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Influence of the Cross-Linker Reactivity on the Formation of Inhomogeneities in Hydrogels

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ABSTRACT: Polyacrylamide hydrogels cross-linked with different types and concentrations of cross-linkers were prepared and characterized by means of static light scattering and elasticity measurements. Big differences in the excess light scattering revealed different tendencies of the networks to form polymer agglomerations and inhomogeneities. Furthermore, the efficiency of the cross-linking reaction changed with the type of cross-linker chosen. A correlation between these two properties has been observed and attributed to the different reactivities of the cross-linker molecules.

Introduction

Hydrogels made by cross-linking copolymerization are interesting materials for a variety of pharmaceutical and hygienic applications. Although the swelling behavior of polymer networks and the elasticity of such systems appears to be understood quite well,[1] there are still questions concerning the structure of real networks and the structure development during the gelation process. In contrast to model networks with constant length of network chains between cross-links, real networks exhibit a wide distribution of chain lengths between network junction points. Furthermore, a variety of network defects, such as dangling ends, elastically ineffective loops, and cross-link agglomerations, are known to occur. These defects change the effective cross-linking density of the networks and thus influence their elastic properties and their swelling behavior. Unfortunately, the exact nature and quantity of network defects are very difficult to evaluate experimentally.

One feature of particular interest is the presence of network inhomogeneities, which was first reported by Weiss et al.[2] These can be visualized as strongly cross-linked regions in a less densely cross-linked environment. The higher the network density, the lower is the swelling capacity. As a result, an inhomogeneously cross-linked hydrogel consists of regions with relatively high polymer concentration and more swollen or diluted regions with lower polymer concentration. The overall swelling capacity of such a heterogeneous system may differ from that of a homogeneously cross-linked network. When gels having high swelling capacity should be designed, the consideration of the inhomogeneity of the network seems necessary. Until now, the mechanism of formation of cross-link agglomerations is little understood. In this paper we try to gain some systematic data which may eventually lead to a fundamental understanding of the mechanisms which lead to inhomogeneous networks.

It has been observed that in a radical cross-linking copolymerization the type of cross-linker chosen decisively affects the efficiency of the cross-linking reaction.[3] Apparently, this is a result of the different reactivities of the cross-linker molecules with respect to the monomer molecules. Different reactivities probably lead to different morphologies of the networks; i.e., network imperfections including inhomogeneities may evolve in different ways and extents. Computer simulations show that there is indeed a big influence of the cross-linker reactivity on the generation of network defects.[4] In our experiments we vary the concentration and type of cross-linker molecules systematically. The networks are then characterized with respect to the formation of inhomogeneities and the efficiency of the cross-linking reaction.

A convenient way to probe concentration fluctuations in a system is by light scattering methods. Dynamic and static light scattering investigations on hydrogels have been carried out in order to obtain information about inhomogeneities,[5−7] cooperative diffusion coefficients,[8] and longitudinal elastic moduli.[9] The static excess scattering of gels, which is the difference of the angle resolved scattering between the cross-linked and the uncross-linked samples, can be analyzed by the Debye−Bueche method in order to obtain the correlation length and the mean square refractive index fluctuation of the gels.[10−12] The excess scattering is given by

$$R_{\mathrm{E}}(q) = \frac{4\pi K\xi^3 \langle\eta^2\rangle}{(1 + q^2\xi^2)^2} \tag{1}$$

with K being the optical constant, $K = 8\pi^2 n_0{}^2 \lambda_0{}^{-4}$, and q the scattering vector, $q = 4\pi/\lambda \sin(\theta/2)$. n_0 is the refractive index and λ the wavelength of the incident light in the medium. ξ is the correlation length of the scatterers and $\langle\eta^2\rangle$ the mean square fluctuation of the refractive index. The slope a and the intercept b of the plot of $R_{\mathrm{E}}(q)^{-1/2}$ vs q^2 (Debye−Bueche plot) gives the correlation length ξ by

$$\xi = \sqrt{a/b} \tag{2}$$

and the mean square fluctuation of the refractive index, $\langle\eta^2\rangle$, by

$$\langle\eta^2\rangle = \frac{1}{4\pi K a^{1.5} b^{0.5}} \tag{3}$$

The efficiency of the cross-linking reaction can be obtained by measuring the shear modulus of the samples. The network density (number of effective network strands per unit volume of the swollen network, ν_{eff}) is given by the shear modulus, G, of a polymer network:[13]

$$G = A\nu_{\mathrm{eff}}RT \tag{4}$$

provided that the measurement of the modulus is made on the gel in the state of formation (no further swelling

