

Entropy-Enthalpy Compensation: Is there an Underlying Microscopic Mechanism ?

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We review here the well-known but still hotly debated notion of entropy-enthalpy compensation (EEC) from an unconventional standpoint: in terms of correlation. Specifically, correlation could mean either that ‘A’ is correlated to ‘B’ due to that ‘A’ directly results from ‘B’, or vice versa, or that there may be some real, but hidden ‘C’ connected to both ‘A’ and ‘B’. In accordance with the second interpretation, we try rationalizing the EEC in terms of hidden, but physically real factors. We conclude that EEC may be rationalized in terms of factors that are not directly measurable but nevertheless could be physically-chemically real. For example, factors involving a Carnot-cycle-type model, with a micro-phase transition (MPT) playing a crucial role. Such MPTs underlying the physically valid EEC could typically be cooperative processes such as the formation of supra-molecular aggregates, including water aggregates at a hydrophobic surface. Thus, the MPT notion may help rationalize EEC in terms of some pertinent microscopic mechanisms.

Keywords entropy; enthalpy; thermodynamics; compensation; correlation; hidden factors

1. Introduction

One of the very recent papers published in the ‘*Journal of Chemical Education*’ [1] has reported on the correlation between standard entropy and standard enthalpy taken from 0° to 298.15° K for a number of organic and inorganic solids. From published experimental data on 77 substances which are solids under normal conditions, the authors find a perfect linear regression fit of the standard entropy, ΔS_0 , to the standard enthalpy, ΔH_0 , of the following form:

$$\frac{\Delta S^0}{\Delta H^0} = 0.0066 \text{ K}^{-1}, \quad (1)$$

and claim that they have therewith revealed “... *important connections between entropy and the concomitant internal energy stored by solids ...*”, which “... *provide a straightforward physical interpretation of entropy, without a recourse to “disorder” or “randomness” ...*”.

However, there is clearly much more to the story. In our opinion, it would be premature to promote the mathematical relationship of Eq 1 as a subject matter for undergraduate lectures or handbooks. Specifically, the authors [1] have set their feet into the ‘swampy realm’ of the so-called “enthalpy-entropy compensation” (EEC), a subject which is of undoubtedly general significance for physics and chemistry, but still hotly debated since many decades – without yet any clear consensus (see, for example, a comprehensive treatise on this topic in [2]).

The objections against the EEC have been three-fold. First, such “marvelous” linear regressions might result from statistically incorrect processing of experimental data. For example: taken together, enthalpy-entropy “couples” obtained each from *one and the same* Arrhenius and/or van’t-Hoff plot deliver linear correlations which obviously bear no physical-chemical meaning. But calorimetric data (or thermodynamic parameters obtained by several independent methods) tend to exhibit statistically significant EEC (see, for example, [2] and the references therein), contrasting that hypothesis as a general explanation. Second, an EEC between apparently chemically unrelated species might be a consequence of so-called “free-energy windows”, again an effect devoid of any physical-chemical sense [3]. Third, many researchers argue that EEC is an “extra-thermodynamic” relationship (see, for example, [4] and the references therein). Whereas the first two points pertain solely to the carefulness of interpretation of experiments and require therefore statistically correct and thoughtful approaches, the third point is much more subtle. For example, the paper [5] shows that a *valid* linear EEC is not in conflict with the conventional thermodynamics. A detailed discussion about the possible physical-chemical backgrounds of valid linear EEC is presented in [3,5-8]. In some cases, a valid EEC may also be *non-linear*, but, again, in full accordance with the conventional thermodynamics [9-11].

We have recently suggested a new generalized model to rationalize the valid EEC phenomena in terms of hidden, but physically real, factors implying a (real or imaginary) Carnot cycle in which some kind of micro-phase transition plays a crucial role [5].

