Supporting Information for: Efficient application of Continuous Fractional Component Monte Carlo in the Reaction Ensemble

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In this Supporting Information, we derive expressions for the partition function and the acceptance rules for the trial moves of the new formulation of the Reaction Ensemble Monte Carlo technique (RxMC) combined with the Continuous Fractional Component Monte Carlo (serial Rx/CFC). We also derive an expression for computing the chemical potential in the Gibbs ensemble for multicomponent mixtures. We extend this derivation to arrive at an expression for chemical potentials in serial Rx/CFC. Details regarding the calculation of equilibrium mixture compositions by thermodynamic modeling using the Peng-Robinson equation of state are provided. We also mentioned how ideal gas partition functions can be computed.

1 Partition function of serial Rx/CFC

In this section, we derive the partition function and acceptance rules for the constant volume version of serial Rx/CFC. In section 5, this is extended to the constant pressure version.[1] We start with the partition function of the Gibbs ensemble for a pure component with a single fractional molecule:[2]

$$
\begin{aligned}
Q_{\mathrm{CFCMC}} =& \frac{1}{\Lambda^{3(N_T+1)} N_T!} \sum_{i=1}^{2} \sum_{N_1=0}^{N_T} \int_0^1 d\lambda \int_0^{V_T} dV_1 V_1^{N_1+\delta_{i,1}} (V_T - V_1)^{N_T - N_1 + \delta_{i,2}} \frac{N_T!}{N_1!(N_T - N_1)!} \times \\
& \int ds^{N_1} \exp[-\beta U_{\mathrm{int},1}(s^{N_1}, V_1)] \int ds^{N_T - N_1} \exp[-\beta U_{\mathrm{int},2}(s^{N_T - N_1}, V_1)] \times \\
& \left(\delta_{i,1} \int ds_{\mathrm{frac}}^1 \exp[-\beta U_{\mathrm{frac},1}(s_{\mathrm{frac}}^1, s^{N_1}, \lambda, V_1)] + \delta_{i,2} \int ds_{\mathrm{frac}}^2 \exp[-\beta U_{\mathrm{frac},2}(s_{\mathrm{frac}}^2, s^{N_T - N_1}, \lambda, V_1)] \right)
\end{aligned}
\tag{S1}
$$

where λ is the scaling parameter with $\lambda \in [0,1]$, V_T is the total volume of the two boxes, V_1 is the volume of box 1, N_T is the total number of whole molecules in the two boxes, N_1 is the number of whole molecules in box 1, $U_{\mathrm{int},i}$ is the total potential energy of whole molecules in box i, and $U_{\mathrm{frac},i}$ is the potential energy of the fractional molecule in box i. The fractional molecule can be either in box 1 ($i = 1$, $\delta_{i,1} = 1$, $\delta_{i,2} = 0$) or in box 2 ($i = 2$, $\delta_{i,1} = 0$, $\delta_{i,2} = 1$). When $\lambda = 0$, the fractional molecule has no interactions with surrounding molecules and when $\lambda = 1$, the fractional molecule has full interactions with surrounding molecules. To derive an expression for the partition function of the reaction ensemble, we consider the case where the volumes of the boxes are fixed and molecules in box 2 do not interact with each other (box 2 is an ideal gas). Later, we will take the limit that box 2 is infinitely large. In this case, Q_{CFCMC} becomes

$$
\begin{aligned}
Q_{\mathrm{CFCMC}} =& \frac{1}{\Lambda^{3(N_T+1)}} \sum_{\delta=0}^{1} \sum_{N_1=0}^{N_T} \frac{V_1^{N_1+\delta}(V_T - V_1)^{N_T - N_1 + 1 - \delta}}{N_1!(N_T - N_1)!} \int_0^1 d\lambda \int ds^{N_1} \exp[-\beta U_{\mathrm{int},1}(s^{N_1})] \\
& \times \left(\int ds_{\mathrm{frac}}^1 \exp[-\beta \delta U_{\mathrm{frac},1}(s_{\mathrm{frac}}^1, s^{N_1}, \lambda)] \right)
\end{aligned}
\tag{S2}
$$

where $\delta = 1$ when the fractional molecule is in box 1 and otherwise $\delta = 0$. Next, we consider a system with multiple components. Each component has ν_i fractional molecules ($\nu_i > 0$). The fractional molecules of component i are either all in box 1 or in box 2. The interaction energy between fractional molecules themselves is included in $U_{\mathrm{frac},i}$. Fractional molecules of type i are distinguishable from the whole molecules in box 1. Since there are no interactions between molecules in the ideal gas reservoir (box 2), fractional molecules are indistinguishable from whole molecules of the same component type in box 2. In this case,

we can write

$$
\begin{aligned}
Q_{\mathrm{CFCMC}} = \sum_{N_1=0}^{N_{T,1}} \sum_{\delta_1=0}^{1} \sum_{N_2=0}^{N_{T,2}} \sum_{\delta_2=0}^{1} \cdots \sum_{N_S=0}^{N_{T,S}} \sum_{\delta_S=0}^{1} \prod_{i=1}^{S} & \frac{V_1^{N_i+\nu_i\delta_i}(V_T-V_1)^{N_{T,i}+(1-\delta_i)\nu_i-N_i}}{\Lambda_i^{3(N_{T,i}+\nu_i)}N_i!\,(N_{T,i}+(1-\delta_i)\nu_i-N_i)!} \\
& \int_0^1 d\lambda_1 \int_0^1 d\lambda_2 \cdots \int_0^1 d\lambda_S \int ds^{N_{\mathrm{int}}} \exp[-\beta U_{\mathrm{int}}(s^{N_{\mathrm{int}}})]\times \\
& \left(\prod_{i=1}^{S} \int ds_{\mathrm{frac}}^{\nu_i} \exp[-\beta\delta_i U_{\mathrm{frac},i}(s_{\mathrm{frac}}^{\nu_i}, s^{N_{\mathrm{int}}}, \lambda_1, \ldots, \lambda_S)] \right)
\end{aligned}
\tag{S3}
$$

where S is the number of components, $N_{T,i}$ is the total number of whole molecules of component i (in box 1 and box 2), N_{int} is the total number of whole molecules in box 1, N_i is the total number of whole molecules of type i in box 1. $\delta_i = 1$ when the ν_i fractional molecules of type i are in box 1, and δ_i is zero otherwise. We assume that box 2 is very large and we want to express the term

$$
\frac{(V_T - V_1)^{N_{T,i}+(1-\delta_i)\nu_i-N_i}}{(N_{T,i}+(1-\delta_i)\nu_i-N_i)!}
$$

as a function of the chemical potential of component i in the reservoir. As V_T is much larger than V_1 and N_T is much larger than N_1, we can write

$$
(V_T-V_1)^{N_{T,i}+(1-\delta_i)\nu_i-N_i} \approx (V_T)^{N_{T,i}+(1-\delta_i)\nu_i-N_i} = (V_T)^{N_{T,i}}(V_T)^{(1-\delta_i)\nu_i-N_i}
\tag{S4}
$$

$$
(N_{T,i}+(1-\delta_i)\nu_i-N_i)! \approx (N_{T,i})^{N_{T,i}+(1-\delta_i)\nu_i-N_i} = (N_{T,i})^{N_{T,i}}(N_{T,i})^{(1-\delta_i)\nu_i-N_i}
\tag{S5}
$$

Therefore, we can write

$$
\frac{(V_T-V_1)^{N_{T,i}+(1-\delta_i)\nu_i-N_i}}{(N_{T,i}+(1-\delta_i)\nu_i-N_i)!} = \frac{(V_T)^{N_{T,i}+\nu_i}(V_T)^{-\delta_i\nu_i-N_i}}{(N_{T,i})^{N_{T,i}+\nu_i}(N_{T,i})^{-\delta_i\nu_i-N_i}} = (\text{constant}) \times \rho_i^{N_i+\delta_i\nu_i}
\tag{S6}
$$

where $\rho_i = N_{T,i}/V_T$ is the number density of component i in box 2 (the ideal gas reservoir). When $N_{T,i} \to \infty, V_T \to \infty$, and ρ_i is a finite number, we can replace the term

$$
\frac{(V_T - V_1)^{N_{T,i}+(1-\delta_i)\nu_i-N_i}}{(N_{T,i}+(1-\delta_i)\nu_i-N_i)!}
$$

with $\rho_i^{N_i+\nu_i\delta_i}$ and we can rewrite the corresponding partition function as

$$
\begin{aligned}
Q_{\text{CFCMC,GC}} = \sum_{N_1=0}^{\infty}\sum_{\delta_1=0}^{1}\sum_{N_2=0}^{\infty}\sum_{\delta_2=0}^{1}\cdots\sum_{N_S=0}^{\infty}\sum_{\delta_S=0}^{1}\prod_{i=1}^{S}\frac{V_1^{N_i+\nu_i\delta_i}\rho_i^{N_i+\nu_i\delta_i}\Lambda_i^{3(N_i+\nu_i\delta_i)}}{\Lambda_i^{3(N_i+\nu_i\delta_i)}N_i!} \\
\int_0^1 d\lambda_1\int_0^1 d\lambda_2\cdots\int_0^1 d\lambda_S\int ds^{N_{\text{int}}}\exp[-\beta U_{\text{int}}(s^{N_{\text{int}}})]\times \\
\left(\prod_{i=1}^{S}\int ds_{\text{frac}}^{\nu_i}\exp[-\beta\delta_i U_{\text{frac},i}(s_{\text{frac}}^{\nu_i},s^{N_{\text{int}}},\lambda_1,...,\lambda_S)]\right)
\end{aligned}
\tag{S7}
$$

