

Networking Properties of Cyclodextrin-Based Cross-Linked Polymers Probed by Inelastic Light-Scattering Experiments

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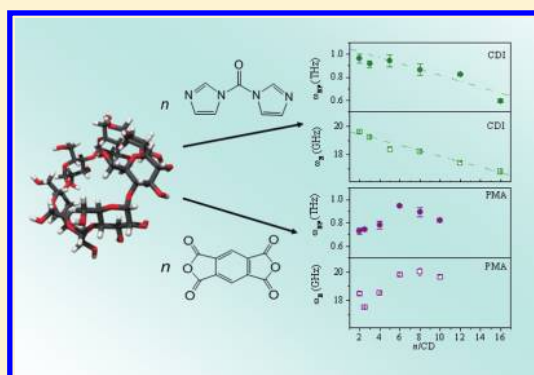
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ABSTRACT: An integrated experimental approach, based on inelastic light-scattering techniques, has been here employed for a multilength scale characterization of networking properties of cyclodextrin nanosponges, a new class of cross-linked polymeric materials built up from natural oligosaccharides cyclodextrins. By using Raman and Brillouin scattering experiments, we performed a detailed inspection of the vibrational dynamics of these polymers over a wide frequency window ranging from gigahertz to terahertz, with the aim of providing physical descriptors correlated to the cross-linking degree and elastic properties of the material. The results seem to suggest that the stiffness of cross-linked polymers can be successfully tuned by acting on the type and the relative amount of the cross-linker during the synthesis of a polymer matrix, predicting and controlling their swelling and entrapment properties. The proposed experimental approach is a useful tool for investigating the structural and physicochemical properties of polymeric network systems.



INTRODUCTION

The continuous search for new materials tailored for specific applications with an expected high technological impact, ranging from drug delivery¹ to tissue engineering and regenerative medicine,^{2,3} demands for an increasingly deeper and broader knowledge of the structural and physicochemical properties of these nanostructured materials up to the mesoscopic scale.

In this scenario, great effort has been recently devoted to the design and characterization of polymeric networks of cross-linked synthetic and/or natural macromolecules and their supramolecular assemblies to be used, for instance, as bioscaffolds for in situ drug release and cell growth or simply as host systems for molecular and cell encapsulation.⁴

Self-assembled polymeric networks synthesized from cyclodextrins (CDs), cyclic oligomers of amilose, appear to be intriguing materials because of their unique physicochemical properties, mainly related to the ability of CD molecules to form inclusion complexes.⁴ More recently, structures involving CD have attracted interest not only as model systems for cross-linked polymeric materials with specific functional properties intimately connected to the cross-linking density but also as

precursors of novel nanomaterials for biomedical and pharmaceutical applications.

Cyclodextrin nanosponges (CDNSs) are a new class of amorphous cross-linked polymers obtained by reacting CD with a suitable polyfunctional agent such as carbonyldiimidazole (CDI) or pyromellitic anhydride (PMA). The reaction products turned out to be highly cross-linked, nanoporous polymers showing interesting inclusion/release properties.^{5–9} Indeed, the presence of the lipophilic cavities of CD units and hydrophilic channels within the porous structure provides the CDNS with the capability of encapsulating a large variety of compounds. Moreover, the type and the amount of cross-linking agent may dramatically modulate important parameters such as the swelling capability and hydrophilicity/hydrophobicity of the final material. These properties make CDNSs highly attractive for several applications in biocatalysis,¹⁰ agriculture and environmental protection,^{11,12} and drug delivery.^{13–15}

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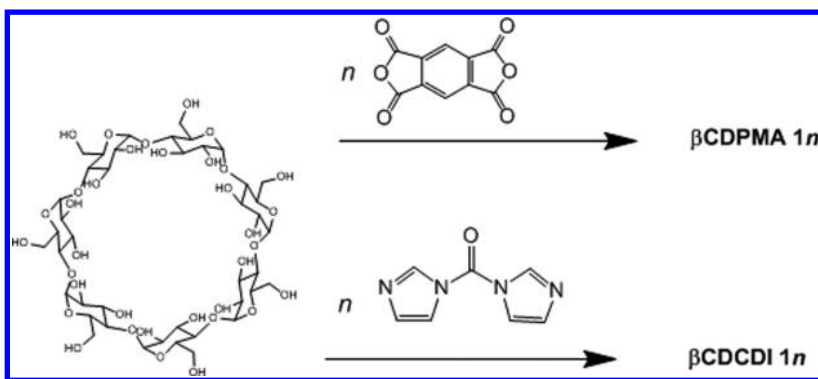


Figure 1. Scheme of synthesis of β CDNS by using PMA and CDI as cross-linking agents; the number n refers to the molar ratio between the reagents.

