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Reply to the Comment on “Relating side chain organization of PNIPAm with its conformation in aqueous methanol” by N. van der Vegt and F. Rodriguez-Ropero, *Soft Matter*, 2017, 13, DOI: 10.1039/C6SM02139E

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In a comment van der Vegt and Rodriguez-Ropero (vdVRR) challenge our explanation of the co-non-solvency effect of PNIPAm in aqueous methanol solutions. They argue, based on a careful selection of published works including some of their own, that direct repulsions between the different constituents are sufficient to understand this phenomenon. According to vdVRR, the emerging view of entropic collapse, put forward by Flory (1910-1985) to explain common polymers in poor solvents, would be enough to explain co-non-solvency. In this reply we attempt to bring this discussion into firmer grounds. We provide a more comprehensive view of available experimental, numerical and theoretical results and review basic concepts of physical chemistry and of statistical mechanics of polymer collapse that show how methanol mediated attractions between chain monomers are required to understand this fascinating behavior.

Poly(N-isopropylacrylamide) (PNIPAm) displays several remarkable properties triggering significant research interests^{1–9}. PNIPAm in water has a lower critical solution temperature (LCST) of about 305 K^{1,2,10}. At the LCST a polymer chain collapses upon increase of temperature, where expelled water molecules, because of the broken hydrogen bonds, gain translational entropy that is larger than the loss of conformational entropy of the chain upon collapse. This presents a situation where energy becomes less relevant compared to entropy^{11–13}. Therefore, it (usually) makes sense to speak of entropy driven transitions. However, when small amounts of alcohol are added the collapse temperature decreases. Eventually upon adding further alcohol the chains expand again. The microscopic origin of this striking behavior has been a matter of controversial discussion for some time already^{4,6–9,14–16}. Therefore, the central question is what causes this reduction and *not* whether the original LCST transition is entropy driven. Furthermore, the very fact that the LCST decreases

upon increasing alcohol concentrations, suggests a shift to enthalpic contributions.

First vdVRR discuss their perspective of the chain collapse, i.e. an equilibrium between a collapsed and an extended state. Although we understand the attempt to describe polymer collapse by tools developed in the biophysical community to quantify denaturation of proteins, we hardly see its relevance to our work here. In the native state protein display a characteristic, well defined folded structure. Despite still existing small fluctuations, this state is qualitatively different than the random globule of a collapsed polymer. In this context, we rather describe this phenomenon at all relevant length scales, connecting the microscopic interactions to the statistical distributions of (co)solvent molecules and chain segments through the appropriate statistical thermodynamic tools such as pair-distribution functions, chemical potential variations, chain structure factors, and potential of mean force (PMF), to name a few. Moreover, we were surprised to learn that the relative abundance of two states depends on the free energy barrier between those two states or that coexistence of those states persists at the Θ point. Statistical mechanics¹⁹ shows that it is the free energy difference between two states that matters for the relative abundance of their populations, the free energy barrier dictating only the kinetics of the process. Furthermore, Θ point is a critical point, i.e. large diverging conformational fluctuations define this point. There are no well defined expanded and collapsed states at a Θ point^{11–13}. The interesting question is whether or not the LCST transition of PNIPAm is a Θ point (i.e. a second order collapse), the experimental data of PNIPAm in water shows hysteresis^{10,17,18} a clear signature of a first order collapse.

We would also like to point out that understanding polymer properties relevant for real chains always require working with the largest possible chains. In the limit of long chains, further away from the transition point, the abundance of non-collapsed polymer configurations vanishes, and the polymer state can only be described by the appropriate statistical analysis of the polymer segment distribution. It is for instance well established that the overall conformation of a collapsed glob-

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ular PNIPAm chain is well characterized by the Porod scaling of the chain form factor $S(q) \sim q^{-4}$ ^{11–13}.

Contrary to previous statements¹⁴ (Ref. 9 of the comment), vdVRR now recognize that “it does not come as a surprise that the polymer collapses when the solvent quality becomes better and better”. It is, however, important to stress here that this is counterintuitive, surprising, and not in line with the well established Flory Huggins scheme for polymer solutions^{11,12,20}. There, upon collapse, solvation of a polymer would become thermodynamically more costly, thus increasing the chemical potential μ (and not decrease). A corresponding coil-globule-coil scenario would mean a low-high-low scenario for μ (see Figs. 5 and 6 in Ref.²⁰). It is one of the main results of our work, that this scheme does not hold for PNIPAm in aqueous alcohol^{7,8}.

