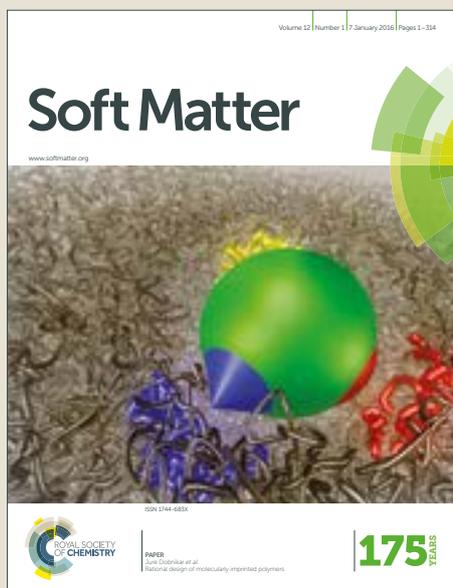


# Soft Matter

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# Reply to the Comment on Relating side chain organization of PNIPAm with its conformation in aqueous methanol by A. Pica and G. Graziano, *Soft Matter*, 2017, 13, DOI: 10.1039/C7SM01065F

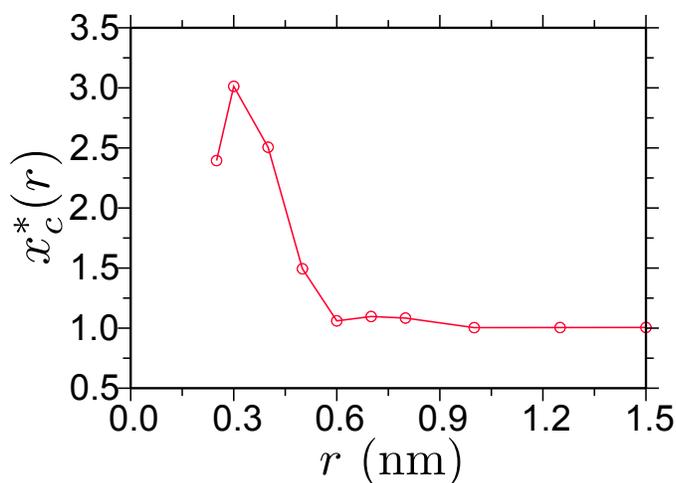
Debashish Mukherji<sup>1</sup>, Manfred Wagner<sup>1</sup>, Mark D. Watson<sup>1,2</sup>, Svenja Winzen<sup>1</sup>, Tiago E. de Oliveira<sup>3</sup>, Carlos M. Marques<sup>4</sup>, and Kurt Kremer<sup>1</sup>

We have recently proposed preferential binding by cosolvent as the mechanism for chain collapse under co-nonsolvency. Here we summarise our earlier works and provide further evidence that alcohol preferentially binds to PNIPAm, forming cosolvent bridges, and thus drives the transition. We also clarify some of the common misconceptions evoked in this debate with Pica and Graziano (PG), reinforcing the arguments of our earlier reply-comment [*Soft Matter*, 2017, 13, 2292] and published works.

Before addressing the comments of PG, we would first like to highlight one statement from the earlier work of PG in Ref.<sup>1</sup> that their comment is based on and thus we believe to be relevant in this context. In this work PG write “Kremer and colleagues [6-8] did not perform MD simulations on a realistic PNIPAM chain immersed in a solution of model H<sub>2</sub>O molecules and model MeOH molecules. They did MD simulations on a bead-spring polymer model immersed in a mixture of two different Lennard-Jones, LJ, spherical particles possessing .....”. Note that in this 2016 article PG claimed to have analyzed, just as in their comment, our earlier articles published between 2013-2015. Now we want to call attention to Fig. 4(a) of Ref. [2] (ref [6] in PG’s paper<sup>1</sup>) where data for all-atom PNIPAM chains with 20 and 40 lengths are shown. Also, Fig. 1(a) of Ref. [3] (ref [7] in PG’s paper<sup>1</sup>), the data with legend “Sim. PNIPAm” corresponds to 40 monomer long all-atom chain.