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or deswelling). A is the structure factor, R is the gas constant, and T is the temperature. Swollen networks are generally considered as phantom networks, hence $A = 0.5$ in the case of tetrafunctional cross-links.[14]

Equation 5 is valid only for slightly swollen polymer networks, where Gaussian chain statistics apply. With more highly swollen networks, more sophisticated formulas have to be employed to calculate the effective network density.[11] The theoretical number of network chains is given by the concentration of the cross-linker in the system, assuming all cross-linker molecules act as tetrafunctional junction points. The ratio of the effective number and the theoretical number of chains is then the efficiency of the cross-linking reaction.

Experimental Section

Materials. Hydrogels were prepared by copolymerizing acrylamide in aqueous solutions with different cross-linkers. The total monomer concentration was held constant at 15% (weight/volume). The cross-linkers used were *N,N′*-methylenebisacrylamide, *N,N′*-ethylenebisacrylamide, *N*-allylacrylamide, *N,N*-diallylacrylamide, and *N,N′*-diallyltartardiamide. As initiator we used a redox mixture comprising sodium peroxodisulphate ($Na_2S_2O_8$, 0.063% w/v) and *N,N,N′,N′*-tetramethylethylenediamine (TEMED, 0.072% w/v).

Sample Preparation. A solution containing 16.7 g of acrylamide, 80 mg of TEMED, and a variable amount of cross-linker (in the range 1−5 mmol) in distilled water to give a total volume of 100 mL was prepared. A second solution contained 0.63 g of $Na_2S_2O_8$ in 100 mL of distilled water. To start the polymerization reaction, 2 mL of the solution containing $Na_2S_2O_8$ and 18 mL of the other solution were mixed. To prepare the solutions of the un-cross-linked polymer, the procedure was the same, except that no cross-linker was added.

It is essential that the prepared gels are completely dust free. Therefore, the polymerizations were carried out in the light scattering cuvettes. All glassware was kept dustfree by rinsing in hot acetone prior to using. The solutions were filtered through Nalgene cellulose−acetate filters (pore size = 0.45 μm) directly into the cuvettes. This process was carried out in a dustfree glovebox. The resultant gels were totally clear and appeared homogeneous to the eye. The concentrations of cross-linkers in the gels prepared are listed in Table 1 together with the results of our experiments.

Light Scattering Experiments. The measurements were carried out in a modernized Sofica apparatus, equipped with a He−Ne laser (λ = 632.8 nm) and a computerized data acquisition system. The system was calibrated against a toluene standard. Since the sizes of the scatterers in gels are generally big and their distribution and orientation is frozen due to permanent cross-links, the scattering volume probed by the instrument is usually too small to average over all configurations of scatterers. Rotation of the cuvette during the experiment can solve this problem.[15] With our systems it was sufficient to average over six positions of the cuvette in order to get well-reproducable data. Specifically, the cuvette was rotated 60° between each cycle of data sampling. The excess scattering of the gels was determined by measuring the total scattering of the gel vs the total scattering of the un-cross-linked sample of the same polymer concentration.

Elasticity Measurements. After measuring the scattering characteristics of the samples, the gels were removed from the cuvettes. The shear modulus was determined by compressing the sample uniaxially and measuring force and deformation. The slope of the plot of the true stress, σ, vs the deformation function, $\lambda^2 - \lambda^{-1}$, gives the shear modulus, G, λ being defined as the length of the deformed sample divided by the length of the undeformed sample, L/L_0.

Results and Discussion

Shear Modulus. The shear modulus was measured directly after the light scattering experiments. The effective network density, ν_{eff}, can be calculated from the shear modulus of the networks according to eq 4. This number divided by the theoretical network density, ν_{th}, gives the efficiency of the cross-linking reaction. ν_{th} can be obtained from the molar concentration of cross-linker molecules, assuming perfect cross-linking without occurrence of network defects. All cross-linkers, including N,N-diallylacrylamide, were treated as leading to tetrafunctional cross-links. (With *N,N*-diallylacrylamide, one has to account for the fact that the two geminal allyl groups polymerize in one step, yielding five-membered rings.[16] That means that the virtual trifunctionality of *N,N*-diallylacrylamide gives rise to tetrafunctional junction points only. Moreover, it should be noted that due to the special reaction mechanism, *N,N*-diallyl groups are regarded as being more reactive than isolated allyl groups.)

