

We would like to thank the second anonymous reviewer for clarifying comments. In the revised version of the manuscript we have carefully taken each comment into account and believe it has improved the study. The reviewer’s comments have been reproduced in [blue text](#) below, followed by our point-by-point replies.

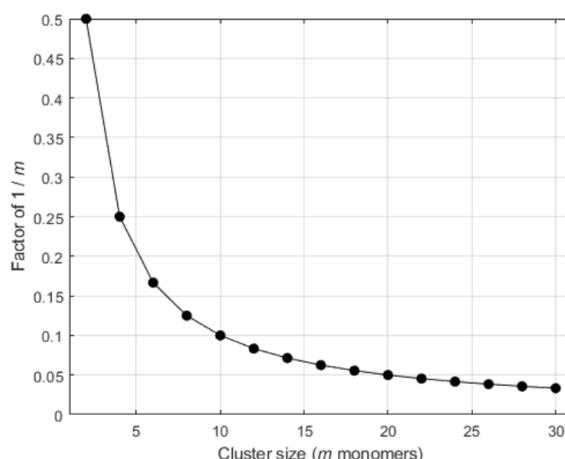
Anonymous Referee 2

I’d like to thank the authors for the replies to mine and other reviewers’ comments, and the clarifications made in the manuscript.

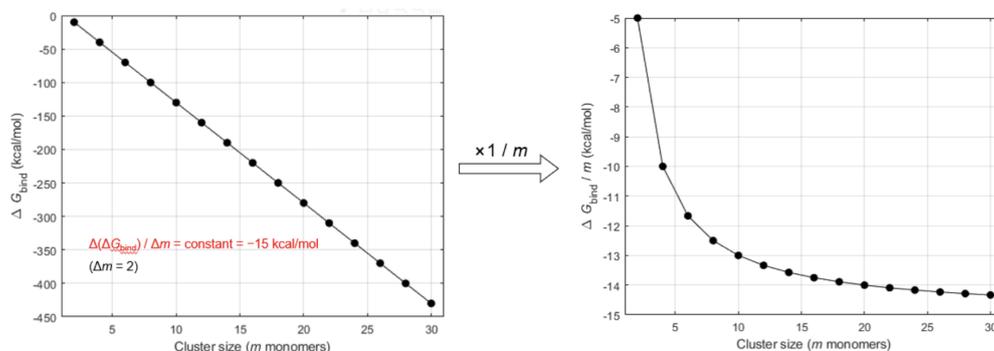
I would like to ask further clarifications related to the reply to my previous comment 2: The authors reply that they did mean that the discussed quantity in relation to Fig. 4b is the actual gradient $\Delta(\Delta G)$, which I suggested to use.

I apologize for being unclear; what I actually meant was to study the gradient $\Delta(\Delta G)$ without dividing the ΔG data by m . This is because the $1/m$ factor will always lead to a similar curve that first changes steeply and then levels off—approximately at m values of ca. 15-20 molecules—regardless of the exact chemical properties.

That is, when you scale the numbers in Fig. 4a by $1/m$, the shape of the curve is determined by this factor, so you are simply bending the graphs in Fig. 4a:



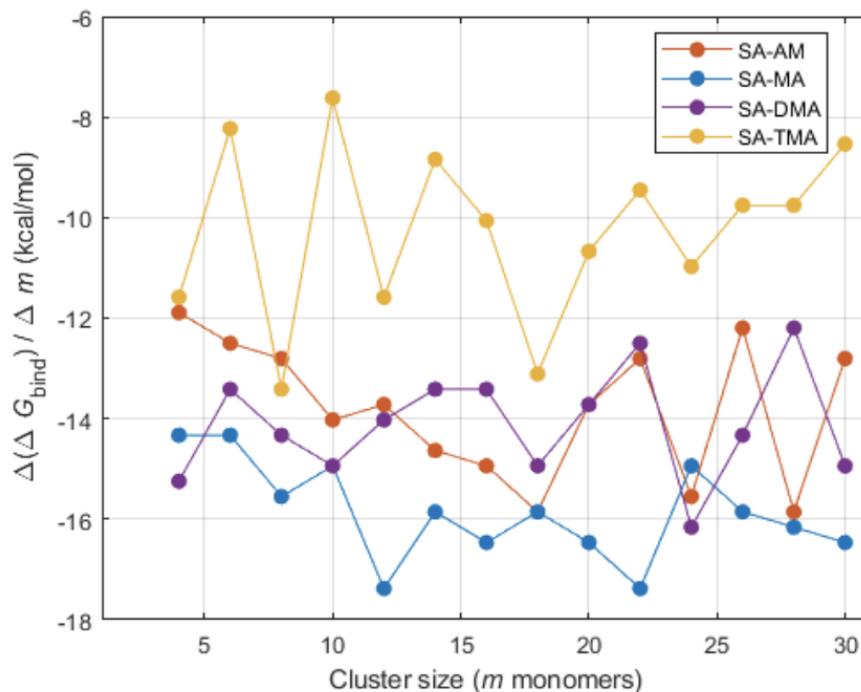
One can think of e.g. an example case of ΔG data where each energy contribution $\Delta(\Delta G)$ upon addition of monomer pair is approximately same, i.e. the gradient is $\Delta(\Delta G)$ constant, and there isn’t any size-dependent transition. However, scaling this data by $1/m$ naturally results in the shape in the plot above:



