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Ultrasound-Induced Cross-Linking and Formation of Macroscopic Covalent Hydrogels in Aqueous Polymer and Monomer Solutions

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ABSTRACT: A new sonochemical method of synthesizing macroscopic permanent hydrogels, that is, water-swellable 3D networks consisting of covalently linked polymer chains, is presented. Subjecting Ar-saturated aqueous solutions of bifunctional monomers, polyethylene glycol diacrylate (PEGDA 700), polyethylene glycol dimethacrylate (PEGDMA 800), and a mixture of PEGDA and vinylpyrrolidone (VP), containing neither initiators nor any other additives to the action of ultrasound leads to the formation of permanent continuous hydrogel filling all of the space previously occupied by monomer solution. For 10% PEGDA solution at an ultrasound frequency of 622 kHz, the reaction time is as short as 30 s. By selecting the appropriate sonication time, frequency of ultrasound, and concentration of substrate, one can control the monomer conversion degree and cross-link density of the resulting gel. Hydrogels can also be obtained by using typical ultrasonic cleaning bath (35 kHz), albeit a higher dose of ultrasound energy (i.e., longer time of expose to ultrasound) is required. In separate experiments, we demonstrate the ultrasound-induced increase in average molecular weight of a polymer (Pluronic F127) in monomer- and initiator-free aqueous solutions, which indicates the prevalence of free-radical cross-linking reactions over degradation. Results are interpreted in terms of ultrasound-induced cavitation leading to the generation of OH radicals, which in turn initiate the monomer/polymer reactions and to a momentary local temperature increase at the surface of cavitation bubbles while undergoing quasi-adiabatic compression.

Introduction

Although the fact that ultrasound can induce chemical reactions in polymers has been known since the 1930s,[1] the scope of studies on such effects has been limited so far to polymerization, synthesis of block copolymers, and degradation,[2] whereas much less is known about ultrasound-induced cross-linking. Heusinger and coworkers demonstrated that some low-molecular-weight compounds that do not possess typical polymerizable groups, such as glucose or glyceraldehyde, can be dimerized or even turned into oligomers by ultrasound.[3] This has been attributed to intermolecular recombination of ultrasound-generated radicals. Isayev et al. have shown that ultrasound treatment of unvulcanized and vulcanized styrene−butadiene rubber induces competing scission and cross-linking reactions.[4] So far, no sonochemical reactions in initiator-free polymer or monomer solution have been reported that lead to cross-linking and, in particular, to the formation of macroscopic ("wall-to-wall") hydrogels, that is, water-swellable 3D networks of covalently bound polymer chains. Taking into account the increasing importance of hydrogels, both "regular" and "smart" (i.e., stimuli-sensitive), as biomaterials,[5] it seems reasonable to search for fast, simple, and clean methods of their synthesis other than classical thermally induced, initiator-based cross-linking polymerization.

To the best of our knowledge, in the only work published so far on ultrasound-assisted gel formation, the synthesis of cross-linked polymer structures was based on ultrasound-induced heating resulting in thermal dissociation of an initiator, which in turn initialized cross-linking polymerization in nonaqueous medium.[6] In our work, we demonstrate direct initiation of cross-linking and gel formation by action of ultrasound on pure aqueous monomer or polymer solutions containing neither initiators nor any other additives. The mechanism of these reactions is based not on thermal dissociation of an initiator but on ultrasound-induced formation of OH radicals (see below), which react with monomer or polymer to initiate cross-linking reactions. In particular, we report two successful attempts of inducing cross-linking processes in aqueous polymeric systems by ultrasound: the formation of permanent, covalently cross-linked, macroscopic hydrogels by cross-linking polymerization of polyethylene glycol diacrylate (PEGDA), polyethylene glycol dimethacrylate (PEGDMA), and a mixture of PEGDA with vinylpyrrolidone (VP), as well as the formation of cross-linked structures (but not yet macroscopic gels) of triblock copolymer of poly(ethylene oxide) and poly(propylene oxide), PEO-*b*-PPO-*b*-PEO (Pluronic F127).