Nevertheless, carrying out a systematic structural and dynamical characterization of CDNS suffers from intrinsic difficulties due to some major factors: (i) the random nature of the growing process of the polymer, (ii) the presence of a large number of reaction sites on each CD unit (14 secondary and 7 primary OH groups per CD residue in the case of β CD), (iii) the extended cross-linking of monomers making the resulting polymer insoluble, and (iv) the nature of the polymerization process yielding a large variety of amorphous systems.

Recently, we presented preliminary structural data obtained on CDNS based on PMA¹⁶ and CDI¹⁷ at different cross-linking agent/ β -CD molar ratios; in fact, the latter parameter is expected to affect the degree of cross-linking of the polymer and, in turn, the observed swelling ability of the material which, in the presence of aqueous solutions, gives rise to gel-like behavior. Moreover, high-resolution magic angle spinning (HR-MAS) NMR spectroscopy of swollen CDNS gave information on the state of confined water, diffusivity of water, and about a probe molecule entrapped inside the swollen polymeric gel.¹⁶

In this paper, the results of an extended investigation of the vibrational dynamics of dry CDNS are reported and discussed. The results are based on the original combined use of Raman and Brillouin light-scattering experiments. This approach allows for the inspection of the vibrational dynamics of the system over two different frequency ranges (gigahertz for Brillouin and terahertz for Raman scattering); in this way, the stiffness properties of these materials can be explored over length scales ranging from a few nanometers up to hundreds of nanometers, thus providing new physical descriptors correlated to cross-linking, stiffness, and swelling attitude of amorphous polymeric networks.

In particular, the low-frequency Raman spectra of dry CDNS were examined, mainly focusing on the frequency position of a prominent feature typically observed in low-frequency inelastic neutron and Raman scattering spectra of amorphous materials, known as “boson peak” (BP). The BP is associated to an excess in the vibrational density of states over the Debye level, observed at terahertz frequencies in a large variety of amorphous solids of different nature and composition. It should be considered a general property of the disordered state^{18–32} and appears to be connected to significant physical parameters, including the elastic properties of the system in the mesoscopic range.^{33–35} On the other hand, the frequency analysis of acoustic phonons propagating into the system in the gigahertz frequency range can be useful to characterize the macroscopic elastic properties of CDNS on a length scale of hundreds of nanometers.³⁶ The frequency evolution of the BP

and the Brillouin peak is investigated as a function of some specific parameters, like (i) the type of cross-linking agent, (ii) type of CD (e.g., α -, β -, and γ -CD), and (iii) the molar ratio between the cross-linking agent and CD used during the synthesis of the final polymer.

■ EXPERIMENTAL SECTION

Synthesis of β CDNS. The nanosponges were obtained following the synthetic procedure previously reported with minor modification^{6,7} (see scheme of Figure 1).

To obtain β CDPMA $1n$ nanosponges, β CD and the cross-linking agent pyromellitic dianhydride (PMA) at 1: n molar ratios (with $n = 2, 2.5, 4, 8, 10$) were dissolved in dimethyl sulfoxide (DMSO) containing triethylamine and allowed to react at room temperature for 3 h. Once the reaction was over, the solid obtained was ground in a mortar and extracted with acetone for 8 h by a Soxhlet apparatus.

The reactions of polymerization between β CD and cross-linking agent carbonyldiimidazole CDI to obtain β CDCDI $1n$ (with $n = 2, 3, 5, 8, 12, 16$) were conducted by dissolving β -CD in anhydrous dimethylformamide (DMF). Once the required molar amount of CDI was added, the mixture was allowed to react for 4 h at 100 °C. Once the reaction was over, a great excess of water was added and the solid recovered by filtration under vacuum, washed with ethanol, and then extracted continuously with ethanol for 10 h.

