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The Lost Work in Dissipative Self-Assembly

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Abstract A general thermodynamic analysis is given of dissipative self-assembly (DSA). Subsequently, the analysis is used to quantify the lost work in a recently published chemical realization of DSA (Boekhoven et al., Angew Chem Int Ed 49:4825, 2010) where a formation reaction produces the monomers that subsequently self-assemble and are finally annihilated by means of a destruction reaction. For this example, the work lost in self-assembly itself is found to be negligibly small compared to the work lost in the reactions driving the non-spontaneous formation reaction and the kinetically hindered destruction reaction.

Keywords Lost work · Non-equilibrium thermodynamics · Self-assembly

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1 Introduction

In order to make artificial self-assembled materials more complex, chemists find inspiration from the highly sophisticated self-assembled systems found in nature. Such systems are not in equilibrium and require transfer of energy to operate: in biological systems it is often the adenosine triphosphate (ATP) hydrolysis that conveys the necessary energy [1]. Many of the systems involve self-assembly which can loosely be defined as the assembly of larger structures from smaller entities [2]. Examples from nature are networks built from for instance microtubules or compartments such as mitochondria. An interesting advantage of using non-equilibrium processes for the formation of self-assembled structures is the fact that the structures are more adaptive to external conditions than their equilibrium counterparts [3].

A particular aspect of non-equilibrium processes is that they are irreversible in the sense that the associated Gibbs energy change is negative, they run spontaneously, and that if this Gibbs energy change is not converted to work, it is dissipated by the environment in the form of heat [4]. It is therefore that the non-equilibrium form of self-assembly as discussed above is also called dissipative self-assembly (DSA) even though it would, in principle, still be possible to convert the Gibbs energy change into work which is not immediately lost. All self-assembly processes—be they equilibrium or non-equilibrium processes [2]—are dynamic, and we therefore prefer the term DSA over dynamic self-assembly to describe the non-equilibrium process [5].

The question that interests us in the present article is the magnitude of the lost work associated with DSA and how this is related to the other energy changes in such systems. For example, standard Gibbs energy changes for equilibrium self-assembly are of the order of $25\,\mathrm{kJ}\cdot\mathrm{mol}^{-1}$ for relatively small molecules. It is for instance yet to be seen whether it is relevant to compare this to the similar Gibbs energy change of $30\,\mathrm{kJ}\cdot\mathrm{mol}^{-1}$ for a driving reaction such as the ATP hydrolysis. To answer this question, we chose a synthetic system that has recently been put forward by some of us [6,7], see Fig. 1. The self-assembly utilizes a low molecular mass hydrogelator, dibenzoyl-(L)-cystine (DBC) in aqueous solution at a pH above its pK_a value of 4.5. Under these conditions, DBC remains isotropically in solution. Methylation of one of the carboxylic groups results in the formation of fibers, and this process can be detected mechanically and optically, using for instance rheometry and turbidity measurements, respectively. Crucially, the methylated DBC molecules are chemically unstable and hydrolyze at a pH-dependent rate. Hence, by tuning the pH and the methylation reaction rate, the self-assembly dynamics of the gel can be controlled. The methylation reaction is not spontaneous and, therefore, it is coupled to a reaction that is spontaneous which in the present case is the conversion of dimethyl sulfate (DMS) into monomethyl sulfate (MMS^-). In actual fact, also the hydrolysis reaction is a coupled reaction that turns the methylated DBC back into DBC itself, see Fig. 1.

2 Self-Assembly

Let us first focus on the self-assembly step in this process, the formation of the linear aggregates from the methylated DBC molecules which from now on will be called

