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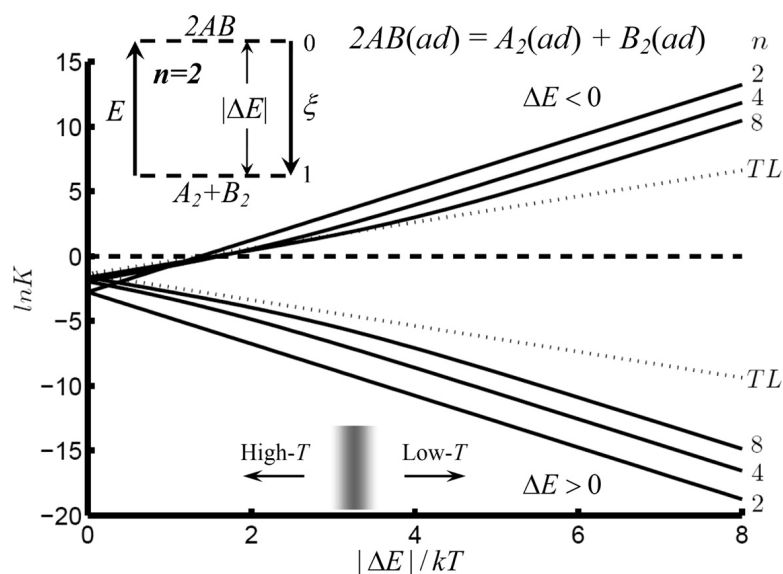
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Nanochemical Equilibrium Involving a Small Number of Molecules: A Prediction of a Distinct Confinement Effect

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ABSTRACT

The equilibrium state of a reaction mixture comprised of a small number of molecules is modeled for three different nanoconfined systems. The issue is relevant to several advanced routes for the synthesis of encapsulated organic molecules, metallic or inorganic nanoclusters, and other nanoscale structures. Canonical-ensemble based formulations and computations predict for the equilibrated closed small systems significant deviations from the (macroscopic) thermodynamic limit. The effects include the enhancement/suppression of the equilibrium extent of the exothermic/endothermic model reactions, associated mainly with reduced numbers of mixed reactant-product microstates in the closed system. Fluctuations in the nanochemical reaction extent, which are found to be closely related to the stoichiometric coefficients, become more dominant for smaller systems and modify considerably the temperature dependence of the equilibrium constant.

Classical thermodynamics of macroscopically large systems is not fully applicable to small groups of molecules or atoms. Already some decades ago Hill¹ modified pertinent thermodynamic state functions for their dependence on the system size and later introduced a more direct approach to “nanothermodynamics”.² More recently, attempts to develop alternative approaches were reported.³ Equilibrium statistical mechanics is basically valid also for small systems,¹ and the specific type of the pertinent statistical–mechanical ensemble depends on the possibility of matter or heat exchange with the surroundings that affects the respective open or closed small system properties.

Besides a pure theoretical interest, the motivation for the present study stems from the increasing research during the past two decades of confined nanospaces where selected chemical reactions can take place very efficiently in controlled environments. A variety of tailor-made “nanoreactors” have been fabricated and studied: (i) molecular capsules, held together either by covalent bonding or by self-assembly via weaker interactions such as metal coordination and hydrogen bonds,^{4,5} for organic and metal catalyzed synthesis; (ii) carbon nanotubes for the synthesis of nanowires,⁶ nanobeads,⁷ or polymeric chains;⁸ (iii) polymeric films used for the fabrication of inorganic semiconductor nanoclusters;⁹ and (iv) self-assembled micelles and vesicles for catalyzed organic reactions and as bionanoreactors.⁴ Crystalline zeolites

with well-defined cavities and pores can be viewed as a separate class (v), common for a long time in the chemical industry, that furnishes nanospaces for catalytic reactions.¹⁰