It clearly doesn’t sound reasonable to interpret this as a physical or chemical transition from clusters to particles. (Note that just to illustrate the risk in such interpretation, this example is qualitatively similar to Fig. 4.)

I’m unsure of the physical interpretation of the $\Delta G/m$ quantity. It is said to be “average binding free energy contribution in the clusters”. Generally, the composition- and size-dependent contribution of monomers (or monomer pairs) to the binding free energy is described by the change upon addition of molecules, i.e. $\Delta(\Delta G)$

; in contrast, the average $\Delta G/m$ doesn't contain any information of these contributions. For the data in Fig. 4a, the actual size-dependent contributions $\Delta(\Delta G)/\Delta m$ look approximately like this:



This is quite different from the curves in Fig. 4b.

Therefore, I would ask the authors to at least add the following:

1. Clarify why dividing the binding free energy by the total number of molecules is expected to give information on the cluster-to-particle transition, and what the physical meaning of this quantity is. Preferably give references, if possible, since I think that this might not be clear to all readers.

Authors' reply: We agree with the reviewer that it would be beneficial to further discuss the physical meaning of the size-averaged binding free energy $\Delta G_{\text{bind}}/m$. Although references on this property are scarce, apart from our own previous work, the recent work by Sindel et al. [1] used a similar definition to study TiO_2 clustering, leading to a convergence in the size-averaged binding free energies toward the formation free energy of the bulk crystal.

The physical interpretation of the size-averaged binding free energy is the binding free energy per monomer in the cluster. This quantity provides insight into the average binding properties of the cluster and offers inferred evidence about the thermochemistry associated with monomer addition. By analyzing how the average binding free energy changes with cluster size, we can understand the stabilization processes occurring during cluster growth.

For example, consider the difference in average binding free energy between a $(\text{SA})_{99}(\text{AM})_{99}$ cluster and a $(\text{SA})_{100}(\text{AM})_{100}$ cluster. In such large clusters, adding one extra acid-base pair results in minimal molecular rearrangement, and thus the average binding free energy remains largely unchanged. This behavior is analogous to condensation thermodynamics. In contrast, adding one $(\text{SA})_1(\text{AM})_1$ pair to form a $(\text{SA})_2(\text{AM})_2$ cluster results a huge drop in the average free energy, as the addition causes a large stabilization at such small cluster sizes by a significant molecular rearrangement. Once the first encapsulated ion is present, further stabilization corresponds to the addition of monomers to an existing solvent shell. This illustrates a gradual transition from single molecules to clusters, highlighting the informative nature of the average binding free energy in this context.

To further elaborate on this aspect, we have added a small section to the methods describing the size-averaged binding free energies in more detail:

Added paragraph, page 4, line 110:

We calculate the binding free energies as the free energy of the cluster with respect to its individual monomers:

$$\Delta G_{\text{bind}} = G_{\text{cluster}} - \sum_i G_{\text{monomers},i} \quad (1)$$

We also calculate the size averaged binding free energies ($\Delta G_{\text{bind}}/m$) of the clusters as the physical interpretation is the binding free energy contribution per monomer in the cluster. This quantity provides insight into the average binding properties of the cluster and offers inferred evidence about the thermochemistry associated with monomer addition. Analyzing how the average binding free energy changes with cluster size will present to us the stabilization processes occurring during cluster growth. A recent work by [1] used a similar definition to study TiO_2 clustering, leading to a convergence in the size-averaged binding free energies toward the formation free energy of the bulk crystal. For example, consider the difference in average binding free energy between a $(\text{SA})_{99}(\text{AM})_{99}$ cluster and a $(\text{SA})_{100}(\text{AM})_{100}$ cluster. In such large clusters, adding one extra acid-base pair results in minimal molecular rearrangement, and thus the average binding free energy remains largely unchanged. This behavior is analogous to condensation thermodynamics. In contrast, adding one $(\text{SA})_1(\text{AM})_1$ pair to form a $(\text{SA})_2(\text{AM})_2$ cluster results a huge drop in the average free energy, as the addition causes a large stabilization at such small cluster sizes by a significant molecular rearrangement.