Table 1. Experimental Results

c (mmol/100 mL)	G (kPa)	ν_{eff}/ν_{th} (%)	ξ (nm)	$\langle\eta^2\rangle \times 10^6$
		N,N′-Methylenebisacrylamide		
1.69	7.6	18.5	14.6	0.62
2.54	10.9	17.6	17.8	0.58
3.38	13.1	15.9	21.2	0.68
4.23	17.2	16.7	31.1	0.895
5.07	18.9	15.3	33.1	1.66
		N,N′-Ethylenebisacrylamide		
1.73	6.3	15.0	20.6	0.16
2.59	7.8	12.4	20.1	0.28
3.45	9.6	11.4	21.3	0.31
5.18	14.8	11.7	24.9	0.51
		N,N-Diallylacrylamide		
1.04	4.7	18.6	12.7	1.35
1.55	6.0	15.9	15.3	2.52
2.07	7.4	14.7	14.0	3.83
2.59	8.5	13.5	15.7	6.2
3.11	9.0	11.9	12.7	7.55
		N-Allylacrylamide		
2.39	7.7	13.2	15.6	1.35
3.59	10.9	12.5	17.4	2.52
4.79	12.2	10.5	17.3	3.83
5.98	15.2	10.4	17.0	6.20
7.18	17.7	10.1	16.9	7.55
		Diallyltartardiamide		
1.73	4.0	9.5	15.6	0.73
2.59	4.9	7.8	13.9	1.66
3.45	5.5	6.5	11.4	4.19
4.32	5.7	5.4	10.7	6.92
5.18	5.9	4.7	10.0	9.64

The modulus values of the networks studied are included in Table 1. Figure 1 shows the efficiency of the cross-linking reaction plotted as a function of the theoretical cross-linking density for different cross-linkers. The cross-linking efficiency is generally low because the networks were synthesized at rather small monomer concentration. In all systems studied, there is a slight decrease of ν_{eff}/ν_{th} with rising concentration of cross-linker. It is furthermore obvious that a clear distinction exists between different cross-linkers: The highest efficiency is achieved with *N,N′*-methylenebisacrylamide, whereas diallyltartardiamide leads to the lowest values. The data for the other cross-linkers employed are close together in an intermediate range.

Light Scattering. As a typical example, Figure 2 shows the Rayleigh ratio $R(q)$ vs the square of the wave vector q^2 for polyacrylamide gels cross-linked with *N*-allylacrylamide. Data for the un-cross-linked solution of the homopolymer and for gels with different concentrations of cross-linker are shown. Already with a small amount of cross-linker, the scattering intensity increases drastically, suggesting the formation of ag-

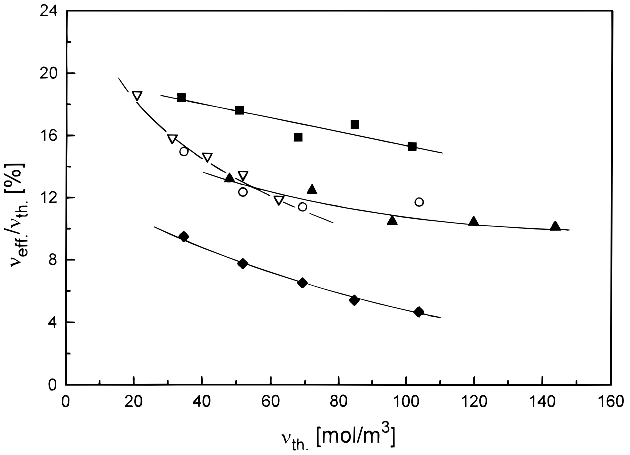

Figure 1. Efficiency ν_{eff}/ν_{th} of the cross-linking reaction vs theoretical network density ν_{th} for PAAm gels (15% polymer concentration); cross-linker: ■, *N,N′*-methylenebisacrylamide; ○, *N,N′*-ethylenebisacrylamide; ▲, *N*-allylacrylamide; ▽, *N,N*-diallylacrylamide, ◆, *N,N′*-diallyltartardiamide.