Sonochemistry of aqueous solutions has been described elsewhere.[7−9] In brief, ultrasound waves propagating in water cause the formation of small voids (cavitation bubbles) filled with water vapor and molecules of dissolved gases and subsequently induce strong volume oscillations of these bubbles. Because of the high frequency of ultrasound, bubble compression is a very fast, quasi-adiabatic process. This leads to a momentary temperature increase in the gas phase to a few thousand kelvins,[10,11] which is high enough to cause the dissociation of water molecules into H and OH. Some of them escape to the surrounding liquid, where they may react with solute molecules. Macromolecules in solution can undergo chemical transformations under the influence of ultrasound by at least three mechanisms: reactions with radicals generated during periodic compression of cavitation bubbles, pyrolysis at the hot bubble−water interface, and mechanochemical effects (resulting from the shear forces generated around collapsing cavitation bubbles), whereas for monomer molecules, only the two former mechanisms may be of importance.

Materials and Methods

PEGDA (Aldrich, nominal average molecular weight 700 Da), PEGDMA (Aldrich, nominal average molecular weight 800 Da), VP (Fluka), PEO-*b*-PPO-*b*-PEO (Pluronic F127, BASF, nominal weight-average molecular weight 12.6 kDa), and *tert*-butanol p.a.

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(Fluka) were used as received. Aqueous solutions were made up in water purified by Nanopure II system (Barnstead).

Sonications were performed in a URS-1000 ultrasonic reactor setup (Allied Signal Elac-Nautik, Germany) consisting of a CESAR wave generator and amplifier, a USW 51-51 ultrasonic transducer, and a thermostatted cylindrical reactor of 500 mL capacity.[9,12,13] The vibrating element of the transducer, covered with stainless steel, formed the bottom of the reactor. A set of ultrasound transducers at a frequency range of 70−1022 kHz was used. The average bulk temperature of sonicated solution was maintained at 22 ± 2 °C by a thermostatted cooling mantle. The dose rates of ultrasound absorption were determined by calorimetry.[9,12,13] For calorimetric measurements, water in the cooling mantle was replaced by air to provide thermal insulation; the reactor was filled with 500 mL of water, and changes in water temperature caused by short sonications (up to 5 min) were followed. In calculations, the thermal losses were assumed to be negligible.

In the case of Pluronic F127 sonications, the reactor filled with polymer solution (500 mL) was covered with a gastight lid and equipped with a gas saturation device. Before sonication, the solution was saturated with argon. The ultrasound frequency was 622 kHz, and the dose rate of ultrasound absorption was 75 W kg^{-1} at the nominal output power of 50 W corresponding to a nominal ultrasound intensity of 2.1 W cm^{-2}.

For PEGDA, PEGDMA, and PEGDA-VP sonications, the reactor was filled with water, and the sample (5 mL) was contained in a flat-bottomed glass ampule fixed in the central part of the reactor. Before sonication, the sample was saturated with argon.

Additionally, sonications of PEGDA solutions in a Sonorex Super 10P ultrasonic cleaning bath (Bandelin, Germany) were performed. The 5 mL sample, prepared in the same way as for experiment in ultrasound reactor, was placed in the central part of the water-filled ultrasonic bath (ultrasound frequency 35 kHz, average temperature ca. 22 °C, nominal output power 60 W, nominal ultrasound intensity ca. 0.2 W cm^{-2}, dose rate estimated at ca. 20 W kg^{-1}).

The equilibrium degrees of swelling (DS) of hydrogels were determined gravimetrically. The gels were kept in distilled water at 25 ± 1 °C to extract the unreacted monomer and to reach the equilibrium swollen state. Distilled water was replaced every second day until no monomer could be detected (2 to 3 weeks). After we determined the mass of the swollen gel, the samples were freeze dried (Labconco) to constant weight. The latter was used to calculate the gel fraction, defined here as the ratio of dry gel weight to the initial weight of monomer in the sample.

Mechanical properties of the synthesized gels were assessed by compressive measurements using an universal testing machine (Zwick BZ5/TN1S) performed on samples obtained by sonication of 10% (w/v) PEGDA (Ar, 622 kHz, 50 W). The samples were of cylindrical shape with diameter of 13 mm and height of 8 mm. A cross-head speed of 1 mm min^{-1} was used, and the maximum load was 100 N. The compressive modulus was calculated as the slope of the initial linear portion of the stress−strain curve and given as an average value of 10 measurements.