Essentially, we have moved to the grand-canonical (GC) ensemble and the sums over the number of molecules run from 0 to ∞. Here, the subscript GC refers to grand-canonical and this is used to emphasize that the reaction ensemble is essentially a grand-canonical ensemble where the chemical potentials of components are constant. For an ideal gas we have[3]

$$
\mu_i = \mu_i^{\circ} + \frac{1}{\beta}\ln\frac{\rho_i}{\beta P^{\circ}}
\tag{S8}
$$

$$
\mu_i^{\circ} = -\frac{1}{\beta}\ln\left(\frac{q_i}{\beta P^{\circ}\Lambda_i^3}\right)
\tag{S9}
$$

where μ_i° is the reference chemical potential, P° is the standard reference pressure (10^5 Pa), Λ_i is thermal wavelength of component i. q_i is the ideal gas phase partition function of an isolated molecule of type i excluding the translational part:[3]

$$
\mu_i = -\frac{1}{\beta}\ln\left(\frac{q_i}{\beta P^{\circ}\Lambda_i^3}\right) + \frac{1}{\beta}\ln\frac{\rho_i}{\beta P^{\circ}}
\tag{S10}
$$

$$
\exp\left[\beta\mu_i\left(N_i+\nu_i\delta_i\right)\right] = \rho_i^{N_i+\nu_i\delta_i}\left(\frac{\Lambda_i^3}{q_i}\right)^{N_i+\nu_i\delta_i}
\tag{S11}
$$

We arrive at

$$
\rho_i^{N_i+\nu_i\delta_i}\Lambda_i^{3(N_i+\nu_i\delta_i)} = \exp\left[\beta\mu_i\left(N_i+\nu_i\delta_i\right)+\left(N_i+\nu_i\delta_i\right)\ln q_i\right]
\tag{S12}
$$

Substituting Eq. S12 into Eq. S7 yields

$$
\begin{aligned}
Q_{\text{CFCMC,GC}} = \sum_{N_1=0}^{\infty}\sum_{\delta_1=0}^{1}\sum_{N_2=0}^{\infty}\sum_{\delta_2=0}^{1}\cdots\sum_{N_S=0}^{\infty}\sum_{\delta_S=0}^{1}\prod_{i=1}^{S}\frac{V_1^{N_i+\nu_i\delta_i}\exp\left[\beta\mu_i\left(N_i+\nu_i\delta_i\right)+\left(N_i+\nu_i\delta_i\right)\ln q_i\right]}{\Lambda_i^{3(N_i+\nu_i\delta_i)}N_i!} \\
\int_0^1 d\lambda_1\int_0^1 d\lambda_2\cdots\int_0^1 d\lambda_S\int ds^{N_{\text{int}}}\exp[-\beta U_{\text{int}}(s^{N_{\text{int}}})]\times \\
\left(\prod_{i=1}^{S}\int ds_{\text{frac}}^{\nu_i}\exp[-\beta\delta_i U_{\text{frac},i}(s_{\text{frac}}^{\nu_i},s^{N_{\text{int}}},\lambda_1,...,\lambda_S)]\right)
\end{aligned}
\tag{S13}
$$

We can rearrange the partition function as follows:

$$Q_{\text{CFCMC,GC}} = \sum_{N_1=0}^{\infty} \sum_{\delta_1=0}^{1} \sum_{N_2=0}^{\infty} \sum_{\delta_2=0}^{1} \cdots \sum_{N_S=0}^{\infty} \sum_{\delta_S=0}^{1} \exp\left[\beta \sum_{i=1}^{S} \mu_i \left(N_i + \nu_i \delta_i\right) + \sum_{i=1}^{S} \left(N_i + \nu_i \delta_i\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{S} \ln N_i!\right]$$

$$\int_0^1 d\lambda_1 \int_0^1 d\lambda_2 \cdots \int_0^1 d\lambda_S \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}})] \times$$

$$\left(\prod_{i=1}^{S} \int ds_{\text{frac}}^{\nu_i} \exp[-\beta \delta_i U_{\text{frac},i}(s_{\text{frac}}^{\nu_i}, s^{N_{\text{int}}}, \lambda_1, ..., \lambda_S)]\right)$$

(S14)

Next, we move to the reaction ensemble and divide the components into reactants (R) and reaction products (P). For simplicity, we only consider systems with a single reaction as extension to systems with multiple reactions is trivial. We consider the case that we either have fractional molecules of reactants $(\delta = 1)$ or fractional molecules of reaction products $(\delta = 0)$. The number of fractional molecules of component i equals the stoichiometric coefficient of component i $(\nu_i > 0)$ in the reaction or equals zero when a component does not participate in the reaction. Furthermore, instead of λ_i for each component, we have an overall λ for the system which translates to λ of individual fractional molecules. Eq. S14 then reduces to

$$Q_{\text{CFCMC,GC}} = \sum_{N_1=0}^{\infty} \cdots \sum_{N_S=0}^{\infty} \sum_{\delta=0}^{1} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right]$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1 - \delta)\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1 - \delta)\right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right]$$

$$\int_0^1 d\lambda \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}})] \left(\prod_{i=1}^{R} \int ds_{\text{frac}}^{\nu_i} \exp[-\beta \delta U_{\text{frac},i}(s_{\text{frac}}^{\nu_i}, s^{N_{\text{int}}}, \lambda)]\right) \times$$

$$\left(\prod_{j=R+1}^{S} \int ds_{\text{frac}}^{\nu_j} \exp[-\beta(1 - \delta) U_{\text{frac},j}(s_{\text{frac}}^{\nu_j}, s^{N_{\text{int}}}, \lambda)]\right)$$

(S15)

where R is the number of reactant components, and P is the number of reaction product components so $R + P = S$. Therefore, the number of reaction product components is ranging from $R + 1$ to S with S being the total number of components.

1.1 Partition function of the reaction ensemble with CFCMC for the ideal gas case

In the ideal gas case, molecules do not interact. Therefore, the energy terms in the partition functions of the conventional reaction ensemble and the reaction ensemble with CFCMC can be disregarded. The partition functions of the conventional reaction ensemble and the reaction ensemble with CFCMC for the ideal gas case are

$$Q_{\text{Conv}}^{\text{IG}} = \sum_{N_1=0}^{\infty} \dots \sum_{N_S=0}^{\infty} \exp\left[\beta \sum_{i=1}^{S} \mu_i N_i + \sum_{i=1}^{S} N_i \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{S} \ln N_i!\right] \tag{S16}$$

$$Q_{\text{CFCMC,GC}}^{\text{IG}} = \sum_{N_1=0}^{\infty} \dots \sum_{N_S=0}^{\infty} \sum_{\delta=0}^{1} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right]$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1 - \delta)\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1 - \delta)\right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] \tag{S17}$$

One can separate the two cases $\delta = 0$ and $\delta = 1$, and rewrite Eq. S17 as

$$Q_{\text{CFCMC,GC}}^{\text{IG}} = \sum_{N_1=0}^{\infty} \dots \sum_{N_S=0}^{\infty} \exp\left[\beta \sum_{i=1}^{R} \mu_i N_i + \sum_{i=1}^{R} N_i \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right] \times$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j\right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] +$$

$$\exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i\right) + \sum_{i=1}^{R} \left(N_i + \nu_i\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right] \times$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j N_j + \sum_{j=R+1}^{S} N_j \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] \tag{S18}$$

$$= \sum_{N_1=0}^{\infty} \dots \sum_{N_S=0}^{\infty} \exp\left[\beta \sum_{i=1}^{R} \mu_i N_i + \sum_{i=1}^{R} N_i \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right] \times$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j N_j + \sum_{j=R+1}^{S} N_j \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] \times$$

$$\left[\exp\left[\beta \sum_{i=1}^{R} \mu_i \nu_i + \sum_{i=1}^{R} \nu_i \ln \frac{V q_i}{\Lambda_i^3}\right] + \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \nu_j + \sum_{j=R+1}^{S} \nu_j \ln \frac{V q_j}{\Lambda_j^3}\right]\right]$$

The last term is simply a constant for given values of μ_i, Λ_i, and q_i for all component. Therefore, we

have

$$Q_{\text{CFCMC,GC}}^{\text{IG}} = \sum_{N_1=0}^{\infty} ... \sum_{N_S=0}^{\infty} \exp\left[\beta \sum_{i=1}^{S} \mu_i N_i + \sum_{i=1}^{S} N_i \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{S} \ln N_i!\right] \times \text{Constant}$$

$$= Q_{\text{Conv}}^{\text{IG}} \times \text{Constant}$$

(S19)

Therefore, ensemble averages computed in the ensemble of Eq. S17 are identical to those computed in the ensemble of Eq. S16, provided that the quantity of which the ensemble average is computed does not depend on λ or δ. By not counting fractional molecules when computing ensemble averages of the number of molecules of a component, one is guaranteed that the ensembles of Eq. S16 and Eq. S17 yield the same results. It is therefore a natural choice not to count fractional molecules when computing ensemble averages for systems with intermolecular interactions.

2 Acceptance rules

Starting from the partition function of Eq. S15, we derive the acceptance rules for the trial moves in serial Rx/CFC.

2.1 Changing the value of λ

This trial move is used to change the value of λ (see Fig. S1) while keeping δ and all molecules positions constant. When the new λ is outside the interval [0,1], this trial move is automatically rejected. In this trial move, the number of whole molecules and fractional molecules remains the same. By changing the value of λ, only the strength of interactions between the fractional molecules and the whole molecules are changed. Therefore, the probabilities of being in the old (o) and new (n) configurations are

$$p_{\text{o}} = \frac{1}{Q_{\text{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right]$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1-\delta)\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1-\delta)\right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\text{o}}]$$

(S20)

$$p_{\text{n}} = \frac{1}{Q_{\text{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right]$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1-\delta)\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1-\delta)\right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\text{n}}]$$

(S21)

where U_{o} and U_{n} are the total potential energies in the old and new configurations, respectively. Therefore the acceptance rule for this trial move is

$$\mathrm{acc}(\mathrm{o} \to \mathrm{n}) = \min\left[1, \exp\left[-\beta \Delta U\right]\right] \tag{S22}$$

in which $\Delta U = U_{\mathrm{n}} - U_{\mathrm{o}}$.