While the equilibrium reaction extent in a small open system is expected to closely resemble the macroscopic case (ignoring possible boundary/molecule interactions), the present work tries to unravel possible effects on the reaction extent related solely to the smallness of a closed reaction mixture (exchanging only heat with the surroundings). Closed system modeling based on the canonical ensemble fits some of the above cases, such as the use of molecular capsules for stoichiometric reactions (e.g., cycloaddition,¹¹ photo-oxidation, and photodimerization¹²) and for the stabilization of reactive intermediates or labile products that are otherwise difficult to isolate and analyze (the stabilization of encapsulated guests could also enable performing reactions disfavored by dilute solution conditions).¹³ Other capsular nanoreactors function as catalytic systems, namely the product leaves the nanospace for new reagent molecules to enter. However, even in catalysis there are situations when an equilibrated reaction mixture is effectively closed, at least temporarily. This includes the occurrence of confined pre-equilibrium reaction steps, which are quite common in organic and biosynthesis, and can exist also in zeolites due to shape and size selectivity.¹⁰ Pre-equilibria can be followed by a slower reaction and release of the final product. (In case of complete “product inhibition”,⁵ which is associated with its relative size or high affinity to the nanoreactor and

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prevents catalytic turnover, chemical denaturation of the capsule can release the product.) Various factors were attributed before to the increased reactivity in nanospaces, such as geometrical constraints preorganizing encapsulated molecules toward the transition state, preferential guest–host interactions and (increased) effective concentrations.⁵ It should be reemphasized that this work focuses only on possible contributions from the smallness of the confined molecular group as a distinct effect. In the context of statistical mechanics of equilibrated small closed systems, it can be noted that only the isomerization reaction was analyzed in ref 1. However, the same reaction extent anticipated for a macroscopic systems was predicted for this case.

The equilibrium constant of a reaction, $\sum_R \nu_R R = \sum_P \nu_P P$, with stoichiometric coefficients ν_R and ν_P and molecular formulas R and P , can be given by means of the product and reactant molecular fractions

$$K = \prod_P f_P^{\nu_P} / \prod_R f_R^{\nu_R} \quad (1)$$

These fractions and the related reaction extent can be obtained by statistical–mechanical averaging over all microstates of the reaction mixture. For convenience, we have chosen to introduce the concept of a “microstate-specific reaction extent”, ξ . A principal distinction of a small reaction mixture comprised of n molecules is that ξ is a discrete variable, while in case of a macroscopic system ($n \rightarrow \infty$, “thermodynamic limit”, TL) it becomes a quasi-continuous variable. (This is formally somewhat similar to a case of electron bands in macroscopic solids versus discrete electron levels in quantum dots, for example.) Thus, the discrete probability distribution of ξ , $p(\xi)$, determining the statistical–mechanical average extent, $\bar{\xi} = \sum_{\xi} \xi p(\xi)$, and its fluctuations, $\Delta \xi^2$, can differ considerably from the sharp Gaussian distribution common in macroscopic systems.¹⁴ Correspondingly, computations of mean values should involve all values of the microstate-specific reaction extent, including the less probable ones. (Approximate formulas, such as the Stirling’s approximation that can become inaccurate for small numbers are avoided in the formulation.) In the following, the smallness effect is explored for three distinct model reactions involving adsorbed, gaseous, and encapsulated molecules with focus on the first case.

The 2AB(ad) = A₂(ad) + B₂(ad) Reaction. A simple “ideal lattice gas mixture” model¹⁵ takes into account the different system microstates, namely the distributions of the three types of molecules, totaling n (the group size), among m geometrically identical chemisorption surface sites. The pertinent three energies, w_{AA} , w_{BB} and w_{AB} , include both the respective molecular bond energy and the chemisorption energy. The model allows an exact solution of the statistical–mechanical problem, yielding the equilibrium molecular fractions. In the TL, the equilibrium constant is given by the well-known expression, $K^{TL} = \exp [-(\Delta E - T\Delta S)/kT]$ with the energy of the reaction given in the present model by $\Delta E = w_{AA} + w_{BB} - 2w_{AB}$, and $\Delta S = -k \ln 4$. The formulation for a closed system is based on the canonical partition function of the n molecule reaction mixture, $Q =$