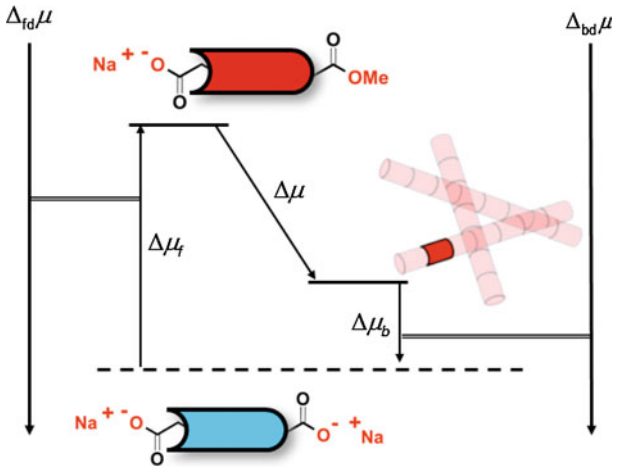

Fig. 1 Dissipative self-assembly process

monomers. We use the simple reaction scheme of

$$N\mathrm{S} \overset{K}{\rightleftharpoons} \mathrm{S}_N, \tag{1}$$

where S denotes the monomer and S_N the aggregate, see Fig. 2a. Although it is an oversimplification to use a single aggregation number N only, for the present purpose of analyzing the energetics of the process, it captures the essential physics of the process. The behavior of this model is, apart from the aggregation number, described by one parameter only, the critical aggregation concentration x_c, that describes the equilibrium, Eq. 1, between monomers and aggregates as

$$\frac{x_N}{N} = \left(\frac{x_1}{x_\mathrm{c}}\right)^N \tag{2}$$

in which x_1 is the mole fraction of free monomers and x_N is the mole fraction of monomers in aggregates. Together with mass conservation, formulated as

$$x_1 + x_N = x_\mathrm{t} \tag{3}$$

this model can be exactly solved, see Fig. 2b, albeit that for large N, there are some numerical issues that need to be taken care of [2]. As long as the total mole fraction x_t remains below the critical aggregation concentration (cac), x_c, no aggregates are formed and the monomer mole fraction follows the total mole fraction. Beyond this cac the monomer mole fraction remains virtually constant at the cac value and the remainder of the total mole fraction of monomers is aggregated. The cac is related to the chemical potential of the monomers, which in terms of their standard chemical potential μ_1^o is written as

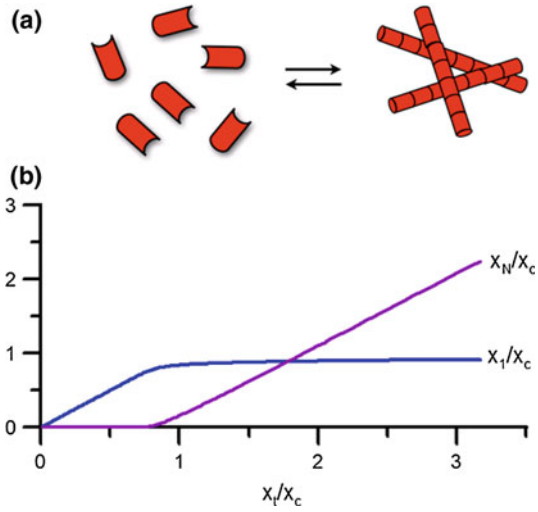

Fig. 2 Schematic representation of self-assembly of monomers in to fibers (*top*) and graph of monomer, x_1 and aggregate mole fraction x_2 as a function of total mole fraction x_t (*bottom*); x_c is the critical mole fraction of the self-assembly process

$$\mu_1 = \mu_1^o + RT \ln x_1, \tag{4}$$

and of the aggregates, written as

$$\mu_N = \mu_N^o + \frac{RT}{N} \ln \frac{x_N}{N}, \tag{5}$$

by

$$x_c = \exp\left\{(\mu_N^o - \mu_1^o)/RT\right\}. \tag{6}$$

Here and in what follows, R is the gas constant and T denotes temperature. The temperature is kept constant during the experiments.

The conversion rate $\dot{r}$ of monomers into aggregates is given by the law of mass action that for the present situation reads

$$\dot{r} = k_1 x_1^N - k_N \frac{x_N}{N} \tag{7}$$

with forward and backward reaction rate constants k_1 and k_N. This rate equation is derived from first principles using mesoscopic non-equilibrium thermodynamics is shown in Appendix [8]. When the conversion rate is cast into the form of

$$\dot{r} = k_1 \mathrm{e}^{N(\mu_1 - \mu_1^o)/(RT)} \left(1 - \mathrm{e}^{N(\mu_N - \mu_1)/(RT)}\right) \tag{8}$$

it is clear that it is proportional to the driving force $\Delta\mu = \mu_N - \mu_1$ when the latter assumes sufficiently small values, i.e., when the system is close to equilibrium where $\Delta\mu \approx 0$. For very large values of the driving force, the conversion rate only depends on the initial or final mole fraction. Assuming a stationary value for the conversion

of monomers into aggregates, which requires a constant supply of monomers and a constant removal of aggregates as shall be discussed later, the driving force is also constant and the available work is then evaluated as

$$\dot{W} = -\dot{r}\Delta\mu \tag{9}$$

A derivation of the above expression can be found in the text book by de Groot and Mazur [9]. It can be understood as being the product of the Gibbs energy difference that gives the available energy and the rate at which the this energy is transferred.