Changes in weight-average molecular weights of Pluronic were determined by multiangle laser light-scattering on a BI-SM 200 setup (Brookhaven Instruments) equipped with an Innova 90C argon ion laser (Coherent, $\lambda = 514.5$ nm). Directly before the light-scattering measurements, aqueous Pluronic solutions were passed through filters (Minisart, Sartorius) of 0.45 μm pore size. The intensity of scattered light was measured at 25.0 ± 0.2 °C for at least five dilutions of each sample in the angular range of 30−120°. Care was taken not to exceed the Pluronic concentration where the onset of micelle formation could take place.[14] The Zimm-plot algorithm was applied for the evaluation of results. The d*n*/d*c* value of Pluronic in water was assumed to be equal to the value for PEO, that is, 0.134 mL g^{-1}.[15]

The net sonochemical yield of cross-linking (ΔG_x, data in Figure 7) was calculated using the following formula[16]

$$\Delta G_x = 4G_x - G_s = \frac{2c}{D\rho}\left(\frac{1}{M_{w0}} - \frac{1}{M_w}\right) \qquad (1)$$

where G_x is the yield of intermolecular cross-linking (number of moles of cross-links formed per unit of absorbed ultrasound energy, in mol J^{-1}), G_s is the yield of scission (number of moles of chain breaks occurred per unit of absorbed ultrasound energy), c is the polymer concentration (in g L^{-1}), ρ is the solution density (kg L^{-1}), D is the absorbed dose of ultrasound energy (amount of ultrasound energy absorbed by 1 kg of the sonicated liquid, in J kg^{-1}), and M_{w0} and M_w are the weight-average molecular weights of the polymer (g mol^{-1}) before and after sonication, respectively.

The ΔG_x values calculated according to eq 1 should be considered to be approximate because in the derivation of this formula, it is assumed that chain scission is a random process, whereas in ultrasound-induced mechanochemical scission some preference for midchain breaks is expected.

The sonochemical yield of OH radicals under our experimental conditions was estimated using Allen dosimetry.[17] The absorbance of I_3^- at 350 nm was measured ($\varepsilon = 25\,500$ dm^3 mol^{-1} cm^{-1}).

Results and Discussion

Ultrasound-Induced Cross-Linking Polymerization in an Initiator-Free Aqueous Solution. Ultrasound can initiate polymerization in an aqueous monomer solution in the absence of initiators because of generation of OH radicals and high local temperatures in the thin solution layers adjacent to the bubble surface. Polymerization of monofunctional monomers, such as vinylpyrrolidone[18] and acrylamide,[19] leads to the formation of linear polymer chains.

Our goal has been to synthesize cross-linked structures by sonochemical polymerization of a bifunctional monomer and to demonstrate that such process finally leads to a covalently bound macroscopic polymer gel. The choice of our main substrate, PEGDA, originates from the works of Kozicki et al.[20] on 3D gel dosimeters for radiotherapy. In these studies, this compound was shown to possess very high gel-formation tendency in aqueous solutions upon absorbing low doses of ionizing radiation (i.e., upon initialization by a very low number of OH radicals).

Figure 1 illustrates gel formation in aqueous PEGDA solutions containing neither initiators nor other additives as a function of sonication time at ultrasound frequency of 622 kHz and dose rate of 75 W kg^{-1}. The onset of gel formation occurred after 30 s, which corresponds to the absorbed dose of ultrasound of 2.25 kJ kg^{-1}.

The gel fraction, that is, the fraction of monomer incorporated into the network, increases with ultrasound dose and reaches a final value of ca. 0.5 (Figure 2).

An important parameter that allows us to assess the cross-link density of a gel is the equilibrium degree of swelling, DS $= (m_s - m_d)/m_d$, where m_s and m_d denote the weight of the gel swollen to an equilibrium and in the dry state, respectively. DS decreases with increasing cross-link density. In our system, DS decreases with increasing dose, indicating that effective cavita-

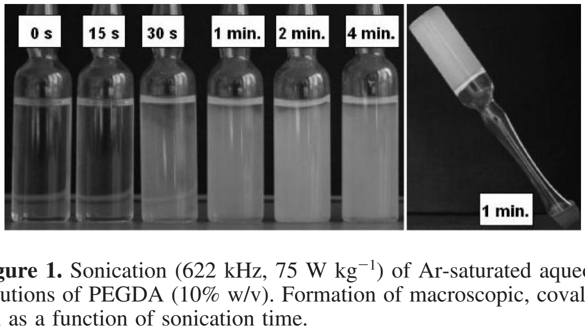

Figure 1. Sonication (622 kHz, 75 W kg^{-1}) of Ar-saturated aqueous solutions of PEGDA (10% w/v). Formation of macroscopic, covalent gel as a function of sonication time.