2.2 Reaction for fractional molecules

In this trial move, the fractional molecules of reactants/reaction products are removed and fractional molecules of reaction/reactants are inserted at random positions (see Fig. S2). The number of whole molecules and also the value of λ are constant but the value of δ changes. This trial move basically mimics the reaction for fractional molecules and is very efficient at low values of λ. Here, we derive the acceptance rule for the forward reaction (reactants $\rightarrow$ reaction products). The acceptance rule for the reverse reaction (reaction products $\rightarrow$ reactants) simply follows by swapping the labels. The direction of the reaction eventually depends on the value of δ for the old configuration (if we have the fractional molecules of reactants or reaction products). The probabilities of being in the old (o) and new (n) configurations are

$$
\begin{aligned}
p_{\mathrm{o}} =& \frac{1}{Q_{\mathrm{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta_{\mathrm{o}}\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta_{\mathrm{o}}\right) \ln \frac{V q_i}{\Lambda_i^{3}} - \sum_{i=1}^{R} \ln N_i!\right] \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1-\delta_{\mathrm{o}})\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1-\delta_{\mathrm{o}})\right) \ln \frac{V q_j}{\Lambda_j^{3}} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\mathrm{o}}]
\end{aligned}
\tag{S23}
$$

$$
\begin{aligned}
p_{\mathrm{n}} =& \frac{1}{Q_{\mathrm{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta_{\mathrm{n}}\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta_{\mathrm{n}}\right) \ln \frac{V q_i}{\Lambda_i^{3}} - \sum_{i=1}^{R} \ln N_i!\right] \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1-\delta_{\mathrm{n}})\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1-\delta_{\mathrm{n}})\right) \ln \frac{V q_j}{\Lambda_j^{3}} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\mathrm{n}}]
\end{aligned}
\tag{S24}
$$

where we have used the notation $\delta_{\mathrm{n}}, \delta_{\mathrm{o}}$ for the value of δ in the new and old configurations, respectively. If $\delta_{\mathrm{o}} = 1$ then $\delta_{\mathrm{n}} = 0$ (and vice versa). For the forward reaction (reactants $\rightarrow$ reaction products), we have $\delta_{\mathrm{o}} = 1$ and $\delta_{\mathrm{n}} = 0$. Therefore, we can rewrite Eqs. S23 and S24 as

$$
\begin{aligned}
p_{\mathrm{o}} =& \frac{1}{Q_{\mathrm{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i\right) + \sum_{i=1}^{R} \left(N_i + \nu_i\right) \ln \frac{V q_i}{\Lambda_i^{3}} - \sum_{i=1}^{R} \ln N_i!\right] \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j N_j + \sum_{j=R+1}^{S} N_j \ln \frac{V q_j}{\Lambda_j^{3}} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\mathrm{o}}]
\end{aligned}
\tag{S25}
$$

$$
\begin{aligned}
p_{\mathrm{n}} =& \frac{1}{Q_{\mathrm{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i N_i + \sum_{i=1}^{R} N_i \ln \frac{V q_i}{\Lambda_i^{3}} - \sum_{i=1}^{R} \ln N_i!\right] \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j\right) \ln \frac{V q_j}{\Lambda_j^{3}} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\mathrm{n}}]
\end{aligned}
\tag{S26}
$$

It is important to note that the number of whole molecules of each component does not change in this trial move. Therefore, we have

$$\frac{p_{\mathrm{n}}}{p_{\mathrm{o}}} = \exp\left[-\beta\sum_{i=1}^{R}\mu_i\nu_i - \sum_{i=1}^{R}\nu_i\ln\frac{Vq_i}{\Lambda_i{}^3} + \beta\sum_{j=R+1}^{S}\mu_j\nu_j + \sum_{j=R+1}^{S}\nu_j\ln\frac{Vq_j}{\Lambda_j{}^3}\right] \times \exp\left[-\beta\Delta U\right] \qquad \text{(S27)}$$

Reaction equilibrium implies $\sum_{i=1}^{R}\mu_i\nu_i = \sum_{j=R+1}^{S}\mu_j\nu_j$. Consequently, Eq. S27 reduces to

$$\frac{p_{\mathrm{n}}}{p_{\mathrm{o}}} = \exp\left[-\sum_{i=1}^{R}\nu_i\ln\frac{Vq_i}{\Lambda_i{}^3} + \sum_{j=R+1}^{S}\nu_j\ln\frac{Vq_j}{\Lambda_j{}^3}\right] \times \exp\left[-\beta\Delta U\right] \qquad \text{(S28)}$$

Therefore the acceptance rule for this trial move is

$$\mathrm{acc}(\mathrm{o}\to\mathrm{n}) = \min\left[1,\left[\prod_{i=1}^{R}\left(\frac{Vq_i}{\Lambda_i{}^3}\right)^{-\nu_i}\right] \times \left[\prod_{j=R+1}^{S}\left(\frac{Vq_j}{\Lambda_j{}^3}\right)^{\nu_j}\right] \times \exp\left[-\beta\Delta U\right]\right] \qquad \text{(S29)}$$

For the limiting case of $\lambda \to 0$, this acceptance rule reduces to

$$\mathrm{acc}(\mathrm{o}\to\mathrm{n}) = \min\left[1,\left[\prod_{i=1}^{R}\left(\frac{Vq_i}{\Lambda_i{}^3}\right)^{-\nu_i}\right] \times \left[\prod_{j=R+1}^{S}\left(\frac{Vq_j}{\Lambda_j{}^3}\right)^{\nu_j}\right]\right] \qquad \text{(S30)}$$

2.3 Reaction for whole molecules

In this trial move, the fractional molecules of reactants/reaction products are transformed into whole molecules of reactants/reaction products while at the same time, randomly selected whole molecules of reaction products/reactants are transformed into the fractional molecules of reaction products/reactants. All molecule positions stay the same. This trial move is illustrated in Fig. S3. The value of λ remains constant during this trial move and the value of δ changes. This trial move can be seen as a reaction for whole molecules. In the forward reaction, whole molecule of reactants are transformed into fractional molecules and, at the same time, fractional molecules of reaction products are turned into whole molecules. Essentially, the number of whole molecules of reactants is reduced and the number of whole molecules of reaction products is increased, according to their stoichiometric coefficients. This trial move is very efficient when the value of λ is close to 1. Trial moves are automatically rejected when there are not enough whole molecules to turn into fractional molecules. Here, we derive the acceptance rule for the forward reaction (reactants $\rightarrow$ reaction products), so the fractional molecules of the reaction products are converted into whole molecules, and ν_i whole molecules of reactants are converted into fractional molecules. The acceptance rule for the reverse reaction (reaction products $\rightarrow$ reactants) simply follows by swapping the labels. The direction of the reaction eventually depends on the value of δ for the old configuration (if we have the fractional molecules of reactants or reaction products). The probabilities of being in the old (o) and new (n) configurations are

$$
\begin{aligned}
p_{\text{o}} =& \frac{1}{Q_{\text{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta_{\text{o}} \right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta_{\text{o}} \right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i! \right] \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j (1-\delta_{\text{o}}) \right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j (1-\delta_{\text{o}}) \right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j! \right] \exp[-\beta U_{\text{o}}] \quad \text{(S31)}
\end{aligned}
$$

$$
\begin{aligned}
p_{\text{n}} =& \frac{1}{Q_{\text{CFCMC,GC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i - \nu_i + \nu_i \delta_{\text{n}} \right) + \sum_{i=1}^{R} \left(N_i - \nu_i + \nu_i \delta_{\text{n}} \right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln \left(N_i - \nu_i \right)! \right] \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j + \nu_j (1-\delta_{\text{n}}) \right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j + \nu_j (1-\delta_{\text{n}}) \right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln \left(N_j + \nu_j \right)! \right] \exp[-\beta U_{\text{n}}] \quad \text{(S32)}
\end{aligned}
$$

For the forward reaction (reactants $\rightarrow$ reaction products) we have $\delta_{\text{o}} = 0$ and $\delta_{\text{n}} = 1$. Therefore, we can write

$$p_{\mathrm{o}} = \frac{1}{Q_{\mathrm{CFCMC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i N_i + \sum_{i=1}^{R} N_i \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i!\right]$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j (N_j + \nu_j) + \sum_{j=R+1}^{S} (N_j + \nu_j) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j!\right] \exp[-\beta U_{\mathrm{o}}] \tag{S33}$$

$$p_{\mathrm{n}} = \frac{1}{Q_{\mathrm{CFCMC}}} \exp\left[\beta \sum_{i=1}^{R} \mu_i N_i + \sum_{i=1}^{R} N_i \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln (N_i - \nu_i)!\right]$$

$$\exp\left[\beta \sum_{j=R+1}^{S} \mu_j (N_j + \nu_j) + \sum_{j=R+1}^{S} (N_j + \nu_j) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln (N_j + \nu_j)!\right] \exp[-\beta U_{\mathrm{n}}] \tag{S34}$$

Since the total number of whole plus fractional molecules of each component remains constant in this trial move, the terms related to the chemical potential and ideal gas partition function are the same for the old and new configurations. Therefore, we have

$$\frac{p_{\mathrm{n}}}{p_{\mathrm{o}}} = \exp\left[\sum_{i=1}^{R} \ln \frac{N_i!}{(N_i - \nu_i)!} + \sum_{j=R+1}^{S} \ln \frac{N_j!}{(N_j + \nu_j)!}\right] \times \exp\left[-\beta \Delta U\right] \tag{S35}$$

in which $\Delta U = U_{\mathrm{n}} - U_{\mathrm{o}}$. Therefore, the acceptance rule is

$$\mathrm{acc}(\mathrm{o} \to \mathrm{n}) = \min\left[1, \prod_{i=1}^{R} \frac{N_i!}{(N_i - \nu_i)!} \times \prod_{j=R+1}^{S} \frac{N_j!}{(N_j + \nu_j)!} \times \exp\left[-\beta \Delta U\right]\right] \tag{S36}$$