We also agree with the reviewer that the leveling off in the $\Delta G_{\text{bind}}/m$ versus m curve alone is not sufficient to classify the transition from clusters to particles. A monomer within the cluster being fully surrounded by adjacent monomers would very likely result a significant difference of binding free energy comparing to the configurations without encapsulated monomer, as the monomer can fully interact with its surroundings. We applied convex-hull analysis to verify that an ion is actually fully encapsulated. In the regime of $4 < m < 16$, we found that the size-averaged binding free energy does not change significantly as a function of m . We preliminarily consider this regime to represent the cluster-to-particle transition. In addition, when combined with the structural changes identified using the convex hull method, it provides additional inferred evidence supporting this transition. We believe this is well captured in the following sentence on page 1, line 7:

“We define the onset of FNPs as when one or more ions are fully solvated inside the cluster and when the gradient of the size-averaged binding free energy approaches zero”

2. Please show and/or discuss how $\Delta G/m$ relates to the actual size-dependent monomer (pair) contribution $\Delta(\Delta G)/\Delta m$, and why $\Delta G/m$ should be used instead of e.g. $\Delta(\Delta G)/\Delta m$. I still recommend to show also $\Delta(\Delta G)$ (it’s okay if it doesn’t look as perfect as the smooth $\Delta G/m$ curves).

Authors’ reply: We agree with the reviewer that the appropriate quantity for estimating stability is the addition free energy ΔG_{add} , as it is related to the evaporation rate. However, our data is limited to clusters with a 1:1 acid-to-base ratio, which means our initial figure only depicted the addition of an acid-base pair. Since dimer evaporation is relatively rare in SA–base clusters, interpreting such a figure in terms of overall stability is challenging. Mathematically, taking the end point (at $m = 30$) of the size averaged binding free energy ($\Delta G/m$) corresponds to taking the average of the addition energetics. We acknowledge that discussion about the mathematical relation between $\Delta(\Delta G)/\Delta m$ and $\Delta G/m$ would be beneficial.

To address this, we have expanded Figure 4 with the acid–base pair addition ΔG_{add} free energies. Instead of $\Delta(\Delta G)/\Delta m$, we opted for ΔG_{add} since it directly represents the addition free energies of a pair of acid–base. As illustrated in the figure, the addition free energies fluctuate around the convergence values (dotted lines). A paragraph was added to describe the relation between $\Delta(\Delta G)/\Delta m$ and $\Delta G/m$.