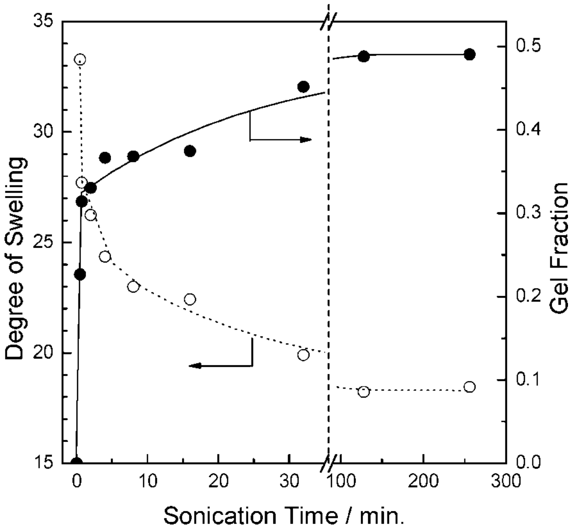

Figure 2. Sonication (622 kHz, 75 W kg^{-1}) of Ar-saturated aqueous solutions of PEGDA (10% w/v). Gel fraction (●) and equilibrium degree of swelling of the gel (○) as a function of sonication time.

tion and further cross-linking take place in the system also after the onset of gel formation, leading to a decrease in average pore size of the 3D polymer network. However, after gelation, cross-linking processes become significantly slower than those at the initial reaction time, when the system is liquid. This is probably due to the fact that very high viscosity of the gel system leads to a considerable decrease in cavitation intensity.

We believe that the initiation of the observed cross-linking polymerization is based on sonochemical OH generation and their subsequent addition to one of the carbon−carbon double bonds in PEGDA. Supplementary series of experiments with the addition of *tert*-butanol as an effective OH radical scavenger were performed. In the presence of 5 mM and 50 mM *tert*-butanol, the dose of ultrasound necessary to obtain gel increases by a factor of 1.4 and 12.8, respectively. Although simple competition kinetics cannot be quantitatively applied to this case for reasons described in detail in refs 11 and 13, these results provide at least qualitative indication that OH radicals play a decisive role in the initiation of polymerization and cross-linking reactions in this system.

To prove that the products are in fact permanent macroscopic hydrogels where polymer chains are bound into a 3D network with covalent bonds, we performed autoclave tests. Hydrogel samples placed in water at 121 °C for 15 min did not visibly change their physical properties, and no dissolution was observed. Physical gels formed by aggregation due to van der Waals forces, hydrophobic interactions, and so on undergo dissolution under such conditions.

The efficiency of gel formation in the studied system (deoxygenated 10% (w/v) PEGDA aqueous solution) depends on ultrasound frequency. This is reflected in differences in gel fraction and degree of swelling and a given dose (Figure 3).

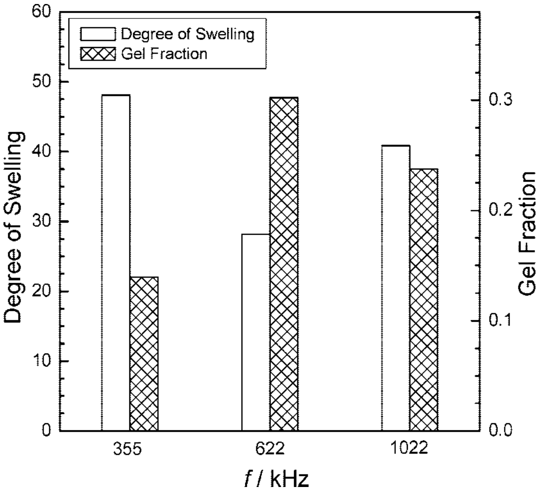

Figure 3. Sonication (50 W, 75 W kg^{-1}, 2 min) of 10% PEGDA in Ar-saturated aqueous solutions. Gel fraction (columns with patterns) and equilibrium degree of swelling of the gel (blank columns) as a function of ultrasound frequency.