2. A Bit Theory ...

Mathematically, the EEC can be expressed as a linear regression of enthalpy H on entropy S , that is,

$$H = aS + b, \quad (2)$$

where a is the so-called "compensation temperature" and b has energy dimension. In our work [5] we have proven a *theorem* that states that "a valid, non-trivial EEC is a necessary and sufficient condition for the existence of a hidden thermodynamic cycle". Besides, Eq 2 can also be easily derived, if we start considering some arbitrary smooth thermodynamic cycle and decompose it into a number of infinitesimal Carnot cycles, as suggested in the book [12]. Then, for each infinitesimal cycle, we have, assuming that the processes under consideration are slow enough and reversible:

$$dS = \frac{\delta Q}{T}; \quad dU = \delta Q - pdV, \quad (3)$$

where the first equation is the Clausius definition of entropy and the second equation just expresses the 1st law of thermodynamics. Q stands for heat, U for internal energy, p for pressure, V for volume and δQ means the *inexact* (path-dependent) differential, as opposed to the *exact* (path-independent) differential, d . And, after eliminating the inexact differential from Eqs 3, we get:

$$dU = TdS - pdV, \quad (4)$$

which is the conventional (Clausius-) Gibbs equation. Integrating the latter, provided that we are dealing with the isobaric-isothermal situation (p constant and T constant) and bearing in mind that $H = U + pV$ by definition, would immediately lead to Eq 2. In other words, the "universal competition between energy and entropy" persuasively demonstrated in the book [12] clearly manifests itself as the EEC for some particular isobaric-isothermal case.

Meanwhile, the EEC concept bears not only a purely academic significance, but might be a handy, versatile and powerful tool in interpreting systematic physical-chemical experimental data as well.

3. The physical sense of the EEC – and how to use this notion properly ...

3.1 Carnot cycle as the physical basis of the EEC

In fact, it is well known that the true, conventional Carnot cycle consists of four basic steps:

- (a) reversible isothermal expansion of the gas at the 'hot' temperature, T_H (in other words, isothermal heat addition or absorption);
- (b) isentropic (in other words, reversible adiabatic) expansion of gas (isentropic work output);
- (c) reversible isothermal compression of the gas at the 'cold' temperature, T_C - where $T_C < T_H$;
- (d) isentropic compression of the gas (in other words, reversible adiabatic work input).

In our earlier work [5], we could rigorously show that it is just the position of the so-called 'enthalpy-entropy compensation (EEC) temperature' with respect to the lab temperature, which is immensely helpful in introducing something like a thermodynamic cycle (hidden, 'imaginary' – or even explicit, depending on the exact experimental conditions) essentially similar to the classical Carnot cycle.

3.2 How to use the EEC notion

Meanwhile, the EEC concept bears not only a purely academic significance, but might be a handy, versatile and powerful tool in interpreting systematic physical-chemical experimental data as well.

For the convenience of our potential readership, we would first of all like to present a concise dictionary of specific terms used in our paper [3] and here. When speaking of the physico-chemically valid EEC, one usually means a linear correlation between enthalpic and entropic parameters obtained through independent systematical experiments. The scope of the latter can be twofold:

- (a) studying one and the same system under the influence of the external parameter(s), or
- (b) investigating a number of systems which are somewhat different from each other (like homological rows of chemical compounds, for example).

In the case (a), we may speak of the real Carnot cycle (a thermodynamic cycle of successive micro-phase transitions) underlying the EEC, whereas in the case (b), it can only be imaginary. Indeed, this same pertains for the notion of real or imaginary 'micro-phase transitions'.

We use the term 'micro-phase transition' – and not just 'phase transition' – for transitions that may take place, for

example, in a macromolecule, such as a protein molecule refolding upon binding of some smaller molecular ligand. The transitions in question are not hidden, unlike the Carnot cycles implied by the EEC – in the sense that our systematic experimental study is usually capable of exploring only some essential part of this cycle, but not the whole one. That we nevertheless may get the information about the whole possible cycle is owing to the specific interpretation of the observable correlation coefficient between the enthalpic and entropic parameters. Specifically, we suggest to interpret such a correlation not as a direct cause-and-effect relationship between these thermodynamic observables (otherwise we would go beyond the thermodynamic modalities), but as an effect of some hidden factors. We call the latter ‘hidden’ ones, because they are not directly measurable with the experimental set-up employed, but still are possessing a clear physical meaning. For the detailed inferences and references, please, consult our earlier paper [3]. A comprehensive treatise on all the possible aspects of EEC [2], although published relatively long time ago, can still be recommended as a thorough introduction to the field.

