The role of the concentration scale in the definition of transfer free energies

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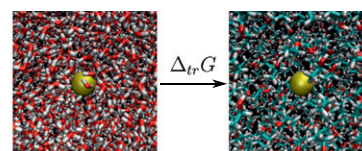
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GRAPHICAL ABSTRACT

Which transfer free energy relates to solute-solvent interactions?

x-scale ✗   c-scale ✓   m-scale ✗

J/mol

Why? Because it corresponds to a hypothetical transfer between solutions with equal volume.

ABSTRACT

The Gibbs free energy of transferring a solute at infinite dilution between two solvents quantifies differences in solute–solvent interactions — if the transfer takes place at constant molarity of the solute. Yet, many calculation formulae and measuring instructions that are commonly used to quantify solute–solvent interactions correspond to transfer processes in which not the molarity of the solute but its concentration measured in another concentration scale is constant. Here, we demonstrate that in this case, not only the change in solute–solvent interactions is quantified but also the entropic effect of a volume change during the transfer. Consequently, the "phenomenon" which is known as "concentration-scale dependence" of transfer free energies is simply explained by a volume-entropy effect. Our explanations are of high importance for the study of cosolvent effects on protein stability.

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1. Introduction

The knowledge of the preference of a solute for one solvent over another is very important in understanding basic processes in biochemistry, biology, solution chemistry, and related natural sciences. Moreover,

it is an important prerequisite in the design of products and production processes in formulation and engineering. Gibbs free energies of transfer (often abbreviated by "transfer free energies" = TFEs) are quantities that are used to quantify the solvent preferences of solutes. Thus, many explanatory models and design principles are based on measured or calculated TFEs. In biochemistry and biology, TFEs are extensively used in the study of chemical denaturation and renaturation of proteins or other macromolecules. In the framework of the transfer model, for example, TFEs can help to unravel which groups of a protein promote
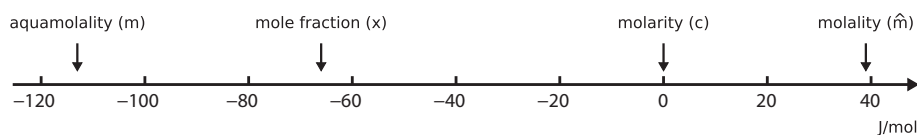
Fig. 1. Illustration of the difference between different STFEs by means of the example of transfers between water and a 1 M urea solution. The molarity-scale STFE is arbitrarily set to zero. The different quantities in Table 1 are in the given example: $d_w = 0.99707$ kg/L, $d_{w + co} = 1.01274$ kg/L [23], $m_{co} = 1.0497$ mol/kg [23], $M_{co} = 60.06$ g/mol, $M_w = 18.015$ g/mol. The molarity-scale STFE of glycine between the two solutions is 17.3 J/mol [2], which demonstrates that the illustrated differences between the different STFEs are not negligible compared to the absolute values.

or prevent unfolding in a denaturant or osmolyte [1,2]. Moreover, commonly used hydrophobicity scales are based on TFEs [3].

The underlying idea in TFE analyses is that a solute favors a solvent 'b' over another ('a'), if the transfer of the solute at infinite dilution from solvent 'a' to solvent 'b' is favorable. Whether this is the case can be quantified by the Gibbs free energy of the transfer (TFE). For a transfer at a constant (infinitely small) concentration ξ of the solute 'i', the TFE $\Delta_{tr}G^0_{i,\xi}(a \rightarrow b)$ is given by the difference of the solute's standard chemical potentials in the two solvents

$$\Delta_{tr}G^0_{i,\xi}(a \rightarrow b) = \mu^0_{i,\xi}(b) - \mu^0_{i,\xi}(a), \tag{1}$$

where ξ can be any common concentration scale (e. g. molarity, molality, or mole fraction). For a long time, it was unclear, whether the change in solute–solvent interactions during a transfer at infinite dilution is best represented by a transfer at constant molarity or at constant mole fraction of the solute. Most researchers favored the mole-fraction scale [4–10] in Eq. (1), whereas others favored the molarity scale [11]. At the latest when one discovered that the sign of the TFE can depend on the used concentration scale [8], it was clear that the choice of concentration scale is highly relevant. In 1978, Ben-Naim was able to resolve the question by means of statistical thermodynamics. In a very in-depth and insightful article [12], he showed that only the Gibbs free energy of a transfer at constant molarity can be interpreted directly in terms of favorable or unfavorable solute–solvent interaction free energy. While Ben-Naim's paper "Standard Thermodynamics of Transfer. Uses and Misuses" [12] by now was cited more than 300 times, the findings reported therein seem to be rather unknown nowadays. This is best illustrated by the fact that there exists a variety of studies, in which TFEs or related quantities are evaluated at constant mole-fraction (e. g. [13,14]) or constant (aqua-)molality (e. g. [15–18]) and nonetheless are interpreted exclusively in terms of solute–solvent interactions. The error due to this can be negligible in some cases, but in others it can be so large that it even affects the classification of the interactions into the categories "favorable" and "unfavorable" as we will show later on in Fig. 1. The fact that the sign of a TFE can depend on the concentration scale for which the standard chemical potentials are defined is sometimes called "concentration-scale dependence" of TFEs and is still described as a source of confusion in the recent literature [19,20].