For sufficiently large values of the aggregation number, the driving force for self-assembly is written as

$$\Delta\mu \approx -RT \ln \frac{x_1}{x_c} \tag{10}$$

which for the example of methylated DBC molecules is evaluated as follows. The critical aggregation constant has been determined by visual inspection to be about 1.2 mM for very slow formation rates. In a typical steady-state experiment with an initial promonomer concentration of 50 mM where the monomer formation rate is $50\,\mathrm{mM}\cdot\mathrm{h}^{-1}$, the value of the free monomer concentration was 2.5 mM [7], whereas the total monomer concentration is 3.9 mM. Hence, $\Delta\mu = -1.8\ \mathrm{kJ}\cdot\mathrm{mol}^{-1}$ and the available work is then calculated to be $90\ \mathrm{J}\cdot(\mathrm{L}\cdot\mathrm{h})^{-1}$.

The available work from the self-assembly, as calculated above, would be lost work only if no other processes are involved. In the present case, where the self-assembly process is coupled to the formation and destruction reactions, the situation is different as discussed below.

3 Self-Assembly Cycle

Consider now in more detail the complete cycle depicted in Fig. 1. It involves three states for the (methylated) DBC molecule: as a promonomer, as a monomer, and as part of an aggregate. For a stationary process, the rates in each of the steps between these three states are identical so that the rate of formation of monomers is equal to the rate of aggregation as well as to the destruction rate of the monomers in aggregated species into promonomers. The driving force for the aggregation step, $\Delta\mu$, has been discussed above and likewise, there are forces for the monomer formation reaction, $\Delta\mu_\mathrm{f}$ and for the back reaction $\Delta\mu_\mathrm{b}$. Their sum is equal to zero, in formula,

$$\Delta\mu_\mathrm{f} + \Delta\mu + \Delta\mu_\mathrm{b} = 0 \tag{11}$$

because after these three steps, the molecules are back in their original state. The immediate consequence of this is, that the total available work in this cycle, being the sum of the work $\dot{W}_\mathrm{f}$ available from the formation reaction, the work $\dot{W}$ available from the self-assembly, and the work $\dot{W}_\mathrm{b}$ available from the backward reaction, also vanishes, i.e.,

$$\dot{W}_\mathrm{f} + \dot{W} + \dot{W}_\mathrm{b} = -\dot{r}\,(\Delta\mu_\mathrm{f} + \Delta\mu + \Delta\mu_\mathrm{b}) = 0. \tag{12}$$

The formation reaction and the destruction reaction involve the same molecule. In the example, it is the DBC molecule that is methylated in the formation step and hydrolyzed in the destruction step. The value of the standard Gibbs energy change of formation is estimated from a comparable reaction, the methylation of acetic acid [10] with a standard enthalpy change of $5.6\,\mathrm{kJ\cdot mol^{-1}}$ and a standard entropy change of $-28.9\,\mathrm{J\cdot mol^{-1}\cdot K^{-1}}$, at $\Delta_\mathrm{r}G^\mathrm{o}_\mathrm{f} = 14\,\mathrm{kJ\cdot mol^{-1}}$. The driving force for the formation is then evaluated as

$$\Delta\mu_\mathrm{f} = \Delta_\mathrm{r}G^\mathrm{o}_\mathrm{f} + RT\ln\left(\frac{x_1}{x_\mathrm{p}}\right) \tag{13}$$

with x_p the mole fraction of the promonomers, in the example, the concentration amounts to 46.1 mM. Note that this driving force is positive as the process does not run spontaneously. It requires the driving reaction to produce monomers. The driving force for the destruction reaction is equal to

$$\Delta\mu_\mathrm{b} = \Delta_\mathrm{r}G^\mathrm{o}_\mathrm{b} + RT\ln\left(\frac{x_N}{x_\mathrm{p}}\right), \tag{14}$$