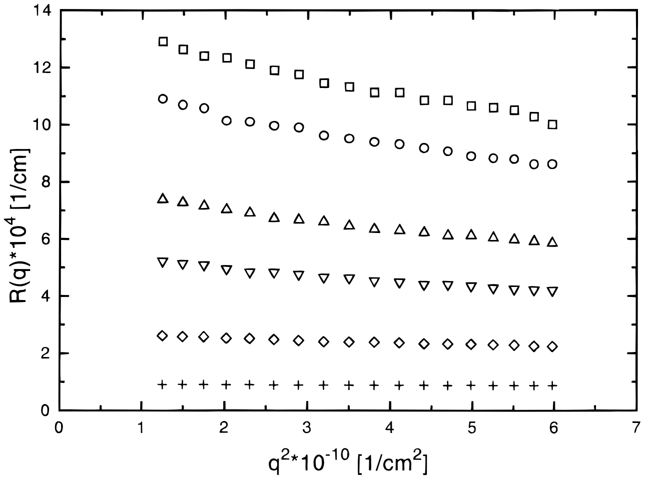

Figure 2. Rayleigh ratio $R(q)$ vs q^2 for PAAm gels (15% polymer concentration) cross-linked with *N*-allylacrylamide; □, 1.47 mol %; ○, 1.23 mol %; △, 0.98 mol %; ▽, 0.74 mol %, ◇, 0.49 mol %; +, un-cross-linked polymer.

glomerations, even at low degrees of cross-linking. At higher degrees of cross-linking, the scattering intensity reaches values which are up to 10 times higher than the intensities obtained from the solution of the un-cross-linked polymer.

In Figure 3, the data points shown in Figure 2 are replotted in the form of a Debye–Bueche analysis, where the inverse square root of the excess scattering is plotted as a function of q^2. The excess scattering is the scattering intensity of the gel minus that of the corresponding un-cross-linked solution. It can be seen that perfectly straight lines are obtained in this type of analysis, implying that the Debye–Bueche approach works well. From the slope and the intercept in this plot, the mean square fluctuation of the refractive index, $\langle\eta^2\rangle$, and the correlation length of the gels, ξ, were obtained according to eqs 2 and 3 (cf. Table 1).

To compare different gels, we will first focus on the excess scattering intensity measured at a fixed angle of 90°. This quantity gives an impression of the homogeneity of the gel without tracing it back to amplitude and correlation length of the fluctuations of the refractive index. Corresponding plots at smaller or larger scattering angles are quite similar. In Figure 4a, the excess scattering intensity $R_E(90°)$ is plotted versus the effective network density, ν_{eff}. These two quantities are directly accessible via light scattering and modulus measurements.

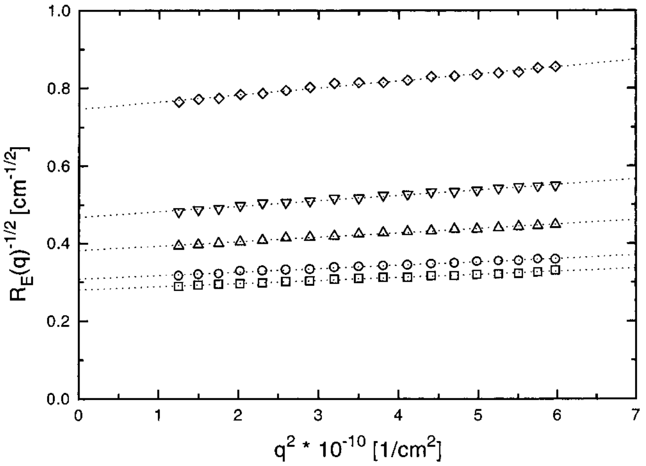

Figure 3. Debye-Bueche plots $(R_E(q))^{-0.5}$ vs q^2 for PAAm gels (15% polymer concentration) cross-linked with *N*-allylacrylamide; ◇, 0.49 mol %; ▽, 0.74 mol %; △, 0.98 mol %; ○, 1.23 mol %; □, 1.47 mol %.

