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# **Understanding Vapor Nucleation on the Molecular Level: A Review**

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**Abstract:**

Gas phase nucleation is a universal phenomenon that plays a crucial role in both natural settings and industrial processes. Despite more than 100 years' work to decipher this highly dynamic process, our understanding of nucleation remains incomplete. In particular, the formation, decay, and structures of the initially formed nucleating clusters critically determine the overall behavior of the nucleation systems, yet they are elusive to conventional experimental methods that only detect grown particles. Filling this gap of understanding calls for the ability to probe nucleation on a molecule-by-molecule basis to retrieve direct evidence of nucleation pathways and the temporal evolution of the nucleating clusters. In this review, we summarize recent modelling and experimental efforts to meet this demand. The techniques discussed here have offered unprecedented molecular level insight into the nucleation process, but they are still subject to constraints in terms of applicable scope and measurement uncertainties. We shall highlight both the advantages and limitations of each technique, with the hope that this review can lead to novel applications and further improvements of the introduced methods.

**Keywords:**

nucleation, new particle formation, molecular-level, clusters, nucleation modelling, nucleation experiment

# 1. Introduction

The formation of new condensed phase particles from gas phase precursors is a crucial element in the atmosphere and in a variety of industrial processes. In the atmosphere, new particle formation influences the concentration of cloud condensation nuclei (Dunne et al., 2016; Kuang, McMurry, & McCormick, 2009; Merikanto, Spracklen, Mann, Pickering, & Carslaw, 2009; Riipinen et al., 2011; Spracklen et al., 2008; Westervelt, Pierce, & Adams, 2014), and relates to hazing episodes with severe adverse health effects (Guo et al., 2020; Guo et al., 2014). In industry, particle formation is sometimes intentionally induced, e.g. to synthesize nanoparticles (Kammler, Madler, & Pratsinis, 2001; Li, Ren, Biswas, & Tse, 2016) or to separate gas mixtures (Haghighi, Hawboldt, & Abedinzadegan Abdi, 2015), but in other circumstances should be carefully regulated as in steam turbines (Ahmad, Casey, & Surken, 2009) and high speed wind tunnels (Daum, 1963). The initial step of particle formation, referred to as nucleation, is the process where molecules interact to form thermodynamically stable molecular clusters. An in-depth understanding of nucleation is critical to quantify nucleation rates in planetary atmospheres and to optimize industrial processes.

Since C. J. Wilson's pioneering expansion cloud chamber experiments (Wilson, 1897), considerable theoretical, modelling and experimental efforts have been devoted to unveiling the detailed mechanisms of nucleation in various systems of interest. Ideally, if we can track the temporal evolution of cluster size distributions in a nucleation event, with the cluster size and composition resolved on the molecular level, all the information required to elucidate nucleation mechanisms can be extracted. However, until recently only the distributions of grown particles, i.e. particles larger in size than the smallest, thermodynamically stable molecular clusters (the critical nucleus), were routinely quantified (with uncertainties, see Kangasluoma and Kontkanen (2017) and Kangasluoma et al. (2020)). Several experimental challenges, the relative importance of which depends on the context, hinder our effort to study nucleation on a molecular basis.

The first and foremost challenge comes from the difficulty in the detection of nucleating clusters. In any nucleation event, the propensity of nucleating clusters to grow and decay essentially determines the nucleation pathways and the nucleation rate. However, nucleating clusters are often **low in concentrations and fragile**, hence their detection is ultra-demanding on instrument sensitivity and the instrument's ability to preserve cluster integrity. For instance, the most frequently applied technique to detect nucleating clusters, i.e. mass spectrometry, requires the neutral nucleating clusters to be ionized for detection. Even with the relatively soft chemical ionization method, the clusters could go through severe transformations upon ionization and during transmission (Brophy & Farmer, 2016; Ortega et al., 2016; Passananti et al., 2019; Zapadinsky, Passananti, Mylly, Kurten, & Vehkamaki, 2019), not to mention if more conventional

ionization methods, e.g. electron ionization, are applied (Fárník & Lengyel, 2018). In fact, recent progress on nucleation characterization critically relies on detection methods that minimize cluster fragmentation to a better extent (Eisele & Hanson, 2000; Eisele & Tanner, 1993; Litman, Yoder, Schläppi, & Signorell, 2013; Schläppi, Litman, Ferreiro, Stapfer, & Signorell, 2015).

The second challenge originates from the complex chemical environments in which nucleation takes place. This is particularly the case for atmospheric nucleation events, where potential nucleation participants are numerous (Kerminen et al., 2018; Kulmala et al., 2014; Lee et al., 2019). It is often difficult to pinpoint which chemical species participates in nucleation since not every nucleating species can be detected by instruments or quantified with a sufficient level of accuracy. A notable example of ‘undetectable species’ in nucleating cluster measurements is water. Although humidity is known to influence nucleation rates (Chen et al., 2015; Dunne et al., 2016; Henschel, Kurtén, & Vehkamäki, 2016; Henschel et al., 2014; Kildgaard, Mikkelsen, Bilde, & Elm, 2018a, 2018b; Yu et al., 2017), water is mostly missing from the mass spectra measured during atmosphere nucleation events. One must resort to indirect measurements and modelling to infer the cluster hydration states.

The third experimental challenge arises from the transient nature of nucleation. This is less of a problem for atmospheric nucleation events that can last up to hours, but poses an obstacle for laboratory nucleation studies that employ highly supersaturated vapors with high nucleation rates. In these studies, nucleation typically runs its course on a millisecond- or microsecond- time scale (Wyslouzil & Wölk, 2016), shorter than the time-resolution of the measuring device. As a result, the measurable quantity from these experiments is the number concentration (in fewer cases, size distributions) of grown particles that does not directly unveil molecular level details of the nucleation process. To extract molecular level information from these studies, the measuring device must be designed to take several snapshots of the cluster size distribution within the time-window of nucleation (Schläppi et al., 2015).

Efforts to improve nucleation instrumentation mainly focus on overcoming the aforementioned challenges. Though a lot of important nucleation scenarios remain unexplored, nowadays nucleation can indeed be observed on the molecular level. Apart from improvement of measurement techniques, the advancement of modelling techniques, e.g. quantum mechanical calculations and molecular dynamic simulations, has greatly facilitated our understanding of the nucleation process. In this review, we set out to summarize and comment on the existing tools that provide molecular-level information on the nucleation process, with the content organized as follows: We begin by introducing basic concepts and theoretical frameworks to understand nucleation in sections 2.1-2.3. We then review modelling techniques including GDE-based kinetic simulations, molecular cluster structure and energy calculations, and molecular dynamics simulations in sections 2.4-2.6, respectively. In section 3, we turn to experimental techniques that

characterize nucleation on the molecular level. Specifically, we focus on nucleation measurements in the postnozzle flow of Laval expansions and the characterization of atmospheric nucleating clusters. We limit ourselves to the 'molecular level' understanding of the nucleation process, hence important techniques that can identify the chemical compositions and size distributions of grown particles are not included here. These important topics are discussed in recent complementary reviews (Johnston & Kerecman, 2019; Kangasluoma et al., 2020). Furthermore, in this review we do not discuss heterogeneous nucleation, i.e. nucleation of vapors on pre-existing nuclei (Gamero-Castaño & de la Mora, 2002; Tauber et al., 2018; Winkler et al., 2008; Winkler et al., 2012). The theoretical aspect of heterogeneous is different from the homogenous nucleation theory presented in section 2.2-2.3, and we refer the reader to the cited works (Fletcher, 1958; Gamero-Castaño & de la Mora, 2002; Vehkamäki et al., 2007) for more details.

## 2. Nucleation theories and modelling techniques

In this section we briefly review gas phase nucleation theories and modelling techniques. Basics of the nucleation thermodynamics and kinetics are introduced in section 2.1, followed by a discussion of the key points in the classical nucleation theory (section 2.2) and the nucleation theorems (section 2.3). Detailed, in-depth accounts of nucleation theories are found in textbooks written by Kashchiev (2000), Vehkamäki (2006), and Kalikmanov (2013). Following the theoretical discussions, we look into three molecular-level modelling techniques applied in nucleation research, i.e. GDE-based kinetic modelling, cluster structure and energy simulations, and molecular dynamic simulations.

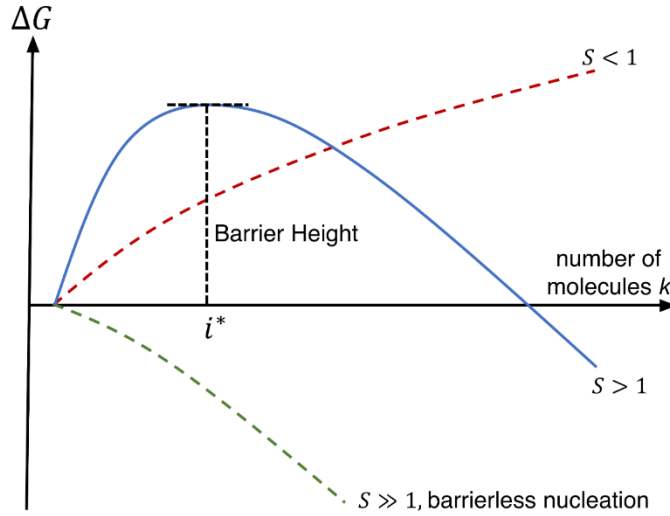
### 2.1 Nucleation thermodynamics and kinetics

Gas phase nucleation can be viewed as the overcoming of an energy barrier by vapor molecules to form clusters that spontaneously grow. As most nucleation experiments take place at (near-) constant pressure and temperature, the Gibbs free energy is the chosen quantity for the cluster free energy of formation. For a system with a single nucleating vapor (unary nucleation), the Gibbs free energy of formation (Oxtoby & Kashchiev, 1994) of a  $k$ -mer (a molecular cluster containing  $k$  molecules) is given by

$$\Delta G_k = k\Delta\mu + F(k) \quad (1)$$

where  $\Delta\mu$  is the chemical potential difference between the condensed and vapor phase,  $F(k)$  is the cluster surface energy. A simplified version of  $\Delta G_k$  variation as a function of  $k$  is shown in Fig. 1. If the vapor saturation ratio  $S$  is less than 1, both  $k\Delta\mu$  and  $F(k)$  are positive and increases with cluster size. Nucleation is forbidden by this ever-increasing energy barrier. As  $S$  rises above 1,  $k\Delta\mu$  becomes negative but nucleation is still hindered by the creation of cluster surface ( $F(k) > 0$ ). This leads to  $\Delta G_k$  to first increase and then decrease with  $k$ , shown by the blue solid line in Fig. 1. Gas-to-particle transition occurs but at a

suppressed rate because the formation of the smallest clusters is thermodynamically unfavorable. Nucleation rates thus represent the frequency at which thermal fluctuations drive the clusters past the energy barrier. The term ‘nucleation’ was coined to refer to phase transition in such a scenario. As  $S$  further increases, the decrease in chemical potential defeats the increase of the surface term for all clusters ( $\Delta G_k < 0$  for  $k \geq 2$ ). Cluster formation thus proceeds without an energy barrier (barrierless nucleation). Barrierless nucleation has been observed in atmospheric nucleation studies (Kürten et al., 2014; Kürten et al., 2018) and in low-temperature nucleation systems (Chakrabarty, Ferreiro, Lippe, & Signorell, 2017; Krohn, Lippe, Li, & Signorell, 2020). In many atmospheric nucleation events, it is unclear if nucleation proceeds with or without a barrier. Therefore, in atmospheric studies the term ‘new particle formation (NPF)’ is often used to describe the gas-to-particle phase transition. In this review, we use ‘nucleation’ as a generic term to describe the gas-to-particle transition because the tools we later introduce apply to nucleation with and without a barrier.



