Effect of Conformers on Free Energies of Atmospheric Complexes

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ABSTRACT: In this article we show how to calculate free energies for atmospherically relevant complexes when multiple conformers and/or isomers are present. We explain why the thermal averaging methods used in several published works are incorrect. On the basis of our two sample cases, the sulfuric acid–pinic acid complex and the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster, we provide numerical evidence that the use of these incorrect formulas can result in errors larger than 1 kcal/mol. We recommend that if vibrational frequencies and thus Gibbs free energies of the individual conformers are unavailable, one should not attempt to correct for the presence of multiple conformers and instead use only the global minimum conformers for both reactants and products. On the contrary, if the free energies for the conformers are calculated for both reactants and products, their effect can be accounted for by the statistical mechanical methods presented in this article.
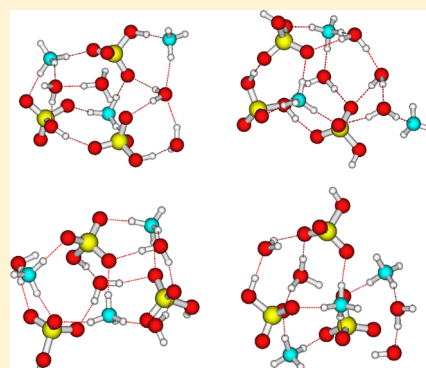
1. INTRODUCTION

Formation and growth of tropospheric aerosols via nucleation is of central importance to the earth's atmosphere and climate.[1,2] Sulfuric acid has been accepted as one of the central molecules for new particle formation, but the effect of several other species ranging from ammonia[3−7] and amines[8−13] to ions[14−22] and various organic compounds[23−32] on the stability of prenucleation clusters has also been examined. Some of the organic compounds and the prenucleation clusters are rather large as they typically contain several tens of atoms. Because of this, there are often multiple low-lying minimum energy configurations in these systems. This number increases rapidly with the size of the system. A major challenge in calculating atmospheric cluster formation is to locate the important cluster configurations efficiently and reliably. This can be accomplished by several different methods, typically in successive stages starting with less accurate approaches based on classical properties followed by more accurate determination of vibrational frequencies, energies, and other properties of the lowest energy conformers necessary for the calculation of the partition functions using *ab initio* methods.[22,33,34]

After the different conformations have been located, a second challenge is to account for not only the global minimum structure but also for the effect of higher energy local minima when thermodynamic properties are calculated. In recent literature, including our own research, an increasingly common approach has been to account for the higher energy conformers by a process of Boltzmann averaging where a thermal average over all the relevant conformers is calculated.[14,22,34−50] We show in the present article that this approach leads to erroneous results even at the qualitative level, as the incorporation of higher energy conformers leads to an increase in the value of the Gibbs free energy, i.e., making the cluster less stable, corresponding to an effective *decrease* in the number of available microstates. In reality, however, the existence of several conformers results in an *increase* in the number of energy levels and available microstates, which should always decrease the value of Gibbs free energy G, as the two are connected by $G = A + pV = -k_B T \ln Z + pV$, where A is the Helmholtz free energy, Z is the canonical partition function obtained as a sum over the energy states, p is the pressure, V is the volume, and k_B is the Boltzmann constant.

We present a rigorous way of accounting for multiple conformers using statistical mechanics. While this approach is not novel (see, for example, ref 51), we feel that the alarmingly growing number of papers using the erroneous averaging formulas warrants a thorough exposition of the correct way to deal with different conformers.

It should be noted that in standard chemical terminology, isomers are compounds that have the same number of atoms
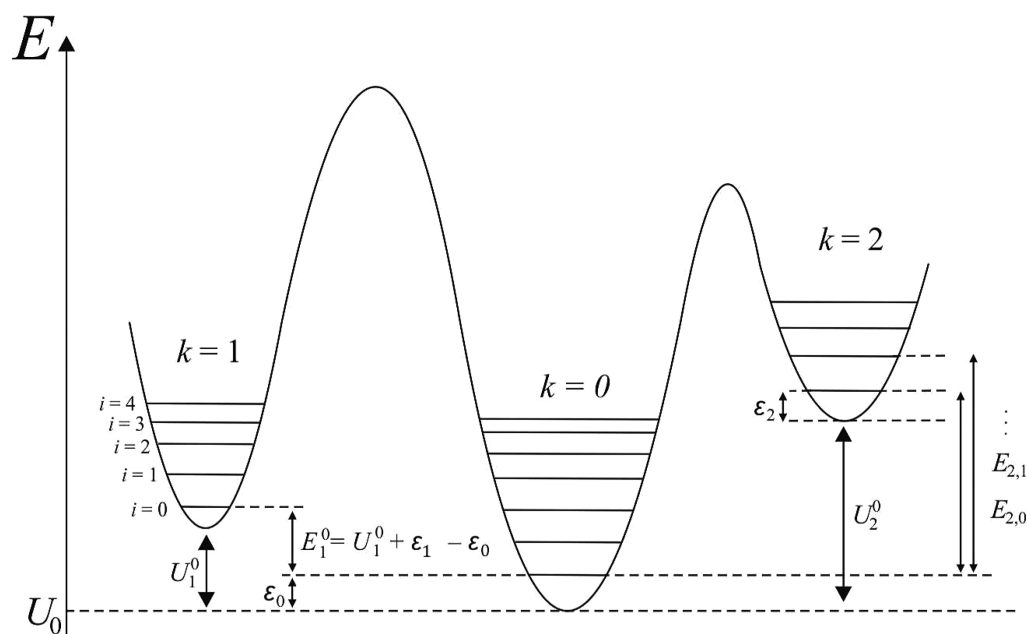
Figure 1. Generic energy level diagram of a molecule with multiple conformers. U_0 is the value of the global minimum of the potential energy surface, ϵ_k is the vibrational zero-point energy of conformer k, measured from the local minimum of k, $E_{k,i}$ is the energy of the ith energy level measured from the quantum mechanical ground state of the system, and U_k^0 is the energy difference between the electronic energy of the kth conformer and the global minimum energy. The energy E_k^0 is the difference between the quantum mechanical ground state energies of conformer k and that of the global minimum, i.e., including the vibrational zero-point energy.

but differ in the way the atoms are arranged, for example in terms of their bonding pattern. Conformational isomers or conformers differ only in the geometric arrangement of the molecules or molecular moieties that enter the compound achieved, for example, through a rotation of a bond. As both of these correspond to minima in the multidimensional potential energy surface (PES), our results are valid for all isomeric structures, but as the conformers are the most relevant, we will use that word in the following.