$\sum_E g(E) \exp(-E/kT)$, where E and $g(E)$ denote the microstate energy and degeneracy, respectively. Instead of the usual summation over E , here the summing is done with respect to the (dimensionless) microstate-specific reaction extent mentioned above, which for an initial composition of n pure reactant molecules is given by $\xi = \{0, 2/n, 4/n, \dots, n/n\}$ with stoichiometric $f_{AB} = 1 - \xi$ and $f_{A_2} = f_{B_2} = \xi/2$. Then, the reaction mixture energy can be written in terms of ξ

$$E(\xi) = n_{AB} w_{AB} + n_{A_2} w_{AA} + n_{B_2} w_{BB} = n \left(w_{AB} + \frac{\xi}{2} \Delta E \right) \quad (2)$$

and the corresponding degeneracy reads,

$$g(\xi) = \frac{m!}{n! (m-n)!} \frac{n!}{n_{AB}! n_{A_2}! n_{B_2}!} 2^{n_{AB}} = \frac{m!}{n! (m-n)!} \frac{n!}{(n-\xi)! [(n\xi/2)!]^2} 2^{n-\xi} \quad (3)$$

In eq 3 the binomial coefficient gives the number of possible ways to fill m chemisorption sites by n molecules, and the trinomial coefficient expresses the number of possible permutations of the three types of molecules among the n sites.

Substitution of eqs 2 and 3, while neglecting ξ -independent terms, leads to

$$Q \propto \sum_{\xi} \frac{2^{-n\xi}}{(n-\xi)! [(n\xi/2)!]^2} \exp \left[-n \frac{\xi}{2} \frac{\Delta E}{kT} \right] = \sum_{\xi} \frac{(K^{TL})^{n\xi/2}}{(n-\xi)! [(n\xi/2)!]^2} \quad (4)$$

Differentiation with respect to K^{TL} provides compact analytical expressions for the average extent, $\bar{\xi}$, its fluctuations, $\Delta \xi^2$, and the slope that reads

$$\frac{d \ln K}{d(1/T)} = - \frac{\Delta E}{k} n \frac{\overline{(\Delta \xi)^2}}{\bar{\xi}(1-\bar{\xi})} \quad (5)$$

This formula signifies the role of fluctuations in the temperature dependence of the equilibrium constant, and agrees with a previous analysis for the specific case of isomeric equilibrium.¹

In the case of a very small group comprised of two molecules, only the two extreme values of the microstate-specific reaction extent are relevant (Figure 1a, inset) and an analytical derivation based on the partition function (eq 4) yields $\ln K = 2 \ln K^{TL}$. Correspondingly, a plot of $\ln K$ versus inverse temperature should have a constant slope, which quite remarkably is twice larger than the TL slope (see $n = 2$ in Figure 1a). Clearly, the group smallness effect is larger at lower temperatures. Regarding its entropic origin, the effect is related to the reduced number of mixed reactant–product microstates in a closed system. In particular, in the case of a two molecule system such microstates are entirely absent (e.g., insets in Figures 1a,b), and hence the (exothermic) reaction can approach completion, which is impeded by mixing entropy in macroscopic systems (TL).

For $n > 2$, computations based on the partition function (eq 4) furnish plots of $\ln K$ versus $|\Delta E|/kT$ (Figure 1a). Generally, the equilibrium constants of the exothermic