**Fig. 1.** The Gibbs free energy of cluster formation as a function of cluster size.

Eq. (1) describes the nucleating clusters from a thermodynamic perspective, but nucleation is fundamentally a kinetic process: monomers/clusters constantly collide with each other to form bigger clusters, while at the same time clusters go through dissociation to replenish monomers/smaller clusters. For a spatially homogeneous, unary nucleation system, the time evolution of the number concentration ( $N_k$ ) of  $k$ -mers is governed by the following equation,

$$\frac{dN_k}{dt} = \frac{1}{2} \sum_{i+j=k} \beta_{i,j} N_i N_j - N_k \sum_{j=1}^{\infty} \beta_{k,j} N_j - E_k N_k + E_{k+1} N_{k+1} - L_k + S_k (k \geq 2) \quad (2)$$

where  $\beta_{i,j}$  is the association rate constant of cluster  $i$  and cluster  $j$ ,  $E_k$  is the evaporation rate of the  $k$ -mers,  $L_k$  and  $S_k$  represent loss and production rates of  $k$ -mers by mechanisms other than coagulation, condensation and evaporation. Eq. (2) and its equivalent variations are referred to as the general dynamic equations (GDE, (Gelbard & Seinfeld, 1979)), the birth-death equations (Vehkamäki & Riipinen, 2012) or population balance equations. Implicit in Eq. (2) are the assumptions that clusters do not fragment upon collisions with monomers or clusters, and that only molecules evaporate from clusters. If spatial inhomogeneity exists, additional terms need to be introduced to account for spatial transport (Cai et al., 2018; Kommu, Khomami, & Biswas, 2004a, 2004b). Provided monomers are much higher in concentration compared to molecular clusters, the cluster-cluster association (coagulation) terms in Eq. (2) can be ignored. With the additional constraint that both  $L_k$  and  $S_k$  are negligible, Eq. (2) reduces to the Becker-Döring equation (Becker & Döring, 1935),

$$\frac{dN_k}{dt} = \beta_{1,k-1}N_1N_{k-1} - \beta_{1,k}N_1N_k - E_kN_k + E_{k+1}N_{k+1} \quad (k \geq 2). \quad (3)$$

The nucleation thermodynamics (Eq. (1)) and kinetics (Eqs. (2) and (3)) are related by detailed balance at equilibrium conditions. For an isothermal nucleation system,  $\beta_{1,k}$ ,  $E_{k+1}$  and  $\Delta G$  are interrelated by the following equation,

$$E_{k+1} = \beta_{1,k}N_1 \exp\left(\frac{\Delta G_{k+1}(T, N_1) - \Delta G_k(T, N_1)}{k_B T}\right). \quad (4)$$

where  $k_B$  is the Boltzmann constant,  $T$  is the temperature and  $\Delta G_k(T, N_1)$  is the Gibbs free energy of formation of  $k$ -mers from monomers at the monomer concentration  $N_1$ . In the next section we show how the classical nucleation theory is formulated based on Eqs. (1), (3) and (4).

## 2.2 The classical nucleation theory

The classical nucleation theory (CNT) is an easy-to-implement theory that only requires bulk material properties as inputs. With the advances in both nucleation theories and modelling techniques, nowadays CNT is less often applied with the purpose to predict nucleation rates, but more often used as a reference for other nucleation theories and experimental studies. Nonetheless, the framework of CNT is fundamentally sound within assumptions and can be quite powerful when combined with more accurate cluster energetics (see section 2.5). Here we give a brief outline of CNT to serve as a basis for further discussion.

The formulation of CNT for a single-component (unary) system starts by assuming nucleation reaches *steady state*, i.e.,  $\frac{dN_k}{dt}$  in Eq. (3) is zero. Eq. (3) can then be analytically solved (Seinfeld & Pandis, 2016) to give the following expression for the nucleation rate  $J$ ,



$$J = N_1 \left( \sum_{i=1}^{\infty} \frac{1}{N_1 \beta_{1,i} \prod_{j=1}^{i-1} \frac{N_1 \beta_{1,j}}{E_{j+1}}} \right)^{-1}. \quad (5)$$

In Eq. (5),  $J$  is expressed as a function of a series of rate coefficients, among which the evaporation rates are largely unknown. As Eq. (4) relates the Gibbs free energy to the kinetic coefficients, we substitute Eq. (4) into Eq. (5), leading to

$$J = \frac{N_1^2}{\sum_{i=1}^{\infty} \frac{\exp\left(\frac{\Delta G_i(T, N_1)}{k_B T}\right)}{\beta_{1,i}}}. \quad (6)$$

Eq. (6) gives a simple formula to calculate the nucleation rate, but requires  $\Delta G_i$ 's as inputs. In CNT,  $\Delta G_i$  is approximated by the capillary approximation, i.e.

$$\Delta G_i = -(i-1)k_b T \ln S + \sigma(A_i - A_1), \quad (7)$$

where  $\sigma$  is the surface tension of the bulk material at temperature  $T$ ,  $A_i$  is the surface area of the cluster  $i$  assuming the clusters are well-defined spheres with a uniform density. Since the denominator of Eq. (6) depends exponentially on  $\Delta G_i$ 's, it can be approximated by integration around the maximum of  $\Delta G_i$ , leading to the simplified form of the nucleation rate,

$$J_{\text{CNT}} = K \exp\left(-\frac{\Delta G^*}{k_B T}\right), \quad (8)$$

where  $K$  is a kinetic prefactor and  $\Delta G^*$  is the formation free energy of the critical nucleus. The size of the critical nucleus at which  $\Delta G_i$  reaches the maximum is given by

$$i^* = \frac{32\pi\sigma^3 v^2}{3(k_B T)^3 (\ln S)^3}, \quad (9)$$

where  $v$  is the volume of the monomer. For binary nucleation, the derivation of CNT is more involved, but the final form of the nucleation rate is similar,

$$J_{\text{bin}} = K_{\text{bin}} \exp\left(-\frac{\Delta G_{\text{bin}}^*}{k_B T}\right), \quad (10)$$

$$\Delta G_{\text{bin}} = n_1 \Delta \mu_1 + n_2 \Delta \mu_2 + \sigma_{\text{bin}} A_{\text{bin}}, \quad (11)$$

where the subscript 'bin' indicates 'binary',  $n_i$  is the number of molecules of component  $i$  in the cluster,  $\Delta \mu_i$  is the change of chemical potential from the vapor phase to the condensation phase.  $\Delta G_{\text{bin}}^*$  is located on a saddle point in the two-dimensional free energy surface.

From the derivation above, some limitations of CNT are easily identifiable. First, CNT calculates the steady-state nucleation rates without providing any information on the process leading to the steady state. Second, CNT only applies to isothermal nucleation, i.e. the nucleating clusters are at the same temperature as the surrounding. This limitation is explicitly manifested by Eq. (7) in which  $T$  is set to the ambient temperature. In experiments/simulations where the carrier gas is not present in sufficiently high concentrations to fully thermalize the nucleating clusters to the ambient temperature (Halonen, Zapadinsky, & Vehkamäki, 2018; Wyslouzil & Seinfeld, 1992), non-isothermal corrections (Feder, Russell, Lothe, & Pound, 1966) must be applied to the nucleation rate. Lastly but most importantly, the capillary approximation leads to large errors of cluster formation energies, in particular for small clusters with highly curved surfaces. Embedded in the capillary approximation is also the wrong interpretation that the nucleating clusters have a uniform density with a well-defined spherical shape, while in reality cluster density should transition gradually from the core to the gas phase (Angélil, Diemand, Tanaka, & Tanaka, 2014) and clusters might be fractal rather than spherical (Kathmann, Schenter, Garrett, Chen, & Siepmann, 2009). These drawbacks of CNT can be partially mitigated by resorting to more advanced computational methods, e.g. quantum chemical calculations, to obtain cluster formation energies (section 2.5).

### 2.3 The nucleation theorems

A powerful, yet often misused tool to retrieve the critical cluster size is the first nucleation theorem. This theorem was first proposed by Kashchiev (1982) for unary, gas phase nucleation systems, with the aim to retrieve critical cluster sizes independent of the underlying nucleation theories; it was later extended to multicomponent nucleation by Oxtoby and Kashchiev (1994). The derivation proposed by Kashchiev is based on thermodynamics, but the first nucleation theorem can also be formulated by a kinetic approach based on the law of mass action (Bowles et al., 2000; McGraw & Wu, 2003). For a unary system, the first nucleation theorem reads

$$i_T^* \cong \left( \frac{d \ln J}{d \ln S} \right)_T - \left( \frac{d \ln K}{d \ln S} \right)_T, \quad (12)$$

where  $i_T^*$  is the number of molecules in the critical nucleus. For binary systems, the first nucleation theorem is given by

$$i_1^* \cong \left( \frac{d \ln J_{bin}}{d \ln a_1} \right)_{a_2, T} - \left( \frac{d \ln K_{bin}}{d \ln a_1} \right)_{a_2, T} \quad (13)$$

and

$$i_2^* \cong \left( \frac{d \ln J_{bin}}{d \ln a_2} \right)_{a_1, T} - \left( \frac{d \ln K_{bin}}{d \ln a_2} \right)_{a_1, T}, \quad (14)$$

where  $l_j^*$  is the number of molecules in the critical nucleus of component  $j$ ,  $a_j$  is the gas phase activity of component  $j$ . The first nucleation theorem has been applied to analyze data from numerous measurements (Brus, Hyvärinen, Ždímal, & Lihavainen, 2005; Kuang, McMurry, McCormick, & Eisele, 2008; Looijmans, Luijten, & van Dongen, 1995; Manka et al., 2010; McGraw & Zhang, 2008; Viisanen & Strey, 1994; Zollner et al., 2012) and molecular dynamics simulations (Matsubara, Koishi, Ebisuzaki, & Yasuoka, 2007; Napari, Julin, & Vehkamäki, 2009). From Eqs. (12-14), the implementation of the nucleation theorem requires a set of nucleation rate measurements at varying saturation levels at a fixed temperature and activities of other components. This requirement might be loosened if the logarithm of the nucleation rate is linear with respect to the logarithm of component concentrations over a wide nucleation rate range (McGraw & Zhang, 2008).