where the standard reaction Gibbs energy $\Delta_\mathrm{r}G^\mathrm{o}_\mathrm{b}$ will have the opposite sign compared to the formation value but slightly different in magnitude as the destruction of monomers in the self-assembled state is slightly different from the destruction of free monomers. Its value could be estimated from the fact that for the cycle the sum of the driving forces vanishes, see Eq. 11. By combining Eqs. 10, 13, and 14 with Eq. 11 one finds that the difference between the standard Gibbs energies of formation and destruction can be evaluated as

$$\Delta_\mathrm{r}G^\mathrm{o}_\mathrm{f} + \Delta_\mathrm{r}G^\mathrm{o}_\mathrm{b} = RT\ln\left(\frac{x_N}{x_\mathrm{c}}\right) \tag{15}$$

which yields $0.4\,\mathrm{kJ\cdot mol^{-1}}$ for the present example.

4 The Complete Process

From the above analysis, it follows that the work lost in the complete process is equal to the work lost in the driving reactions. To estimate the latter for the present example, it suffices to consider the overall reaction, that is the result of the methylation reaction,

$$\mathrm{DMS} + \mathrm{H_2O} \rightarrow \mathrm{MMS^-} + \mathrm{MeOH} + \mathrm{H^+} \tag{16}$$

and the hydrolysis reaction,

$$\mathrm{H^+} + \mathrm{OH^-} \rightarrow \mathrm{H_2O} \tag{17}$$

that reads

$$\mathrm{DMS} + \mathrm{OH}^- \rightarrow \mathrm{MMS}^- + \mathrm{MeOH} \tag{18}$$

For this reaction, the standard Gibbs energy change is estimated at $\Delta_r G^o = -398\ \mathrm{kJ \cdot mol^{-1}}$ (from [11] and standard data [12]), and the reaction rate is 50 $\mathrm{mM \cdot h^{-1}}$. Neglecting concentration contributions to the Gibbs energy change, the lost work is evaluated to be $5.5\,\mathrm{W \cdot L^{-1}}$. In the present example, the heat produced will be transferred to the environment by the temperature controlled heat bath.

The chemical energy that is brought into the cycle is the amount that is necessary for the formation of monomers. In the present example, this is the methylation reaction for which we estimated an amount of $14\ \mathrm{kJ \cdot mol^{-1}}$, again neglecting concentration contributions. If compared to the Gibbs energy of the driving reaction, this transferred amount is about 4 % of the driving work. Of course, the destruction reaction returns most of the formation work with a minor loss to the self-assembly, as calculated above, about $0.4\ \mathrm{kJ \cdot mol^{-1}}$.

5 Conclusion

The above analysis demonstrates how to evaluate the lost work in a DSA process. The self-assembly process itself is evaluated by means of a commonly used model and for the present example yields a relatively low amount of lost work, about $0.4\,\mathrm{kJ \cdot mol^{-1}}$. The process depicted in Fig. 1 gives the situation where the formation, self-assembly, and destruction form a cycle because one single molecule is involved. In that case at least one of the steps is irreversible and needs to be coupled to a spontaneous driving reaction. The present process in addition has a spontaneous process coupled to the destruction reaction. The total amount of transferred work is for such a situation largely determined by the coupling reactions. The coupling efficiency is rather low in the present example, about 4 %; in natural processes the coupling efficiency is usually much larger [1].

One might imagine a DSA process where the formation and destruction of monomers is not a cycle, for instance where the assembled monomer is irreversibly destructed and no longer available as promonomer. In such cases where there is no internal self-assembly cycle, more work will be lost in the total process. The present situation, where both formation and destruction steps require a spontaneous driving process poses the interesting option of energy storage: when only the formation reaction is driven and the destruction reaction is—either kinetically or thermodynamically—blocked, the formation work will be stored in the self-assembled state. This stored energy becomes available with the reaction driving the destruction which for instance could deliver work in the form of electrical energy if coupled to an electrochemical reaction. In actual fact, this is very similar to the many other chemical energy storage mechanisms which for instance utilize a phase transition. The choice of self-assembling systems is, however, far larger and hence poses an interesting option for further study.