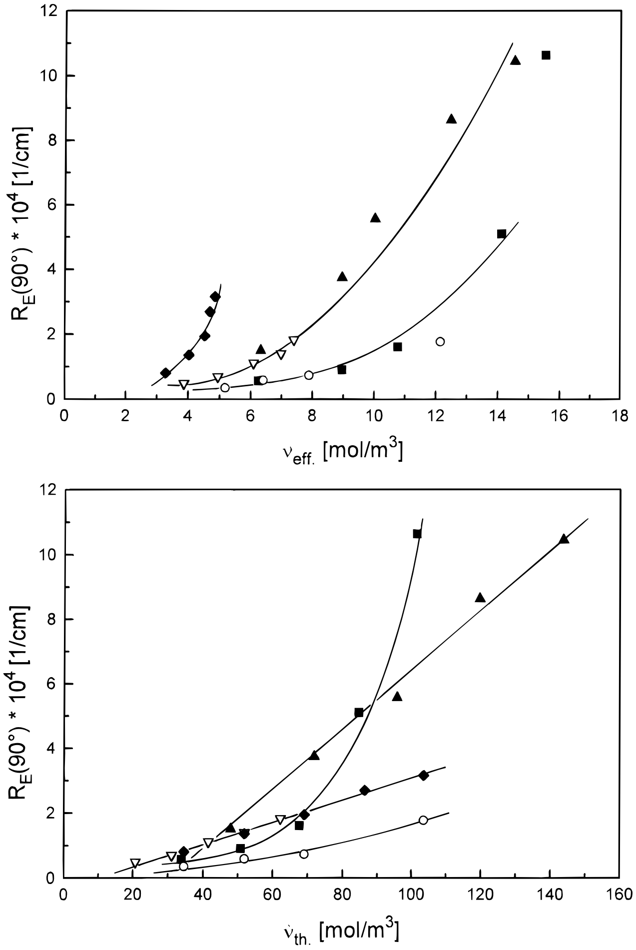

Figure 4. Excess scattering at 90° vs the effective network density, ν_{eff} (a) and vs the theoretical network density, ν_{th} (b). Cross-linker: ■, *N,N′*-methylenebisacrylamide; ○, *N,N′*-ethylenebisacrylamide; ▲, *N*-allylacrylamide; ▽, *N,N*-diallylacrylamide; ◆, *N,N′*-diallyltartardiamide.

Again, a clear distinction between gels made with different cross-linkers can be made; the experimental data fall into three different categories. The upturn of the scattering intensity with increasing effective network density starts at different levels, depending on the

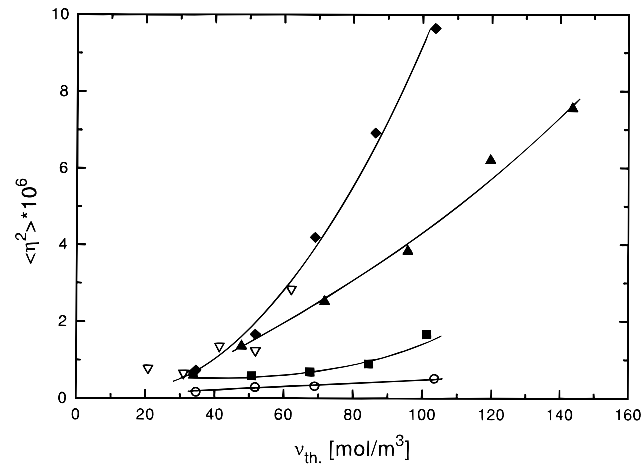

Figure 5. Mean square fluctuation of refractive index $\langle\eta^2\rangle$ vs theoretical network density ν_{th} for PAAm gels (15% polymer concentration); cross-linker: ■, *N,N′*-methylenebisacrylamide; ○, *N,N′*-ethylenebisacrylamide; ▲, *N*-allylacrylamide; ▽, *N,N*-diallylacrylamide; ♦, *N,N′*-diallyltartardiamide.

type of cross-linker. The first category includes the diallyl cross-linker and shows a steep upturn of the scattering intensity at low network densities. Allylacryl cross-linkers show an upturn at intermediate levels of cross-linking, and diacryl cross-linkers fall into the last category, where the upturn occurs at much higher cross-linking densities. This is essentially the same sequence as observed with the cross-linking efficiency.