Despite being a convenient tool to derive critical cluster sizes, the first nucleation theorem has rather restrictive underlying assumptions. These assumptions have been summarized and tested against simulations by Kupiainen-Määttä et al. (2014) (see Table 1 in the cited work; other works that discuss the restrictions of the nucleation theorem include Ehrhart and Curtius (2013), Vehkamäki et al. (2012) and Malila, McGraw, Laaksonen, and Lehtinen (2015)). Some of these restrictions include the single high nucleation energy barrier, negligible coagulation, and the absence of external particle losses. In general, the first nucleation theorem cannot be naively applied without all inherent assumptions satisfied. For instance, the scavenging of nucleating clusters by pre-existing particles can affect the power dependence of the nucleation rate on the concentration of the nucleating species, leading to wrong interpretation of the critical cluster size if Eqs. (12-14) are applied (see Fig. 3 and Fig. 4 in Kupiainen-Määttä et al. (2014)). Therefore, literature-reported critical cluster sizes determined from the nucleation theorem should be treated critically, especially in atmospherically relevant studies in which particle sinks (particle wall losses, scavenging by pre-existing particles) strongly affect the nucleation process.

The second nucleation theorem (Ford, 1996, 1997; Vehkamäki & Ford, 2000) gives the excess internal energy of the critical cluster,  $E_x(n^*)$ , which is the energy difference between molecules in the cluster and molecules in the bulk condensed phase. For a unary system, the second nucleation theorem reads

$$E_x(n^*) \cong k_B T^2 \left( \frac{d \ln J}{dT} \right)_{\ln S} + k_B T - L, \quad (15)$$

where  $L$  is the latent heat of condensation per molecule.  $E_x(n^*)$  retrieved with the second nucleation theorem can be compared with theoretical predictions to better understand the nucleation mechanisms. Tanimura, Pathak, and Wyslouzil (2013) compared the excess energy of pure water clusters from the second nucleation theorem and that from quantum chemical calculations. This comparison suggests a constant

nucleation prefactor independent of monomer concentration, which might be caused by insufficient cooling of the critical nucleus at highly saturated conditions. Ogunronbi and Wyslouzil (2019) calculated  $E_x(n^*)$  for the critical clusters during pentane, hexane and heptane nucleation and found an overall stronger dependence of  $E_x(n^*)$  on  $n^*$  than predicted by the capillary approximation.

## 2.4 GDE-based kinetic simulations

Solving the general dynamic equations (GDE, Eqs. (2) and (3)) produces the cluster size distributions as a function of time (Ehrhart et al., 2016; Lovejoy, Curtius, & Froyd, 2004; McGrath et al., 2012; McMurry & Li, 2017; Wyslouzil & Wilemski, 1995; Yu, 2006; Yu et al., 2018). Added to that, using numerical approximation methods, e.g. the discrete-sectional method or the collocation method (Gelbard & Seinfeld, 1978; Gelbard, Tambour, & Seinfeld, 1980; Wu & Flagan, 1988), particle size distributions up to tens of micrometers can be computed at a small computational cost. This coverage of the whole particle size range makes GDE-based simulations a powerful tool, allowing the testing of the proposed nucleation mechanisms/theories against the experimentally observable particle size distributions (Kürten et al., 2018). To date, GDE-based kinetic analysis have been applied to predict nucleation rates (Yu, 2006; Yu et al., 2018), extract rate constants (Jen, McMurry, & Hanson, 2014; Li, Lippe, Krohn, & Signorell, 2019), identify nucleation mechanisms (Kürten et al., 2018), and examine the significance of physical/chemical processes (Kupiainen-Määttä et al., 2014; Li & McMurry, 2018; Liu et al., 2019; McMurry & Li, 2017). The kinetic equations can be further coupled with gas phase reaction schemes to incorporate gas phase chemistry (Carlsson et al., 2020; Carlsson & Zeuch, 2018), or combined with fluid dynamics equations to capture spatial characteristics of particle nucleation and growth (Kommu et al., 2004a, 2004b).

Despite being a straightforward approach, a few challenges stand in the way of wider applications of the GDE-based kinetic simulations. Elm et al. (2020) put up a checklist that researchers should consult while implementing GDE-based kinetic simulations (the terminology used in their work is ‘cluster dynamics simulations’). Here we selectively comment on two challenges complementary to their work. First, we note that a full kinetic modelling of multi-component nucleation systems inclusive of all possible cluster compositions is exceedingly complex. To mitigate the complexity one can either truncate some of the nucleation pathways (Jen et al., 2014), or to adopt simplification methods to replace kinetics with equilibrium distributions (Carlsson et al., 2020; Yu et al., 2018). For instance, in systems that contain a less volatile nucleating species X and a more volatile species Y, a cluster experiences many collisions with Y-molecules in between collisions with X-molecules. This allows modelling the distribution of clusters  $X_iY_j$  as in thermal equilibrium with species Y. Yu et al. (2018) adopted this strategy in their modelling of the multicomponent system including sulfuric acid, water, ammonia and ions: the clusters are assumed to be in equilibrium with both gas phase ammonia and water.

Second, the solution of the GDE equations requires rate constants as inputs, i.e. the evaporation rate of a  $j$ -mer ( $E_j$ ) and association rate between an  $i$ -mer and a  $j$ -mer ( $\beta_{i,j}$ ) must be fed into a numerical GDE solver. In practice,  $E_j$  is computed with Eq. (4) for a fully thermalized cluster at temperature  $T$ , while  $\beta_{i,j}$  can be approximated by the hard-sphere collision rate frequency function ( $\beta_{i,j,hs}$ ). Apparently, the computation of  $E_j$  requires  $\Delta G_j$ , which used to be approximated with the liquid droplet model as in CNT (Rao & McMurry, 1989), but is increasingly obtained from the quantum chemical calculations (see section 2.5). Because of the exponential dependence,  $E_j$  is highly sensitive to the accuracy of  $\Delta G_j$ . This introduces large uncertainties to the kinetic modelling even if  $\Delta G_j$  is based on quantum chemistry (with the best achievable accuracy around  $\pm 1$  kcal/mol). In contrast, using  $\beta_{i,j,hs}$  as a substitute for  $\beta_{i,j}$  usually leads to smaller errors, but  $\beta_{i,j}$  can still deviate from  $\beta_{i,j,hs}$  in both directions. First, in the calculation of  $\beta_{i,j,hs}$ , the cluster shape is often assumed to be spherical with its density taken to be the bulk density – this can be a very rough approximation for the molecular clusters (Ang elil et al., 2014). Second, long range interactions, e.g. Van der Waals forces, dipole-dipole interactions, dipole-ion interactions, can lead to enhanced  $\beta_{i,j}$ . This enhancement has been known in the aerosol community for particle coagulations (Ouyang, Gopalakrishnan, & Hogan, 2012; Scaats, 1989) and has been investigated on the molecular level using molecular dynamics simulations (Halonen, Zapadinsky, Kurt en, Vehkam aki, & Reischl, 2019; Yang, Goudeli, & Hogan, 2018) and through experiments (Krohn et al., 2020; Li et al., 2019; Stolzenburg et al., 2020). Third,  $\beta_{i,j}$  can be smaller than the hard sphere rate as ‘collisions’ does not necessarily lead to formation of newly coalesced clusters, i.e. the accommodation coefficient is less than unity. This may originate from steric effects specific to the molecular and cluster structures, or from energy nonaccommodation, i.e. the excess translational energy released in cluster formation (Yang, Drossinos, & Hogan, 2019) leads to instant breakup of the newly formed, metastable clusters (Kurt en et al., 2010). At atmospheric conditions, energy non-accommodation is less of a concern because the high-concentration air molecules instantly take away the excess energy to stabilize the clusters. Hydration of the colliding entities, common at atmospheric conditions, also facilitates the allocation of the excess energy (Kurt en et al., 2010; Loukonen, Bork, & Vehkam aki, 2014a). However, at low pressures,  $\beta_{i,j}$  can deviate from  $\beta_{i,j,hs}$  by orders of magnitude. For instance, the association rate of two water monomers have been found to be considerably lower than the monomer-monomer collision rates from both theories and experiments (Bourgalais et al., 2016; Lippe, Chakrabarty, Ferreiro, Tanaka, & Signorell, 2018). It is currently unclear to what extent the deviation of  $\beta_{i,j}$  from collision rates can affect nucleation estimation under various experimental conditions, but one could expect energy non-accommodation to play a more important role at reduced pressures.

## 2.5 Cluster structure and free energy calculations

GDE-based kinetic simulations are useful for generating cluster size distributions but shed no light on cluster structures and formation energies. Three molecular-level computational methods, i.e. quantum chemistry (QC) calculations, Monte-Carlo (MC) simulations and molecular dynamics (MD) simulations, help fill this gap. Among these methods, QC calculation is based on first principles of quantum mechanics with the highest level of accuracy in terms of cluster energy (uncertainties down to  $\pm 1$  kcal/mol). However, accurate QC calculations are limited to relatively small clusters because of computational cost. In contrast, both MC and MD simulations (Frenkel & Smit, 2002) are mostly based on atomic force fields and are applicable to larger clusters with decreased accuracy. Since the experimental detection and analysis of molecular clusters is still exceedingly challenging, these simulations offer insight on nucleating cluster properties that are otherwise unavailable.