The first question that PG raised is whether in our simulation methanol preferentially binds to the PNIPAm chain, thus leading to the possibility of cosolvent bridges. In Fig. 1 we show that even at a methanol mole fraction of only 10% we observe a significant aggregation of methanol onto the PNIPAm surface, there is an excess of about three times within the first solvation shell, i.e., within  $0.15 \text{ nm} < r < 0.45 \text{ nm}$ , in agreement with our NMR results<sup>5</sup>.

PG also claim that we did not provide other data than the



**Fig. 1** Normalized methanol mole fraction  $x_c^*(r) = x_c(r)/x_c$  as a function of radial distance from the polymer backbone. Here  $x_c$  is the reference mole fraction of methanol in bulk solution. The results are shown for a chain length  $N_l = 256$ , at temperature  $T = 298 \text{ K}$ , and for  $x_c = 0.1$ . Data is taken from<sup>4</sup>.

gyration radius  $R_g$ , refereeing to table 1 and Figs. 1 and 2 of Ref.<sup>5</sup>. PG clearly overlooked the chain structure factor presented in Fig.4<sup>5</sup>. This key probe of chain structure shows that while the chain remains collapsed globally, it is in a better-than-theta solvent at short length scales. This is expected for a polymer in a good solvent forced to collapse by a finite fraction of bridging interactions.

In paragraph 3, PG state that a single methanol binding is only about  $0.5 k_B T$ , with  $k_B T$  being the thermal energy, and therefore can not form sticky contacts. We would first like to recall that this comment is *identical to* one of the points in Ref. [6] of the comment of PG, which was already addressed in Ref.<sup>6</sup> (see page 2, left column, paragraph 5 and lines 4 to 10). We would also like to clarify that, contrary to statements of PG in their comment and also in their earlier work<sup>1</sup>, we did never state that a single molecule bridges two monomers. In fact it is a collection of alcohols that helps forming cosolvent bridges providing sufficient binding (free) energy as frequently stated. For example, page 3, right column, discussion

<sup>1</sup>Max-Planck Institut für Polymerforschung, Ackermannweg 10, 55128 Mainz Germany

<sup>2</sup>University of Kentucky, Lexington, KY 40506-0055, USA

<sup>3</sup>Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

<sup>4</sup>Institut Charles Sadron, Université de Strasbourg, CNRS, Strasbourg, France

section, lines 4 to 6 of Ref. [3] that states “*c molecules can bind to two distinctly far monomers inducing bridges that initiate the collapsing process*”, here *c* stands for cosolvents or the minor components. Such statements are also mentioned several places in Ref. [3], including in the supplementary material, page 6, supplementary note 2. Additionally, in page 6, right column, second paragraph and last sentence of Ref. [5], we clearly state “*Therefore, it should still be mentioned that the enthalpic interactions (or bridging) are usually not given by a single methanol molecule, rather a few collectively lead to sticky contacts.*”

We are also surprised by the text written in the reference 17 of the PG comment. Here PG makes connections to the cases discussed in references 18 and 19 of their comment stating that for high chemical potentials (or densities) phase separation occurs in the solution with pure repulsive components. In this regard, we would first like to call attention to page 5, Method and models section, equations 7, 8, and 9 with the appropriate combination rules<sup>3</sup>. In our generic case, parameters are chosen such that the polymer mimics good solvent conditions in both (co)solvents. We further tune the attractive interaction between monomer-cosolvent in our generic model to represent correct relative interaction strengths between two (co)solvents known from all atom simulations<sup>2</sup>. Note that this can be achieved by a number of different combinations (see also for example Fig. 3 in Ref.<sup>7</sup>). It should also be noted here that references 18 and 19 of the comment deal with poor solvent conditions of a polymer chain, a very different regime of the parameter space.

We also would like to rebuke PG’s statement that we have only shown data for a single monomer in our earlier works<sup>2,3,7</sup> and for a single alcohol, by pointing for instance to Fig. 5 in Ref.<sup>2</sup>, where data for two chain lengths are compared. There it is shown that the correction factor between the solvation of a single monomer and a polymer is due to the difference in the solvation volume, which is spherical for a monomer and gets modified when monomers are connected into a chain. As usual in polymer science, we *normalize* these polymer data by the chain length.

PG further attempt to strengthen their explanation based on configurational entropy by pointing at Fig. 3 of Ref. [9] in their comment. They, however, seem not to have noticed that the abstract of the same paper states that “*Our results show that at low alcohol content of the solution methanol preferentially binds to the PNIPAM globule and drives polymer collapse*”.