For the limiting case of $\lambda \to 1$, the acceptance rule reduces to

$$\mathrm{acc}(\mathrm{o} \to \mathrm{n}) = \min\left[1, \prod_{i=1}^{R} \frac{N_i!}{(N_i - \nu_i)!} \times \prod_{j=R+1}^{S} \frac{N_j!}{(N_j + \nu_j)!}\right] \tag{S37}$$

3   Chemical potential of mulitcomponent mixtures in the conventional Gibbs ensemble

We start with the partition function of the conventional Gibbs ensemble of a mixture of S components[1]

$$Q_{\text{normal,GE}} = \sum_{N_1=0}^{N_{T,1}} \sum_{N_2=0}^{N_{T,2}} \cdots \sum_{N_s=0}^{N_{T,S}} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{S} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}} N_i! \, (N_{T,i}-N_i)!} \right) \int ds^{N_{\text{total}}} \exp[-\beta U(s^{N_{\text{total}}}, V_1)] \tag{S38}$$

We know that[1]

$$\mu_i = \left(\frac{\partial F}{\partial N_i} \right)_{V,T,N_{j\neq i}} \approx \frac{F_{N_{\text{total}}+1} - F_{N_{\text{total}}}}{1} \approx \frac{F_{N_{\text{total}}+\nu_i} - F_{N_{\text{total}}}}{\nu_i} \tag{S39}$$

Therefore, we have

$$\nu_i \mu_i = F_{N_{\text{total}}+\nu_i} - F_{N_{\text{total}}} = \frac{-1}{\beta} \ln \left(\frac{Q_{N_{\text{total}}+\nu_i}}{Q_{N_{\text{total}}}} \right) \tag{S40}$$

We can extend this to mixtures and write

$$\sum_{i=1}^{R} \nu_i \mu_i = \frac{-1}{\beta} \ln \left(\frac{Q_{N_{\text{total}}+\sum_{i=1}^{R} \nu_i}}{Q_{N_{\text{total}}}} \right) \tag{S41}$$

In this case, we have

$$\begin{aligned}
Q_{N_{\text{total}}+\sum_{i=1}^{R} \nu_i} &= \sum_{N_1=0}^{N_{T,1}+\nu_1} \cdots \sum_{N_R=0}^{N_{T,R}+\nu_R} \cdots \sum_{N_{R+1}=0}^{N_{T,R+1}} \cdots \sum_{N_s=0}^{N_{T,S}} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}+\nu_i-N_i}}{\Lambda^{3(N_{T,i}+\nu_i)} N_i! \, (N_{T,i}+\nu_i-N_i)!} \right) \\
&\quad \left(\prod_{i=R+1}^{S} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}} N_i! \, (N_{T,i}-N_i)!} \right) \int ds^{N_{\text{total}}+\sum_{i=1}^{R} \nu_i} \exp[-\beta U(s^{N_{\text{total}}+\sum_{i=1}^{R} \nu_i}, V_1)]
\end{aligned} \tag{S42}$$

where $Q_{N_{\text{total}}+\sum_{i=1}^{R} \nu_i}$ is the partition function of Gibbs ensemble when for each reactant i, ν_i molecules of type i are added to the system. Therefore, we can write

$$\frac{Q_{N_{\text{total}}+\sum_{i=1}^{R} \nu_i}}{Q_{N_{\text{total}}}} = \frac{\begin{pmatrix} \sum_{N_1=0}^{N_{T,1}+\nu_1} \cdots \sum_{N_R=0}^{N_{T,R}+\nu_R} \cdots \sum_{N_{R+1}=0}^{N_{T,R+1}} \cdots \sum_{N_s=0}^{N_{T,S}} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}+\nu_i-N_i}}{\Lambda^{3(N_{T,i}+\nu_i)} N_i! \, (N_{T,i}+\nu_i-N_i)!} \right) \\ \left(\prod_{i=R+1}^{S} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}} N_i! \, (N_{T,i}-N_i)!} \right) \int ds^{N_{\text{total}}+\sum_{i=1}^{R} \nu_i} \exp[-\beta U(s^{N_{\text{total}}+\sum_{i=1}^{R} \nu_i}, V_1)] \end{pmatrix}}{\sum_{N_1=0}^{N_{T,1}} \cdots \sum_{N_s=0}^{N_{T,S}} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{S} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}} N_i!(N_{T,i}-N_i)!} \right) \int ds^{N_{\text{total}}} \exp[-\beta U(s^{N_{\text{total}}}, V_1)]} \tag{S43}$$

Following Frenkel and Smit and separating the terms $N_i = 0$ to $N_i = \nu_i - 1$ for reactants leads to[4]

$$
\frac{Q_{N_{\text{total}}+\sum_{i=1}^{R}\nu_i}}{Q_{N_{\text{total}}}} = \frac{\left(\begin{array}{c}\sum\limits_{N_1=\nu_1}^{N_{T,1}+\nu_1}\sum\limits_{N_R=\nu_R}^{N_{T,R}+\nu_R}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{R}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}+\nu_i-N_i}}{\Lambda^{3(N_{T,i}+\nu_i)}N_i!\,(N_{T,i}+\nu_i-N_i)!}\right)\\ \left(\left(\prod\limits_{i=R+1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!\,(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i}\exp[-\beta U(s^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i},V_1)]\right)\end{array}\right)}{\sum\limits_{N_1=0}^{N_{T,1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}}\exp[-\beta U(s^{N_{\text{total}}},V_1)]} +
$$

$$
\frac{\left(\begin{array}{c}\sum\limits_{N_1=0}^{\nu_1-1}\sum\limits_{N_2=0}^{\nu_2-1}\cdots\sum\limits_{N_R=0}^{\nu_R-1}\cdots\sum\limits_{N_{R+1}=0}^{N_{T,R+1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{R}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}+\nu_i-N_i}}{\Lambda^{3(N_{T,i}+\nu_i)}N_i!\,(N_{T,i}+\nu_i-N_i)!}\right)\\ \left(\left(\prod\limits_{i=R+1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!\,(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i}\exp[-\beta U(s^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i},V_1)]\right)\end{array}\right)}{\sum\limits_{N_1=0}^{N_{T,1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}}\exp[-\beta U(s^{N_{\text{total}}},V_1)]}
$$

(S44)

By re-indexing the sums, we obtain

$$
\frac{Q_{N_{\text{total}}+\sum_{i=1}^{R}\nu_i}}{Q_{N_{\text{total}}}} = \frac{\left(\begin{array}{c}\sum\limits_{N_1=0}^{N_{T,1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!\,(N_{T,i}-N_i)!}\right)\\ \left(\prod\limits_{i=1}^{R}\left(\frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}}{\frac{(N_i+\nu_i)!}{N_i!}}\right)\exp[-\beta\sum\limits_{j=1}^{\nu_i}\Delta U_j^{+}]\right)\int ds^{N_{\text{total}}}\exp[-\beta U(s^{N_{\text{total}}},V_1)]\end{array}\right)}{\sum\limits_{N_1=0}^{N_{T,1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}}\exp[-\beta U(s^{N_{\text{total}}},V_1)]} +
$$

$$
\frac{\left(\begin{array}{c}\sum\limits_{N_1=0}^{\nu_1-1}\sum\limits_{N_2=0}^{\nu_2-1}\cdots\sum\limits_{N_R=0}^{\nu_R-1}\cdots\sum\limits_{N_{R+1}=0}^{N_{T,R+1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{R}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}+\nu_i-N_i}}{\Lambda^{3(N_{T,i}+\nu_i)}N_i!\,(N_{T,i}+\nu_i-N_i)!}\right)\\ \left(\left(\prod\limits_{i=R+1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!\,(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i}\exp[-\beta U(s^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i},V_1)]\right)\end{array}\right)}{\sum\limits_{N_1=0}^{N_{T,1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T}dV_1\left(\prod\limits_{i=1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}}\exp[-\beta U(s^{N_{\text{total}}},V_1)]}
$$

(S45)

where $\sum_{j=1}^{\nu_i}\Delta U_j^{+}$ is the total change in the potential energy of the system due to the addition of ν_i molecules of component i for reactants only. As the first term on the right hand side of Eq. S45 corresponds to an

ensemble average in the conventional Gibbs ensemble, we can write

$$
\frac{Q_{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i}}{Q_{N_{\text{total}}}} = \left\langle \prod_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\text{normal,GE}} +
$$

$$
\frac{\left(\sum\limits_{N_1=0}^{\nu_1-1}\sum\limits_{N_2=0}^{\nu_2-1}\cdots\sum\limits_{N_R=0}^{\nu_R-1}\cdots\sum\limits_{N_{R+1}=0}^{N_{T,R+1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{R}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}+\nu_i-N_i}}{\Lambda^{3(N_{T,i}+\nu_i)}N_i!\,(N_{T,i}+\nu_i-N_i)!}\right)\right)}{\sum\limits_{N_1=0}^{N_{T,1}}\cdots\sum\limits_{N_s=0}^{N_{T,S}}\int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}}\exp[-\beta U(s^{N_{\text{total}}},V_1)]}
$$

$$
\frac{\left(\left(\prod\limits_{i=R+1}^{S}\frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda^{3N_{T,i}}N_i!\,(N_{T,i}-N_i)!}\right)\int ds^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i}\exp[-\beta U(s^{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i},V_1)]\right)}{}
$$

(S46)

where the last term corresponds to configurations where the numbers of molecules of reactants in box 1 are less than their stoichiometric coefficient. These configurations have very limited contribution to the statistical weight[1,4] and therefore we can neglect this term. Therefore, we have

$$
\frac{Q_{N_{\text{total}}+\sum\limits_{i=1}^{R}\nu_i}}{Q_{N_{\text{total}}}} = \left\langle \prod_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\text{normal,GE}}
$$

(S47)

so that

$$
\sum_{i=1}^{R} \nu_i \mu_i = \left\langle \prod_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\text{normal,GE}}
$$

(S48)