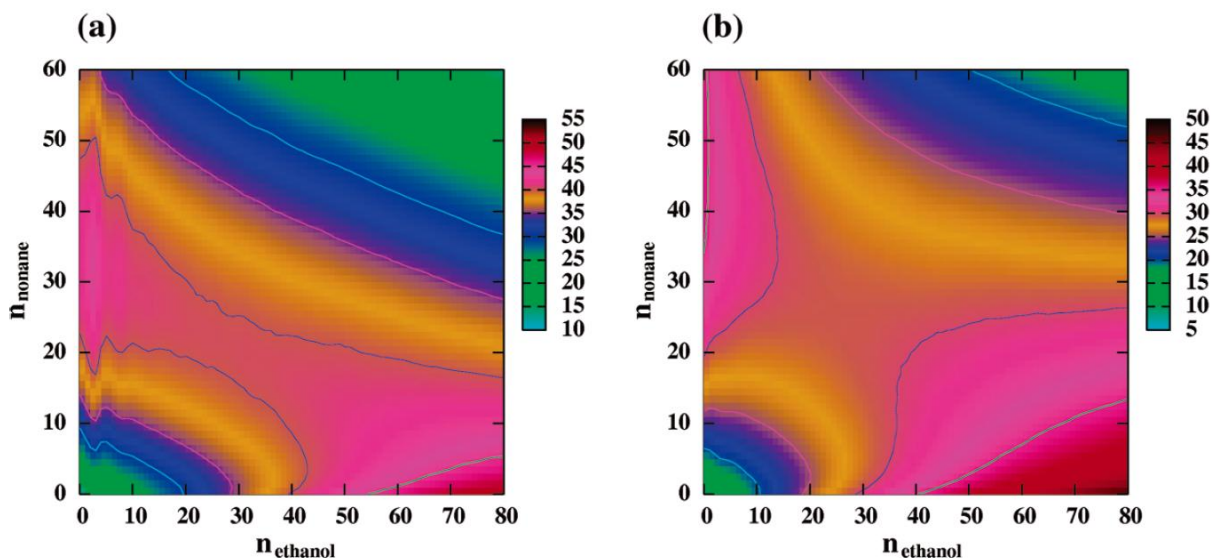
The application of QC to simulate nucleating clusters has seen rapid increase in recent years, especially in atmospheric-relevant nucleation studies. State-of-the-art QC methods applied to atmospheric nucleating clusters are comprehensively reviewed by Elm et al. (2020). Here we only briefly summarize the main applications of QC simulations:

1. QC-based cluster Gibbs free energies can be substituted into the CNT framework, e.g. Eq. (5), to calculate nucleation rates. Nucleation rates calculation with QC-based free energies often show improved performance compared to CNT predictions (Bromley, Gómez Martín, & Plane, 2016; Du, Nadykto, & Yu, 2009; Duplissy et al., 2016; Goumans & Bromley, 2012; Krohn et al., 2020; Merikanto et al., 2016).
2. Through Eq. (4), QC-based cluster free energy can be used to infer cluster evaporation rates, which are inputs to GDE-based kinetic models introduced in the previous section (Carlsson et al., 2020; McGrath et al., 2012). These evaporation rates also provide a benchmark against which experimentally extracted rates can be compared (Jen et al., 2014; Ortega et al., 2012).
3. QC calculations play an essential role in estimating the extent of hydration for the atmospheric nucleating clusters (Henschel et al., 2016; Henschel et al., 2014; Kildgaard et al., 2018a, 2018b; Kurtén, Noppel, Vehkamäki, Salonen, & Kulmala, 2007; Loukonen et al., 2010; Rasmussen et al., 2020; Temelso et al., 2012) since water molecules evaporate almost completely even in the state-of-the-art atmospheric cluster detection methods.
4. QC calculations help identify the key nucleating species and potential nucleation pathways by examining the cluster stability (Bork, Elm, Olenius, & Vehkamäki, 2014; Elm, Jen, Kurtén, & Vehkamäki, 2016; Elm, Kurtén, Bilde, & Mikkelsen, 2014; Elm, Passananti, Kurtén, & Vehkamäki, 2017; Lin et al., 2019; Myllys, Elm, Halonen, Kurtén, & Vehkamäki, 2016; Ortega et al., 2016;

Ortega et al., 2012; Xu & Zhang, 2012; Zhao, Khalizov, Zhang, & McGraw, 2009). For instance, through QC simulations Elm, Myllys, and Kurtén (2017) proposed that an organic oxidation product can stabilize sulfuric acid clusters if the molecule has no or weak intramolecular hydrogen bonds and at least two carboxylic acid groups. Another example is the computational study by Liu et al. (2019), in which methanol is found to have a quenching effect on NPF by scavenging SO<sub>3</sub> to form methyl hydrogen sulfate.

QC calculations are performed on many different levels, leading to difficulties of data inter-comparison from different works. Recently, 633 unique atmospherically relevant molecular clusters were compiled into a database with the cluster structure and vibrational frequency calculated on the  $\omega$ B97X-D/6-31++G(d,p) level of theory and single point cluster energy calculated with DLPNO-CCSD(T)/aug-cc-pVTZ (Elm, 2019). Such a database is one step towards constructing comprehensive kinetic models to simulate atmospheric new particle formation.

Compared to QC, MC simulations have seen more applications in fundamental nucleation studies. Nucleating clusters examined by MC mainly include Lenard-Jones clusters (ten Wolde & Frenkel, 1998), water clusters (Merikanto, Vehkamäki, & Zapadinsky, 2004; Merikanto, Zapadinsky, Lauri, & Vehkamäki, 2007) and clusters formed in binary/multicomponent systems (Chen, Siepmann, & Klein, 2003; Chen, Siepmann, Oh, & Klein, 2001; McKenzie & Chen, 2006; Nellas & Chen, 2008; Nellas, Keasler, Siepmann, & Chen, 2010; Ogunronbi, Sepehri, Chen, & Wyslouzil, 2018). In the works of Chen, Siepmann, and co-workers (Kathmann et al., 2009), a combination of aggregation-volume-bias Monte Carlo, umbrella sampling, and histogram reweighting is applied to elucidate the structure and formation energy of the nucleating clusters. One finding of their work is that as the nucleating cluster grows in size, the shape of the cluster transitions from fractal-like to spherical (Chen, Siepmann, Oh, & Klein, 2002). Their work has also provided insight into the microheterogeneity (nonbulk-like mixing) of the nucleating clusters, e.g. core-shell structures and dumbbells (Nellas, Chen, & Ilja Siepmann, 2007). Through the construction of nucleation free energy surfaces, distinct nucleation pathways are identifiable in various combinations of nucleating vapors. For instance, in McKenzie and Chen (2006), binary nucleation of water-ethanol, water-nonane and ethanol-nonane are shown to follow different pathways: 1. water-ethanol vapors nucleate through the formation of mixed nuclei; 2. water-nonane vapors have two independent nucleation channels, with water or nonane enriched nuclei; 3. ethanol-nonane mixtures can nucleate through multiple nucleation pathways with varying cluster compositions. The nucleation energy surfaces for an ethanol-nonane system at 300 K and 360 K are shown in Figs. 2a and 2b, respectively, indicating that the formation free energy is similar for a range of cluster compositions.



**Fig 2.** Contour plots for the nucleation free energy surface for a binary ethanol-nonane system at the following conditions (a)  $T = 300 \text{ K}$ ,  $N_{\text{nonane}} = 1.7 \times 10^{-5} \text{ \AA}^{-3}$ ,  $N_{\text{ethanol}} = 4.2 \times 10^{-6} \text{ \AA}^{-3}$  (b)  $T = 360 \text{ K}$ ,  $N_{\text{nonane}} = 1.7 \times 10^{-5} \text{ \AA}^{-3}$ ,  $N_{\text{ethanol}} = 3.8 \times 10^{-6} \text{ \AA}^{-3}$ . The color corresponds to cluster free energies of formation in units of  $k_{\text{B}}T$ .  $n_{\text{ethanol}}$  and  $n_{\text{nonane}}$  are the numbers of ethanol and nonane molecules in the clusters, respectively. [Reprinted with permission from McKenzie & Chen (2006), *The Journal of Physical Chemistry*, 110, 3511-3516. Copyright 2006 American Chemical Society.]

Similar to MC, MD simulations can also be applied to simulate equilibrium cluster properties (Horsch, Vrabec, & Hasse, 2008; Julin, Napari, Merikanto, & Vehkamäki, 2008; Laasonen, Wonczak, Strey, & Laaksonen, 2000; Napari et al., 2009). Additionally, first-principles MD simulations have been applied to understand the formation and the stability of atmospheric relevant clusters (Loukonen et al., 2014a; Loukonen, Kuo, McGrath, & Vehkamäki, 2014b). However, MD is more powerful as a method to directly mimic gas-to-particle transitions, as introduced in the next section.

## 2.6 Molecular dynamics simulations

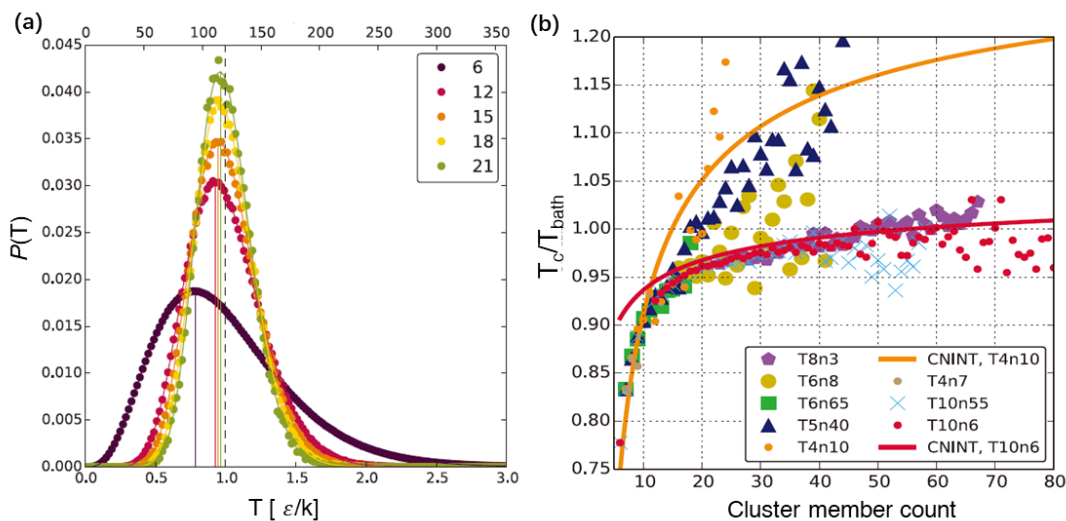
Through tracking down every atom in a simulation domain, MD simulations offer a way to directly simulate the highly dynamic nucleation processes. As MD uses force fields to describe atomic/molecular interactions, the mostly investigated nucleating species by MD are Lenard-Jones molecules, the simplicity of which help rule out complicating factors and speed up simulation (Angélil et al., 2014; Halonen et al., 2018; Napari et al., 2009; Salvalaglio, Tiwary, Maggioni, Mazzotti, & Parrinello, 2016; Tsai, Smith, & Tiwary, 2019; Zhukhovitskii, 2016). Another substance that has attracted a significant amount of attention is water (Angélil, Diemand, Tanaka, & Tanaka, 2015; Dumitrescu, Huinink, Smeulders, Dam, & Gastra-Nedeia, 2018; Dumitrescu, Smeulders, Dam, & Gastra-Nedeia, 2017; Duška, Němec, Hrubý, Vinš, & Planková, 2015; Matsubara et al., 2007; Tanaka, Kawano, & Tanaka, 2014; Yasuoka & Matsumoto, 1998b;



Zipoli et al., 2013). Metal, binary and ternary nucleation systems have also been investigated by MD (Braun, Kalikmanov, & Kraska, 2014; Braun & Kraska, 2012; Lümmen & Kraska, 2006; Römer & Kraska, 2007).