3.3 And as soon as we get the physically-chemically valid EEC, what can we do ?

Here we would like to present the simple interpretational algorithm:

1. Thorough and systematical experimental data on EEC must first be obtained. But mind that not every experimentally revealed EEC is a valid one ! Typically, one must use independent experimental approaches for one and the same specimen (set of specimens) to get enthalpy and entropy. If the latter both are obtained, say, as a result of the conventional Arrhenius or van't Hoff analyses, this is not a physically-chemically interpretable EEC.
2. The conventional linear regression of the experimental enthalpy on the experimental entropy data must be found in the standard way, to reliably evaluate the a and b parameters in Eq 2. Only then, the “Carnot entropic parameter”, b/a , can be determined.
3. The results thus obtained can be interpreted using the own experimental data and the information known from the literature.

The algorithm in itself is pretty easy, with the third step being surely the most non-trivial one. But this should not constitute any “inviolable fortification” for the specialists in the respective fields.

To this end, it is very important to summarize the intrinsic difficulties, as well as the positive breakthroughs connected with employing the EEC concept in different fields of physical chemistry.

Specifically, first of all, we have to mention here the simple intrinsic relationship between the effect of solvent and temperature on the chromatographic retention in the reversed-phase-chromatography (RPC) that arises from the previously observed enthalpy-entropy compensation, which ought to be *an “extrathermodynamic” relationship*, as several author groups conclude, after the detailed statistical-mechanical analysis and careful, systematical experimental work [13].

Along with this, the EEC phenomenon has even been considered something “which ought to be *overcome*” (!) to achieve the proper molecular host-guest “binding affinity” [14]. On the other hand, the EEC can in principle be treated as a kind of driving force when studying protein folding and hydration [15,16] (especially, in dealing with the salt and osmolytic effects on the molecular-scale hydrophobic hydration and interactions [17]).

Still, as concerns the molecular/macromolecular binding (or combined binding-folding/refolding) processes, the role of the EEC phenomenon is not just unambiguously “impeding”, as one might immediately conclude after carefully reading, say, the work [14], as clearly demonstrated in the recent papers [18-20]. The EEC phenomenon is, furthermore, definitely relevant to enzymatic processes, to the interaction of amino-acid residues in proteins with the water of hydration, in particular, as well as – most probably – to the molecular/supramolecular-crowding-induced self-assembly, in general [21-23].

Interestingly, several recent works devoted to the EEC phenomenon completely support the standpoint that the EEC is of essential mechanistic significance for the processes involving the host-guest (supra)molecular binding, as well as the physical-chemical events triggered by the latter ones. And, along with all this, the EEC phenomenon ought to be deeply rooted in the thermodynamics [24-28].

Remarkably, all the most recent works are completely in line with the above conclusion, for they are demonstrating examples of the correct and successful usage of the EEC concept when trying to explain systematical experimental data obtainable in different fields of physical chemistry [29-32].

Among all the above points, when investigating the physical-chemical significance of the enthalpy-entropy compensation principle, it is extremely important to find the detailed connection of the latter to the basics of thermodynamics, as well as to properly refine the sense of the entropy notion. And such studies are also underway in several groups all over the world, see, e. g., the recent works [33-37].

3.4 Micro-phase transitions – or – real phase transitions: How microscopy could be of help ?

For example, the work [30] stresses that “*most readers, who have reached this ultimate part of the present Perspective, would object that such detailed understanding of the Ni–N interactions is of very limited interest for global science, except for specialists in coordination chemistry, and we fully share their opinion. However, let’s apply the same*