4 Chemical potentials in the new reaction ensemble with CFCMC

Consider the reaction: $\nu_1 r_1 + \nu_2 r_2 + ... + \nu_R r_R \rightleftharpoons \nu_{R+1} p_1 + \nu_{R+2} p_2 + ... + \nu_S p_P$

We start the derivation by not yet considering the contribution of internal degrees of freedom to the chemical potential of each component i, as we add these effects at the very end. We start again from the Gibbs ensemble where molecules only interact in box 1, and box 2 is an ideal gas reservoir. Eq. S3 then reduces to

$$
Q_{\text{CFCMC}} = \sum_{N_1=0}^{N_{T,1}} ... \sum_{N_S=0}^{N_{T,S}} \sum_{\delta=0}^{1} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{R} \frac{V_1^{N_i+\nu_i\delta}(V_T-V_1)^{N_{T,i}+(1-\delta)\nu_i-N_i}}{\Lambda_i^{3(N_{T,i}+\nu_i)} N_i!\,(N_{T,i}+(1-\delta)\nu_i-N_i)!} \right)
$$
$$
\times \left(\prod_{j=R+1}^{S} \frac{V_1^{N_j+\nu_j(1-\delta)}(V_T-V_1)^{N_{T,j}+\delta\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\delta\nu_j-N_j)!} \right) \int_0^1 d\lambda \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}}, V_1)]
$$
$$
\times \left(\prod_{i=1}^{R} \int ds_{\text{frac}}^{\nu_i} \exp[-\beta\delta U_{\text{frac},i}(s_{\text{frac}}^{\nu_i}, s^{N_{\text{int}}}, \lambda, V_1)] \right) \times \left(\prod_{j=R+1}^{s} \int ds_{\text{frac}}^{\nu_j} \exp[-\beta(1-\delta)U_{\text{frac},j}(s_{\text{frac}}^{\nu_j}, s^{N_{\text{int}}}, \lambda, V_1)] \right)
$$

(S49)

We can write

$$
\left\langle \delta'_{\lambda=0,\delta=1} \frac{1}{\prod_{i=1}^{R}\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}} \right\rangle =
$$
$$
\left(\sum_{N_1=0}^{N_{T,1}} ... \sum_{N_S=0}^{N_{T,S}} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{R} \frac{V_1^{N_i+\nu_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3(N_{T,i}+\nu_i)} N_i!\,(N_{T,j}-N_i)!} \right) \right.
$$
$$
\left. \times \left(\prod_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \frac{1}{\prod_{i=1}^{R}\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}} \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}}, V_1)] \right)
$$

(S50)

$\frac{}{Q_{\text{CFCMC}}}$

$\delta'_{\lambda=0,\delta=1}$ equals one when $\lambda=0$ and $\delta=1$ and otherwise this term equals zero. When $\delta=1$, all reactants have fractional molecules in box 1. Therefore,

$$
\left\langle \delta'_{\lambda=0,\delta=1} \frac{1}{\prod_{i=1}^{R}\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}} \right\rangle =
$$
$$
\left(\sum_{N_1=0}^{N_{T,1}} ... \sum_{N_S=0}^{N_{T,S}} \int_0^{V_T} dV_1 \left(\prod_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3N_{T,i}} N_i!\,(N_{T,i}-N_i)!} \right) \right.
$$
$$
\left. \left(\prod_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}}, V_1)] \right)
$$

(S51)

$\frac{}{Q_{\text{CFCMC}}}$

We can also write

$$
\left\langle \delta'_{\lambda=1,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \right\rangle =
$$

$$
\frac{\left(\sum\limits_{N_1=0}^{N_{T,1}} \cdots \sum\limits_{N_S=0}^{N_{T,S}} \int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{R} \frac{V_1^{N_i+\nu_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3(N_{T,i}+\nu_i)} N_i!\,(N_{T,j}-N_i)!} \right) \left(\prod\limits_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \right.}{Q_{\mathrm{CFCMC}}}
$$
$$
\left. \frac{1}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \int ds^{N_{\mathrm{int}}} \exp[-\beta U_{\mathrm{int}}(s^{N_{\mathrm{int}}},V_1)] \times \left(\prod\limits_{i=1}^{R} \int ds_{\mathrm{frac}}^{\nu_i} \exp[-\beta U_{\mathrm{frac},i}(s_{\mathrm{frac}}^{\nu_i}, s^{N_{\mathrm{int}}},\lambda=1,V_1)] \right) \right)
$$

$$\text{(S52)}$$

$$
= \frac{\left(\sum\limits_{N_1=0}^{N_{T,1}} \cdots \sum\limits_{N_S=0}^{N_{T,S}} \int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3N_{T,i}} N_i!\,(N_{T,j}-N_i)!} \right) \left(\prod\limits_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \right.}{Q_{\mathrm{CFCMC}}}
$$
$$
\left. \frac{\prod\limits_{i=1}^{R} \left(\frac{V_1}{\Lambda_i^3} \right)^{\nu_i}}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \int ds^{N_{\mathrm{int}}} \exp[-\beta U_{\mathrm{int}}(s^{N_{\mathrm{int}}},V_1)] \times \left(\prod\limits_{i=1}^{R} \int ds_{\mathrm{frac}}^{\nu_i} \exp[-\beta U_{\mathrm{frac},i}(s_{\mathrm{frac}}^{\nu_i}, s^{N_{\mathrm{int}}},\lambda=1,V_1)] \right) \right)
$$

At this condition, fractional molecules interact just like whole molecules and we can write

$$
\left\langle \delta'_{\lambda=1,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \right\rangle =
$$

$$
\frac{\left(\sum\limits_{N_1=0}^{N_{T,1}} \cdots \sum\limits_{N_S=0}^{N_{T,S}} \int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3N_{T,i}} N_i!\,(N_{T,j}-N_i)!} \right) \left(\prod\limits_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \right.}{Q_{\mathrm{CFCMC}}}
$$
$$
\left. \frac{\prod\limits_{i=1}^{R} \left(\frac{V_1}{\Lambda_i^3} \right)^{\nu_i}}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \left[\prod\limits_{i=1}^{R} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^{+}] \right] \int ds^{N_{\mathrm{int}}} \exp[-\beta U_{\mathrm{int}}(s^{N_{\mathrm{int}}},V_1)] \right)
$$

$$\text{(S53)}$$

By combining Eqs. S51 and S53, we can write:

$$
\frac{\left\langle \delta'_{\lambda=1,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \right\rangle}{\left\langle \delta'_{\lambda=0,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}} \right\rangle} =
$$

$$
\frac{\left(\sum\limits_{N_1=0}^{N_{T,1}} \cdots \sum\limits_{N_S=0}^{N_{T,S}} \int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3N_{T,i}} N_i!\,(N_{T,j}-N_i)!} \right) \left(\prod\limits_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \right)}{\left(\sum\limits_{N_1=0}^{N_{T,1}} \cdots \sum\limits_{N_S=0}^{N_{T,S}} \int\limits_0^{V_T} dV_1 \left(\prod\limits_{i=1}^{R} \frac{V_1^{N_i}(V_T-V_1)^{N_{T,i}-N_i}}{\Lambda_i^{3N_{T,i}} N_i!\,(N_{T,i}-N_i)!} \right) \right)}
$$
$$
\frac{\frac{\prod\limits_{i=1}^{R}\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}}{\prod\limits_{i=1}^{R}\frac{(N_i+\nu_i)!}{N_i!}} \prod\limits_{i=1}^{R} \exp[-\beta \sum\limits_j^{\nu_i} \Delta U_j^+] \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}},V_1)]}{\left(\prod\limits_{j=R+1}^{S} \frac{V_1^{N_j}(V_T-V_1)^{N_{T,j}+\nu_j-N_j}}{\Lambda_j^{3(N_{T,j}+\nu_j)} N_j!\,(N_{T,j}+\nu_j-N_j)!} \right) \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}},V_1)]}
\tag{S54}
$$

This leads to

$$
\frac{\left\langle \delta'_{\lambda=1,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \right\rangle}{\left\langle \delta'_{\lambda=0,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}} \right\rangle} = \left\langle \prod\limits_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\text{normal,GE}}
\tag{S55}
$$

Note that the right hand side of Eq. S55 is directly related to the chemical potential (see Eq. S48). If we assume that number of whole molecules and volume of the box are independent of the value of λ, we can write

$$
\frac{\left\langle \delta'_{\lambda=1,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \right\rangle}{\left\langle \delta'_{\lambda=0,\delta=1} \frac{1}{\prod\limits_{i=1}^{R} \left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}} \right\rangle} \approx \left\langle \frac{\prod\limits_{i=1}^{R}\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}}{\prod\limits_{i=1}^{R}\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle \frac{\langle \delta'_{\lambda=1,\delta_1=1} \rangle}{\langle \delta'_{\lambda=0,\delta_1=1} \rangle} \approx \left\langle \prod\limits_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\text{normal,GE}} = \sum\limits_{i=1}^{R} \nu_i \mu_i
\tag{S56}
$$

which leads to

$$
\left\langle \frac{\prod\limits_{i=1}^{R}\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}}{\prod\limits_{i=1}^{R}\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle \frac{p(\lambda_R \uparrow 1)}{p(\lambda_R \downarrow 0)} \approx \left\langle \prod\limits_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum\limits_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\text{normal,GE}} = \sum\limits_{i=1}^{R} \nu_i \mu_i
\tag{S57}
$$

where $\lambda_{\mathrm{R}} = \lambda$ when we have the fractional molecules of reactants ($\delta = 1$). In this equation, $p(\lambda_R \uparrow 1)$ is the probability that λ_R approaches 1, and $p(\lambda_R \downarrow 0)$ is the probability that λ_R approaches 0.

$$\left\langle \frac{\prod_{i=1}^{R} \left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}}{\prod_{i=1}^{R} \frac{(N_i+\nu_i)!}{N_i!}} \right\rangle \approx \left\langle \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i}}{\prod_{i=1}^{R} N_i^{\nu_i}} \right\rangle = \left\langle \prod_{i=1}^{R} \left(\frac{1}{\Lambda_i^3 \rho_i}\right)^{\nu_i} \right\rangle \tag{S58}$$