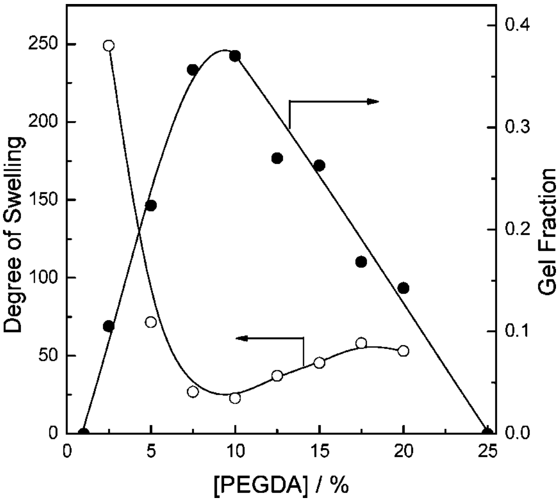

Figure 4. Sonication (622 kHz, 50 W, 75 W kg^{-1}, 6 min) of PEGDA in Ar-saturated aqueous solutions. Gel fraction (●) and equilibrium degree of swelling of the gel (○) as a function of substrate concentration (% w/v).

Two effects contribute to this dependence. The sonochemical yield of OH radicals in aqueous solutions exhibits a broad maximum at the frequency of ca. 300 kHz (refs 8 and 9; our own data: $G_{OH} \approx 6.7 \times 10^{-11}$, 2.1×10^{-9}, 5.9×10^{-10}, and 2.2×10^{-10} mol J^{-1} at 70, 355, 622, and 1022 kHz, respectively), whereas the efficiency of mechanochemical degradation strongly decreases with increasing frequency in the studied range. As a result of the interplay of these two counteracting processes, that is, OH-induced cross-linking polymerization and mechanochemical chain scission, maximum net efficiency of gel formation (the highest gel fraction and the lowest degree of swelling) is observed at 622 kHz. At 355 kHz, despite a somewhat higher OH yield, there is strong influence of mechanochemistry,[12,13] whereas at 1022 kHz, where, in practical terms, no mechanochemical effects take place, the yield of OH is already noticeably lower than that at 355 and 622 kHz.

However, we found that gelation of aqueous PEGDA solutions can also be achieved, albeit at significantly higher doses, by sonication at low ultrasound frequency (35 kHz, typical ultrasonic bath), where the OH generation yield is much lower than that at 622 kHz. Most likely, the local, momentary strong rises in temperature of the liquid layers adjacent to the collapsing bubbles may cause thermal self-initiation of cross-linking polymerization in addition to the OH-induced initiation. However, owing to different geometry, instability of temperature and power, and lack of possibility of carrying out precise dosimetric measurements in the simple ultrasonic bath, it is difficult to make such measurements quantitatively and compare the yield of cross-linking to the results obtained using the ultrasound reactor. Nevertheless, the observation on the possibility of synthesizing hydrogels in a typical ultrasonic bath may be of some importance from a practical point of view because of the low cost and broad use of ultrasonic baths in chemical laboratories.

Figure 4 illustrates the dependence of gel fraction and equilibrium degree of swelling of obtained gels on PEGDA

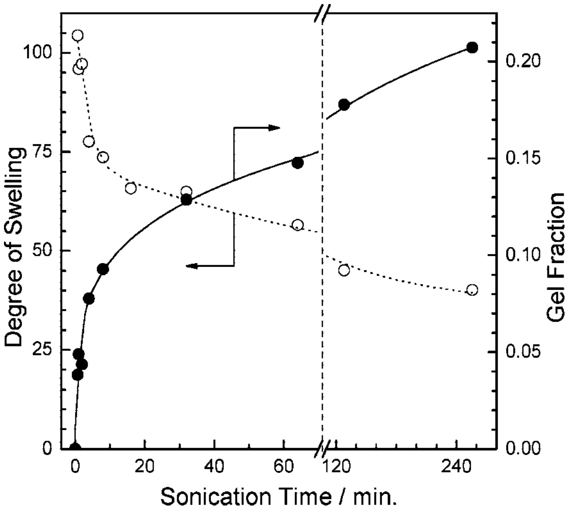

Figure 5. Sonication (622 kHz, 75 W kg^{-1}) of Ar-saturated aqueous solutions of 5% PEGDA and 5% VP (w/v). Gel fraction (●) and equilibrium degree of swelling of the gel (○) as a function of sonication time.

