*, 15. doi:10.1016/J.MOLLIQ.2004.07.004

[19] D. T. Richens, *The Chemistry of Aqua Ions* **1997**, Ch. 1, pp. 3–7 (Wiley & Sons: Chichester).

[20] N. T. Skipper, A. K. Soper, M. V. Smalley, *J. Phys. Chem.* **1994**, *98*, 942. doi:10.1021/J100054A033

[21] M. Y. Kiriukhin, K. D. Collins, *Biophys. Chem.* **2002**, *99*, 155. doi:10.1016/S0301-4622(02)00153-9

[22] N. Katsura, *Dent. Jpn. (Tokyo)* **1990**, *27*, 57.