approach to self-assemblies controlling recognition processes in physiology, medicine and biology. A thorough understanding of the underlying intermolecular connection of an effector to a receptor could be at the origin of some novel design for drugs, agonists or antagonists, and of the discovery of the mechanism of their action in term of entropy and enthalpy control." Indeed, the work [30] follows our earlier results [5] and rationalizes the enthalpy–entropy compensation (EEC) in intermolecular associations as a *'hidden' structural constraint*. Physically seen, the work [30] goes even farther than the work [1] in immediately interpreting the EEC – and we find in the Chapter 4 of the work [30] the following statement: *"single-step H/S compensations have been mainly investigated in melting processes involving solid → liquid or solid → liquid crystalline phase transitions (the corresponding Gibbs free energy, enthalpy, entropy: ΔG_m , ΔH_m , ΔS_m), or during the reverse physical transformations, where liquids or liquid crystals condensate to give some organized solid-state materials (the corresponding Gibbs free energy, enthalpy, entropy: ΔG_{asso} , ΔH_{asso} , ΔS_{asso})"* (cf. also the corresponding references in the work [30]). In such a representation – these are, generally speaking, not more just 'micro'-phase transitions, these are – fully real phase transitions. Therefore, what in effect ought to be the real scale ('micro' or 'macro') of our observations is also completely dependent on the dimensions of our sample under study. And, if we are working with 'microscopic' samples, we may anyway efficiently use the proper kind of microscopy to check, what is happening in effect behind the observed EEC.

Meanwhile, other authors [23,32,38] devote a lot of attention to physical-chemical consequences of molecular crowding and the 'self-assembly induced by the latter'. The main idea here could be formulated as follows. A polymer-induced intermolecular assembly is also relevant to methods for protein separation by the addition of synthetic macromolecules. The conventional theoretical approaches to the problem usually stop at taking into account purely repulsive excluded volume interactions between flexible polymers and some supramolecular associating species M . And the works [23,32,38] analyze in detail the significant alteration of crowding induced by attractive interactions between the polymers and the assembling species, as reflected in the equilibrium constants K governing self-assembly in the systems with additives that have both attractive and repulsive short range interactions with M , after clearly separating the contributions of attractive and repulsive intermolecular interactions in fluid mixtures.

The mutual virial coefficient B between polymers and monomers of the associating species dominates the changes in their solubility induced by the proper polymer additive, leading to an exponential dependence of the solubility on the polymer concentration, as observed experimentally (cf. the works [23,32,38] and Refs therein). The attractive (enthalpic) and repulsive (entropic) interactions are found to balance at a compensation temperature T_c , where the polymer additive essentially exerts no effect on the assembly, thus providing a physically transparent theoretical explanation of the enthalpy-entropy compensation (EEC) effect [39-42].

Further, the solubility of M is defined in terms of K , so that the molecular additives causing the change in K , ought to affect the solubility as well. However, this additive-induced alteration in solubility is distinct from how molecular additives influence the phase separation (cf. the works [23,32,38] and Refs therein), although the both effects are intrinsically connected to the EEC. The repulsive polymer-protein interactions thus provide the entropic contribution to the protein solubility, which diminishes protein solubility and enhances the protein assembly, i. e., stabilization of the assembled form of M , while attractive interactions exert an opposing trend. The entropy-enthalpy compensation occurs when these factors exactly balance each other – something like the occurrence of the Boyle point in some nonideal gas.

The entropy-enthalpy compensation effect in the influence of polymer additives on protein solubility is directly reflected in the variation of K with the temperature T or the concentration of these additives.

Specifically, the solubility characteristically exhibits an Arrhenius T dependence. As the additive concentration is changed, the Arrhenius slope of the solubility rotates and then vanishes. Alternatively, if the additive concentration is varied at some fixed T , then the solubility varies linearly with the additive concentration, and the Arrhenius slope of the solubility vs the additives concentration shifts progressively from positive to negative upon cooling (cf. the works [23,32,38] and Refs therein). Here we could only add that, if speaking about the EEC phenomena, it is not correct to draw the conclusions based exclusively upon the Arrhenius- and/or van't-Hoff-type plots only, an additional thermochemical argumentation (some microcalorimetry data, for example) is extremely necessary, if one looks for the physically-chemically valid EEC.

Generally speaking, equilibrium constants and rate constants exist for diverse associations, reactions, and relaxation processes in condensed state mixtures, and a lot of of these processes is amenable to the one and the same type of statistical mechanical formalism. Evidently, with this in mind, the entropy-enthalpy compensation must be a rather generic phenomenon in condensed matter equilibria and reaction dynamics.