In the second paragraph vdVRR claim that PMFs presented in Figs. 8 and 9 are incorrectly interpreted. However, they also say that there is a preferential binding between alcohol and PNIPAm, which is what we have proposed^{7,8,20,21}. This leads to the peculiar chain structure vdVRR ignore completely. The static structure factor in Fig. 4 of Ref 21 reveals that the chain globally collapses (i.e. $S(q) \sim q^{-4}$ for small q) but remains in good solvent on short lengths scales, i.e. $S(q) \sim q^{-5/3}$ for larger q ^{11–13}. This represents a good solvent polymer segment enriched by methanol rich sticky contacts, which is further supported by increased solvent quality for PNIPAm as described above.

vdVRR also find Fig. 8 in Ref.²¹ to be insufficient to explain preferentiability and thus the local excess of methanol near PNIPAm. In this context, we first want to call the attention to the pair distribution function $g(r)$ calculated in Fig. 4 of Ref.²². If we now consider the first guess of PMF $v(r) = -k_B T \ln[g(r)]$, it does not come as a surprise that methanol-NIPAm minima in PMF is $0.5k_B T$. Furthermore, it is the relative methanol-NIPAm and water-NIPAm fraction within the first solvation shell that dictates polymer solvation, which is correctly presented by our analysis²¹. Furthermore, vdVRR seem not to have noticed that a certain number of methanol molecules are most probably needed to form co-solvent bridges^{8,21}. Straightforward geometry arguments and simple physics^{23,24} tells us that because of the smaller sizes of methanol in comparison to NIPAm, one can pack more methanol molecules within the first shell. This explains why a methanol-NIPAm binding of $\sim 0.5k_B T$ ²¹ can still lead to large energy density within solvation volume⁸.

Also recall that there is an excess of hydrogen bonding between methanol and NIPAm as seen from Fig. 10(a) in Ref.²¹. There are experimental^{25,26} and combined simulation-experimental²⁷ works, though not cited by vdVRR, showing that hydrogen bonded bridging of distal NIPAm monomers is the driving force for PNIPAm collapse. Therefore, hydrogen bonding does play a key role in describing the polymer col-

lapse transition of PNIPAm, unlike the claims made by vdVRR in their earlier work¹⁴ and Refs. [7,9] of their comment.

Additionally, upon decrease of temperature, water-NIPAm hydrogen bonding becomes more relevant and thus reduces preferentiability with methanol, as shown in Fig. 9 in Ref.²¹.

In the second last paragraph vdVRR claim that in Ref.²¹: “NMR experiments cannot answer whether methanol sit in between the buried side groups of PNIPAm” and “Fig. 10b and 10c presents hypothetical arrangement”. By carefully looking into Figs. [5,6,10] in Ref.²¹ and the explanation therein, the NMR experiments indeed point at the interstitial solvents. To further validate this scenario, one could also perform quadrupolar splitting experiments. We are, however, happy to know that vdVRR also see the same, as proposed by us in Refs.^{8,20,21}, in their simulations¹⁴.

The last paragraph of the comment compares alkanes to PNIPAm. We start by mentioning that alkanes are quite insoluble in water, while PNIPAm is soluble below 305 K. For instance, the solubility of methane in water is only below 22.3 mg/L (or a mole fraction of 0.000025) and even much lower for longer alkanes²⁸. This leads to collapsed chains in pure water and to somewhat swollen ones in pure methanol, being a standard poor solvent collapse. Note that the collapse of PNIPAm in aqueous methanol is not a standard poor solvent collapse. Furthermore, alkanes and tertiary butanol are insoluble in aqueous methanol, leading to direct CH₃-CH₃ contacts between solutes^{29,30} and is not driven by interstitial (co)solvents, in striking difference to PNIPAm. As it seems vdVRR misinterprets our analysis^{8,20,21} and analysis in^{29,30}. Moreover, our scenario presented in Figs. 10 (b) and 10(c) of Ref.²¹ is consistent with the observations^{29,30}. More specifically, -CH₃ group of methanol can form sticky contacts with isopropyl group of NIPAm or -CH₃ group of another methanol sticking to another NIPAm monomer, while -OH group of methanol is hydrogen bonded with amide group of NIPAm. In this process, expelled water molecules obtain a large translational entropy gain.