Light-Scattering Measurements. Raman spectra of dry CDNS were recorded over the wavenumber range between 1.5 and 400 cm^{-1} ($1 \text{ cm}^{-1} = 30 \text{ GHz}$) at room temperature by using a triple-monochromator spectrometer (Horiba-Jobin Yvon, model T64000) set in double-subtractive/single configuration and equipped with 1800 grooves/mm. The spectra were registered in backscattering geometry, in crossed polarization. Micro-Raman spectra were excited by the 647.1 nm wavelength of an argon/krypton ion laser and detected by a CCD detector cryogenically cooled by liquid nitrogen. Exciting radiation was focused onto the sample surface with a spot size of about $1 \mu\text{m}^2$ through a 100 \times objective with NA = 0.9. To avoid unwanted laser-induced transformations, neutral filters of different optical densities were used, whenever necessary. The scattered radiation, filtered by the fore double-monochromator, was detected at the spectrograph output. The resolution was about $0.36 \text{ cm}^{-1}/\text{pixel}$.

For Brillouin light-scattering measurements, the excitation radiation at 514.5 nm, vertically polarized with respect to the scattering plane, was provided by a single mode Ar⁺ laser (Coherent-Innova) with a typical power of 100 mW. The light

scattered by the sample in a back-scattering configuration was analyzed by means of a Sandercock-type 3 + 3-pass tandem Fabry–Pérot interferometer, characterized by a finesse of about 100 and a contrast ratio higher than 10^9 .

RESULTS AND DISCUSSION

Cross-polarized Raman intensity I values recorded from β CDPMA1*n* nanosponges, in a dry state, at several values of n/β CD molar ratios are shown in Figure 2 (a) and (b), over the

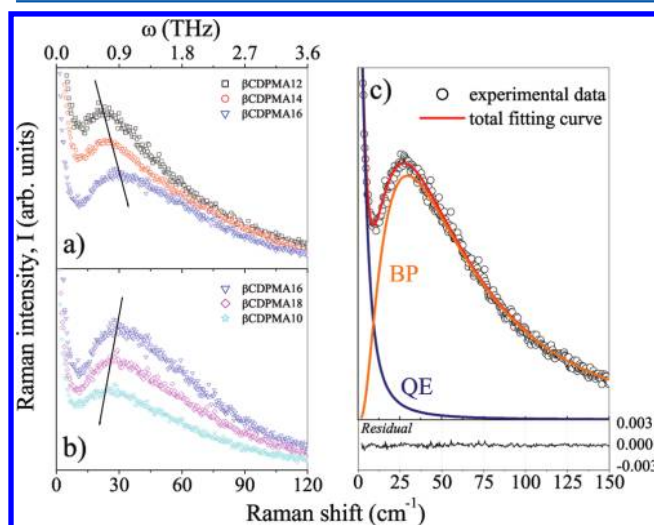


Figure 2. (a),(b) Cross-polarized Raman spectra of β CDPMA1*n* nanosponges obtained by using different PMA/ β CD molar ratios; the spectra are vertically shifted to better highlight the evolution of the boson peak frequency. (c) Typical example of the fitting procedure results: the experimental data (empty circles) are shown together with the total fitting curve and the different components (QE, quasi-elastic; BP, boson peak).

wavenumber range 1–120 cm^{-1} . All the spectra show in this region two main features: a quasi-elastic (QE) relaxational part and an inelastic vibrational component, in the form of a broad bump, centered at about 20–30 cm^{-1} and extending up to about 100 cm^{-1} , which is referred to as the boson peak (BP). As already mentioned, this feature is a general property of amorphous systems and appears to be connected to significant physical parameters, including the elastic properties of the system in the mesoscopic range.