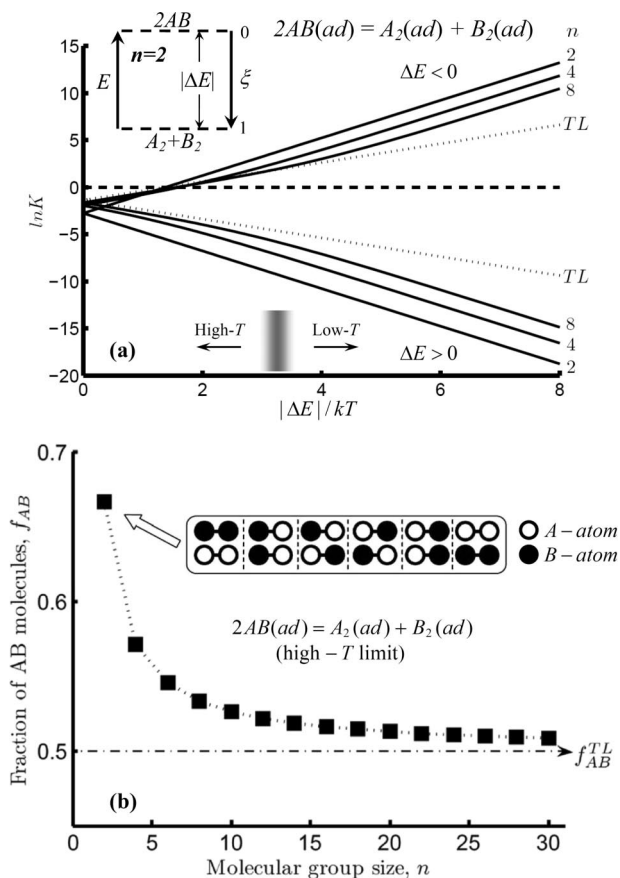


Figure 1. (a) The temperature dependence of the equilibrium constant computed using the ideal lattice gas model for different group sizes (n) of the closed stoichiometric reaction mixture. Inset: Schematics of the two energy levels of a mixture comprised of two molecules. (b) High- T limit fractions of the AB reactant molecules vs group size compared to the thermodynamic limit (TL) value. Inset: Schematics of the six microstates possible for $n=2$ (4 pure reactant microstates, $\xi=0$, and 2 pure product microstates, $\xi=1$).

reaction ($\Delta E < 0$) are significantly enhanced, whereas for the endothermic reaction ($\Delta E > 0$) suppression of K below the TL values is the dominant effect in the same temperature range. Although the plots exhibit distinct group-size dependent variations relative to the TL values, their low- T doubled slopes are identical to the all- T $n=2$ case. The minor backward shift in K relative to K^{TL} predicted for high temperatures (Figure 1a) is also entropic in nature, and it can be verified by a straightforward evaluation of the corresponding molecular fractions in the high- T limit. Thus, unlike the TL case, in a small closed system the presence of a specific atom (e.g., A) in a molecule affects the number of available A atoms for bonding in this or in other molecules, thereby diminishing f_{A_2} (and increasing f_{AB}). For example, for $n=2$ $f_{A_2} = 1/6$ (see inset in Figure 1b), whereas in the TL it equals $f_{A_2}^{TL} = 1/4$. For larger n , the deviations from the TL values are reduced, until the effect almost disappears for a group of few tens of molecules (Figure 1b).

The dependence of the normalized fluctuations in the reaction extent, $(\Delta\xi)^2/\xi(1-\xi)$, on the inverse group size as computed numerically (using eq 5) is given in Figure 2. The predicted linear dependence (see also refs 1, 16) exhibits in

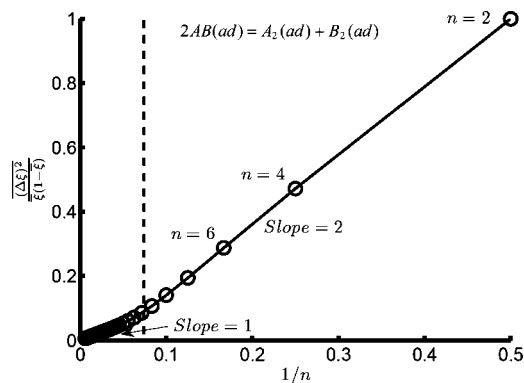


Figure 2. The dependence of the normalized fluctuations in the extent of the indicated reaction on the inverse group-size ($kT/|\Delta E| = 0.25$).