In the case of small molecules, one may be able to use accurate methods for obtaining the partition function. For small systems, such as a water or an ammonia molecule, it is possible to calculate all the relevant energy levels[52−54] and thus obtain the partition function as a simple sum over these. On the contrary, for small complexes such as the water dimer, water−ammonia cluster, and water−sulfuric acid cluster, the presence of other conformers can be accounted for by focusing on the large amplitude vibrational motions that connect the separate local minima.[53−56] Thus, by treating the high-frequency vibrations separately from the low-frequency ones, it is possible to reduce the dimensionality of the large amplitude potential energy surface to a manageable size so that the presence of the different conformers can be accounted for quantum mechanically, and an exact counting procedure can be implemented.[55] This, however, does not remove the need to address the question raised here, because increased computing power will reveal an increasing number of conformers for larger clusters, and the quantum mechanical treatment of different conformers remains laborious even for relatively small atmospherically interesting systems such as the sulfuric acid monohydrate.

We illustrate the proper statistical mechanical accounting of the high-energy conformers by focusing on two example systems: the complex formed by sulfuric acid and pinic acid and the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster. In the atmosphere, pinic acid originates from the oxidation of α- or β-pinene, organic

compounds emitted by vegetation such as pine trees. Its involvement in the initial clustering steps is a subject of intense research, and together with other oxidized organic compounds it is known to be involved in subsequent particle growth.[1,57,58] Also the significance of ammonia, sulfuric acid, and water clusters for new particle formation has been widely studied.[5,6,59] In our previous research, we have looked at the stability of these two complexes solely on the basis of the global minimum Gibbs free energy structures,[59,60] and in this study we investigate how the higher energy conformers change the Gibbs free energies relative to that calculation.

The remainder of the paper is structured as follows: In section 2, we derive two formulas for the accounting of different energy conformers at varying levels of sophistication for both the Gibbs and the Helmholtz free energies. In section 3, we give a detailed description of what goes wrong in the naive approaches for the inclusion of the conformers. In section 4, we outline the computational methods used for our two case studies. Our results are presented and discussed in section 5, and the paper ends with conclusions in section 6.

2. HOW TO ACCOUNT FOR MULTIPLE CONFORMERS

The effect of conformers in the quantitative description of chemical reactions is most concisely accounted for by statistical mechanics. The molecular (equilibrium) partition function is

$$z = \sum_i e^{-\beta E_i} \tag{1}$$

where the sum is over all quantum states i of the molecule, E_i is the energy of quantum state i, and $\beta \equiv 1/k_B T$. If the molecules are noninteracting and indistinguishable, then the molecular partition function is connected to the canonical partition function of the system Z by the well-known formula $Z = \frac{z^N}{N!}$, where N is the number of molecules. Two properties that also

pertain to the equations below should be noted for eq 1. First, if one wishes to use molar (free) energies instead of (free) energies per molecule, all the results below hold if you substitute the molecular energies and free energies with their molar counterparts and replace k_B with R, the molar gas constant. Second, to conform as closely as possible to standard chemical convention for zeros of energies, we have chosen to calculate the vibrational and electronic parts of the molecular partition function starting from the quantum mechanical vibrational or electronic ground state, respectively, consistent with the convention adopted in several of the physical chemistry textbooks widely used today.[61,62] An alternative frequently used convention is to express the energies relative to the energy when the constituent atoms are infinitely far apart.[63] The choice is a matter of preference: physical results do not depend on the choice of zero of energy.

In the absence of multiple conformers, the sum in eq 1 can be calculated with an expansion of the nonrotational and nontranslational motion of the atoms around the single minimum energy configuration. When more than one well-defined minimum is present, eq 1 can be rearranged as

$$z = \sum_k e^{-\beta E_k^0} \sum_i e^{-\beta(E_{k,i} - E_k^0)} \tag{2}$$

where the index k runs over all the different local minima (conformers) with $k = 0$ corresponding to the global minimum, i.e., k labels the conformer configurations and $E_{k,i}$ denotes the energy of quantum state i of conformer k, measured from the quantum mechanical ground state of the system. The term E_k^0 is the zero of energy of the conformer relative to the minimum energy conformer, including the difference in vibrational zero point energies:

$$\epsilon_k^0 = U_k^0 + \epsilon_{k,0} - \epsilon_{0,0} \tag{3}$$

where U_k^0 is the separation between the global minimum of the potential energy surface U_0 and the local minimum k. Finally, $\epsilon_{k,0}$ is the zero point vibrational energy of the minimum k, as illustrated in Figure 1.

With the natural definition of the molecular partition function for conformer k as

$$z_k \equiv \sum_i e^{-\beta(E_{k,i} - E_k^0)} \tag{4}$$

we can also write the canonical partition function in eq 2 in the more compact form[33]

$$z = \sum_k z_k e^{-\beta E_k^0} \tag{5}$$

If energy levels can be unambiguously assigned to different conformers, eq 5 holds in equilibrium irrespective of whether the heights of the barriers between the local minima allow conformer interconversion or not, as shown in Appendix 1. Another consideration is that the lifetimes of the clusters or molecules in the atmosphere may not be long enough to establish an equilibrium population, in which case eq 5 and the results that follow cannot be applied. This is, however, a different issue from the question of barrier heights.

The Helmholtz free energy is connected to the molecular partition function z by the equation

$$A - A(0) = -kT \ln Z = -NkT \ln \frac{z}{N} - NkT \tag{6}$$

where the second equality follows from the insertion of $Z = \frac{z^N}{N!}$ and the use of Stirling's approximation. For an ideal gas $G = A + pV = A + NkT$ so that the corresponding relation for the Gibbs free energy is

$$G - G(0) = -NkT \ln \frac{z}{N} \tag{7}$$

Focusing on the free energies per molecule $g = \frac{G}{N}$, one can write the connection between g and z as

$$g - g(0) = -1/\beta \ln \frac{z}{N} \Leftrightarrow \frac{z}{N} = e^{-\beta(g - g(0))} \tag{8}$$

where $g(0)$ is the zero temperature value of g. Lowercase letters g and a are used for Gibbs and Helmholtz free energies per molecule, respectively. Assuming ideal gas behavior, the Gibbs free energy at absolute zero temperature $g(0)$, is equal to the internal energy at absolute zero $g(0) = U_0 + \epsilon_0$. Thus, we can express eq 5 in terms of the Gibbs free energies of the separate conformers g_k by

$$\frac{z}{N} = \sum_k \frac{z_k}{N} e^{-\beta E_k^0} = \sum_k e^{-\beta(g_k - g_k(0) + E_k^0)} \tag{9}$$

where g_k, the Gibbs free energy of the conformer k, is defined accordingly by equation

$$e^{-\beta(g_k - g_k(0))} = \frac{z_k}{N} = \frac{1}{N} \sum_i e^{-\beta(E_{k,i} - E_k^0)} \tag{10}$$

We can calculate the total free energy by combining the Gibbs free energies calculated separately for each conformer. We have

$$g = g(0) - k_B T \ln \frac{z}{N} = g(0) - k_B T \ln\left(\sum_k e^{-\beta(g_k - g_k(0) + E_k^0)}\right)$$
$$= -k_B T \ln\left(e^{-\beta g(0)} \sum_k e^{-\beta(g_k - g_k(0))}\right) = -k_B T \ln\left(\sum_k e^{-\beta g_k}\right) \tag{11}$$

which agrees with the result given in ref 51. The third equality follows because $g_k(0) = U_0 + U_k^0 + \epsilon_k = g(0) + E_k^0$ (see eq 3 and Figure 1). The corresponding equations for enthalpy and entropy can be obtained by substituting eq 5 for the partition function in the relevant expressions, and will not be represented here.