The raw spectral profiles in Figure 2 show a clear evolution of the frequency of maximum BP, ω_{BP} , as a function of the PMA/ β CD molar ratio used for polymerization; the latter parameter is, in turn, expected to modulate the cross-linking degree of the final product. This finding supports the use of the BP frequency as an experimental descriptor of the elastic medium properties strictly related to the vibrational dynamics of cross-linked polymeric systems. This is in agreement with previous works that suggested a clear relationship between the changes in the frequency position of the BP and the transformation of the elastic properties of material.^{34,35} In particular, the frequency shift and intensity decrease of the BP in a reactive epoxy–amine mixture during isothermal polymerization were correlated to the increasing number of covalent bonds among the constituent molecules, showing the existence of a scaling law for the BP related to the elastic medium transformation.³⁴

The spectra reported in Figure 2 show that the BP maximum moves to higher wavenumbers with increasing the PMA/ β CD molar ratio up to a value of about 6 (Figure 2 (a)). Further increase of the cross-linker amount leads to a shift of ω_{BP} to lower frequencies (Figure 2 (b)).

A more quantitative analysis of the modifications occurring on BP can be achieved by inspecting the vibrational component of the total experimental spectra only. In fact, the total Raman scattering intensity can be reasonably approximated by the sum of two contributions: the quasi-elastic scattering related to relaxational dynamics and the BP related to the pure vibrational dynamics. To evaluate the QE contribution, a well-assessed fitting procedure can be employed.^{33,35} The total experimental profiles $I(\omega)$ can be fitted by the sum of two contributions (eq 1): (i) a Lorentzian function, centered at zero wavenumber, with width ω_0 and amplitude A to reproduce the QE contribution, and (ii) a log-normal distribution function that well describes the shape and the position of the BP^{32,33,35} with width W , amplitude B , and peak frequency ω_{BP} .

$$I(\omega) = \frac{A\omega_0}{\omega_0^2 + \omega^2} + B \exp \left\{ -\frac{\left[\ln \left(\frac{\omega}{\omega_{\text{BP}}} \right) \right]^2}{2W^2} \right\} \quad (1)$$

Figure 2(c) shows a typical best-fit result obtained for the β CDPMA14 nanosponge with the two distinct components of QE and BP plotted separately. It should be pointed out that the analysis here proposed allows us to better quantify the modifications occurring to the vibrational profiles of different polymers, although the overall trend of the BP component, obtained after subtraction of the QE contribution, is the same as observed in the raw profiles of Figures 2 (a) and (b), thus confirming that the described subtraction procedure of the QE contribution does not affect the final results.

The spectra in Figure 2(a) and (b) point out significant variations of the BP features in the samples synthesized, thus suggesting a relationship between the low-wavenumber vibrational dynamics and the chemical characteristics of the polymeric network, related in turn to the molar ratio n/CD (defined as the ratio between the amount n of cross-linker and CD in the synthesis of the polymer, see scheme in Figure 1). In particular, the best-fit values of the wavenumber positions of the boson peak ω_{BP} , estimated by using the data handling procedure described above, suggest a clear dependence of the ω_{BP} from the PMA/ β CD molar ratio of the examined samples.

For PMA/ β CD < 6, ω_{BP} shifts to higher wavenumbers with increasing amount of cross-linker, and it reaches a broad maximum at molar ratios around 6 ($\omega_{\text{BP}} = 31 \text{ cm}^{-1}$) and then decreases for PMA/ β CD > 6. A possible rationale for such trend of the BP frequency can be based on the sensitivity of the BP to the degree of cross-linking. Indeed, the reticulation in cyclodextrin nanosponges is expected to grow to a saturation level beyond which steric effects tend to prevent further cross-linking of the polymer. In the case of β CDPMA nanosponges, the saturation effect requires about a 6-fold excess of cross-linker (PMA) with respect to the monomer (β -CD). For high molar ratios, i.e., $n > 6$, the excess of PMA is likely to provide branching of cyclodextrin units rather than further increasing of the cross-linking of the whole system. The conformational degrees of freedom of the branches, in turn, cause the decrease of the whole system stiffness, with a decrease of the BP frequency.

To explore the elastic properties of the system, and to proceed to a comparative analysis among the different polymeric compounds, Brillouin light-scattering experiments were carried out. Indeed, the frequency position of the Brillouin peaks, ω_B , is related to the longitudinal elastic modulus of the material, a parameter usually adopted to characterize the stiffness of the whole structure of materials.³⁶ In our case, an increase of the polymer cross-linking is expected to reduce the conformational flexibility of the whole structure, in turn affecting the Brillouin sound velocity.