In Figure 4b, the same excess scattering intensities are plotted, but now as a function of the theoretical network density, ν_{th}, which reflects the molar concentration of the cross-linker molecules. Increasing cross-linker concentrations always led to higher excess scattering, but the distinction between the different cross-linkers is less clear because the curves are shifted closer together.

We will now turn the discussion of the parameters obtained from the Debye–Bueche analysis of the measurements. Figure 5 shows the mean square fluctuation of the refractive index, $\langle\eta^2\rangle$, for different gels as a function of the theoretical network density ν_{th}. $\langle\eta^2\rangle$ always increases with increasing cross-linker concentration, independent of the type of cross-linker. However, the extent of this increase again depends markedly on the cross-linker chosen. $\langle\eta^2\rangle$ reaches much higher values in the case of systems which contain little reactive allyl-type crosslinkers than in gels cross-linked with highly reactive acryl-type cross-linkers.

Apparently, the lower reactivity of the allyl-type cross-linkers leads to a higher degree of inhomogeneity. When the reactivity of a cross-linker is low, a bigger fraction of the cross-linker will react only at higher conversion of the polymerization reaction. It has to be concluded that this portion is particularly prone to forming cross-link agglomerations or network inhomogeneities, simply because of an enhanced statistical probability that cross-linkers react with each other. When one plots $\langle\eta^2\rangle$ versus the effective network density (not shown), the differentiation between different categories of cross-linkers is even more pronounced. Hence $\langle\eta^2\rangle$ is still more sensitive then $R_E(q)$ to capture the difference in network topology.

The correlation length, on the other hand, seems not to be related to the cross-linker concentration in a definite matter (Figure 6). With some cross-linkers, the correlation length rises with increasing concentration, whereas with others there is a slight decrease or no significant change at all. Generally, there seems to be a relation between this slope and the cross-linker efficiency. Bisacrylic crosslinkers exhibit a positive slope, whereas allylacryl and bisallyl cross-linkers show no or negative slopes, respectively. The largest correlation lengths are observed with the highly reactive cross-linkers methylene- or ethylenebisacrylamide.

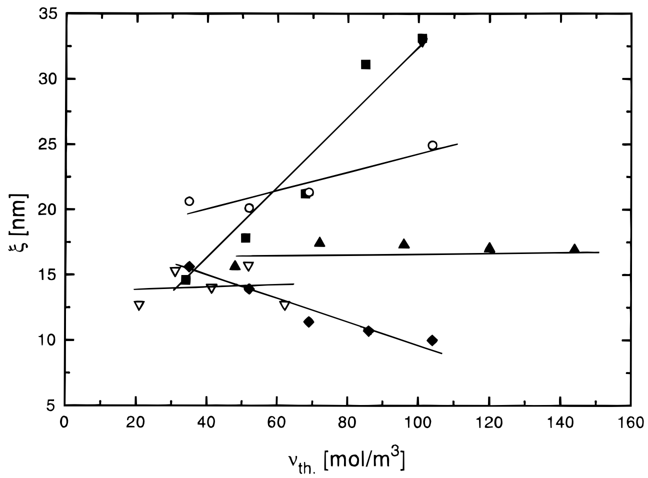

Figure 6. Correlation length ξ vs theoretical network density ν_{th} for PAAm gels (15% polymer concentration); cross-linker: ■, *N,N′*-methylenebisacrylamide; ○, *N,N′*-ethylenebisacrylamide; ▲, *N*-allylacrylamide; ▽, *N,N*-diallylacrylamide; ♦, *N,N′*-diallyltartardiamide.

Combining the observations from Figures 5 and 6, it has been established that gels made with diallyl-type cross-linkers or allylacryl cross-linkers show an increase of the mean square fluctuation of the refractive index with rising network density, while the correlation length remains more or less unaffected. With the significantly more reactive bisacrylic crosslinkers, the mean square fluctuations are appreciably smaller, and the correlation length increases considerably with rising network density.

Conclusion

It has been demonstrated that by means of static light scattering, inhomogeneities of gels prepared with different cross-linkers can be characterized. There is a clear correlation between the reactivity of the cross-linkers, the efficiency of the cross-linking reaction, and the size and density of agglomerations within the gels. Apparently, the cross-linking efficiency with cross-linkers exhibiting a low reactivity is small because the cross-linker is mainly used to build up the highly cross-linked agglomerations instead of yielding a more homogeneous network.

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