MD simulations come on different scales. Reliable nucleation statistics can either be extracted by many repetitions of nucleation in small-scale systems (a few hundred atoms), or fewer runs of large-scale systems (up to  $10^9$  atoms). Corresponding to the simulation scale, different methods are available to analyze the simulation results. For small-scale systems, the mean first-passage time (MFPT) method (Hänggi, Talkner, & Borkovec, 1990) is often employed to calculate nucleation rates. This method fits a three-parameter expression to the mean first passage time of  $k$ -mers, retrieving the nucleation time  $\tau_J$ , the Zeldovich factor (Zeldovich, 1943), and the critical cluster size. The nucleation rate is then given by the inverse of the simulation domain volume multiplied by  $\tau_J$ . For large-scale simulations, the Yasuoka–Matsumoto method (Yasuoka & Matsumoto, 1998a) is often applied. This method tracks the total number of clusters greater than threshold sizes, and the nucleation rate is given by derivativizing the cluster concentrations with respect to time. Chkonia, Wölk, Strey, Wedekind, and Reguera (2009) compared four methods to retrieve nucleation rates from MD simulations (the other two methods are the ‘direct observation method’ and the ‘survival probability method’). They concluded that when applied properly, the nucleation rates derived from the four methods differ within a factor of two.

MD arguably provides the most comprehensive information of the nucleation process, as the distribution of nucleating cluster properties can be retrieved by taking snapshots of a fast-evolving nucleation system. These properties include cluster temperatures, density profiles, potential energies and shapes (Angélil et al., 2014; Ayuba, Suh, Nomura, Ebisuzaki, & Yasuoka, 2018; Wedekind, Reguera, & Strey, 2007). Take the cluster temperature distribution in a Lennard-Jones nucleation system (Angélil et al., 2014) as an example. Fig. 3a shows the temperature distribution of selected clusters from a single MD run, while Fig. 3b shows the ratio between the most probable cluster temperature and bath temperature as a function of cluster sizes for multiple MD runs. Fig. 3a clearly indicates that clusters of the same size have a non-Gaussian temperature distribution rather than a single, uniform temperature. This temperature distribution is fitted with the probability distribution function derived by McGraw and LaViolette (1995) (solid lines). Fig. 3b shows that although sub-critical clusters have most probable temperatures slightly lower than the bath temperature, post-critical clusters can retain much of the heat released upon argon phase transition, leading the temperature to rise well-above the bath temperature. This rise of cluster temperature as a function of cluster size is also discussed by Wedekind et al. (2007).



**Fig. 3.** (a) Temperature probability distributions (circles) for selected cluster sizes (see legend) in an MD nucleation simulation of Lennard-Jones molecules. The solid distribution curves are obtained through fitting the temperature distribution function proposed by McGraw and LaViolette (1995). The vertical solid lines indicate the most probable cluster temperature and the vertical dashed line shows the average bath temperature. (b) The ratio of the most probable cluster temperatures,  $T_c$ , to the bath temperature  $T_{\text{bath}}$ . The solid lines indicate the predictions from the classical non-isothermal theory (CNINT) from Feder et al. (1966) for runs T4n10 and T10n6. The labels indicate different MD simulation runs with in the format TXnY. X indicates system temperature and is equal to  $10 \times \frac{\epsilon}{k_B}$ ; Y indicates the concentration of the Lennard-Jones molecules at the beginning of the simulation (see Table 1 in the cited work for details).  $\epsilon$  is the potential well depth in the Lennard-Jones model. [Reprinted from Angéilil, R. et al. (2014) *Journal of Chemical Physics*, 140, 074303-074303, with the permission of AIP Publishing]

With ease of scanning through simulation parameters, MD simulations facilitate tests of nucleation theories that are difficult to verify experimentally. One persisting problem in nucleation studies is the effect of carrier gas pressure and composition on nucleation rates, with literature reporting mixed evidences. Wedekind, Hyvärinen, Brus, and Reguera (2008) devised MD simulations to test their proposed mechanism on the effect of carrier gas pressure: higher carrier gas pressure increases nucleation rates by suppressing the non-isothermal effects, but decreases nucleation rates by adding extra volume work to the cluster formation process. They were able to vary the ratio between the carrier gas (helium) to the nucleating species (argon) from 1 to 20 in their MD simulations, which is hardly achievable by any given nucleation apparatus. Also dealing with the effect of carrier gas, Yasuoka and Zeng (2007) used carrier gas molecules with different interaction potentials in their simulations. They found that the effect of carrier gas pressure depends strongly on the potential model of the carrier gas molecules.

As a brute force method, MD simulation tracks the motion of every atom in the simulation domain, hence computational cost poses a major limit for MD applicability. Accurate simulation of atomic movements requires the time step used in MD to be a few femtoseconds, with the total simulation time

typically up to microseconds. Experimentally accessible nucleation rates of up to  $10^{17} \text{ cm}^{-3} \text{ s}^{-1}$  (Wyslouzil & Wölk, 2016), once converted to the units more relevant for MD simulations, i.e.  $\text{nm}^{-3} \mu\text{s}^{-1}$ , are only  $10^{-10}$  in value. This implies that nucleation is a truly ‘rare’ event from an MD perspective: to capture these events large simulation domains and long simulation times are needed. Limited by computational cost, most MD simulations use high supersaturation ratios to produce nucleation rates much higher than the experimentally accessible rates. Exceptions are the large-scale MD simulations performed by Tanaka and co-workers. For Lenard-Jones (LJ) systems,  $10^8$ - $10^9$  atoms have been simulated for a time duration of up to  $1.2 \mu\text{s}$  (Diemand, Angélil, Tanaka, & Tanaka, 2013). The scale of their simulation allows a nucleation rate as low as  $10^{17} \text{ cm}^{-3} \text{ s}^{-1}$  to be achieved, overlapping with nucleation rates obtained from supersonic nozzles experiments (Sinha et al., 2010). For water nucleation, Angélil et al. (2015) performed the largest MD simulation so far: They simulated water nucleation containing  $4 \times 10^6$  molecules, achieving a nucleation rate as low as  $10^{19} \text{ cm}^{-3} \text{ s}^{-1}$ . Recently, Salvalaglio et al. (2016) proposed using Well Tempered Metadynamics to further extend the accessible nucleation rates by MD simulations. Using small scale simulations with only 512 argon molecules, their results are in quantitative agreement with nucleation rates from the aforementioned large scale simulations (Diemand et al., 2013). Very importantly, Salvalaglio et al. retrieved nucleation rates as low as  $10^{13} \text{ cm}^{-3} \text{ s}^{-1}$ , showing great promise to perform parallel MD simulations and experiments that can be directly compared in future investigations.

A more nuanced aspect of MD simulations concerns the utilization of ‘thermostats’, which remove the latent heat released upon phase transition. Ideally, carrier gas should be used to remove heat from the nucleating clusters to mimic real experiments, but the incorporation of high-concentration carrier gas molecules incurs extra computational cost. Halonen et al. (2018) compiled MD-simulated nucleation rates from studies (Diemand et al., 2013; Napari et al., 2009; Tanaka, Tanaka, Yamamoto, & Kawamura, 2011; Wedekind et al., 2007) in which four thermostats (velocity scaling, Nose-Hoover, Berendsen, and stochastic Langevin) are applied. These rates were compared with reference rates assuming the clusters are fully thermalized, with cluster free energy determined from Monte-Carlo simulations. It is found that the MD-simulated nucleation rates are consistently lower than the MC-based rates. At low temperature, the deviation exceeds the non-isothermal effects predicted by Feder et al. (1966). This raises questions as to if an MD simulation with an artificial thermostat could represent a real nucleation experiment. A number of MD simulations have been performed using carrier gases as the thermostat (Wedekind et al., 2008; Wedekind et al., 2007; Yasuoka & Matsumoto, 1998b; Yasuoka & Zeng, 2007). However, to date there are no definitive guidelines as to the choice of thermostats or carrier gas concentrations. Systematic investigation on this front is still needed.

The application of MD simulations to atmospheric nucleation is very challenging. Compared with fundamental nucleation studies, atmospheric nucleation is characterized by even lower nucleation rates, making it extremely difficult to for MD to capture the nucleation events. Besides, MD simulation of atmospheric nucleation in general requires reactive force fields (Senftle et al., 2016) or even *ab initio* MD simulations to accurately simulate chemical reactions. *Ab initio* MD simulations of atmospheric nucleation are currently not feasible, but might come into reach as massive parallel Car-Parrinello type *ab initio* MD codes and computing infrastructures continue to develop.