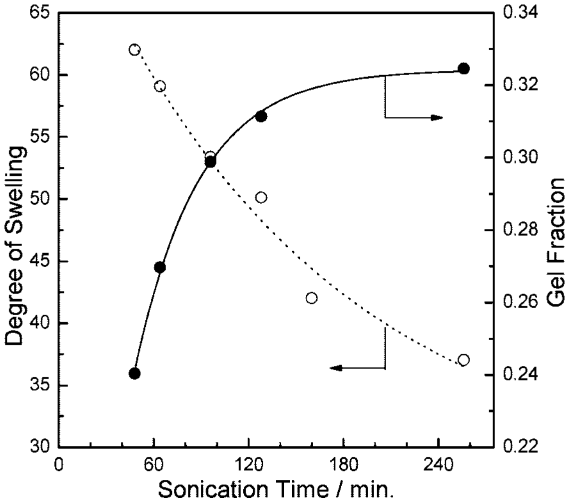

Figure 6. Sonication (622 kHz, 75 W kg^{-1}) of Ar-saturated aqueous solutions of PEGDMA (10% w/v). Gel fraction (●) and equilibrium degree of swelling of the gel (○) as a function of sonication time.

concentration under constant sonication conditions. These data clearly indicate the existence of an optimum concentration range at ca. 5−15% w/v. At a constant rate of radical formation in the system, low monomer concentration results in too slow propagation and cross-linking in comparison with radical recombination. This results in the formation of short, oligomeric chains that are not linked into a 3D network. Furthermore, taking into consideration the relatively high local OH concentrations under sonication close to the surface of cavitation bubbles, at low monomer concentrations, some OH radicals may be "lost" because of rapid self-termination ($2k = 1.1 \times 10^{10}$ M^{-1} s^{-1}).[21] At high monomer concentrations, the gel fraction decreases because of at least two factors. One of them is the statistics of gel formation. If we want to obtain a gel with given parameters (e.g., given amount of cross-linking bonds in relation to the number of monomer units), the number of cross-links necessary to reach that aim is expected to increase proportionally with the concentration. In other words, if the number of generated radicals (and cross-linking bonds) is constant, then an increase in monomer concentration should lead to lower gel fraction and increased degree of swelling. Additionally, at high monomer fractions in the system, the yield of OH generation decreases and thus lowers the cross-linking yield.

Mechanical tests indicated that the hydrogels synthesized by sonicating 10% PEGDA solutions (Ar, 622 kHz, 50 W, 75 W kg^{-1}, 64 min) have compression strength of 10.3 kPa and elastic modulus of 4.0 kPa. These values are lower than those characteristic of strongly chemically or photochemically cross-linked PEGDA gels[22] but are similar as determined for some other gels used for practical purposes, for instance, hydrogels obtained by radiation cross-linking of poly(glutamic acid)[23] or typical calcium alginate gels.[24]

Whereas PEGDA was chosen for the initial tests because of its known high gel-forming ability, it may be interesting to see whether the range of applications for the proposed sonochemical method of hydrogel synthesis can be made to be somewhat broader. Whereas answering this question requires, of course, broader studies, here a first step has been made by testing either PEGDA in combination with a monofunctional monomer or PEGDMA as another bifunctional monomer.

Figure 5 illustrates the results obtained for a mixture of 5% PEGDA and 5% vinylpyrrolidone (VP) in aqueous solution. Similarly as for 10% PEGDA, sonolysis of PEGDA-VP solution leads to the formation of a macroscopic hydrogel in a relatively short time, and the equilibrium degree of swelling may be controlled by means of ultrasound dose. The obtained gel fraction is significantly lower than that for pure PEGDA, but the product still has good mechanical properties. Elementary analysis of dried PEGDA-VP gels that were previously subjected to swelling and long-term rinsing in water to remove sol fraction from the sample indicates that the molar fraction of VP units in the product amounts to 60%. This value is somewhat lower than the molar fraction of VP monomer in the initial mixture of substrates (86%); nevertheless, it indicates that vinylpyrrolidone participated in the propagation reaction effectively, and a significant part of this monomer was built into the structure of the formed hydrogel.