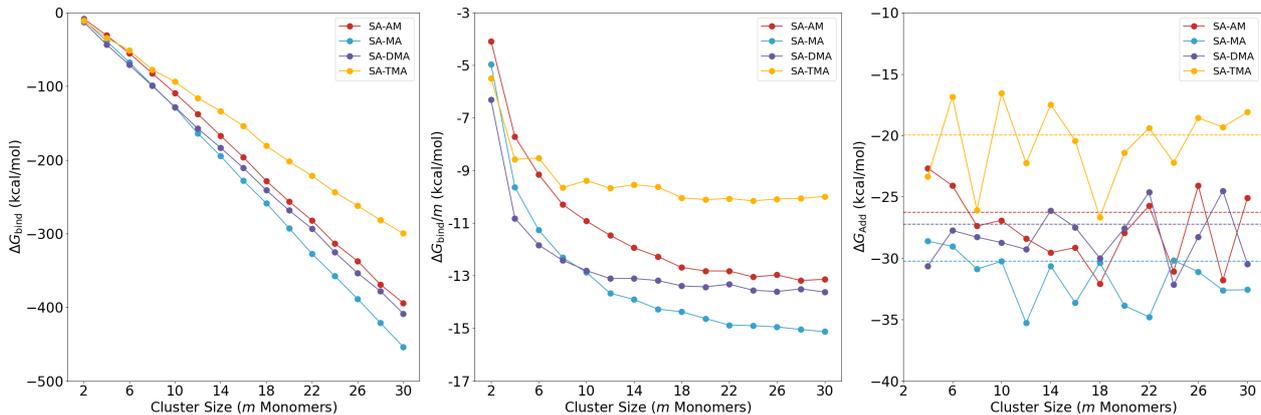


Figure 1: *Left:* Total binding free energies of $(SA)_n(AM/MA/DMA/TMA)_n$ clusters, $n = 1-15$. *Middle:* Size-averaged binding free energy contribution in the clusters. *Right:* Acid-base pair addition free energies ΔG_{add} of the four SA-Base clusters. (The dot line indicates the values of $2 \times \Delta G_{\text{bind}}/m$ with $m = 30$, the values were multiplied by two as we present pair wise addition here.) Data of SA-AM/DMA are from our prior work [2], with additional sampling carried out in this work.

Added paragraph, page 10, Line 237:

As shown in the right panel of Figure 1, the acid-base pair addition free energies ΔG_{add} fluctuate around the convergence value of the size-averaged binding free energy per monomer, $\Delta G_{\text{bind}}/m$ (indicated by the dotted lines). Since the addition free energy ΔG_{add} is the accurate quantity for estimating cluster stability, the relation between addition free energy ΔG_{add} and size-averaged binding free energy $\Delta G_{\text{bind}}/m$ is significant. Mathematically, taking the endpoint at m of the size-averaged binding free energy $\Delta G_{\text{bind}}/m$ corresponds to calculating the average of the addition free energies up to cluster size m . This approach helps determine the cluster size m at which fluctuations in ΔG_{bind} become negligible relative to the entire system. Furthermore, the convergence value of $\Delta G_{\text{bind}}/m$ can be used to estimate the free energies of acid-base pair additions to large clusters.

3. Explain that the general shape and leveling off of the $\Delta G/m$ curves is primarily not related to the chemical properties or composition, but simply follows from the $1/m$ factor which is same for all chemistries.

Authors' reply: Indeed, while multiplying a linear ΔG_{bind} curve by $1/m$ will always produce a bend, the linearity of the binding free energy ΔG_{bind} as a function of m is dependent on the chemical composition of the system. In our case, we study strongly bound systems and observe a linear trend. However, this is not always given *a priori*. For instance, in the previous work done by Myllys *et al.*[3] (See their Figure 1, 6 and 10), the ΔG_{bind} of $(SA)_1(\text{Base})_1(\text{H}_2\text{O})_n$ is plotted against the number of water molecules n (where $n = m - 2$, with m being the total monomer count, including one SA and one base molecules). In all these cases the free energy is not simply linearly decreasing as these interactions are quite weak. For instance, hydration of bases even gives an increasing free energy as a function of water molecules (Ref [3], Figure 1). This further supports the idea that the behavior of $\Delta G_{\text{bind}}/m$ is system-specific and underscores the importance of considering both energetic and structural factors when interpreting these curves. To further clarify this aspect, we have added the following sentence when first discussing the linear trend in the binding free energies.

Added paragraph, page 8, line 201:

It should be noted that the linearly decreasing trend is dependent on the cluster composition and requires strongly binding clusters. For instance, in the previous work done by [3] (As shown in Figure 1, 6 and 10 of their paper), the ΔG_{bind} of $(SA)_1(\text{Base})_1(\text{H}_2\text{O})_n$ is plotted against the number of water molecules n (where $n = m - 2$, with m being the total monomer count, including one SA and one base molecules). In all these cases the free energy is not simply linearly decreasing as the inter-molecular interactions are quite weak. For instance, hydration of bases even gives an increasing free energy as a function of water molecules (see [3], Figure 1).

References

- [1] J. P. Sindel, D. Gobrecht, Ch. Helling, and L. Decin. Revisiting Fundamental Properties of TiO₂ Nanoclusters as Condensation Seeds in Astrophysical Environments. *Astron. Astrophys*, 668:A35, 2022.
- [2] H. Wu, M. Engsvang, Y. Knattrup, J. Kubečka, and J. Elm. Improved Configurational Sampling Protocol for Large Atmospheric Molecular Clusters. *ACS Omega*, 8(47):45065–45077, 2023.
- [3] N. Myllys, D. Myers, S. Chee, and J. N. Smith. Molecular Properties Affecting the Hydration of Acid–base Clusters. *Physical Chemistry Chemical Physics*, 23(23):13106–13114, 2021.