The sum of chemical potentials of all reactants times their stoichiometric coefficients equals

$$\left\langle \prod_{i=1}^{R} \left(\frac{1}{\Lambda_i^3 \rho_i}\right)^{\nu_i} \right\rangle \frac{p(\lambda_R \uparrow 1)}{p(\lambda_R \downarrow 0)} \approx \left\langle \prod_{i=1}^{R} \frac{\left(\frac{V_1}{\Lambda_i^3}\right)^{\nu_i} \exp[-\beta \sum_{j=1}^{\nu_i} \Delta U_j^+]}{\frac{(N_i+\nu_i)!}{N_i!}} \right\rangle_{\mathrm{normal,GE}} \tag{S59}$$

At this point, it is important to note that so far we did not consider the internal contribution of the partition function of component i. The corrected expression including the correct reference state for the chemical potential of component i equals

$$\sum_{i=1}^{R} \nu_i \mu_i = -\frac{1}{\beta} \ln \left\langle \prod_{i=1}^{R} \left(\frac{q_i}{\Lambda_i^3 \rho_i}\right)^{\nu_i} \right\rangle - \frac{1}{\beta} \ln \left(\frac{p(\lambda_R \uparrow 1)}{p(\lambda_R \downarrow 0)}\right) \tag{S60}$$

where q_i is the ideal gas partition function of component i, excluding the translational part.[3] Eq. S60 allows for an independent check of reaction equilibria without any additional calculations (e.g. Widom's test particle insertion method).[1] By coupling the interactions of different components in smart way to the order parameter λ_R, we are able to compute the chemical potentials of all components participating in the reaction. If we only scale the interactions of the fractional molecule of one of the reactant components (for instance component i) from no interactions to full interactions when $\lambda \in \langle 0, A \rangle$, we can write

$$\nu_i \mu_i = -\frac{1}{\beta} \ln \left(\frac{q_i}{\Lambda_i^3 \rho_i}\right)^{\nu_i} - \frac{1}{\beta} \ln \left(\frac{p(\lambda_R \uparrow A)}{p(\lambda_R \downarrow 0)}\right) \tag{S61}$$

The first term on the right hand side accounts for the ideal gas part of the chemical potential including the internal degrees of freedom, and the second term account for the excess part of the chemical potential (due to the interactions of molecules with the surrounding). To validate Eq. S61, excess chemical potentials obtained from serial Rx/CFC for the reaction A $\rightleftharpoons$ B, where A and B have identical interaction potentials, are compared with the values obtained from Widom's test particle insertion method[1,5,6] in the NPT ensemble and values computed from from the equation of state of the Lennard-Jones interaction potential.[7] As shown in table S1, values obtained from the three methods are in excellent agreement. The chemical

potential of component i for a non-ideal gas equals[8] (see also Eqs. S8 and S9)

$$\mu_i = \frac{1}{\beta} \ln \frac{\beta P_0 \Lambda_i^3}{q_i} + \frac{1}{\beta} \ln \frac{y_i P \varphi_i}{P_0} \tag{S62}$$

in which φ_i and y_i are the fugacity coefficient and mole fraction of component i. P_0 is the reference pressure (1 bar) and P is the pressure of the mixture. Therefore, we have

$$\sum_{i=1}^{R} \nu_i \mu_i = \frac{1}{\beta} \ln \left(\prod_{i=1}^{R} \left[\frac{\beta \Lambda_i^3 y_i P \varphi_i}{q_i} \right]^{\nu_i} \right) \tag{S63}$$

Combining this with Eq. S60 immediately leads to

$$\prod_{i=1}^{R} \varphi_i^{-\nu_i} = \left(\frac{\beta y_i P}{\rho_i} \right)^{\nu_i} \frac{p(\lambda_R \uparrow 1)}{p(\lambda_R \downarrow 0)} \tag{S64}$$

We define the term z_i by

$$z_i = \frac{\beta y_i P}{\rho_i} \tag{S65}$$

Therefore, we can write for φ_i

$$\varphi_i^{-\nu_i} = z_i^{\nu_i} \frac{p(\lambda_R \uparrow A)}{p(\lambda_R \downarrow 0)} \tag{S66}$$

5 Extension to the constant pressure version of serial Rx/CFC

In this section, we extend the expressions derived for the partition function and acceptance rules for the constant volume version of serial Rx/CFC to the constant pressure version by multiplying the partition function by a term $\exp[-\beta PV]$.[1] The partition function for the constant pressure version of serial Rx/CFC is therefore given by

$$
\begin{aligned}
Q_{\text{CFC,P}} = {}& \beta P \sum_{N_1=0}^{\infty} \cdots \sum_{N_S=0}^{\infty} \sum_{\delta=0}^{1} \int dV \exp[-\beta PV] \exp\left[\beta \sum_{i=1}^{R} \mu_i \left(N_i + \nu_i \delta\right) + \sum_{i=1}^{R} \left(N_i + \nu_i \delta\right) \ln \frac{V q_i}{\Lambda_i^3} - \sum_{i=1}^{R} \ln N_i! \right] \times \\
& \exp\left[\beta \sum_{j=R+1}^{S} \mu_j \left(N_j + \nu_j(1-\delta)\right) + \sum_{j=R+1}^{S} \left(N_j + \nu_j(1-\delta)\right) \ln \frac{V q_j}{\Lambda_j^3} - \sum_{j=R+1}^{S} \ln N_j! \right] \times \\
& \int_0^1 d\lambda \int ds^{N_{\text{int}}} \exp[-\beta U_{\text{int}}(s^{N_{\text{int}}})] \left(\prod_{i=1}^{R} \int ds_{\text{frac}}^{\nu_i} \exp[-\beta \delta U_{\text{frac},i}(s_{\text{frac}}^{\nu_i}, s^{N_{\text{int}}}, \lambda)] \right) \times \\
& \left(\prod_{j=R+1}^{S} \int ds_{\text{frac}}^{\nu_j} \exp[-\beta (1-\delta) U_{\text{frac},j}(s_{\text{frac}}^{\nu_j}, s^{N_{\text{int}}}, \lambda)] \right)
\end{aligned} \tag{S67}
$$

where P is the pressure of the system. The term βP is used to make the partition function dimensionless.[1] In the constant pressure version of the serial Rx/CFC method, the volume of the simulation box remains unchanged in all reaction trial moves. Therefore, the acceptance rules for these trial moves in the constant volume and constant pressure versions of serial Rx/CFC Eqs. S22, S29 and S36 are identical. The only additional trial move in the constant pressure versions of serial Rx/CFC is the trial move to change the volume of the simulation box. In this trial move, the volume of the simulation box is changed while the number and relative coordinates of the whole molecules and fractional molecules stay the same. Here, the random walk is performed in V and not in $\ln(V)$. The acceptance rule for this trial move is[1]

$$\text{acc}(\text{o} \to \text{n}) = \min \left[1, \left(\frac{V_\text{n}}{V_\text{o}} \right)^{\sum\limits_{i=1}^{R} (N_i + \nu_i \delta) + \sum\limits_{j=R+1}^{S} (N_j + \nu_j (1-\delta))} \exp \left[-\beta \left(\Delta U + P \left(V_\text{n} - V_\text{o} \right) \right) \right] \right] \qquad \text{(S68)}$$

As we assume that the probability distribution of λ does not depend on volume, the expression derived for the chemical potential for the constant volume version of serial Rx/CFC can also be used for the constant pressure version of the serial Rx/CFC method, as is the same for the conventional NVT and NPT ensembles.[1]

6 Thermodynamic modeling of ammonia synthesis reaction

The ammonia synthesis reaction is modeled using the Peng-Robinson Equation of State (PR-EoS)[9] and the mixture compositions at equilibrium are obtained for different temperatures and pressures. These results are compared to those obtained from serial Rx/CFC simulations. The equilibrium constant is only a function of temperature and defined by[8]

$$K = \frac{\prod\limits_{j=R+1}^{S} \left(q_j / \Lambda_j^3 \right)}{\prod\limits_{i=1}^{R} \left(q_i / \Lambda_i^3 \right)} \qquad \text{(S69)}$$

where Λ_i is the de Broglie thermal wavelength of component i, and q_i is the ideal gas partition function excluding the translational part. At equilibrium, the equilibrium constant is also given by

$$K = \frac{\prod_{j=R+1}^{S} \left(\frac{y_j P \varphi_j}{k_{\mathrm{B}} T}\right)^{v_j}}{\prod_{i=1}^{R} \left(\frac{y_i P \varphi_i}{k_{\mathrm{B}} T}\right)^{v_i}} \tag{S70}$$

where P is the total pressure, and y_i and φ_i are the mole fraction and the fugacity coefficient of component i, respectively. For a non-linear polyatomic molecule, the ideal gas partition function excluding the translational part is[8]

$$\frac{q_i(T)}{\Lambda_i^3} = \left(\frac{2\pi M_i k_{\mathrm{B}} T}{h^2}\right)^{3/2} \frac{\pi^{1/2}}{\sigma} \left(\frac{T^3}{\Theta_{\mathrm{rot,A},i} \Theta_{\mathrm{rot,B},i} \Theta_{\mathrm{rot,C},i}}\right) \prod_{j=1}^{3n-6} \frac{1}{1-\exp\left(-\Theta_{\mathrm{vib},j,i}/T\right)} g_{e1,i} \exp[D_0/k_{\mathrm{B}} T] \tag{S71}$$

where $\Theta_{\mathrm{rot,A},i}$, $\Theta_{\mathrm{rot,B},i}$, and $\Theta_{\mathrm{rot,C},i}$ are the characteristic rotational temperatures in terms of three principal moments of inertial.[8] M_i is the molecular mass of component i, $\Theta_{\mathrm{vib},j}$ is the characteristic vibrational temperature corresponding to normal mode j. D_0 is the atomization energy at 0K. σ is the symmetry number of molecules of component i. h is the Planck constant. $g_{e1,i}$ is the degeneracy of the electronic ground state, and k_B is the Boltzmann constant. As the atomization energies D_0 appear in the exponential, small differences in D_0 may lead to large differences in the computed partition functions. Deviations are observed between the experimental atomization energies and those obtained from the Gaussian09. These values are reported in table S2. table S3 summarizes the computed partition functions both based on experimental data from literature[8,10] and quantum computations using Gaussian09.[11] It is important to note that for the latter, the atomization energies from McQuarrie were used, and not the ones computed from Gaussian09. Using the atomization energies computed from Gaussian09, results in equilibrium constants that are 5 times larger than experimentally measured equilibrium constants. In all QM computations, the optimized molecular structures for nitrogen, hydrogen and ammonia were obtained at the B3LYP level of theory with a 6-31G** basis set. A frequency analysis was carried out on the optimized geometries to compute the partition functions.