In paragraph 5, PG comment on our NMR data<sup>5</sup>, stating that it does not provide evidence of bridging methanol. We would like to first call attention to page 2, right column, 2nd paragraph of Ref.<sup>6</sup>, where this point was already addressed. PG further comment on Fig. 7 of Ref.<sup>5</sup>. In this regard, note that the preferential binding of the methanol with PNI-

PAM is calculated by monitoring the methanol mole fraction in the lower panel of the NMR tube consisting of only aqueous methanol solution. Therefore, considering the actual volume of the tube, 3% depletion in methanol mole fraction corresponds to a rather strong preference for PNIPAm. Otherwise the bulk solution would not have shown any observable methanol depletion within our resolution.

In view of the last two paragraphs of the comment it is important to reiterate that we are not discussing the LCST in water, but the reduction of the LCST upon the addition of methanol. Moreover, we would still like to comment on a few points:

(a) PG claim that water has preferential binding with amide group and methanol interact strongly with the isopropyl group. There, however, is also a preferential hydrogen bonding of methanol with NIPAM monomer as shown in Fig. 10(a) in Ref.<sup>5</sup> (see also Fig. 5 in Ref.<sup>8</sup>). We are, however, happy to learn that PG acknowledge that there is competitive coordination between water-NIPAM and methanol-NIPAM interaction as earlier proposed by us (see for example page 4, right column, after Eq. 4, and between lines 7-9 in Ref.<sup>3</sup> and was further tested in Fig. 3 in Ref.<sup>7</sup>).

(b) PG state that “*If MeOH molecules were sticky for PNIPAM chains, an increase in  $\Delta H$  (collapse) would be expected because several MeOH-PNIPAM attractions would be lost upon collapse (i.e., the number of MeOH-PNIPAM interactions should be markedly larger with coil conformations which possess a larger solvent-accessible surface area)*”. As shown in Fig. 1, preferential binding of methanol with PNIPAM implies that when a small amount of methanol is added, it binds two monomers (far) along the PNIPAM backbone and thus reduce energy, while the complete decoration of PNIPAM with methanol leads to the observed reopening at higher methanol concentrations<sup>3</sup>.

(c) In support of their explanation for PNIPAm collapse PG write in the abstract that “*cononsolvency is caused by the geometric-energetic frustration experienced by the polymer when it can interact with both water and methanol molecules at the same time*”. The argument seems to be that the contact of MeOH with the propyl group precludes contact of water with the peptidic part and that the chain undergoes the coil-to-globule transition to release this geometric-energetic frustration. Therefore, when two monomers get close (in a globule state), this expels out the MeOH and allows the water back in. This scenario does not, however, make sense from a thermodynamic point of view. Indeed, if a methanol spontaneously blocks water, it must lower the free energy. Consequently, expulsion of methanol would *increase* the free-energy. PG further iterate that such an explanation would be required to understand the case of PDEAM that does not show co-nonsolvency in aqueous methanol. However, PG seem to have not noticed that PDEAM shows co-nonsolvency in aqueous

ethanol<sup>9</sup>. Since systems with similar chemical species should show similar microscopic behavior. Therefore, if the arguments of PG were correct, PDEAM should not display co-nonsolvency in aqueous ethanol, as it does!

In summary, we have shown that the suggestion by PG to reinterpret our results as a support to their own explanation of co-nonsolvency does not hold. We remind that in order to unveil the possible microscopic origin of this phenomenon, we have used all-atom simulations<sup>2,5</sup>, generic simulations<sup>3,7</sup> and experiments<sup>5</sup>. The body of evidence coming out of this effort shows that polymer collapse is induced by a bridging mechanism due to the competitive preferential adsorption of the cosolvent on the polymer chain. Moreover, our simple explanation rationalizes a generic behaviour found in many mixed solvent polymer solutions (see Table 1 in Ref.<sup>7</sup>).

As we conclude this reply to the second comment on our paper, we cannot but notice that the experimental, numerical and theoretical contributions of our work have nucleated ardent discussions on the relevance of previous different attempts to explain co-nonsolvency. We hope that by consolidating here the efforts engaged in our reply (Ref. [6]) to the first comment, we have further anchored the discussion on the floor of scientific arguments.

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