While the compensation phenomenon in question has long been observed for equilibrium association and kinetic measurements (rates of chemical reactions, dielectric relaxation) in diverse materials, a profound statistical mechanical explanation has been drastically lacking. And now the works [23,32,38,39-43] still manage to clearly demonstrate that the EEC might naturally arise as a consequence of a balancing between repulsive and attractive interactions among the associating species and the additives. The "mystery" regarding the EEC could thus be considered partially resolved, although explaining the near constancy of the compensation temperature for large numbers of the related reactions and association processes, especially those occurring in water, certainly remains an obvious challenge. Still, in our opinion, microscopy could be of immense help to visualize the consequences ("molecular crowding", self-assembly, (micro)phase-transitions) of the above-mentioned compensation effects.

3.5 Valid EEC in physical chemistry of biopolymers or related supra-molecular systems: how microscopy can be of help ?

In studying such parameters of supra-molecular aggregation phenomena as critical aggregation concentrations (CACs), adsorption (at air/water interface) and thermodynamic parameters of aggregation, it becomes clear that the aggregation process is driven by both favorable enthalpy and favorable entropy contributions. For example, the work [44] aims at examining the morphological features of the aggregates in water using SANS and SAXS methods, while the taken SANS and SAXS curves exhibit some diffuse structural peaks that could not be satisfactorily explained using the available conventional models. These aggregates can at best be considered as clusters of ionic liquid (IL) molecules packed in cubical order through several types of interactions, namely $\pi \dots \pi$ interactions and H-bonding interactions between the aromatic cations of the ILs and Cl^- -anion, the water and Cl^- -anions, acidic protons of the aromatic rings in the IL molecules' and water, etc. And the calculations carried out in the work [44] based upon concentration averaged numbers, plus the observed increase in the mean aggregation number with the concentration, indicate that more and more IL molecules can participate in the aggregation, as a result of the favorable environment facilitated by the IL–IL interactions. However, the presence of small aggregates could still be detected [44].

Therefore, all the results of the work [44] taken together show that within the concentration regime under study, the aqueous systems may consist of polydisperse nanostructured pseudophases, a situation that is usually expected in the open type aggregation. Moreover, in the IL molecules investigated in the work [44], a methyl group is attached to the carbon opposite to the nitrogen of pyridine ring, and thus, it is capable of exerting some steric effect. But, along with this, the mean aggregation numbers increased quite expectedly for the 1-octylpyridinium chloride and decreased for the 1-octyl-4-methylpyridinium chloride. To this end, it is well-known that the chloride ions have in general high hydration radii – hence, they hold more water and dehydrate the aggregates in such a way (see the work [44] and the references therein). At the same time, the increase in Cl^- -anion concentration in the stern layer at the surface would help neutralize the positive charge (i. e., promoting the counterion condensation effect). These conditions facilitate the growth of the aggregates in terms of number, as well as geometry. The case of 1-octylpyridinium chloride definitely falls in this category [44]. The exception shown by the 1-octyl-4-methylpyridinium chloride aggregates in the presence of sodium chloride may perhaps enable one to draw a conclusion that the methyl group on pyridine ring sterically prevents the close packing. For more and deeper understanding of the aggregation phenomenon in the ILs under study, detailed microscopic studies – in addition to the conventional experimental ‘machinery’ – would be highly advisable, in our opinion. The values of the aggregation numbers obtained are about 25 Å, which are still in a reasonable accordance with the corresponding molecular chain length value of 24.6 Å for the straight chain configuration of a 1-octylpyridinium chloride molecule in a bi-layered structure, whereas the aggregate structures seem to be smaller in size with high packing density. This means that at high IL concentrations, their volume number density increases so much that the IL \dots IL intermolecular interactions ought to predominate over the IL \dots water intermolecular interactions, thus leading to the formation of heterogeneous phases with cubical packing [44].