An alternative bifunctional water-soluble monomer, PEGDMA, is a PEGDA analogue with more hydrophobic properties. The course of PEGDMA reaction under sonication considerably differs from cross-linking of PEGDA. In the first stage of sonication, which lasts for many minutes, no gel formation was observed, most probably because of the formation of microgels not connected into a macroscopic structure. This could possibly be interpreted as a result of aggregation tendency among the highly hydrophobic PEGDMA molecules in water. After a longer sonication time, a macroscopic gel was formed (Figure 6). The final content of gel fraction was somewhat lower than that for PEGDA (0.32 for PEGDMA and 0.49 for PEGDA after 256 min of sonication). The macroscopic PEGDMA hydrogel was characterized by an equilibrium degree of swelling that was somewhat higher than that observed for PEGDA despite the theoretically lower capability of water binding because of the more hydrophobic nature of its chains in the network. This clearly indicates the lower cross-linking density of PEGDMA networks.

In all experiments described above, solutions have been saturated with argon before sonication. Both accumulated knowledge[9,25] and our own experience[26] favor using argon for the saturation of water in sonochemical experiments. It provides maximum yield of radicals (high C_p/C_v of argon, and its low heat conductivity promotes temperature rise in the quasi-adiabatic compression phase of cavitation bubbles) and also prevents both the formation of peroxyl radicals, which may cause chain scission, and the oxidation of products. To test the influence of oxygen on the cross-linking process, we have performed experiments on sonication of 10% PEGDA solutions where argon has been substituted by oxygen. In contrast with Ar-saturated systems, no gel formation could be detected as a

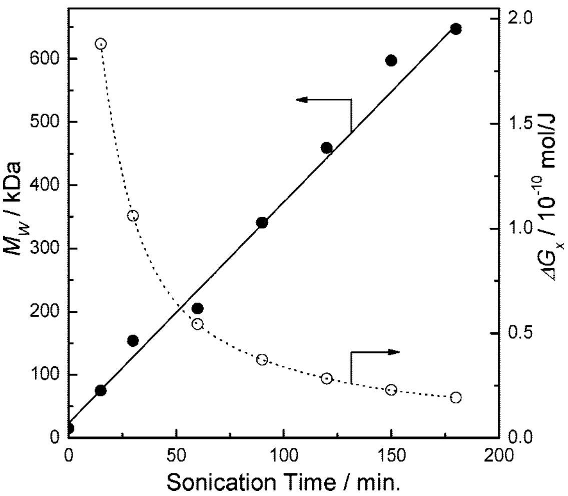

Figure 7. Sonication (622 kHz, 75 W kg^{-1}) of Ar-saturated aqueous solutions of Pluronic F127 (0.475 g L^{-1}). Weight-average molecular weight (M_w, ●) and net cross-linking yield (ΔG_x, ○) as a function of sonication time.

result of sonication in oxygen-saturated solutions, even at reaction times up to 2 h.

Cross-Linking of Macromolecules in Monomer-Free Aqueous Solution. Whereas inducing polymerization and cross-linking of monomers by ultrasound is relatively easily achieved, it is more challenging to initialize cross-linking of macromolecules in a monomer- and cross-linker-free system. The idea behind attempting this apparently more difficult approach is to allow the use of biocompatible medical-grade polymers as substrates and thus to have no traces of monomer, cross-linking agent (potentially irritant or harmful and usually difficult to remove), or both in the product. OH-radical-induced cross-linking of polymers in aqueous solutions is well-known from radiation chemistry and technology, where OH radicals are formed upon radiolysis of water.[27] Because ultrasound of appropriate frequency range also generates OH radicals in water, it should be, in principle, possible to transfer the synthetic methods from radiation chemistry to sonochemistry. In the latter, however, two specific factors should be taken into consideration. Strong gradients of liquid velocity in the vicinity of oscillating cavitation bubbles cause mechanochemical chain scission and efficiently counteract any potential cross-linking process taking place in the system. The yield of mechanochemical degradation is dependent on the chain length, with long chains being more susceptible. Another important aspect is that the generation of OH radicals in sonochemistry takes place only locally in the collapsing bubbles; therefore, considerable OH concentration in the liquid phase is present only at the immediate vicinity of the bubble−water interface. Actually, in the studies on sonication of polymers in solution, no net increase in the average molecular weight has been reported so far.