We are glad to recognize that vdVRR acknowledge that “the co-nonsolvency effect may well be independent of specific chemical details”, in contrast to previous published statements (see for instance conclusion in Ref.¹⁴ where the authors state that “polymer collapse by cosolvent adsorption is not a generic phenomenon”). Furthermore, while Refs. [7,9] in the comment deal with PNIPAm in aqueous urea mixtures and vdVRR take Ref. [23] of the comment to their support, we do not see how this can support vdVRR’s statement (see for example the abstract of Ref.¹⁶ written by the same authors of Ref. [23] and also Ref. [23] itself). Instead the authors of Ref.¹⁶ present their alternative explanation of co-non-solvency, which seem to be based on the relative interaction strengths. We are also puzzled by the adjective “emerging” used to characterize entropy driven collapse, a description used for more than half a

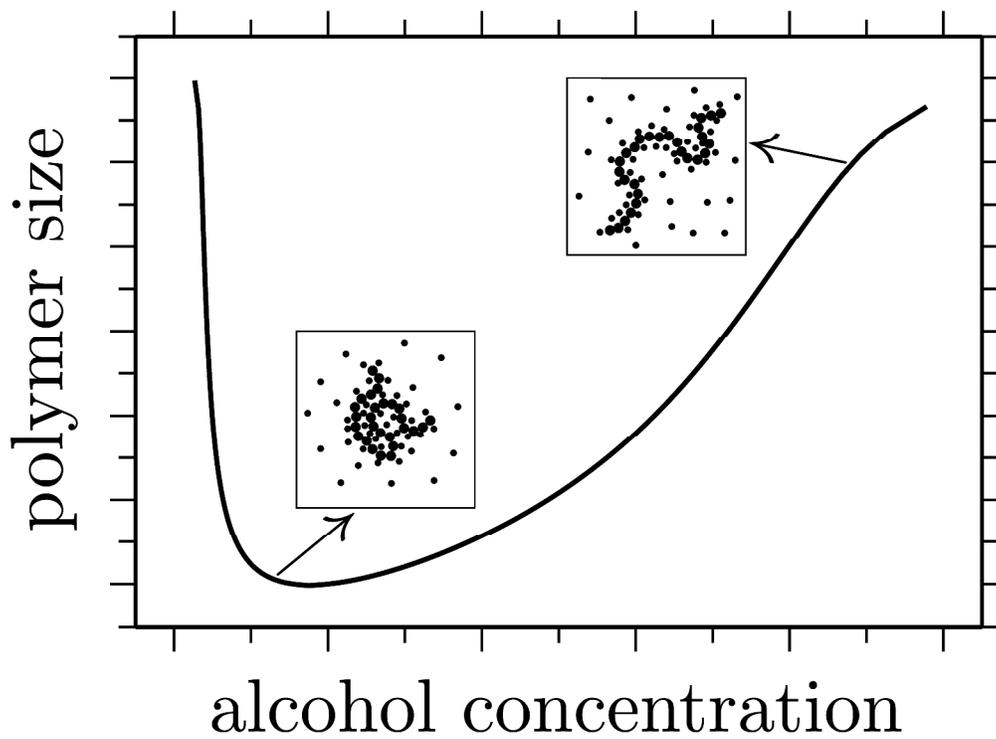
century in the context of an LCST for polymer solutions^{11–13}.

In our reply we answered questions related to our recent contributions to the understanding of co-non-solvency phenomena in general, and to our recent work on the reduction of the collapse temperature of PNIPAm in water upon addition of alcohol. We clarified that such effects are of a generic nature^{8,20}, driven by the enthalpic preferential adsorption of one of the co-solvents to the chain monomers²¹ and that the polymer collapses in good solvent, making mean-field arguments incapable of describing this phenomenon²⁰. We hope, the present discussion will put further contributions to this field by its main protagonists in scientifically firmer grounds.