For the ammonia synthesis reaction $N_2 + 3H_2 \rightleftharpoons 2NH_3$, the equilibrium constant of Eq. S70 becomes

$$K = \frac{(y_{NH_3}P\varphi_{NH_3})^2}{(y_{N_2}P\varphi_{N_2})(y_{H_2}P\varphi_{H_2})^3}(k_B T)^2 \tag{S72}$$

The fugacity coefficients of ammonia, nitrogen and hydrogen are obtained from the Peng-Robinson Equation of State:[12]

$$P = \frac{RT}{V-b} - \frac{a}{V(V+b)+b(V-b)} \tag{S73}$$

$$\ln \varphi_i = \frac{b_i}{b_m}(Z_m - 1) - \ln(Z_m - B_m) - \frac{A_m}{2\sqrt{2}B_m}\left(\frac{2\sum_{k=1}^{S} y_k a_{ik}}{a_m} - \frac{b_i}{b}\right)\ln\left(\frac{Z_m + 2.414B_m}{Z_m - 0.414B_m}\right) \tag{S74}$$

S is the number of components, Z_m is the compressibility factor, and A_m and B_m are defined as[12,13]

$$A_m = a_m(T)P/R^2 T^2 \ , \ B_m = b_m P/RT \ , \ Z_m = PV/RT \tag{S75}$$

a_m and b_m are constants taking into account the molecular interactions in the mixture and co-volume, respectively. For mixtures, a and b in Eq. S73 are replaced by a_m and b_m, respectively. The van der Waals mixing rules are used to compute these values:[12,13]

$$a_m = \sum_{i=1}^{S}\sum_{j=i}^{S} x_i x_j a_{ij}$$

$$b_m = \sum_{i-1}^{S}\sum_{j=i}^{S} x_i x_j b_{ij} \tag{S76}$$

where x_i is the mole fraction of component i. In the above equation, a_{ii} and b_{ii} correspond to pure component i and are defined as[12,13]

$$a_{ii}(T) = 0.45724\frac{R^2 T_c^2}{P_c}\left[1 + \left(0.37464 + 1.54226\omega - 0.26992\omega^2\right)\left(1 - T_r^{1/2}\right)\right]^2$$

$$b_{ii} = \frac{0.0778RT_c}{P_c} \tag{S77}$$

ω is the acentric factor of the component which can be found in literature.[14] T_c and P_c are the critical temperature and critical pressure of the component, respectively. Critical points and acentric factors for nitrogen, hydrogen and ammonia are taken from the REFPROP database[15] and are listed in table S4. a_{ij} and b_{ij} corresponds to unlike-interaction parameters and defined as

$$
\begin{aligned}
a_{ij} &= (a_{ii}a_{jj})^{1/2}\left(1 - k_{ij}\right) \\
b_{ij} &= \frac{(b_{ii} + b_{jj})}{2}
\end{aligned}
\tag{S78}
$$

k_{ij} is the coupling interaction parameter. For a given temperature and pressure, the right hand side of Eq. S72 is defined by mixture compositions at equilibrium. To obtain the mixture compositions at equilibrium using the PR-EoS, the reaction is started with 360 moles of H_2 and 120 moles of N_2 and no ammonia (see Fig. 7 of the main text). The reaction coordinate $\varepsilon \in [0,1]$ is defined as a measure of the extent of the reaction. The value 0 meaning the reaction has not taken place and the value 1 meaning all reactants are converted into reaction products. Knowing the initial composition, the mixture composition at equilibrium is defined by the value of ε, when equilibrium is reached. Using Eq. S72 and the Peng-Robinson equation of state, the value of ε can be found iteratively and this directly leads to the composition of the mixture at chemical equilibrium.

7 Interactions for the ammonia synthesis reaction

For Lennard-Jones interactions, the cutoff radius is set to 12.0Å. The Lorentz-Berthelot mixing rules and tail corrections are used.[6] For fractional molecules, Lennard-Jones interactions are scaled as:[16]

$$
u(r,\lambda) = \lambda 4\epsilon \left(\frac{1}{\left[\frac{1}{2}\left(1-\lambda\right)^2 + \left(\frac{r}{\sigma}\right)^6\right]^2} - \frac{1}{\left[\frac{1}{2}\left(1-\lambda\right)^2 + \left(\frac{r}{\sigma}\right)^6\right]} \right)
\tag{S79}
$$

For the interactions between two different fractional molecules, the minimum of the two values of λ is used. The tail corrections energy for two atom types i and j is:[1]

$$u_{\text{tail}}^{ij} = \frac{16\pi N_i N_j \epsilon_{ij}}{V} \left(\frac{\sigma_{ij}^{12}}{9r_{\text{cut}}^9} - \frac{\sigma_{ij}^6}{3r_{\text{cut}}^3} \right) \tag{S80}$$

where N_i and N_j are the total number of atoms of type i and j in the simulation box, V is the volume of the simulation box and r_{cut} the cutoff radius. An atom of a fractional molecule is counted as λ. The total energy tail correction of the system is then:

$$U_{\text{tail,total}} = \frac{1}{2} \sum_{i=1}^{M} \sum_{j=1}^{M} u_{\text{tail}}^{ij}$$

where M is the number of different atom types and the factor $\frac{1}{2}$ corrects for counting contributions double. Coulombic interactions are calculated with the Wolf method.[17] Here, also a cutoff radius of 12.0Å is used and the damping parameter was set to $\alpha = 0.10\text{Å}^{-1}$. In the Wolf method, Coulombic interactions are calculated in two parts. The first part is a damped pairwise potential:

$$u(r, \lambda) = \frac{q_i q_j}{4\pi\epsilon_0} \left(\frac{\text{erfc}(\alpha r)}{r} - \frac{\text{erfc}(\alpha r_{\text{cut}})}{r_{\text{cut}}} \right) \tag{S81}$$

where α is a damping parameter, r_{cut} the cutoff radius, and $\text{erfc}(x)$ is the complementary error function. For fractional molecules we use a slightly different form:

$$u(r) = \frac{\lambda q_i q_j}{4\pi\epsilon_0} \left(\frac{\text{erfc}(\alpha r)}{r + \frac{1}{2}(1-\lambda)^2} - \frac{\text{erfc}(\alpha r_{\text{cut}})}{r_{\text{cut}} + \frac{1}{2}(1-\lambda)^2} \right) \tag{S82}$$

This ensures that for $\lambda = 1$ we have the original interaction potential and for $\lambda = 0$ interactions are switched off, and no singularities are present when $\lambda \to 0$. The second term is a correction term called the self term:[17]

$$u_{\text{self}} = -\frac{1}{4\pi\epsilon_0} \left(\frac{\text{erfc}(\alpha r_{\text{cut}})}{2r_{\text{cut}}} + \frac{\alpha}{\sqrt{\pi}} \right) \sum_{i=1}^{N} q_i^2 \tag{S83}$$

where the sum is over all atomic charges so that N is the total number of atoms in the system. Fractional molecules are included by substituting N by $N + N_{\text{frac}}$ (N_{frac} is the total number of atoms of fractional molecules). For fractional molecules, the term q_i^2 is replaced by λq_i^2. By comparing the total electrostatic energy of several configurations using the Wolf method and the Ewald summation,[1,18] we verified that the electrostatic energies computed using the Wolf method are nearly identical.

Force field parameters used for ammonia, nitrogen and, hydrogen are listed in table S5 and were taken from Refs.[19–22] Hydrogen is modeled by a single chargeless Lennard-Jones interaction site. For nitrogen, bond lengths and angles are:

- $d(\text{N}_{\text{N}_2}, \text{M}_{\text{N}_2}) = 0.55\text{Å}$

- $d(\text{N}_{\text{N}_2}, \text{N}_{\text{N}_2}) = 1.10\text{Å}$

- $\theta(\text{N}_{\text{N}_2}, \text{M}_{\text{N}_2}, \text{N}_{\text{N}_2}) = 180 \text{ deg}$

M_{N_2} is a dummy site which only carries a partial charge and is located in between the two N atoms (see also table S5). For ammonia, bond lengths and angles are:

- $d(\text{N}_{\text{NH}_3}, \text{H}_{\text{NH}_3}) = 1.012\text{Å}$

- $d(\text{N}_{\text{NH}_3}, \text{M}_{\text{NH}_3}) = 0.080\text{Å}$

- $\theta(\text{H}_{\text{NH}_3}, \text{N}_{\text{NH}_3}, \text{H}_{\text{NH}_3}) = 106.7 \text{ deg}$

- $\theta(\text{H}_{\text{NH}_3}, \text{N}_{\text{NH}_3}, \text{M}_{\text{NH}_3}) = 67.9 \text{ deg}$

M_{NH_3} is a dummy site which only carries a partial charge (see also table S5).