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Appendix

In the mesoscopic description, we use a coordinate γ to describe the chemical reaction [13]. This coordinate is dimensionless and varies between 0 and 1. The existence of local equilibrium along the reaction path enables us to use the Gibbs relation,

$$\delta S = -\frac{1}{T}\int_0^1 \mathrm{d}\gamma\, \mu(\gamma, t)\delta P(\gamma, t), \tag{19}$$

where $\mu(\gamma, t)$ is the molar Gibbs energy of the reaction complex along the reaction coordinate and $P(\gamma, t)$ is the probability that the reaction complex is in the state γ at time t. The evolution of the probability density along the γ-coordinate is governed by the continuity equation,

$$\frac{\partial P(\gamma, t)}{\partial t} = -\frac{\partial}{\partial \gamma} \cdot J(\gamma, t), \tag{20}$$

where $J(\gamma, t)$ is a current along the γ-coordinate which has to be specified. Substitution in Eq. 19 gives for the contribution to the entropy production after integration by parts,

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{1}{T}\int_0^1 \mathrm{d}\gamma\, J(\gamma, t) \cdot \frac{\partial \mu(\gamma, t)}{\partial \gamma}, \tag{21}$$

where we used that the fluxes are zero on the surface of the integration domain. From Eq. 21, we find the most general linear law for the current along the γ-coordinate,

$$J(\gamma, t) = -\frac{L(\gamma, t)}{T} \cdot \frac{\partial \mu(\gamma, t)}{\partial \gamma}. \tag{22}$$

The molar Gibbs energy of the reaction complex for reaction along the γ-coordinate is given by

$$\mu(\gamma, t) = RT \ln P(\gamma, t) + \Phi(\gamma). \tag{23}$$

Here $\Phi(\gamma)$ is the enthalpy profile through which the diffusion process takes place. This enthalpy of the reaction complex is characterized by two minima at $\gamma = 0$ and 1 related to the states of reactants and products, respectively, separated by a maximum

which will be assumed large compared to RT. The activation energy for the forward reaction is the difference between the maximum of the curve E and the left hand value $\mu(0)$.

To simplify notation we will further suppress the dependence on t. Using the fact that the Onsager coefficient $L(\gamma)$ is in very good approximation proportional to $P(\gamma)$, we introduce the constant diffusion coefficient D by

$$L(\gamma) = \frac{D}{R} P(\gamma) \tag{24}$$

The linear laws can then be written as

$$J(\gamma) = -D \exp\left(\frac{-\Phi(\gamma)}{RT}\right) \frac{\partial}{\partial \gamma} \exp\left(\frac{\mu(\gamma)}{RT}\right). \tag{25}$$

When the enthalpy barrier along the γ-coordinates is high enough, diffusion along these coordinates is very slow and becomes quasi-stationary, $J(\gamma) = J$. If we now multiply Eq. 25 with $\exp(\Phi(\gamma)/RT)$ and use the constant nature of the flux, we can integrate and obtain

$$J = -\frac{D}{\int_0^1 \mathrm{d}\gamma \exp(\Phi(\gamma)/RT)} \left[\exp\left(\frac{\mu(1)}{RT}\right) - \exp\left(\frac{\mu(0)}{RT}\right)\right]. \tag{26}$$

For the self-assembly reaction (Eq. 1), the boundary conditions for the chemical potentials along the γ-coordinates are, using Eqs. 4 and 5, written as

$$\mu(1) = N\mu_N \quad \text{and} \quad \mu(0) = N\mu_1 \tag{27}$$

For the flux along the γ coordinate, and using Eqs. 4 and 5, this implies

$$J = \frac{D}{\int_0^1 \mathrm{d}\gamma \exp(\Phi(\gamma)/RT)} \left[\exp\left(\frac{N\mu_1^o}{RT}\right) x_1^N - \exp\left(\frac{N\mu_N^o}{RT}\right) \frac{x_N}{N}\right] \tag{28}$$

This expression for the rate coincides with the one obtained in the chemical kinetic description (Eq. 7). We hence find for the rate coefficients

$$k_1 = \frac{D}{\int_0^1 \mathrm{d}\gamma \exp(\Phi(\gamma)/RT)} \exp\left(\frac{N\mu_1^o}{RT}\right) \tag{29}$$

and

$$k_N = \frac{D}{\int_0^1 \mathrm{d}\gamma \exp(\Phi(\gamma)/RT)} \exp\left(\frac{N\mu_N^o}{RT}\right) \tag{30}$$

These expressions show that we can understand each reaction as a diffusional process across an activation energy barrier [14], the barrier effects included in the kinetic constants k_1 and k_N, respectively.

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