If the conformers are sufficiently similar, in the sense that the vibrational frequencies and rotational constants are similar, the free energies differ mainly by their electronic energies U_k^0 and we have

$$g_k \approx g_0 + E_k^0 \approx g_0 + U_k^0 \tag{12}$$

In this case, we can find the total Gibbs free energy of the system by the approximate formula

$$g = -k_B T \ln\left(\sum_k e^{-\beta g_k}\right) \approx g_0 - k_B T \ln \sum_k (e^{-\beta U_k^0}) \tag{13}$$

where g_0 is the Gibbs free energy of the lowest energy conformer.

Using expression 11 or 13 for the Gibbs free energy, we find the corresponding results for the Helmholtz free energy from $a = g - pv$, where $v = \frac{V}{N}$ is in units of volume/molecule. By subtracting the pv term on both sides of eq 11, we obtain

$$a = g - pv = -k_{B}T \ln\left(\sum_{k} e^{-\beta g_{k}}\right) - pv$$

$$= -k_{B}T \ln\left(e^{\beta pv} \sum_{k} e^{-\beta g_{k}}\right) = -k_{B}T \ln\left(\sum_{k} e^{-\beta a_{k}}\right) \tag{14}$$

showing how the Helmholtz free energy can be calculated from the Helmholtz free energies of the different conformers. The simple relation follows because both the external pressures, and the system volumes are identical for all conformers.

Again, if the conformers are similar enough that the a_k's differ mainly by their electronic energies U_k^0, we have $a_k \approx a_0 + U_k^0$, where a_0 is the Helmholtz energy of the lowest energy conformer, and subtracting pV on both sides of eq 13 results in the approximate formula

$$a = g - pv = g_0 - pv - k_{B}T \ln \sum_{k} (e^{-\beta U_k^0})$$

$$= a_0 - k_{B}T \ln \sum_{k} (e^{-\beta U_k^0}) \tag{15}$$

We emphasize again that the main result derived in this article does not depend on this approximation.

When calculating the free energies of individual conformers, one may for convenience make the usual separation between the different degrees of freedom for z_k of conformer k: $z_k = z_{k,trans} z_{k,rot} z_{k,vib} z_{k,el}$. This will be done here in the discussion of numerical examples, but it is not essential for the discussion of conformer or isomer free energies. The nuclear partition function $z_{k,nuc}$ has been left out because it depends only weakly on the molecular configuration and is constant to a good approximation for both clusters and free molecules at the relevant temperatures. We will disregard effects on the rotational and vibrational partition functions caused by quantum constraints on molecular wave functions, such as those that appear for ortho and para hydrogen. Except for the Boltzmann factor for the ground state energy, the electronic partition function is typically equal to the degeneracy of the lowest electronic state. Apart from linear molecules, this will be a spin degeneracy only because of the lifting of the degeneracy by the Jahn–Teller effect. The translational partition functions are identical for all conformers and separates out exactly from the other degrees of freedom. It is proportional to the volume and the ensemble free energy therefore depends logarithmically on the vapor density.

3. ENTROPY, OR WHY THERMAL AVERAGING DOES NOT ALWAYS WORK

Recently, in the literature, there have been several articles with thermal averages for free energies, enthalpies, and entropies calculated using formulas akin to the standard averaging formula

$$\langle O \rangle = Z^{-1} \sum_{i} O_i e^{-\beta E_i} \tag{16}$$

where O_i is the value of the observable O in state i, and Z is the canonical partition function as before. With more than one conformer present, the averages are taken over the energies of different conformers,[34,64,65]

$$\langle O \rangle = \frac{\sum_{k} O_k e^{-\beta E_k}}{\sum_{k} e^{-\beta E_k}} \tag{17}$$

where E_k and O_k are the energy and observable O values of conformer k, respectively. In other works,[14,22,35−50] Gibbs free energies are used to obtain the average free energy value

$$\langle g \rangle = \frac{\sum_{k} g_k e^{-\beta g_k}}{\sum_{k} e^{-\beta g_k}} \tag{18}$$

where g_k is the Gibbs free energy of conformer k.

The thermal averaging represented by eq 17 gives the mean value of the observable O when it only depends on the specific state i (or point in phase space, in classical statistical mechanics). Such local variables include energy, momentum, angular momentum, and location. Dipole moments, for example, have been calculated successfully with this kind of averaging.[64,65] Variables such as free energies, entropies, or the partition functions themselves that reflect the properties of the whole set of energy states (classically the system's phase space), sometimes called integral quantities, cannot be calculated with the averaging given by eq 17. This is a known problem in numerical simulations, for which special methods have been designed to calculate free energies; see, e.g., refs 66 and 67. Using averaging as in eqs 17 and 18 for such quantities gives trivial identities because they are independent of the states in the summand. However, when integral quantities are calculated as sums over integral quantities that are in turn calculated over a restricted set of states, such as free energies of different conformers, the result becomes incorrect. Specifically, eq 18 is always incorrect.

An illustrative example where this type of averaging does not work is entropy. Procedures, such as eqs 17 and 18, that average similar values over different conformers, will tend to leave the entropy unchanged. It will be rigorously unchanged if the vibrational and rotational parameters of all conformers are identical. As a simple concrete example, assume that the system has two different conformers with N microstates each. According to eq 17 the entropy would be $k_B \ln(N)$, whereas by Boltzmann's formula it is $k_B(\ln(N) + \ln(2))$. Generally, you therefore do not get an average entropy by averaging entropies of conformer states. In reality, the entropy increases with every conformer present in the system, because entropy is essentially the logarithm of the number of states. The effect of the entropy increase will be larger than the effect of the increase in average energy due to the higher energy of the conformers, and the Helmholtz or Gibbs free energy will decrease and not increase as the incorrect averaging formula states.

The correct expression for entropy is obtained by considering the Helmholtz free energy of the system $A = U - TS$, where $U = \langle E \rangle$, and the canonical partition function $Z = e^{-\beta(A-A(0))}$. Insertion gives

$$Z = e^{-\beta(\langle E \rangle - TS - \langle E \rangle_{T=0})} \tag{19}$$

where $A(0) = U(0) = \langle E \rangle_{T=0}$ and $\langle E \rangle$ is calculated, e.g., with eqs 9 and 16. The entropy becomes

$$S = k_B \ln Z + \frac{\langle E \rangle - \langle E \rangle_{T=0}}{T}$$

$$= k_B N \ln\left(\sum_{k} e^{-\beta(g_k - g_k(0) + E_k^0)}\right) + N k_B$$

$$+ \frac{1}{TZ} \sum_{i} (E_i - \langle E \rangle_{T=0}) e^{-\beta E_i} \tag{20}$$

The nonadditivity of the first term is the reason for the nonaveraging properties of entropy.