To sum up, the pyridinium-based short chain ionic liquids are capable of undergoing aggregation in water beyond CAC. The nature of the aggregation phenomenon and aggregates themselves is, however, rather complex. The aggregation process as such is facilitated by favorable IL \dots IL interactions, but overall it is entropy-driven (*well, in our opinion, to put this more properly, in view of the observed EEC for this case, we may follow the above-mentioned works [23,32,38,39-41] and remark that the whole process is in effect driven by some fine balance between repulsive (entropic factor) and attractive (enthalpic factor) interactions*). The CAC data for short alkyl-chain-pyridinium-based ILs [44], as well as similar data for higher homologous compounds ($n = 10-18$) (for details, see references to the work [44]) were all successfully approximated using the Stauff–Klevens rule ($\log \text{CMC} = a - Bn_c$), and the results yielded the slope value of 0.28 (which is in the range of 0.28–0.30, and therefore is expected for the [mim]-based ILs – or surfactants with the single ionic head group (for details, see references to the work [44])). The observed upfield $^1\text{H-NMR}$ chemical shifts corresponding to the terminal methyl units of 1-butyl-pyridinium chloride, as compared to the down-field shifts for the other two ILs clearly revealed that the nature of the aggregates of the butyl chain based IL ought to be different from those of hexyl- and octyl-pyridinium based ILs (for details, see references to the work [44]). Otherwise, the clustering of IL molecules ought to occur through an open aggregation process: the SANS and SAXS results [44] indicate clearly that the overall nature of the aggregates of short chain ILs is quite different from those of pyridinium-based long chain classical cationic surfactants. These aggregates can at best be considered as clusters of closely packed molecules or small aggregates stabilized by several types of interactions, namely $\pi \dots \pi$ interactions between the pyridine rings and H-bonding interactions between the cations of the ILs and Cl^- -anions, the water and Cl^- -anions, the ring acidic protons and water etc. The methyl groups in substituted pyridines hinder sterically any closer packing of molecules, and hence, an addition of sodium chloride to the system has opposite effect on the growth of aggregates of simple octyl-pyridinium-based ILs as compared to the 1-alkyl-methyl substituted pyridine ILs. More measurements on higher homologs of ILs of this series under variable concentrations are definitely required to gain further understanding and analyze these systems in more detail. Short-chain-based pyridinium based ILs are promising, as they are not only surface active, but also capable of forming an effective biodegradable soft matter (for more details, see the work [44] and the references therein).

Most recently, another very interesting study has been published, *viz.*, on the kinetics of the amorphous silicon crystallization [45]. Remarkably, it is well and long known that the crystallization enthalpy measured in a large series of amorphous silicon (a-Si) materials varies within a factor of 2 from sample to sample. According to the classical theory of nucleation, this variation should produce large differences in the crystallization kinetics leading to crystallization temperatures and activation energies exceeding 550°C and 1.7 eV, respectively, that is, the ‘standard’ values measured for the a-Si obtained by self-implantation. Contrary to all expectations, the observed crystallization kinetics is very similar for all the samples studied and has no correlation with the crystallization enthalpy. Still, such a discrepancy could also bear witness that crystallization in a-Si begins in microscopic domains in almost identical way for all the samples under study, independently of their crystallization enthalpy [45].

In principle, the existence of some microscopic inhomogeneities might also play a crucial role in the crystallization kinetics of other amorphous materials and glasses. One could also think about some other explanation of the non-conventional crystallization effects observed and studied in [45] (with the only reference to the enthalpy, but without any reference to the equally possible entropic effects !): namely, the so-called “Meyer-Neldel-Rule” directly connected to the EEC and well known in different physical-chemical aspects of amorphous materials – but, in fact – not only of the latter ones [46].

There are also lots of other important aspects of the EEC connected with the equilibrium, kinetic, structural and other materials’ properties [47-51], where microscopic investigations might also be of real use and help in deciphering the EEC mechanisms. But the ways of microscopy application will not be analyzed here in detail, owing to the limited space available – the motivated readership is very welcome to cast a professional look at the cited works ...