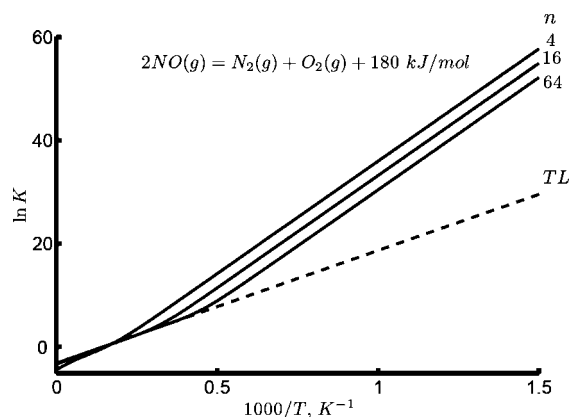


Figure 3. The equilibrium constant vs inverse temperature computed for different group sizes of the indicated exothermic gaseous reaction, in comparison to the TL dependence.

the present case a change of slope from ≈ 1 to ≈ 2 around $n < 10$ for $kT/|\Delta E| = 0.25$. This doubling of the slope is obviously compatible with the fluctuation-related $\ln K$ versus $|\Delta E|/kT$ doubled slope described above for small n (Figure 1a).

The Gaseous Exothermic Reaction $2NO(g) = N_2(g) + O_2(g)$. The modeling is extended to the gaseous phase using the “harmonic oscillator-rigid rotor” approximation.¹⁷ Again, the pertinent partition function of the molecular group is given by the rhs of eq 4, but with $K^{TL} = q_{N_2}q_{O_2}/q_{NO}^2$, where q_{N_2} , q_{O_2} and q_{NO} denote the single-molecule partition functions of N_2 , O_2 and NO , respectively. The similar enhancement trends shown in Figure 3 and Figure 1a ($\Delta E < 0$) demonstrate the generality of the confinement effect, which for very small values of n and low- T is enormous in magnitude.

Addition Reaction of Encapsulated Molecules. Since the addition reaction $A + B = C$ has been rather common in studies and syntheses of encapsulated organic molecules, it has been chosen to be modeled too. As an illustration, the characteristics of an exothermic addition reaction in a tetrahedral capsule are computed assuming that the binding sites are vertexes for the reactant molecules and edges for the product molecule (Figure 4). The enhanced $\ln K$ versus $|\Delta E|/kT$ low- T slope (≈ 2) persists at practical temperatures

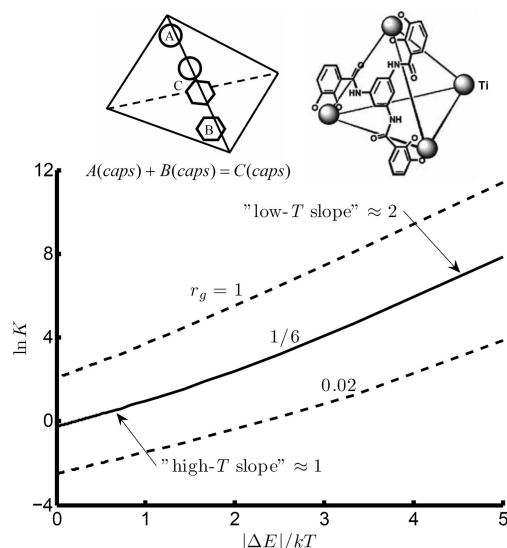


Figure 4. Modeling of an exothermic addition reaction $A + B = C$ taking place in a hypothetical tetrahedral nanoreactor cage (top left; top right: sketch of a real tetrahedral molecular capsule based on a hexadentate 3-fold symmetric ligand as taken from ref 20). The equilibrium constant temperature dependence is shown for different product/reactant degeneracy ratios, $r_g \equiv g_P/g_R$. (e.g., $r_g = 1/6$ corresponds to the symmetry related degeneracies $g_R = 72$ and $g_P = 12$ for the A, B, and C hypothetical molecules having 1, 6, and 2 distinguishable positions on the respective binding sites.)

even for relatively low values of ΔE (say, -10 kJ/mol). Similarly to the trends found for the above two model reactions, the slope changes from ~ 2 to ~ 1 with increasing temperature. Moreover, a similar slope change can be induced by decreasing r_g , namely by increasing the number of reactant microstates relative to the product microstates (e.g., by using different nanoreactors). This entropic effect results in lower K values and even a reversal of the equilibrated reaction direction (Figure 4, $r_g = 0.02$).