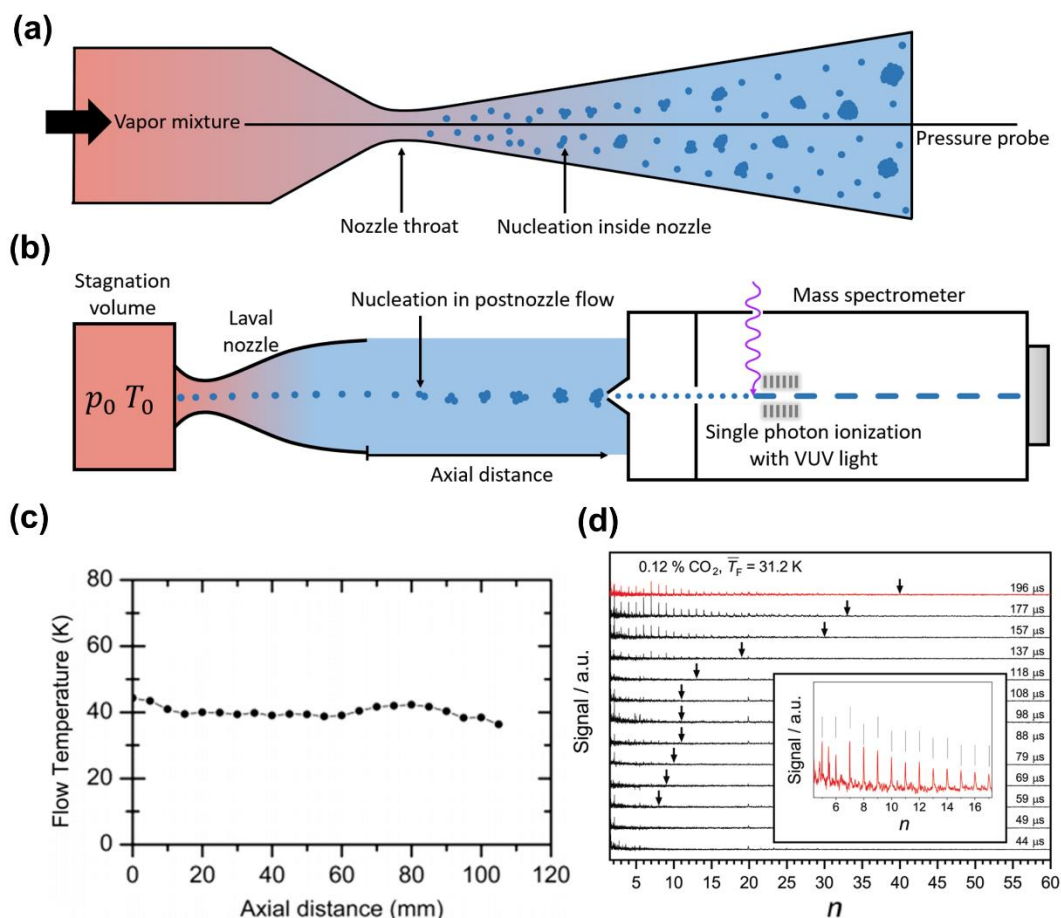
### 3. Experimental measurements of nucleation

Experimental nucleation studies mainly belong in two categories: those that examine nucleation from a fundamental point of view (Wyslouzil & Wölk, 2016) and those that focus on nucleation relevant to Earth's atmosphere (Lee et al., 2019). In the former category, the nucleating vapors selected often have (relatively) simple molecular structures, i.e. water, CO<sub>2</sub>, alkanes, alcohols, and noble gases. The concentrations of the nucleating vapors are usually known, hence the major experimental challenges to retrieve molecular level information are the successful detection of nucleating clusters and resolving nucleation dynamics within the experimental time scale. In the latter category, i.e. atmosphere-relevant nucleation studies, the time scale of nucleation is less of a concern (minutes to hours), but it is challenging to identify all the species that contribute to nucleation. Over the years, a wide range of techniques have been developed to understand nucleation of both categories, but not many directly provide molecular level information. In the following, we focus on two techniques that explicitly resolve nucleating cluster compositions and concentrations. The first one is controlled Laval expansion coupled with time-of-flight mass spectrometry, mainly applied in fundamental nucleation studies; the second is atmospheric pressure inlet-mass spectrometry, the current go-to technique for atmospheric nucleating cluster measurements. Other than these two techniques, direct experimental information of the nucleating clusters are not available, though constraining equations (e.g. heat and mass balance equations) can be applied to infer molecular cluster concentrations in some systems (Tanimura, Wyslouzil, & Wilemski, 2010). For a detailed account of other nucleation setups, we refer to reader to the excellent review by Wyslouzil and Wölk (2016).

#### 3. 1 Nucleation in postnozzle flows of Laval expansions

Laval nozzles (or converging-diverging nozzles) allow gas expansion to proceed in a well-controlled manner with a strong cooling effect. The variation of pressure, temperature, gas speed inside the nozzle are known functions of nozzle geometries (Saad, 1985). This precise knowledge of gas properties makes Laval expansion suitable for nucleation studies. Wegener and co-workers were the first to study gas phase nucleation inside Laval nozzles (Wegener, 1975; Wegener & Wu, 1976). Later, Wyslouzil and co-

workers further developed this technique by incorporating a range of nucleation characterization techniques including pressure trace measurements, infra-red spectroscopy and small angle X-ray scattering (Ghosh et al., 2010; Khan, Heath, Dieregswiler, Wyslouzil, & Strey, 2003; Pathak, Wölk, Strey, & Wyslouzil, 2014; Tanimura, Dieregswiler, & Wyslouzil, 2010; Wyslouzil, Wilemski, Strey, Seifert, & Winans, 2007). Although molecular level information on the smallest nucleating cluster are not directly available, valuable information on nucleation rates, nucleated particle phase transition has been obtained with this method. An illustration of nucleation inside Laval nozzles is shown in Fig. 4a.



**Fig. 4.** (a) An illustration of gas phase nucleation inside Laval nozzles. The pressure probe is used to measure the gas pressure inside the nozzle, the deviation of which from theoretical values could indicate a nucleation event. (b) A simplified schematic of the nucleation setup developed by Signorell and co-workers. See the text for a detailed explanation of its working principles. In both (a) and (b), the transition of color from red to blue indicates the drop in temperature of the carrier gas. (c) Flow temperature characterization in the axial direction of the postnozzle flow of the ETH setup. [Reprinted with permission from Schläppi et al. (2015), *Physical Chemistry Chemical Physics*, 17 (39), 25761-25771—Published by the PCCP Owner Societies] (d) Cluster size distribution measured at different nucleation times (axial distances) during a  $\text{CO}_2$  nucleation event.  $n$  is the number of molecules within the clusters; the black arrows indicate the position of the largest observable clusters. The inset plot is a zoomed-in spectrum of the uppermost trace. [Reprinted from

A recent, novel application of the Laval nozzle to nucleation studies does not induce nucleation inside the nozzle, but rather in a uniform postnozzle flow. The uniform postnozzle flow has previously found applications in chemical kinetics by several groups (Dupeyrat, Marquette, & Rowe, 1985; Lee, Hoobler, & Leone, 2000; Rowe, Marquette, & Rebrion, 1989), but its application to gas phase nucleation has been mainly explored with the Cinétique de Réaction en Ecoulement Supersonique Uniforme (CRESU) setup developed by Rowe and co-workers (Bourgalais et al., 2016; Sabbah, Biennier, Klippenstein, Sims, & Rowe, 2010), and the setup in ETH Zürich developed by Signorell and coworkers (Chakrabarty et al., 2017; Ferreira, Chakrabarty, Schläppi, & Signorell, 2016; Li et al., 2019; Lippe et al., 2018; Lippe et al., 2019; Schläppi et al., 2015). Since the ETH setup is equipped with soft ionization techniques to better preserve cluster integrity (in contrast to electron impact ionization used in the CRESU by Bourgalais et al. (2016)), in the following we use the setup schematic from the Signorell group (Fig. 4b) to demonstrate the working principles of this technique.

In a typical experiment, one or more nucleating vapors along with a carrier gas (usually nitrogen, argon and their mixtures) is supplied to the stagnation volume (red shaded area) of a Laval nozzle with pulsed valves. As the gas expands through nozzle, the flow speed increases while the flow temperature and pressure quickly drop (the temperature drop is indicated by the color shift from red to blue in Fig. 4b), leading to supersaturations of the nucleating vapors. By matching the chamber pressure to the flow pressure at the nozzle exit, the postnozzle flow achieves and maintains uniformity in speed, temperature, and pressure within a  $\sim 10$  cm distance. This is in contrast to a free gas expansion process with strong spatial gradients of flow properties. The flow uniformity is the key to nucleation experiments, not only because nucleation is extremely sensitive to ambient conditions, but also because flow uniformity guarantees that the nucleation-related rate constants remain the same in the postnozzle region, enabling detailed kinetic analysis. Fig. 4c illustrates the flow uniformity by showing the temperature fluctuations as a function of the axial distance (Schläppi et al., 2015). The nucleating clusters formed in the postnozzle flow are sampled by a skimmer that connects to a differential chamber at  $10^{-5}$  Pa, and are then directed into a time-of-flight chamber at  $10^{-7}$  Pa, where the clusters are ionized by single photon ionization with a vacuum ultraviolet (VUV) laser (Belau, Wilson, Leone, & Ahmed, 2007; Chakrabarty et al., 2017; Litman et al., 2013). We note that the clusters remain neutral until they are ionized in a collision-less, low pressure environment. This avoids collision-induced dissociation (CID) of the ionized clusters in ion optics (compare to the APi-Tof introduced in the next section). With the combination of VUV ionization and lack of CID, the integrity of weakly-bound clusters is well-preserved. The laser-ionized clusters are then extracted by an electrostatic

lens and detected by a microchannel plate. To increase instrument sensitivity, the voltage applied to the electrostatic lens is up to 30 kV.

To capture the temporal variation of the cluster size distributions in the nucleation process, the distance between the nozzle exit and the skimmer is adjustable by mounting the Laval nozzle on a translation stage. At constant flow speed, the distance between the nozzle-exit and the skimmer translates to nucleation time, and the allowable time resolution is down to  $\sim 2 \mu\text{s}$ . As an example, Fig. 4d shows  $\text{CO}_2$  cluster size distributions at different nucleation times measured at 31.2 K and a  $\text{CO}_2$  percentage of 0.12% (Krohn et al., 2020). By adding a gas standard such as  $\text{CH}_4$  with known photoionization cross section into the carrier gas, the absolute concentration of each detectable cluster can be quantified by the following equation,

$$N_n^a = \frac{I_n}{I^s} \frac{\sigma^s}{n \cdot \sigma^a} \cdot N^s \quad (16)$$

where  $N_n$  stands for the number concentration of clusters containing  $n$  monomers,  $I$  for the ion signal and  $\sigma$  for the molecular photoionization cross section. The superscripts 'a' and 's' stand for 'analyte' and 'standard', respectively.

Through the combination of the above techniques, weakly-bound clusters can be detected and quantified, with their temporal variations resolved. To date, the Laval-based setups have provided unprecedented details on the unary homogeneous nucleation of propane (Ferreiro et al., 2016; Schläppi et al., 2015), toluene (Chakrabarty et al., 2017), water (Bourgalais et al., 2016; Li et al., 2019; Lippe et al., 2018) and  $\text{CO}_2$  (Krohn et al., 2020; Lippe et al., 2019). Apart from the quantities available from conventional nucleation measurements, e.g. onset conditions of nucleation and the nucleation rates, the time-resolved cluster size distributions enable the determination of dimerization rate constants and monomer-cluster association rate constants (Li et al., 2019; Lippe et al., 2018). The extracted rate constants further allow direct comparison between experiments and calculations based on first principles (Bourgalais et al., 2016; Sabbah et al., 2010). By changing nozzle geometries and carrier gas compositions, the relative magnitude of the monomer association rate and cluster evaporation rate can also be measured as a function of temperature, providing evidence of shifting nucleation barrier heights as temperature varies (Krohn et al., 2020).