Conf #1 (0.0 kcal/mol)

Conf #5 (1.9 kcal/mol)

Conf #12 (3.7 kcal/mol)

Conf #38 (10.1 kcal/mol)
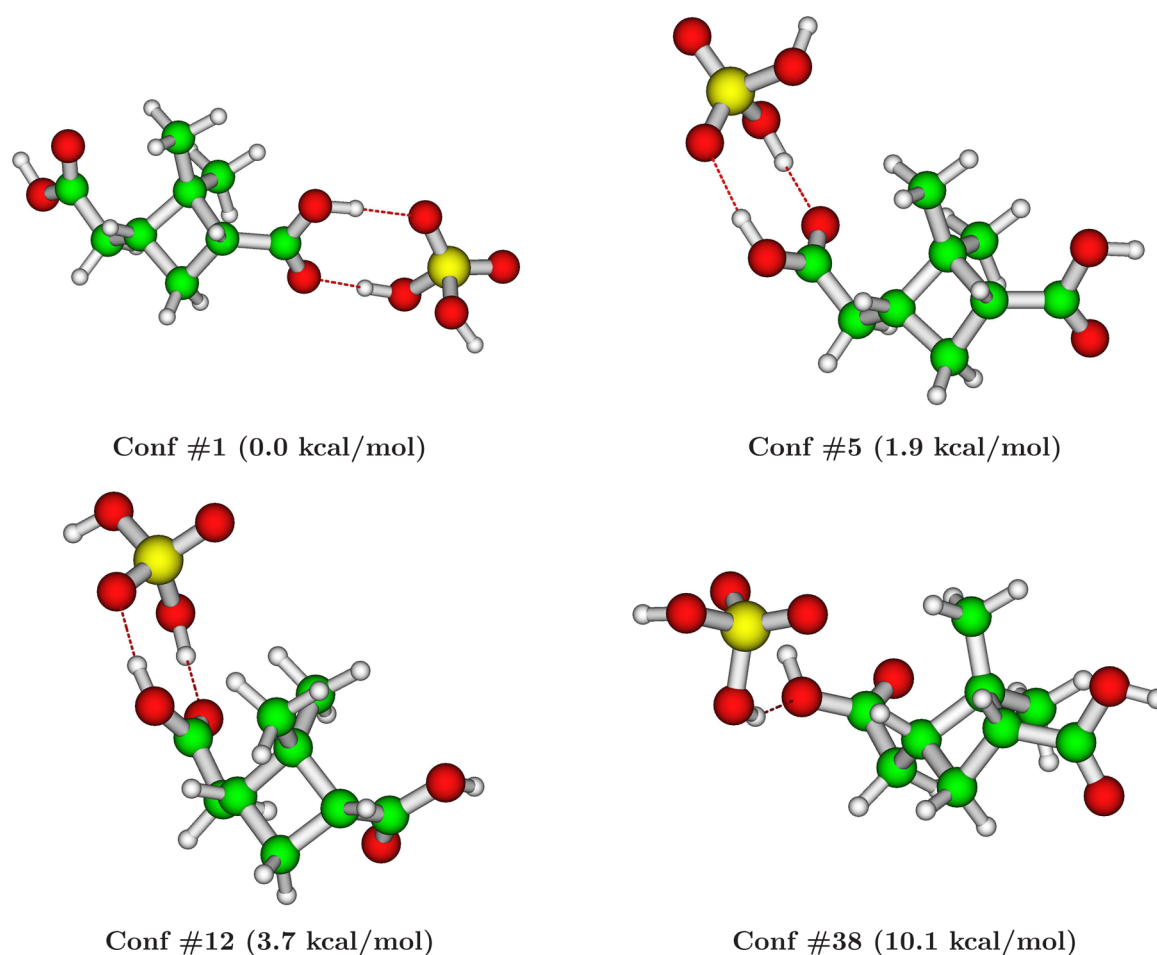
Figure 2. Molecular structure of four different conformers (#1, #5, #12, and #38) of the pinic acid−sulfuric acid complex. The relative stability is given in the brackets in kcal/mol (where 1 kcal/mol = 4.184 kJ/mol).

We should point out that the statements here do not imply that entropy would not be an extensive quantity in thermodynamics. The additivity of the entropy from two different parts of a system derives because the total number of quantum states in the combined system is essentially the product of the number of states of each of the two subsystems. The situation addressed here is different, namely, that of a system that has several alternative (competing) configurations, of which only one can be realized physically at any given time.

4. EXAMPLES

Geometry optimizations of the sulfuric acid−pinic acid complex and the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster were performed using the Gaussian09 program package.[68] Frequency calculations were made of all optimized geometries, confirming them as minima without any imaginary frequencies. The frequencies obtained were used without scaling for the calculation of Gibbs free energies using rigid rotor, harmonic oscillator approximations at 298.15 K and 1 atm.

In the original pinic acid study[60] 10 initial guess geometries were constructed of the isolated pinic acid reactant. The lowest identified conformer was used for further cluster formation with sulfuric acid, utilizing a semiempirically PM6-guided sampling technique relying on several thousand guess structures in each cluster formation step. The identified different conformers of the $(pinic\ acid)_n(H_2SO_4)_m$ clusters were further optimized using the M06-2X[69] functional. M06-2X was chosen on the

basis of its performance in calculating the Gibbs free energies and binding energies of sulfuric acid-containing clusters.[70−72] To be able to explore the configuration space, the small 6-31+G(d) basis set was utilized. In this work we use a more systematic approach to sample the pinic acid reactant conformers. The pinic acid molecule was sampled using a systematic rotor approach as implemented in Avogadro.[73] This led to a total 7 distinct conformers, with the lowest one being 1.0 kcal/mol more stable than our previously identified global minimum energy conformer.

The initial guess geometries of the sulfuric acid, base, and water clusters were constructed on the basis of previously published clusters without water present.[74] Cluster geometry optimization and frequency calculations were performed using the B3LYP functional with the CBSB7 (6-311G(2d,d,p)) basis set. This level of theory was chosen as it is the basis of the B3RICC2 method, which has been shown to yield reliable quantitative trends for atmospheric molecular cluster formation.[74] For more computational details of the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster and the pinic acid−sulfuric acid complex, see the studies by Henschel et al.[59,75] and Elm et al.,[60] respectively.

5. RESULTS AND DISCUSSION

5.1. Case 1: Sulfuric Acid−Pinic Acid Complex. In our previous study the thermochemical analysis relied solely on the global minimum structure seen in Figure 2 as conformer Conf

#1. With relative free energies ranging up to 11.6 kcal/mol, we identified 44, 7, and 2 conformers for the complex, pinic acid, and sulfuric acid, respectively, with our M06-2X/6-31+G(d) approach. For the complex, some of these higher energy conformers are shown in Figure 2 together with their relative free energies and display the wide range of structures found within the investigated free-energy range. The stability of each conformer is well reflected by the number of hydrogen bonds in the structures. Conformers #5 and #12 each have two donor–acceptor pairs, whereas conformer #38 only possesses a single hydrogen bond.