We believe that promoting OH-induced sonochemical cross-linking of macromolecules in aqueous solutions so that it can dominate over scission processes and lead to a net increase in the average molecular weight requires the following conditions to be met. The substrate polymer should be relatively hydrophobic (but, of course, water-soluble) to have a tendency to accumulate at the surface of cavitation bubbles,[11] that is, at the source of OH radicals, the starting molecular weight should be moderate, and the ultrasound frequency should be chosen to maximize the OH yield versus intensity of mechanochemical scission. In our previous studies,[9] we used oligomeric poly(ethylene glycol), but Pluronic molecules seem to fulfill the two former conditions (water-soluble but hydrophobic, $M_w \approx 12.6$ kDa) even better. The intensity of mechanochemical scission decreases with increasing ultrasound frequency, whereas OH yield exhibits a maximum at ca. 300 kHz.[6,7] Our tests indicate that somewhat higher frequencies (on the order of 600 kHz) provide the optimum cross-linking-to-scission ratio.

Although macroscopic gel formation has not been reached in the studied system, data shown in Figure 7 clearly indicate that under the chosen conditions, in the absence of any monomer or cross-linking agent, Pluronic molecules in aqueous solution become linked together by action of ultrasound.

From these data, one can calculate the time dependence of cross-linking yield (moles of cross-links formed per unit of ultrasound energy delivered to unit mass of the solution, cf. eq 1) or, more precisely, of the difference between the yields of cross-linking and scission (Figure 7). It should be noted that the initial ΔG_x (when almost no degradation takes place, i.e., $\Delta G_x \approx 4G_x$) is in the same range as the sonochemical yield of OH radicals in water under the same conditions ($G_{OH} = 5.9 \times 10^{-10}$ mol J^{-1}). Cross-linking yield decreases with sonication time because of the increasing susceptibility of growing chains to mechanochemical scission; therefore, the formation of macroscopic gel by ultrasound-induced cross-linking of polymers is difficult to achieve, and it has not been reached in the described system. Nevertheless, we believe that finding the substrate and conditions where cross-linking dominates scission in the ultrasound-treated polymer solution is a first step in this direction.

Conclusions

The action of ultrasound on aqueous solutions of bifunctional monomers, PEGDA and PEGDMA, leads to the formation of macroscopic permanent hydrogels where the polymer chains are linked by covalent bonds to form a 3D network. Under optimum conditions, gelation of PEGDA solutions can be reached in 30 s. Properties of the gels can be adjusted by controlling the ultrasound dose. Experiments with scavengers indicate that polymerization and cross-linking is mainly initiated by OH radicals produced upon sonication of water. Reaction efficiency (and, in turn, the ultrasound dose necessary to obtain the gel) depends on ultrasound frequency, with an optimum at ca. 600 kHz, albeit gel formation can also be achieved at low frequencies, such as those typical of simple laboratory ultrasonic baths. Another parameter that influences the efficiency of gel formation is the initial substrate concentration. For PEGDA, the highest gel yield is reached at ca. 10% (w/v). Gelation by ultrasound can also be achieved in solutions containing a mixture of bifunctional and monofunctional monomers, as shown in the example of PEGDA and VP.

Keeping in mind the potential applications of hydrogels in the biomedical field, where monomer residues in the products are not desirable, a test of an alternative approach with no monomers present has been made. Sonication of aqueous solutions of a model polymer, Pluronic F127, in the absence of any monomers and cross-linking agents, albeit not leading to the formation of macroscopic gels under the tested conditions, results in a pronounced increase in the average molecular weight, indicating the dominance of cross-linking reactions.

The elaborated fast, simple, one-stage sonochemical synthesis of hydrogels seems to be a potentially interesting alternative method, besides radiation-induced cross-linking, to synthesize permanent hydrogels with controlled properties in a system containing neither initiators nor any other additives.

To the best of our knowledge, our results are the first observation of a permanent hydrogel formation initiated by ultrasound in an initiator-free system.

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