Despite its great potential to unveil the nucleation process on the molecular level, currently there are a few limiting factors for this Laval-based technique. First, even though single photon ionization is in general a soft ionization technique, it still leads to composition-dependent cluster fragmentation and intra-cluster chemistry. Water clusters may only lose a monomer upon single photon ionization (Belau et al.,

2007; Litman et al., 2013), but intra-cluster chemical reactions can follow ionization for other species, e.g. dimethyl ether and acids (Litman et al., 2013). Second, to date nucleation experiments with the Laval-based setups have been limited to low-temperatures (under 100 K). While this temperature range is advantageous for understanding nucleation by weakly-interacting species, substances with stronger intermolecular interactions, e.g. those of atmospheric relevance, may not exhibit nucleation behavior of interest. To study nucleation of these substances, the accessible temperature of the postnozzle flow need to be expanded.

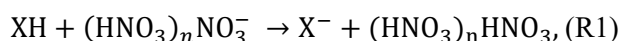
### **3.2 Detection of nucleating clusters at atmospheric conditions**

Atmospheric nucleation (or new particle formation, NPF) is the most extensively studied nucleation phenomenon because of its influence on the climate, on human health and its inherent complexity (Chu et al., 2019; Gordon et al., 2017; Guo et al., 2014; Kazil et al., 2010; Lee et al., 2019; Merikanto et al., 2009; Spracklen et al., 2008; Wang et al., 2017; Zhang, Khalizov, Wang, Hu, & Xu, 2012). Elucidation of the NPF mechanisms is a twofold problem that entails (a) identification and quantification of the nucleating vapors and ions in the atmosphere (Johnston & Kerecman, 2019; Junninen et al., 2010; Mirme & Mirme, 2013; Zhao, 2018), and (b) determination of the chemical composition and concentration of the nucleating clusters. Here we focus on the latter and look into the instruments that are the work horses for detection of atmospheric nucleating clusters, i.e. the Cluster-CIMS and (CI)-APi-TOF.

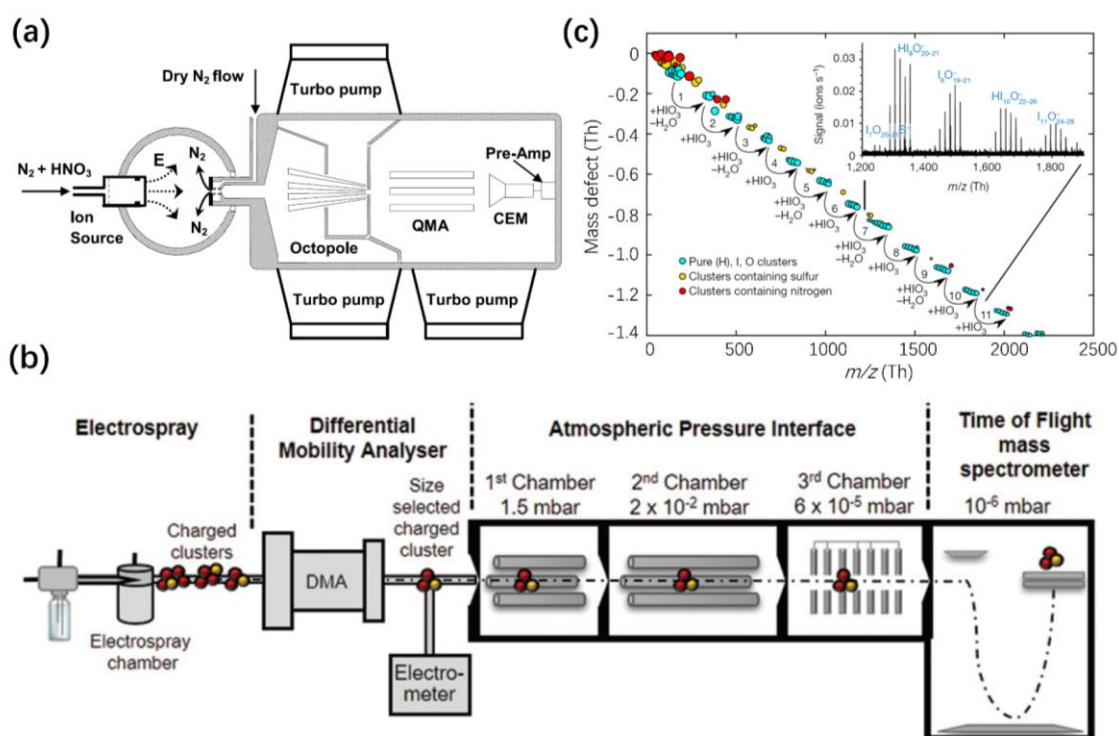
Nucleating clusters formed in atmospheric nucleation events are both low in concentration and fragile, hence the detection and quantification of these clusters demand not only high instrument sensitivity, but also cluster integrity being preserved to a good extent. Eisele and co-workers (Ball, Hanson, Eisele, & McMurry, 1999; Eisele & Hanson, 2000; Eisele & Tanner, 1993; Hanson & Eisele, 2002) were the first to explore utilizing chemical ionization to detect atmospherically-relevant, neutral nucleating clusters and laid the ground for the current detection methods. They carried out mass spectrometric analysis of nucleating vapors and clusters, preceded by analyte chemical ionization with nitrate ions at atmospheric pressure. Ionization in the atmosphere is essential to avoid dilution of the nucleating clusters, and chemical ionization with nitrate ions ensures that the ionization process is ‘soft’ to minimize cluster fragmentation. The prototype instrument used in their works later evolved into the Cluster-CIMS, i.e. cluster chemical ionization mass spectrometer (Chen et al., 2012; Jen, Bachman, Zhao, McMurry, & Hanson, 2016a; Jen et al., 2014; Jen, Zhao, McMurry, & Hanson, 2016b; Jiang et al., 2011; Zhao, Eisele, Titcombe, Kuang, & McMurry, 2010; Zhao et al., 2011). Fig. 5a shows a schematic of this instrumentation consisting of (from the left to the right) the ionization source, the atmospheric pressure interface, an octupole to facilitate ion transmission, a quadrupole for ion separation and an ion detector. Nitrate ions are produced by passing trace amounts of nitric acid vapors nearby a radioactive source, with chemical ionization taking place in either a



flow tube operation mode or a traverse ion operation mode (the mode is unspecified in Fig. 5a) following the reaction schemes:



R1 indicates ionization by proton transfer reaction and R2 indicates ionization by adduct formation. By changing the chemical ionization reaction time, reagent ion-induced cluster formation and the original neutral clusters can be distinguished (Eisele & Hanson, 2000; Zhao et al., 2010).



**Fig. 5.** (a) The instrument schematic of the Cluster-CIMS developed by Zhao et al. [Reprinted with permission from Zhao et al. (2010), *Journal of Geophysical Research: Atmospheres*, 115(D8). Copyright 2010 by the American Geophysical Union] (b) An illustrative instrument schematic of the API-ToF. A cluster generation setup is connected to the front of the API to produce clusters of known compositions to facilitate instrument calibration. The API consists of three chambers with sequentially decreasing pressures, with the third chamber connected to the time-of-flight chamber. [Reprinted with permission from Passananti et al. (2019), *Chemical Communications*, 55(42), 5946-5949 – Published by The Royal Society of Chemistry] (c) CI-API-ToF measured mass defect plot as a function of cluster mass-to-charge ratio ( $m/z$ ) during a nucleation event initiated by HIO<sub>3</sub>. The clusters are hypothesized to form via sequential addition of HIO<sub>3</sub>. The area of the symbols are proportional to the observed signal. The inset plot is a portion of the recorded raw mass spectrum. Refer to the cited work for chemical reactions of 1-11. [Adapted with permission by Springer Nature: *Nature*, Molecular-scale evidence of aerosol particle formation via sequential addition of HIO<sub>3</sub>, Sipilä et al. (2016). Copyright 2016]

The application of cluster-CIMS to atmospheric field measurements marked an important step in detecting atmospheric neutral clusters (Chen et al., 2012; Jiang et al., 2011; Zhao et al., 2010). However, the Cluster-CIMS uses a quadrupole to separate charged clusters and only has unit-mass resolution, which is insufficient to fully resolve the exact molecular content of the nucleating clusters. This limitation was lifted through coupling time-of-flight spectrometry (Tof), chemical ionization (CI) and an atmospheric pressure inlet (APi), i.e. the CI-APi-Tof (Jokinen et al., 2012). Without the chemical ionization inlet, the CI-APi-Tof reduces to an APi-Tof (Junninen et al., 2010), which is suitable for the detection of naturally charged nucleating species and ion-induced nucleation (Duplissy et al., 2016; Kirkby et al., 2016). Fig. 5b shows a schematic of the APi-Tof connected to a cluster-generation setup used for instrument calibration. The (CI-)APi-Tof has a resolving power between 3000 and 7000  $m/z$ , enabling it to determine the exact molecular composition of neutral nucleating clusters. The mass-spectrometric data retrieved from (CI-)APi-Tof measurements are usually presented as mass defect plots, as demonstrated in Fig. 5c. With the (CI-)APi-Tof, a wide range of atmospheric nucleating clusters have been identified, including but not limited to sulfuric acid-amines/ammonia-oxidized organics clusters (Almeida et al., 2013; Kürten et al., 2014; Riccobono et al., 2014; Yao et al., 2018), iodine oxoacids and iodine oxide clusters (Sipilä et al., 2016) and clusters containing only ions and highly oxidized molecules (Frege et al., 2018; Kirkby et al., 2016). These works in total suggest that sulfuric acid is a necessary ingredient for atmospheric nucleation, with water, ammonia/amines, and organics facilitating the nucleation process. Exceptions are the nucleation in coastal regions, which could mainly involve iodine containing clusters, and ion induced nucleation, which does not require the presence of sulfuric acid.