The first three rows of Table 1 show the differences relative to the lowest energy conformer for both the reactants and the

Table 1. Gibbs Free Energies (kcal/mol) Calculated with the Different Statistical Mechanical Methods Presented in This Article for the Pinic Acid–Sulfuric Acid Complex Formation Reaction[a]

	no correction eq. (21)	correct-approximate eq.(13)	correct-accurate eq.(11)	naive eq.(18)	naive eq.(17)
δG(PA)	-	-0.17	-0.31	0.44	0.28
δG(SA)	-	-1.65	-0.30	0.10	0.24
δG(PA+SA)	-	-0.45	-0.25	0.49	0.87
$\Delta_{\mathrm{p}}G$	-7.83	-8.28	-8.08	-7.34	-6.95
$\Delta_{\mathrm{r,p}}G$	-7.83	-6.45	-7.48	-7.87	-7.47

[a]The first three rows show Gibbs free energies for pinic acid (PA), sulfuric acid (SA), and the complex (PA + SA) relative to the G value of the lowest energy conformer for each reactant or product (δG). The last two rows show the formation reaction free energies with only the product conformers included in the calculation ($\Delta_{\mathrm{p}}G$) and with both product and reactant conformers included ($\Delta_{\mathrm{r,p}}G$). The line types are identical to the ones used in Figures 3 and 4.

products of the complex formation reaction calculated with the four methods for the accounting of higher energy conformers presented in sections 2 and 3 by eqs 11, 13, 17, and 18. In the last two rows of the first column, the reaction free energies are calculated as the difference in free energies between minimum energy conformers of products and reactants, i.e.

$$\Delta G = \sum_i \nu_i G_{0,i} \tag{21}$$

where ν_i is the stoichiometric coefficient of species i. Columns two to five in the last two rows show the reaction free energies with only the product conformers included in the calculation ($\Delta_{\mathrm{p}}G$), and reaction free energies with both product and reactant conformers included ($\Delta_{\mathrm{r,p}}G$). With eqs 17 and 18 the actual calculation was done by subtracting the lowest state (free) energy from the (free) energies of the individual conformers in both the nominator and the denominator, which, for example, in the case of eq 17 results in the energies E_k being replaced by the relative energies E_k^0. Inspection of the first three rows of Table 1 shows that, for both reactants and products, adding more conformers increases the stability, manifested as a more negative Gibbs free energy, of the molecule when the rigorous eqs 13 and 11 are used and decreases the stability when the erroneous eqs 17 and 18 are used. Due to the low number of conformers, for sulfuric acid the differences between the thermal averaging results of eqs 17 and 18 are smaller than for pinic acid or the complex. In general, the largest differences in δG values between the different methods are observed when the number of conformers is the largest, i.e., in the case of the

sulfuric acid–pinic acid complex where the differences are more than 0.7 kcal/mol between the correct and incorrect approaches. The predicted differences between eqs 13 and 11 are seen to be small for both pinic acid and the complex but for sulfuric acid the difference exceeds 1 kcal/mol, with the simplified approach of eq 13 giving a significantly more negative value. This occurs because, for sulfuric acid, the lowest energy conformer is different from the lowest free energy conformer at the M06-2X/6-31+G(d) level of theory, which results in a large negative contribution to the free energy from the second term in eq 13. The free energies of the two conformers of sulfuric acid are only 0.25 kcal/mol apart, which shows in Table 1 in that the addition of the second conformer results in a free energy decrease of −0.3 kcal/mol with eq 11. Alternatively, one could approximate eq 11 analogously to eq 13 by taking the Gibbs free energy of the lowest energy conformer out of the logarithm instead of the lowest free energy conformer (G_0). This results in an unphysical increase of 0.18 kcal/mol in the free energy compared to the value for the lowest energy conformer, implying that this approach is not feasible either.

The results in the fourth row show that when only the conformers of the complex product are taken into account, the predictions of the thermal averaging schemes are more than 0.7 kcal/mol off again, reflecting the difference in the δG values, making this an important correction if one wishes to obtain reaction free energy values within the kcal/mol range. On the contrary, eqs 13 and 11 yield roughly the same result. The $\Delta_{\mathrm{p}}G$ values of Table 1 are plotted in Figure 3 for the complex
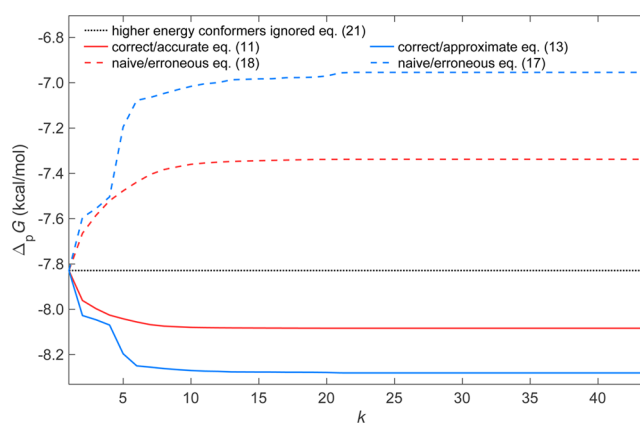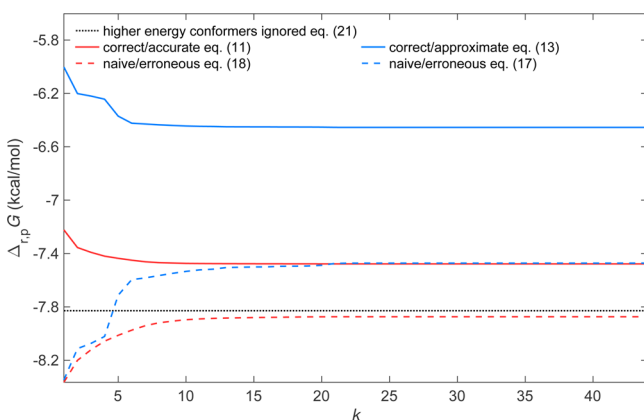

Figure 3. Formation free energies of the pinic acid–sulfuric acid complex when only product conformers are included in the calculation as a function of the number of conformers included.

formation as a function of the number of product conformers included in the calculation when the presence of multiple conformers for the reactants is ignored. The values corresponding to the $\Delta_{\mathrm{p}}G$ values shown in Table 1 can be read from the rightmost side of Figure 3, when all the conformers have been taken into account. The conformers have been included in order of increasing free energy, which results in the stepped structure for eqs 13 and 17 when the ordering of the electronic energies does not match the free energy order. The difference between the theoretically correct averaging schemes and the incorrect ones is very clear from Figure 3, with the correct ones decreasing the free energy of the product and thus the $\Delta_{\mathrm{p}}G$ value for the reaction. Figure 3 also shows that due to the logarithmic dependence on the free energies of the

conformers, convergence with respect to the free energy of the added conformers is obtained faster with formulas 11 and 13 than with the incorrect thermal averaging counterparts. In the case of the pinic acid–sulfuric acid complex, only about the first ten conformers have a significant effect when the correct formulas are used, implying that the free energy range that needs to be considered in identification of important conformers is narrow, once the global minimum has been located. As seen in Figure 2, this implies that only conformer #5 with the relative stability of 1.9 kcal/mol will contribute the formation free energy. Conformers #12 and #38 with relative stabilities of 3.7 and 10.1 kcal/mol, respectively, show negligible contributions. When erroneous thermal averaging is used, the convergence is slower and conformer #12 also contributes to the reaction free energy.