The Two Energy Level Approximation. This analysis helps to comprehend the generally similar trends predicted above for quite different three model reactions. As noted above, the probability distribution, $p(\xi)$, in small systems can differ greatly from the case of macroscopic systems characterized by quasi-continuous ξ . In particular, below a low but finite T ($T < |\Delta E|/k$) all except two $p(\xi)$ values can be ignored, and correspondingly only two ξ values are practically involved in computing average values (e.g., see inset in Figure 1a). Specifically, in the case of an exothermic reaction at low T the stoichiometric reactants (R) tend to have very small equilibrium concentrations with ξ equals either 1, or a value (ξ') corresponding to only one reaction step backward. Since $p(\xi')$ is proportional to the Boltzmann factor, in the present approximation, $f_R \sim \exp(\Delta E/kT)$ for all reactants. Substitution in eq 1 gives $\ln K \approx -\omega_{\text{exo}}\Delta E/kT$ with ω_{exo} being the sum of the reactant stoichiometric coefficients, $\omega_{\text{exo}} = \sum_R \nu_R$, in complete agreement with the three model computations given above ($\omega_{\text{exo}} = 2$). Moreover, the normalized fluctuations in the reaction extent are obtained as $(\Delta\xi)^2/\bar{\xi}(1 - \bar{\xi}) \approx \omega_{\text{exo}}/n$, by noting that for two levels $\xi = 1 - (\omega_{\text{exo}}/n)\delta$ with $\delta = 0$ or 1 (hence, $\delta^2 = \delta$ and $(\Delta\delta)^2 = \bar{\delta}(1 - \bar{\delta})$). Substitution of the normalized fluctua-

tion expression in eq 5 gives again the predicted slope enhancement factor (ω_{exo}). With slight modifications, the above arguments are valid also for endothermic reactions, leading to $\ln K \approx -\omega_{\text{endo}}\Delta E/kT$ with $\omega_{\text{endo}} = \sum_P \nu_P$. (For off-stoichiometric reaction mixtures the sums can involve fewer coefficients.)

At higher T the number of “excited” energy levels increases and the situation starts to resemble the TL case. Hence, the small group ($n > 2$) $\ln K$ versus $|\Delta E|/kT$ slopes gradually approach the TL value ($=1$, e.g., Figure 1a). Yet, the two energy level approximation can be used with reasonable accuracy at practical temperatures depending mainly on n and ΔE of the specific reaction.

As shown, the molecular group size can considerably affect chemical equilibria in confined reaction mixtures, relevant to real situations in nanoreactors. Thus, imposing closure on a small system at the “low- T ” range leads to significant increase/decrease of the reaction extent in case of exothermic/endothermic reactions. This effect is universal in a sense that it stems only from the limited amount of molecules in a reaction mixture, resulting in a reduced number of certain microstates. It should be noted that the stoichiometric coefficients are among principal factors determining the reaction extent fluctuations, which play a significant role in the smallness effect. Unlike the three cases treated above having two reactant molecule stoichiometry ($\omega_{\text{exo}} = 2$), in the isomerization reaction $\omega_{\text{exo}} = 1$ and no effect is expected. On the other hand, when in a gaseous reaction the overall number of molecules changes, preliminary work indicates that the system volume too plays a role in the smallness effect, demonstrating its dependence on the nature of the specific reaction. It can be also noted that due to the relationships between chemical equilibria and corresponding reaction rates, smallness-induced effects should be reflected also in the kinetics of the reactions. Attempts to analyze reaction kinetics in confined geometries involving fluctuations in small groups of molecules, such as hydrogen adsorbed on the surfaces of tiny dust grains in interstellar clouds, were reported recently.^{18,19} Moreover, enhanced rates observed for organic syntheses in molecular capsules⁵ might originate partially from the confinement-smallness effect introduced in this letter. Since it is one of several expected concurrent confinement effects, its distinct experimental verification may be quite difficult. This renders theoretical-computational modeling, like the present one, a powerful means to evaluate the smallness effect significance and implications in closed reaction nanomixtures.

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