Typical Brillouin spectra (longitudinal part connected to bulk modulus) of β CDPMA12 and β CDPMA16 in the dry state are shown in Figure 3 where the frequency position of the Brillouin

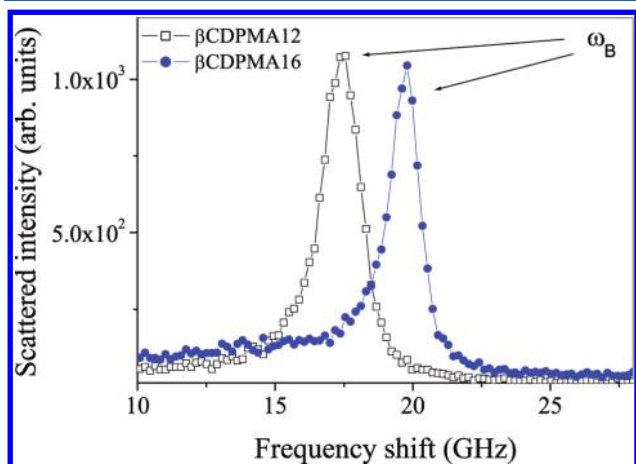


Figure 3. Brillouin light-scattering spectra for β CDPMA12 (empty squares) and β CDPMA16 (full circles). The arrows indicate the frequency of the Brillouin peak ω_B .

peak ω_B is indicated by arrows. The raw Brillouin spectra show a shift of about 2 GHz of ω_B with increasing the PMA/ β CD molar ratio, giving a further indication of the strong influence of the cross-linker amount on the rigidity of the final polymers.

The frequency positions obtained for the BP (panel at the top) and the Brillouin peak (panel at the bottom) as a function of the molar ratio between PMA and β CD are compared in Figure 4 for all the examined samples of β CDPMA nanosponges; the maximum values measured for both ω_B and ω_{BP} correspond, within the experimental error, to the samples obtained with a molar ratio 1:6 of β -CD and PMA, confirming that the greatest stiffness of the polymer is reached when the amount of PMA is about 6 times higher than that of β -CD.

More interestingly, it should be noted that the overall trend observed for the ω_B data is in qualitative agreement with that estimated for ω_{BP} ; this suggests that the increasing (decreasing) degree of cross-linking among the CD units in the polymeric matrix, as evidenced by the BP evolution, involves the whole system even on a larger range of lengths, leading to a general hardness (softness) of the material. This finding can be conveniently exploited for controlling the properties of swelling and entrapment of guest molecules in the polymeric network of nanosponges by preliminarily tuning the grade of networking of the final product.

This conclusion is doubly supported by comparing the frequency shifts of ω_B and ω_{BP} as observed in nanosponges obtained by polymerization of β CD with carbonyldiimidazole and shown in Figure 4. It is known that CDI is an efficient carbonylating agent, allowing us to obtain highly cross-linked

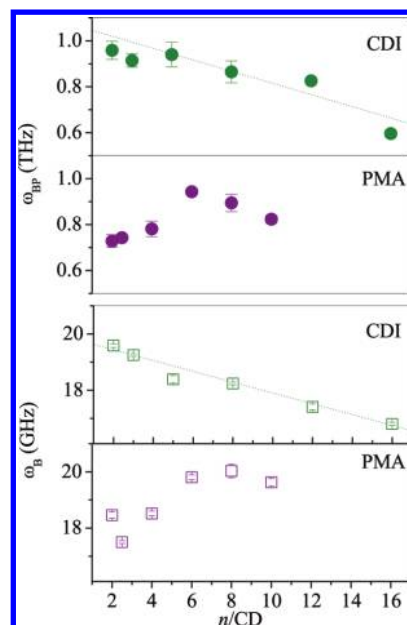


Figure 4. Frequency position estimated for ω_{BP} (panel at the top) and ω_B (panel at the bottom) as a function of the molar ratio n/CD for β CDPMA (violet full circles and violet empty squares) and β CDPMA nanosponges (green full circles and green empty squares).