Accounting only for the global minimum structures for both products and reactants, the Gibbs free energy for the complex formation between sulfuric acid and pinic acid has the value of −7.83 kcal/mol, as seen in Table 1. Using eq 11 with all the higher lying local minima taken into account increases this to −7.48 kcal/mol due to the presence of a greater number of low-lying conformers for the reactants than for the product, which, however, has in total significantly more conformers in the investigated range. With the approximate formula of eq 13, where only the Gibbs free energy of the lowest conformer is taken into account, and higher lying conformers are contributing with their electronic energies, a value of −6.45 kcal/mol is obtained. The discrepancy with the more accurate result arises largely from the problems this approximation has in the case of sulfuric acid and clearly shows that (13) is not applicable when the lowest energy conformer is not the same as the lowest free energy one. The first of the two thermal averaging schemes, eq 18, gives results within 0.4 kcal/mol of the eq 11 whereas the one based on electronic energies, eq 17, yields virtually the same value as eq 11. To obtain a better idea of how the Gibbs free energy behaves as a function of the number of product conformers, the $\Delta_{r,p}G$ value is plotted in Figure 4 where all the reactant conformers are taken into account in all the values. As in Figure 3, the conformers are arranged in the order of increasing Gibbs free energy and the values shown in Table 1 can be read from the rightmost edge of Figure 4. The inclusion of the reactant conformers stabilizes the reactants when formulas 11 and 13 are used and has the effect

of decreasing the reaction Gibbs free energy. The opposite is true for the thermal averaging approaches, leading to an offset in the free energies at the leftmost edge of Figure 4, where only the reactant conformers have been accounted for. Due to the relatively large number of relevant reactant conformers, we see that the offset from the dashed black line corresponding to the case where neither reactant nor product conformers have been incorporated in the calculation is about 0.6 kcal/mol in all cases except for the blue curve representing results obtained with eq 13. The significant differences between Figures 3 and 4 underline the importance of accounting for the reactant conformers when the reactants include larger molecules with multiple low-lying conformers, such as pinic acid.

5.2. Case 2: $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ Clusters. For the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster, a total of 305 conformers were identified using the B3LYP functional with the CBSB7 basis. At this level of theory, the lowest energy conformer of sulfuric acid coincided with the lowest free energy one. Figure 5 displays some of the different cluster conformations found, with the lowest identified structure shown as conformer #1. Already at #100, the free energy difference relative to the lowest free energy structure is large, implying that only a few of the 305 identified conformers actually contribute to the formation free energies of the cluster. The higher formation free energies of these conformers are related to the number of hydrogen bonds to sulfuric acid, which decreases with decreasing stability, leading to more direct ammonia–water hydrogen bonds.

Table 2 summarizes the results from the cluster calculation using the five different methods adopted in this study. As in the case of the pinic acid–sulfuric acid complex, the first two rows of Table 2 show the differences relative to the lowest energy conformer for both the reactants and the products of the cluster formation reaction. The last two rows show the cluster formation free energies with only the product conformers included in the calculation (Δ_pG), and reaction free energies with both product and reactant conformers included ($\Delta_{r,p}G$). Similarly to the results shown in Table 1, adding more conformers for both reactants and products increases the stability of the molecule or cluster when treated with eq 11 or 13, whereas for eqs 17 and 18 a decrease in stability is observed. In the case of sulfuric acid, the differences between eq 11 and the incorrect averaging methods are small, whereas in the case of the cluster the differences are more than 0.9 kcal/mol. In contrast to the pinic acid–sulfuric acid case, the results from eq 11 or 13 agree well, as seen from the first row of Table 2.