The Cluster-CIMS and (CI-)APi-TOF are the current go-to techniques for the detection of atmospheric clusters (especially the latter). Recently, Riva et al. (2019) coupled atmospheric CI with an orbitrap, which further increases the instrument resolution (up to 140,000 at  $m/z = 200$ ) and allows tandem mass spectrometry to elucidate molecular structures. Since CI-Orbitrap is yet to be widely applied in nucleation studies, in the following we shall classify the significant amount of effort that has been devoted to the characterizations of Cluster-CIMS and (CI-)APi-TOF:

**a. Mass dependent transmission efficiency.** By comparing the signal of the Cluster-CIMS to that of an electrometer, Zhao et al. (2010) showed that the ion transmission efficiency in the Cluster-CIMS is ion mass dependent and is a function of the applied frequency to the octupole. Their calibration setup is similar to the one presented in Fig. 5b, i.e. using calibration ions produced by electrospray and selected by a high resolution differential mobility analyzer (Rosser & de la Mora, 2005). A similar calibration procedure is

reported for the APi-Tof (Junninen et al., 2010). Heinritzi et al. (2016) incorporated the ionization step into the mass dependency calibration by adding perfluorinated acids to deplete primary nitrate ions. They showed that there is a non-negligible mass discrimination effect in the CI source: the relative transmission efficiency increases by a factor around 5 as  $m/z$  of the ions increase from 62 to 550. This mass dependency is applied in recent atmospheric nucleation and growth measurements to correct the raw data (Stolzenburg et al., 2018).

**b. Ionizing Reagents.** To date, the detection of atmospheric nucleating clusters has mostly been accomplished with nitrate ions as the ionizing reagent ions. Nitrate ions have shown good sensitivity for sulfuric-acid containing clusters, but its charging efficiency is composition dependent and low for less oxidized species (Rissanen, Mikkilä, Iyer, & Hakala, 2019). Compared to nitrate ions, acetate ions allow detection with higher efficiency (Berndt et al., 2016; Berndt et al., 2015), but acetate ionization chemistry is more complex, characterized by a broader range of ionizing clusters that are strongly influenced by relative humidity (Brophy & Farmer, 2016). Because of these complicating factors, acetate ions have seen limited applications in cluster detection (Jen, Hanson, & McMurry, 2015; Jen et al., 2016b). Other ionizing reagents, including iodide ions (Iyer, Lopez-Hilfiker, Lee, Thornton, & Kurtén, 2016) and bisulfate ions (Sipilä et al., 2015), are mainly used for detecting gaseous species instead of molecular clusters. Since different ions have varying sensitivities and compound selectivity, instruments that feature switchable ionization schemes have the potential to provide a more complete picture of nucleation pathways (Brophy & Farmer, 2015; Rissanen et al., 2019). Besides experimental characterization, our understanding of ionization chemistry is also facilitated by quantum chemistry computations of ion-neutral binding energies (Hytinen et al., 2018; Hytinen, Rissanen, & Kurtén, 2017; Iyer et al., 2016).

**c. Cluster transformation upon ionization.** Even though chemical ionizations are relatively soft, clusters are likely to go through composition transformation upon ionization. Ortega et al. (2014) calculated the evaporation rates of charged sulfuric acid-base clusters and found that negative charging will lead to the increase of sulfuric-acid: base ratios, while positive charging will decrease the ratio. It has also been shown that charged sulfuric acid clusters are less hydrated than their neutral counterparts (Ehrhart et al., 2016); this could contribute to water evaporation upon ionization of sulfuric acid clusters.

**d. Collision-induced dissociation.** Upon entrance into the APi, clusters ionized at the atmospheric pressure are accelerated at reduced pressures by the ion optics, which leads to collision-induced cluster fragmentation. Passananti et al. (2019) experimentally measured and simulated the fragmentation of  $(\text{H}_2\text{SO}_4)_2\text{HSO}_4^-$  in an APi-Tof. The experimental setup is shown in Fig. 5b. They found that the voltage configuration of the second chamber in the APi has the strongest influence on  $(\text{H}_2\text{SO}_4)_2\text{HSO}_4^-$  fragmentation. In the first chamber, the clusters do not accumulate enough kinetic energy in between collisions with carrier

gas molecules to induce fragmentation, while in the third chamber the clusters rarely collide with carrier gas molecules because of the low pressure. No voltage configurations of the ion optics would eliminate fragmentation of  $(\text{H}_2\text{SO}_4)_2\text{HSO}_4^-$ , but some configurations lead to complete fragmentation of the cluster. Leiminger et al. (2019) used hexapoles in lieu of quadrupoles to decrease cluster fragmentation during transmission. With the  $\text{H}_3\text{O}^+(\text{H}_2\text{O})_{n=0-3}$  model system, they estimated clusters with binding energies higher than  $19 \text{ kcal mol}^{-1}$  can be transmitted through the APi without significant fragmentation. This is lower than a previously reported value of  $25 \text{ kcal mol}^{-1}$  for quadrupole-based instruments (Iyer et al., 2016). Currently, thorough characterization of collision-induced fragmentation of atmospherically relevant clusters is still limited, but in the future the simulation framework developed by Vehkamäki and coworkers (Passananti et al., 2019; Zanca et al., 2020; Zapadinsky et al., 2019) can be utilized to estimate cluster survival ratios.

**e. Calibration factor.** With proper calibration standards, a calibration factor for a given analyte can be empirically obtained for an instrument setting, which encompasses all the factors (a-d) mentioned above and converts measured signals to analyte concentrations. For CI-APi-Tof measurements, the calibration factor for sulfuric acid monomer is derived from measurements using a well-characterized  $\text{H}_2\text{SO}_4$  generator (Kürten, Rondo, Ehrhart, & Curtius, 2012). For most highly oxygenated molecules (HOMs), however, authentic calibration standards are not available, hence the quantification of HOMs are achieved by using the same calibration factor as sulfuric acid molecules (Berndt et al., 2015; Lehtipalo et al., 2018; Tröstl et al., 2016), or determined with a surrogate molecule with a gravimetrically calibrated permeation source (Ehn et al., 2014). This is a major source of uncertainty for CI-APi-Tof data, especially for compounds that may exhibit lower levels of ionization efficiency (Berndt et al., 2016; Berndt et al., 2015; Hyttinen et al., 2015; Hyttinen et al., 2018; Hyttinen et al., 2017). For nucleating clusters, although studies have indicated that detection efficiency is cluster composition and instrument-setting dependent (Kürten et al., 2014; Passananti et al., 2019), calibration standards are not available.

**f. Missing hydrated clusters.** Theoretical and experimental evidence suggests that under atmospheric conditions, the nucleating clusters are hydrated (Ahonen et al., 2019; Hanson & Lovejoy, 2006; Henschel et al., 2016; Henschel et al., 2014; Kildgaard et al., 2018a; Thomas et al., 2016). However, for both the Cluster-CIMS and (CI-)APi-Tof, water molecules quickly evaporate from the clusters once they enter the mass spectrometer since the atmospheric hydration equilibrium is no longer maintained. This is even the case for binary sulfuric-water nucleation in which water definitively participates in the nucleation process (Eisele & Hanson, 2000). The loss of water makes it difficult to directly examine the role of water in the atmospheric nucleation process.

**g. Comparison with measurements of nucleated particles.** The molecular level information obtained by either the Cluster-CIMS or the (CI-)APi-Tof needs to be compared with other established methods for the

detection of nanometer range nucleated particles (Kangasluoma et al., 2020). Jen et al. (2015) compared the particle number concentrations predicted based on Cluster-CIMS measurements and those measured by a scanning mobility particle spectrometer equipped with a diethylene glycol condensation particle counter (DEG-SMPS). Good agreement was achieved except at low sulfuric acid concentrations. However, studies on the reconciliation between molecular level measurements and particle level measurements are still lacking.

As detailed above, although atmospheric nucleating clusters can be detected by the Cluster-CIMS and (CI-)APi-Tof, there exists a level of uncertainty in data interpretation, especially when it comes to quantification of the nucleating clusters. Further systematic and innovative work is needed to constrain experimental uncertainties caused by cluster fragmentation and variable ionization efficiency. The identification of nucleating clusters, the composition of which correspond to different nucleation pathways, is an ongoing effort: The existing research works cannot rule out the possibility that a subset of atmospheric trace species, similar to water, participate in atmospheric nucleation but are hitherto unidentified in nucleating clusters. These species may cluster with low-volatility species such as sulfuric acid in the atmosphere and enhance nucleation, but the clusters are relatively weakly bound and severely fragment inside the detection instrument. With existing experimental setups (i.e. flow reactors, smog chambers) robust experiments can be devised to identify species that enhance nucleation (Arquero, Gerber, & Finlayson-Pitts, 2017; Perraud, Xu, Gerber, & Finlayson-Pitts, 2020; Yu, McGraw, & Lee, 2012; Zhang et al., 2004). Future improvement of instrumentation should aim at reconciling observed nucleating clusters and nucleation enhancement measurements.

## 4. Summary and Outlook

In this review, we summarized the techniques to probe nucleation on the molecular level. The introduced modeling methods facilitate the interpretation of the experimental data and give insight into the nucleation process. In particular,

- GDE-based kinetic simulations are routinely applied to understand atmospheric nucleation (the critical rates in the model are often obtained by QC calculations). GDE-based kinetic simulations work best for simulating nucleation when the major nucleation participants are known. Molecular level information retrieved from the Laval-based experiments have also been analyzed by GDE-based kinetic simulations.
- QC calculations are extremely valuable in evaluating cluster stability. This helps identify/rule out nucleation participants. Some well-controlled nucleation experiments, e.g. sulfuric acid-water binary nucleation studies in the CLOUD chamber, are nicely explained by QC-based theories. QC also

facilitates constraining experimental uncertainties in terms of analyte dissociation, hydration, and ionization.

However, as explained in this review, each method has its limitations, hence the task of improving individual techniques and bringing modeling and experiments together to characterize nucleation requires continued efforts. For future scientific endeavors in gas phase nucleation, we believe the following general directions may be considered:

- For GDE-based kinetic simulations, further development should focus on efficient simulation of more complex systems, with user-friendly interfaces to large quantum mechanical cluster energy databases. Coupling of the GDE with gas phase chemistry, multi-phase chemistry should facilitate simulating the entire evolution of atmospheric particles.
- For molecular dynamics simulations, recent developments (Diemand et al., 2013; Salvalaglio et al., 2016) have shown the possibility to reach a true overlap between simulated nucleation rates and experimental nucleation rates. Joint efforts between experimental and modelling groups are in need to implement direct comparison between experimental and simulation data. Development of guidelines for simulations, e.g. the proper choice of thermostats, is needed.
- For nucleation measurements in the postnozzle flow of Laval nozzles, multicomponent nucleation pathways are yet to be fully explored. Expanding the accessible temperature range by the postnozzle flow should open the door to more nucleation systems of interest and facilitate comparison with results measured with other experimental techniques.
- For the measurement of atmospherically relevant nucleating clusters, efforts to constrain the uncertainties in cluster detection and quantifications are still much needed. Minimizing cluster fragmentation may help reveal unidentified nucleation pathways.

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## **Declaration of competing interest**

The authors declare no competing interest.

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