nanosponges.³⁷ Both Raman and Brillouin spectra of β CDPMA nanosponges show a systematic decrease of the frequency position of both the BP and the Brillouin peak with increasing the amount of cross-linker with respect to β CD within the explored CDI/ β CD molar ratios. Thus, the saturation effect mentioned above is reached for a low cross-linker/cyclodextrin ratio (CDI/CD = 2) in this class of nanosponges, differently from what was found for PMA-based nanosponges (PMA/CD = 6). In addition, the comparison between the BP frequency positions for the two different types of nanosponges before the PMA saturation point shows that a high cross-linking degree is obtained even in the presence of a small molar excess of a CDI with respect to monomeric β -CD. This finding is consistent with the fact that the corresponding nanosponges are more rigid and not swellable compared to the nanosponges obtained with PMA.

The different behavior of β CDPMA nanosponges compared to β CDPMA analogues can be explained by the different chemical nature of the cross-linker: the carbonate functional group generated by CDI is conformationally more rigid than the ester group formed by condensation of PMA with the OH groups of cyclodextrins which probably leads to a structure less strongly interconnected.

Finally, the BP frequency for PMA nanosponges close to the saturation point seems to be slightly dependent on the macrocycle size of the cyclodextrin, as indicated by the low-frequency vibrational spectra of three samples of nanosponges synthesized by using the same cross-linker (PMA), different cyclodextrins (α -, β -, and γ -CD), and constant molar ratio PMA/CD = 4.

Figure 5(a) shows the cross-polarized Raman intensity for α -, β -, and γ -CDPMA14 after subtraction of the QE contribution, for better inspection of the evolution of the vibrational features of the experimental data.

The estimated BP and Brillouin frequencies as a function of the size of the CD's macrocycle are reported in Figure 5(b) and

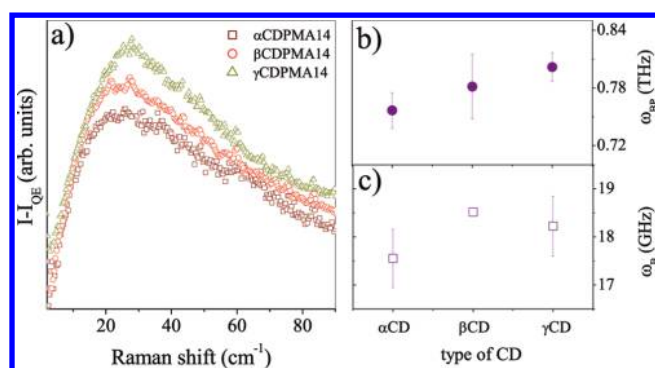


Figure 5. (a) Raman intensity (after subtraction of I_{QE} contribution) for CDPMA nanospheres obtained by polymerization of α - (squares), β - (circles), and γ - (triangles) cyclodextrin with PMA in a molar ratio of 1:4, respectively. (b),(c): Frequency position estimated for ω_{BP} (full circles) and ω_B (empty squares) as a function of the type of CD used for the polymerization.

(c), respectively. The values show that the position of ω_{BP} and ω_B for α -, β -, and γ -CDPMA14 does not change significantly, giving an indication that, within the experimental error, the stiffness of the polymeric network of the three nanospheres is the same. This finding seems to suggest, as expected, that the type and amount of cross-linker most significantly affect the cross-linking density of the final polymer, rather than the type of CD used.

CONCLUSIONS

The combined use of two inelastic light-scattering techniques allowed both nano- and macroscale characterization of the networking properties of a new class of cross-linked polymeric systems synthesized from natural oligosaccharide cyclodextrins. These polymers can be assumed as a model for cross-linked systems for which the use of X-ray diffraction as the structural investigation method is seriously hampered by the low or absent level of crystallinity. The thorough analysis of the spectral modifications of the so-called boson peak and the changes of the Brillouin frequency provide indications that the cross-linking degree and the elastic properties of the cyclodextrin nanospheres can be successfully modulated by acting on the type and the relative amount of the cross-linker during the synthesis of the polymer matrix, while the size of the macrocycle does not seem to affect significantly the stiffness of the material. These findings appear to be of fundamental importance for the purpose of predicting and controlling the swelling and entrapment properties of these cross-linked systems.

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Notes

The authors declare no competing financial interest.

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