The cluster formation free energies Δ_pG and $\Delta_{r,p}G$ are much lower for the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster than for the pinic acid–sulfuric acid complex due to the larger number of bonds created in the reaction and the increased size of the system. The overall trend in the energies is the same as in section 5.1. Figure 6 shows Δ_pG plotted as a function of the number of product conformers included in the calculation in the order of increasing Gibbs free energy. The predictions from eqs 11 and 13 are less than 0.3 kcal/mol apart. On the contrary, the differences between the erroneous averaging methods and the correct value given by eq 11 are clearly larger than for the pinic acid–sulfuric acid complex due to the larger number of contributing conformers for the product. In both Figures 3 and 6, it is seen that the approximate eq 13 tends to overestimate the stability of the cluster, whereas for single pinic acid molecules, for example, it underestimates the stability, indicating that there is no systematic way to know a priori what will be the case for any particular molecule or cluster. The
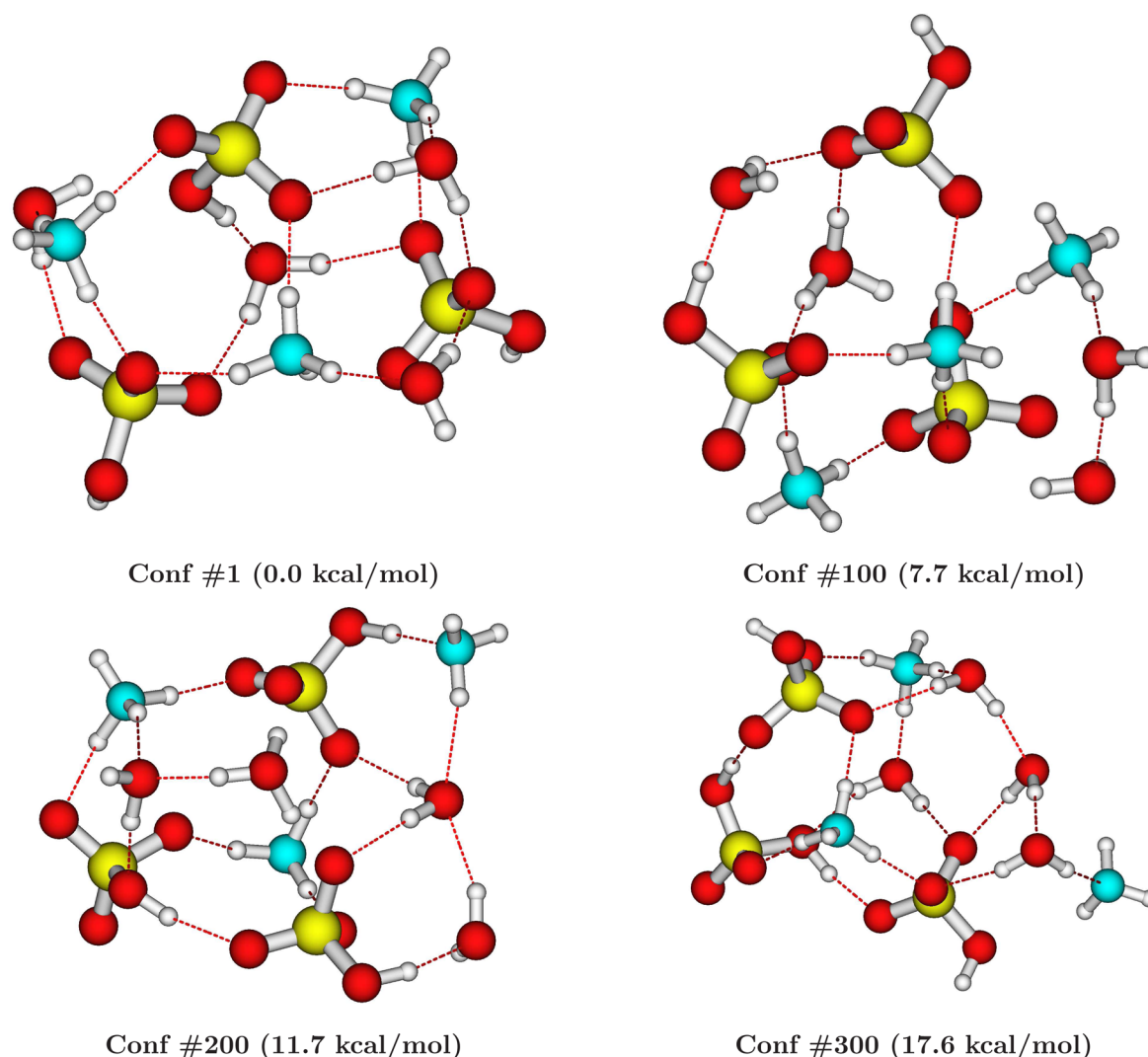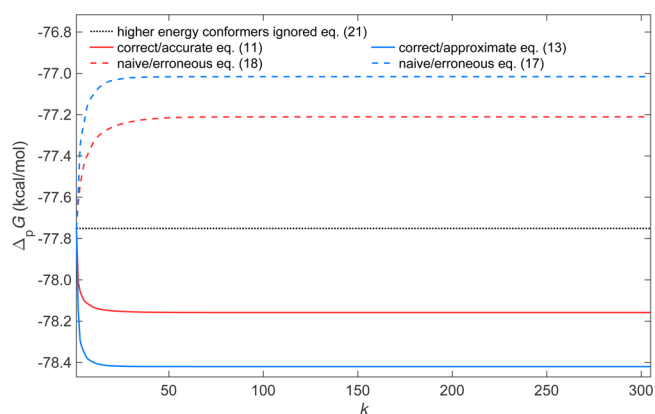

Figure 4. Formation free energies of the pinic acid–sulfuric acid complex when reactant and product conformers are included in the calculation as a function of the number of product conformers included.

Conf #1 (0.0 kcal/mol)   Conf #100 (7.7 kcal/mol)

Conf #200 (11.7 kcal/mol)   Conf #300 (17.6 kcal/mol)

Figure 5. Molecular structure of four different conformers (#1, #100, #200, and #300) of the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster. The relative stabilities are given in the brackets in kcal/mol.

Table 2. Gibbs Free Energies (kcal/mol) Calculated with the Different Statistical Mechanical Methods Presented in This Article for the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ Cluster Formation Reaction^a

	no correction eq. (21)	correct-approximate eq. (13)	correct-accurate eq. (11)	naive eq.(18)	naive eq.(17)
δG(SA)	-	-0.05	-0.23	0.14	0.03
δG(SA3+W4+A3)	-	-0.67	-0.41	0.54	0.73
$\Delta_p G$	-77.75	-78.42	-78.16	-77.21	-77.02
$\Delta_{r,p}G$	-77.75	-78.28	-77.47	-77.64	-77.12

^{a}The first two rows show Gibbs free energies for reactants and products relative to the G value of the lowest energy conformer for each reactant or product (δG). The last two rows show the formation reaction free energies with only the product conformers included in the calculation ($\Delta_p G$) and reaction free energies with both product and reactant conformers included ($\Delta_{r,p}G$).

Figure 6. Formation free energies of the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster when only product conformers are included in the calculation as a function of the number of conformers included.

same also applies for the two erroneous averaging schemes, as can be seen from Table 2 where for sulfuric acid eq 17 gives results closer to those obtained from eq 11 whereas the opposite is true for the cluster. In terms of convergence of the different approaches, Figure 6 indicates that only a few tens of

the 305 conformers have significant contribution to the free energy values. It is seen that the logarithmic sum formulas 13 and 11 again show faster convergence than eqs 17 and 18. On the basis of these two cases, we suggest a threshold criterion of 3.0 kcal/mol, at which point the addition of one extra

conformer with this energy will change the Gibbs free energy by less than 0.004 kcal/mol in eq 11 at 298.15 K. Considering the conformers with free energies within 10 kcal/mol from the lowest energy conformer, the difference between a conformer free energy and the minimum structure free energy was on average shifted 0.85 kcal/mol from the difference between the conformer minimum energy and the minimum energy of the global minimum structure. This implies that to include free energy conformers within 3 kcal/mol, frequency calculations should be performed on all the conformers with energies within 3.85 kcal/mol from the lowest energy state.

The $\Delta_{r,p}G$ values for the cluster reported in row four of Table 2 are displayed as a function of the number of product conformers in Figure 7, analogously to Figure 4. The
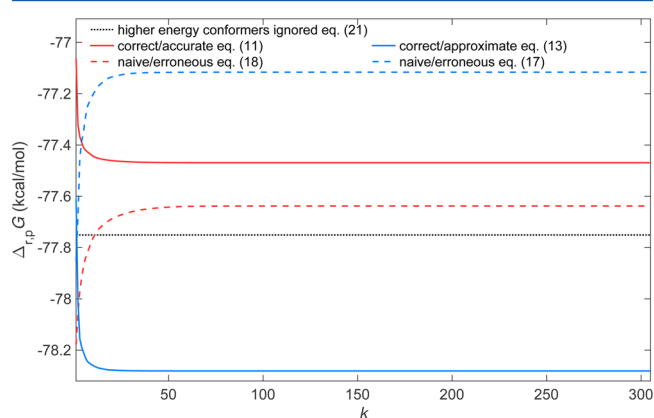
Figure 7. Formation free energies of the $(H_2SO_4)_3(NH_3)_3(H_2O)_4$ cluster when reactant and product conformers are included in the calculation as a function of the number of product conformers included.