In the article at hand, we didactically explain why TFEs calculated by Eq. (1) only yield the desired information about solute–solvent interaction free energy if the molarity-scale standard chemical potentials are used. We start out by recapitulating that depending on the choice of concentration scale in Eq. (1), the calculated TFE corresponds to a different *hypothetical* transfer process (insofar as the infinitely small concentration of the transferred substance is kept constant in a different concentration scale). This fact is nowadays often not paid attention to. Subsequently, we show how the TFEs of the different transfer processes can generally be converted into one another and provide a convenient table with explicit conversion terms. A discussion of the conversion equation reveals that even in the limit of infinite dilution of the transferred substance it matters in which concentration scale the concentration is kept constant. Considering this, we address the question which of the different transfer processes at infinite dilution should

be used to quantify the solvent preference of a solute. We show that this is the transfer at constant molarity and we explain comprehensibly how the TFEs corresponding to the other processes can be interpreted. Our results also affect TFE-related quantities as e. g. "chemical potential derivatives".

2. Different transfer processes at infinite dilution

In the recent literature, the TFE of a solute 'i' between two solutions 'a' and 'b' is often said to be the difference of the solute's standard chemical potentials in the two solutions $\mu^0_i(b) - \mu^0_i(a)$ [19,20]. Even though a standard chemical potential is only defined in connection with a concentration scale (see Appendix B.2), a concentration scale is often not specified. This suggests (incorrectly) that the choice of concentration scale for the standard chemical potential is of no significance. However, here, we show that depending on the concentration scale of the standard chemical potentials, a different TFE is obtained that corresponds to a different transfer process. This was already discussed in the early days of TFE studies [4,11].

We start our reasoning by considering a general transfer of a single solute molecule 'i' from a solution 'a' to a solution 'b'. The Gibbs free energy associated with the removal or the addition of a single solute molecule from respectively to a large solution is by definition the solute's chemical potential μ_i in the considered solution (respectively the negative thereof in case of removals). Hence, the Gibbs free energy of the transfer of a single molecule from a *given* solution 'a' to a *given* solution 'b' is

$$\Delta_{tr}G_i(a \rightarrow b) = \mu_i(b) - \mu_i(a). \tag{2}$$

Given that this is a general transfer between two solutions, we realize that a TFE expressed by the difference of standard chemical potentials must correspond to a transfer between special solutions — i. e. solutions for which $\mu_i(b) - \mu_i(a)$ reduces to $\mu^0_i(b) - \mu^0_i(a)$. To learn under which conditions this is the case, it is instructive to express Eq. (2) in an arbitrary concentration scale ξ[1]:

$$\Delta_{tr}G_i(a \rightarrow b) = \mu^0_{i,\xi}(b) - \mu^0_{i,\xi}(a) + kTln\left(\frac{\gamma_{i,\xi}(b) \cdot \xi_i(b)}{\gamma_{i,\xi}(a) \cdot \xi_i(a)}\right). \tag{3}$$

The ξ_i describe the concentrations of the solute 'i' in the two solutions 'a' and 'b' and the $\mu^0_{i,\xi}$ and $\gamma_{i,\xi}$ are the standard chemical potentials and activity coefficients of the solute in the two solutions in the concentration scale ξ. From Eq. (3), it is evident that a TFE calculated by the difference of standard chemical potentials corresponds to a transfer process for which the third term on the rhs is zero. This is the case if the solute has the same infinitely small concentration ξ_i in both solutions so that $\gamma_{i,\xi}(b) = \gamma_{i,\xi}(a) = 1$ and $\xi_i(b)/\xi_i(a) = 1$. The condition $\xi_i(b) = \xi_i(a)$ is necessary because the third term on the rhs of Eq. (3) does not vanish if $\xi_i(b) \approx 0$ and $\xi_i(a) \approx 0$ but $\xi_i(b) \neq \xi_i(a)$. Hence,

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[1] ξ may stand for any of the concentration scales listed in Appendix A or more generally for any concentration scale that fulfills the three criteria listed in Appendix B.2.2.