References

- Schild, H. G.; Muthukumar, M.; Tirrell, D. A. *Macromolecules* **1991**, *24*, 948-952.
- Winnik, F. M.; Ringsdorf, H.; Venzmer, J. *Macromolecules* **1990**, *23*, 2415-2416.
- Zhang, G.; Wu, C. *Phys. Rev. Lett.* **2001**, *86*, 822-825.
- Walter, J.; Sehr, J.; Vrabc, J.; Hasse, H. *J. Phys. Chem. B* **2012**, *116*, 5251-5259.
- Kojima, H.; Tanaka, F.; Scherzinger, C.; Richtering, W. *J. Pol. Sci. B* **2013**, *51*, 1100-1111.
- Tanaka, F.; Koga, T.; Winnik, F. M. *Phys. Rev. Lett.* **2008**, *101*, 028302.
- Mukherji, D.; Kremer, K. *Macromolecules* **2013**, *46*, 9158-9163.
- Mukherji, D.; Marques, C. M.; Kremer, K. *Nat. Commun.* **2014**, *5*, 4882.
- Kyriakos, K.; Philipp, M.; Lin, C.-H.; Dyakonova, M.; Vishnevetskaya, N.; Grillo, I.; Zaccone, A.; Miasnikova, A.; Laschewsky, A.; Mller-Buschbaum, P.; Papadakis, C.M. *Macromol. Rapid Commun.* **2016**, *37*, 420-425.
- Wu, C.; Wang, X. *Phys. Rev. Lett.* **1998**, *80*, 4092-4094.
- Gennes, P.-G. de *Scaling Concepts in Polymer Physics*, Cornell University Press: London, 1979.
- Des Cloizeaux, J.; Jannink, G. *Polymers in Solution: Their Modelling and Structure*, Clarendon Press: Oxford, 1990.
- Rubinstein, M.; Colby, R. H. *Polymer Physics*, Oxford University Press, 2003.
- Rupero, F. R.; Hajari, T.; and van der Vegt, N.; *J. Phys. Chem B* **2015**, *119*, 15780-15788.
- Budkov, Y. A.; Kolesnikov, A. L.; Kalikin, N. N.; Kiselev, M. G. *EPL* **2016**, *114*, 46004.
- Pica, A.; Graziano, G. *Phys. Chem. Chem. Phys.* **2016**, *18*, 25601-25608.
- Ray, B.; Okamoto, Y.; Kamigaito, M.; Sawamoto, M.; Seno, K.; Kanaoka, S.; Aoshima, S. *Polym. J.* **2005**, *37*, 234-237.
- Hirano, T.; Okumura, Y.; Kitajima, H.; Seno, M.; Sato, T. *J. Polym. Sci. A: Polym. Chem.* **2006**, *44*, 4450-4460. DOI: 10.1039/C7SM00041C
- Pathria, R. K. *Statistical Mechanics*, Elsevier, 1996.
- Mukherji, D.; Marques, C. M.; Stuehn, T. Kremer, K. *J. Chem. Phys.* **2015**, *142*, 114903.
- Mukherji, D.; Wagner, M.; Watson, M. D.; Winzen, S.; de Oliveira, T.; Marques, C. M.; Kremer, K. *Soft Matter* **2016**, *12*, 7995.
- Oliveira, T. E. de; Netz, P. A.; Mukherji, D.; Kremer, K. *Soft Matter* **2015**, *11*, 8599-8604.
- Halliday, D.; Resnick, R. *Fundamentals of Physics*, John Wiley & Sons, Inc., 1960.
- Kittel, C. *Introduction of Solid State Physics 8th Edition*, John Wiley & Sons, Inc., 2013.
- Sagle, L. B.; Zhang, Y.; Litosh, V. A.; Chen, X.; Cho, Y.; Cremer, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 9304-9310.
- Wang, J.; Liu, B.; Ru, G.; Bai, J.; Feng, J. *Macromolecules* **2016**, *49*, 234-243.
- Micciulla, S.; Michalowsky, J.; Schrör, M. A.; Holm, C.; von Klitzing, R.; Smiatek, J. *Phys. Chem. Chem. Phys.* **2016**, *18*, 5324-5335.
- Atkins, P. W.; de Paula, J. *Physical Chemistry 9th Edition*, Oxford University Press (2010).
- Mochizuki, K.; Koga, K. *Phys. Chem. Chem. Phys.* **2016**, *18*, 16188-16195.
- Mochizuki, K.; Pattenaude, S. R.; Ben-Amotz, D. *J. Amer. Chem. Soc.* **2016**, *138* 9045-9048.

The puzzle of co-non-solvency



A response to the comments raised by N. van der Vegt and F. Rodriguez-Ropero in their reply to our recently published article in *Soft Matter*.