significance of accounting for the reactant conformers is again visible in the large differences of the starting values as seen from the leftmost side of the plot. In terms of $\Delta_{r,p}G$, the difference between the values for eqs 11 and 13 is about 0.8 kcal/mol. This large difference arises from, on one hand, eq 13, which predicts a more stable cluster by about 0.3 kcal/mol, and on the other hand, eq 11, which predicts sulfuric acid to be more stable than does eq 13, by about 0.2 kcal/mol. This shows that even fairly small differences in the free energies quickly add up when multiple molecules of a given species participate in the reaction, making it even more important to account for conformers in these cases. A striking feature when Figure 7 is compared with Figure 4 is that the ordering of the other approaches relative to the accurate treatment with eq 11 changes greatly depending on the compound considered. Looking at the figures it is evident that resorting to one of the thermal averaging methods or even eq 13 can lead to results that are worse than the ones obtained just by employing the lowest energy conformers for each species with eq 21. When both reactant and product conformers are taken into account, the differences in formation Gibbs free energy between the correct accounting method of eq 11 and the least accurate incorrect averaging method are still relatively small, about 0.4 kcal/mol in both cases of this study. It is, however, noteworthy that the method giving the worst prediction is different in each case and by looking at Figures 3 and 6 it is likely that these differences can be much larger.

6. CONCLUSIONS AND IMPLICATIONS FOR FURTHER RESEARCH

In this article we have given a thorough accounting of how to correctly deal with the presence of multiple conformers in molecules and clusters when calculating the reaction free energies. We have shown that the thermal averaging-type approaches used in several published works are incorrect and provided numerical evidence that the use of these erroneous formulas can result in errors larger than 1 kcal/mol, especially if this is coupled with the typical approach of only taking product conformers into account. When both reactants and products have numerous conformers, the differences between thermal averaging approaches and the correct value are difficult to predict beforehand, further implying that the averaging schemes should not be used for the calculation of reaction free energies under any circumstances. In two case studies, the simplified version of the correct equation, which requires that the free energy is calculated only for the lowest energy conformer, performs worse than the erroneous averaging formulas. We consider this fortuitous but take it as a caveat that by accounting for the presence of multiple low-lying minima only through their electronic energies may not reduce errors. Furthermore, the approximate equation is inapplicable when the lowest energy conformer of the species is not the same as the lowest free energy conformer, as is typically the case for sulfuric acid, for example. Thus, if it is not feasible to compute the free energies of all the energetically low-lying conformers of both reactants and products, one should just neglect the presence of higher energy conformers. If free energies are available for all the conformers, then the accurate equation should be employed.

It should be borne in mind that very different results for the thermodynamic properties are obtained with different methods and basis sets mostly due to basis set superposition errors as demonstrated by Kurtén et al.[3] Thus, the actual values of the thermodynamic properties for the example systems used to illustrate the different statistical mechanical approaches should be taken with the reservation that the relatively large system sizes in this study mandate the combination of DFT methods with relatively small basis sets. Additionally, in this paper we chose to focus exclusively on the effects of global anharmonicity, i.e., the presence of higher energy conformers on the thermodynamic properties[76] and have not addressed the effect of the local anharmonicity present in the vibrational degrees of freedom of the individual conformers. To estimate the effect of the incorrect averaging formulas when local anharmonicity is accounted for, we recalculated new Gibbs free energies of reaction for the different sulfuric acid hydrates reported by Temelso et al.[36] using the correct formulas and the average difference between the two was 0.78 kcal/mol. This indicates that especially in cases where a large number of low-lying conformers is present, global anharmonicity likely has a larger impact on the thermodynamic properties than local anharmonicity whose effects have been previously estimated to be around 0.4 kcal/mol.[3]

Due to the logarithmic dependence on free energies in the correct free-energy formulas, the number of conformers making significant contributions to the free energy of the molecule or cluster is smaller than suggested by the incorrect thermal averaging equations. However, the differences in free energies between different conformers can be well over 10 kcal/mol, making it crucial that the correct global minimum conformer is

identified. This means that even though only a handful of conformers are important in terms of the free energy values, one will still need to perform a large conformational search to be sure that the lowest energy conformer found is the global minimum. On the basis of this study, we suggest a Gibbs free energy threshold criterion of 3.0 kcal/mol relative to the free energy of the global minimum energy structure. At this point the addition of one extra conformer with this energy will change the Gibbs free energy by less than 0.004 kcal/mol at 298.15 K when the accurate equation is used. This corresponds to performing free energy calculations on all conformers with electronic energies within 3.85 kcal/mol of the global minimum energy structure.

■ APPENDIX 1

Proof That Eq 5 Holds Irrespective of the Barrier Heights
It is worth considering if the results of this article apply to situations where the barriers between the conformers are so high that interconversion does not happen, or does not happen on a relevant time scale. One may argue that in this case each conformers is a distinct chemical species. The fact that they have the same mass does not make them identical; there are a lot of conformer specific properties that make them distinct. This means that the summation over states should be restricted to those states that sit in a single conformer minimum, with concomitant consequences for the entropy and free energy.

The question is relevant for the concentrations of the particles, so let's focus on this question and compare the number of particles of a certain mass in the two different scenarios, one where the conformers are readily interconverted as above and thus cannot be treated as distinct molecules, and another where they are not interconvertible. For the first case the partition function for N particles is given by the well-known expression

$$Z = \frac{z^N}{N!} \tag{22}$$

where z is the partition function for a single particle. With application of Stirling's approximation for the factorial the chemical potential of the system becomes[77]

$$\mu = -k_B T \frac{d \ln Z}{dN} = -k_B T (\ln z - \ln N) \tag{23}$$

or, equivalently,

$$N = z e^{\mu/k_B T} \tag{24}$$

In equilibrium the chemical potential is equal to the sum of the chemical potentials of the constituent molecules or atoms in gas phase. Denoting the sum of these chemical potentials by μ_c we have

$$\mu \equiv \mu_c \tag{25}$$

This holds for all distinct conformers of the non-interconversion equilibrium situation, and together with eq 24 this gives the conformer concentrations

$$N_k = z_k e^{-E_k^0/k_B T} e^{\mu_c/k_B T} \tag{26}$$

where the Boltzmann factor $e^{-E_k^0/k_B T}$ takes into account the convention used for the zero of energy in the calculation of partition functions. Adding the conformer populations give

$$\sum_k N_k = \sum_k z_k e^{-E_k^0/k_B T} e^{\mu_c/k_B T} = z e^{\mu_c/k_B T} \tag{27}$$

where the last equality follows from

$$z = \sum_k z_k e^{-E_k^0/k_B T} \tag{28}$$

This is identical to the result for interconverting conformers, and thus the total equilibrium population of the species is identical in the two situations.

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Notes
The authors declare no competing financial interest.

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