Table S1: Computed excess chemical potentials of Lennard-Jones particles (with analytic tail corrections [1,6]) at different pressures obtained from serial RX/CFC and Widom's test particle insertion method [5] in the NPT ensemble are compared with values computed from the Equation Of State (EOS) from Kolafa and Nezbeda.[7] In the second column, the values obtained with the serial Rx/CFC method for the reaction A $\rightleftharpoons$ B are shown. In the third column, values obtained from NPT simulations (400 particles) with Widom's test particle insertion method are shown. The numbers between brackets denote the uncertainty in the last digit. All values are reported in dimensionless units. The cutoff radius was set to 2.5 in dimensionless units. $T=2$.

P	Serial RX/CFC	Widom	EOS
1.0	-0.646(9)	-0.645(8)	-0.646
3.0	1.91(2)	1.91(3)	1.910
5.0	4.34(2)	4.37(4)	4.342

Table S2: Experimental atomization energies[8] and atomization energies computed for nitrogen, hydrogen, ammonia using Gaussian09 using the B3LYP level of theory with a 6-31G** basis set.[11]

Component	D_0 / [kJ/mol]	
	McQuarrie	Gaussian
N_2	941.6	917.6
H_2	432.1	432.1
NH_3	1158	1149.8

Table S3: Computed ideal gas partition functions of nitrogen, hydrogen, ammonia obtained as defined in section 6 of the SI. The reported values are based on experimental data[8,10] and quantum computations using Gaussian09 (B3LYP level of theory, 6-31G** basis set).[11] It is important to note that for the values obtained from Gaussian09, the experimental atomization energies provided by McQuarrie[8] are used (see table S2) and *NOT* the ones obtained from Gaussian09. One can easily see that using the atomization energies from Gaussian09 (as listed in table S2) results in large deviations. For serial Rx/CFC simulations, values reported in the first column (McQuarrie) were used.

	q/Λ^3 [N_2]/[Å^{-3}]			q/Λ^3 [H_2]/[Å^{-3}]			q/Λ^3 [NH_3]/[Å^{-3}]		
T/K	McQuarrie	JANAF	Gaussian	McQuarrie	JANAF	Gaussian	McQuarrie	JANAF	Gaussian
573	$2.60 \cdot 10^{90}$	$2.63 \cdot 10^{90}$	$2.65 \cdot 10^{90}$	$6.46 \cdot 10^{40}$	$6.46 \cdot 10^{40}$	$5.95 \cdot 10^{40}$	$1.50 \cdot 10^{110}$	$1.44 \cdot 10^{110}$	$1.50 \cdot 10^{110}$
673	$6.89 \cdot 10^{77}$	$6.99 \cdot 10^{77}$	$6.99 \cdot 10^{77}$	$1.28 \cdot 10^{35}$	$1.35 \cdot 10^{35}$	$1.25 \cdot 10^{35}$	$5.42 \cdot 10^{94}$	$5.22 \cdot 10^{94}$	$5.42 \cdot 10^{94}$
773	$3.44 \cdot 10^{68}$	$3.50 \cdot 10^{68}$	$3.49 \cdot 10^{68}$	$8.28 \cdot 10^{30}$	$8.75 \cdot 10^{30}$	$8.09 \cdot 10^{30}$	$2.12 \cdot 10^{83}$	$2.05 \cdot 10^{83}$	$2.12 \cdot 10^{83}$
873	$2.42 \cdot 10^{61}$	$2.47 \cdot 10^{61}$	$2.77 \cdot 10^{61}$	$5.08 \cdot 10^{27}$	$5.36 \cdot 10^{27}$	$4.96 \cdot 10^{27}$	$3.65 \cdot 10^{74}$	$3.56 \cdot 10^{74}$	$3.65 \cdot 10^{74}$

Table S4: Critical temperatures (T_c), pressures (P_c) and acentric factors (ω) of the components used in the PR-EoS modeling.[14]

Component	T_c /[K]	P_c /[Pa]	ω
N_2	126.19	3395800	0.0372
H_2	33.14	1296400	-0.219
NH_3	405.4	11333000	0.25601

Table S5: Force field parameters (Lennard-Jones parameters, and partial charges of interaction sites) used for ammonia, nitrogen and, hydrogen.[19–22] The different interaction sites are defined in section 7 of the SI. Lennard-Jones interactions between unlike atoms are calculated using the Lorentz-Berthelot mixing rules.[6]

Site	σ /[Å]	ϵ/k_B /[K]	q /[e]
N_{N_2}	3.32	36.4	-0.40505
M_{N_2}	0.0	0.0	0.8101
H_2	2.915	38.0	0.0
N_{NH_3}	3.420	185.0	0.0
H_{NH_3}	0.0	0.0	0.410
M_{NH_3}	0.0	0.0	-1.230
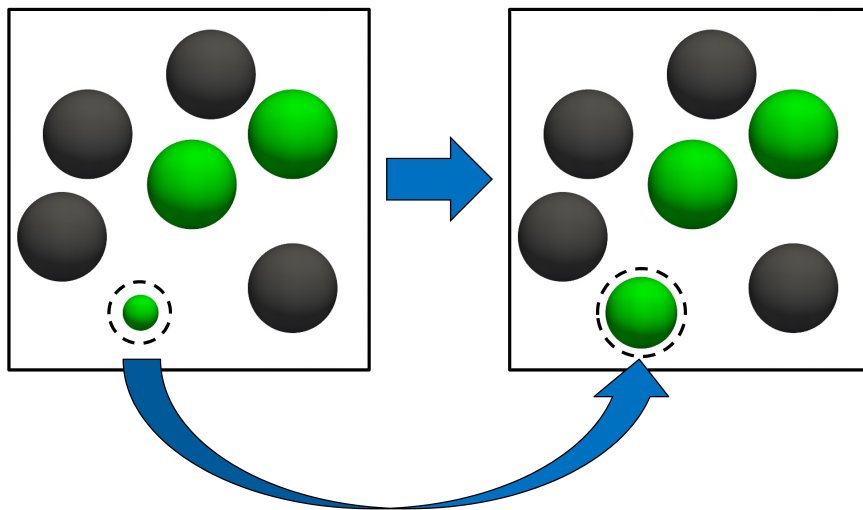
Figure S1: Schematic representation of the trial move attempting to change the coupling parameter λ. In this trial move, δ and the positions of all molecules remain the same. We consider the reaction A $\rightleftharpoons$ B in which A=green and B=black. The dashed spheres represent fractional molecules.
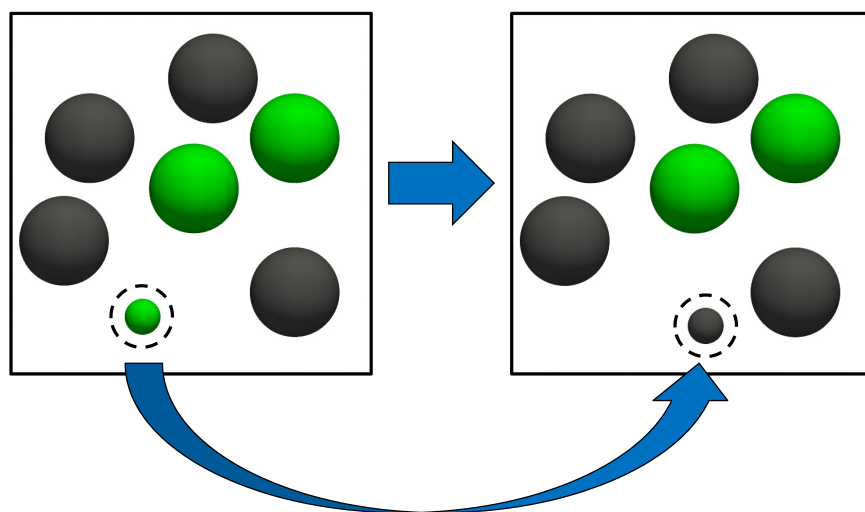
Figure S2: Schematic representation of the trial move attempting to perform the reaction for fractional molecules. In this trial move, the number of the whole molecules and also the value of λ are constant. We consider the reaction A $\rightleftharpoons$ B in which A=green and B=black. The dashed spheres represent fractional molecules. The fractional molecule of A is removed and a fractional molecule of B is inserted at a randomly selected position.
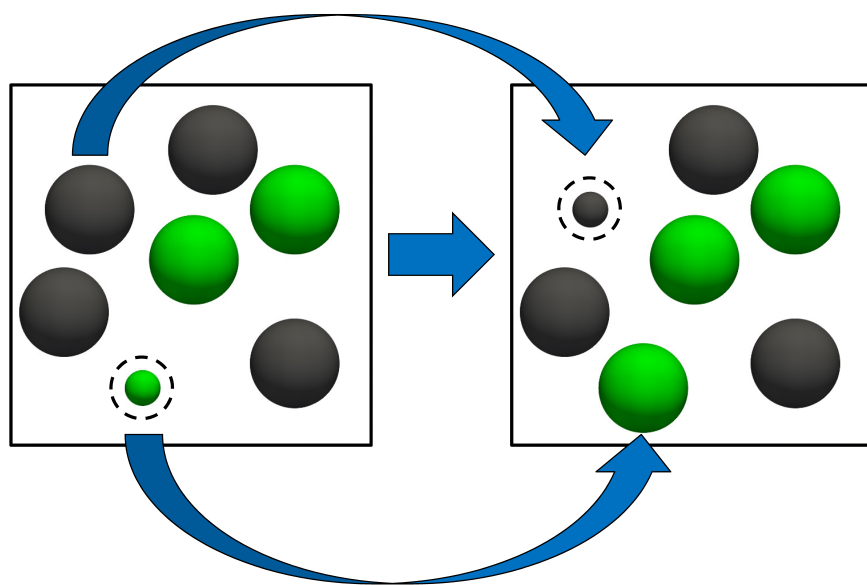
Figure S3: Schematic representation of the trial move attempting to perform the reaction for whole molecules. In this trial move, the value of λ and all positions of all molecules remain the same. We consider the reaction A $\rightleftharpoons$ B in which A=green and B=black. The dashed spheres represent fractional molecules. The fractional molecule of A is transformed into a whole molecule of A while at the same time, a randomly selected whole molecule of B is transformed into a fractional molecule of B.

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