We have just mentioned above the work [46] which underlines the immense importance of the EEC notion for catalytic systems as a whole – among other cases. Interestingly, the most recent work [52] is also devoted to this theme. Specifically, a bright example of the acidic zeolites which are well-known to be indispensable catalysts in the petrochemical industry, because they are capable of selecting reactants and their chemical pathways based upon their size and shape. The voids of molecular dimensions would confine reactive intermediates, as well as the transition states that mediate chemical reactions, in stabilizing them by van der Waals interactions. This behavior is reminiscent of the solvation effects prevalent within the enzyme pockets – and thus has analogous consequences for the catalytic specificity. The voids in question may also provide the “right fit” for certain transition states, reflected in their lower free energies, thus extending the catalytic diversity of zeolites well beyond the simple ‘size discrimination’. This catalytic diversity is even more remarkable, because acid strength is essentially unaffected by confinement among the known crystalline alumino-silicates. The work [52] discusses factors that determine the “right fit” for a specific chemical reaction, exploring predictive criteria that extend the prevailing discourse based on size and shape. The structures of reactants, transition states, and confining voids could in principle be linked to the details of chemical reactivity and selectivity – and this opens, in our opinion, an interesting field for successful microscopy applications.

Furthermore, the work [52] shows that the spatial confinement in question mediates enthalpy-entropy compromises that determine the Gibbs free energies of the relevant transition states and reactants; these activation free energies determine turnover rates *via* transition state theory. At low temperatures (400-500° K), dimethyl ether carbonylation occurs with high specificity within small eight-membered ring (8-MR) voids in FER and MOR zeolite structures, but at undetectable rates within larger voids (MFI, BEA, FAU, and SiO₂Al₂O₃). More effective van der Waals stabilization within 8-MR voids leads to lower ion-pair enthalpies but also lower entropies; taken together, the carbonylation activation free energies are lower within 8-MR voids. The “right fit” is a “tight fit” at low temperatures, a consequence of how temperature appears in the equation for the Gibbs free energy, owing to the enthalpic effects domination.

Contrariwise, entropy effects dominate in high-temperature alkane activation (700-800° K), for which the “right fit” becomes a “loose fit”. Indeed, alkane activation turnovers appear to be still faster on 8-MR MOR protons, because these transition states are confined only partially within shallow 8-MR pockets; this way they ought to retain higher entropies than those ion-pairs fully confined within 12-MR channels at the expense of enthalpic stability. Selectivities for *n*-alkane dehydrogenation (relative to cracking) and isoalkane cracking (relative to dehydrogenation) can be shown to be higher on 8-MR than 12-MR sites, because the partial confinement preferentially stabilizes looser ion-pair structures; so, these structures ought to occur later along the pertinent reaction coordinates and are higher in energy, in accordance with the conventional Marcus’ theory for charge-transfer reactions. At the same time, the enthalpy differences between cracking and dehydrogenation ion-pairs for a given reactant appear to be independent of the zeolite structure (FAU, FER, MFI, or MOR) and predominantly reflect the different gas-phase proton affinities of alkane C-C and C-H bonds, as expected from the Born-Haber thermochemical cycles. These thermochemical relations, together with statistical mechanics-based treatments, predict that rotational entropy differences between intact reactants and ion-pair transition states should cause intrinsic cracking rates to increase with *n*-alkane size [52].

Using the above-mentioned illustrative examples, the work [52] highlights the effects of reactant and catalyst structures on ion-pair transition state enthalpies and entropies. It is very important that the detailed discussion presented in the work [52] underscores the role of the environmental temperature in mediating enthalpic and entropic contributions to the Gibbs free energies and, in turn, to the rates and selectivities in the field of zeolite acid catalysis.

Another topic highly related to the catalytic activity discussed above is touched in detail in the most recent work [53], where the problem of interpretation of the experimental data related to the thermodynamics of metal ions binding

by alginate-based biosorbents. When considering the thermodynamic parameters (i. e., changes in the enthalpy and entropy values, ΔH and ΔS , respectively), perceivably large discrepancies are observable between their values, even if the systems under study are sufficiently similar to each other. For instance, the binding of copper, cadmium, and lead can be entropy-driven, enthalpy-driven or both entropy- and enthalpy-driven, depending on the considered report. The work [53] aims at revealing the physical-chemical reason(s) for such a paradox and discusses the proper ways of avoiding any misinterpretation of the data conventionally used to estimate ΔH and ΔS values. Remarkably, both experimental (e. g., pH, ionic strength) and theoretical model-related (e. g., mono-dentate vs. bi-dentate binding models) parameters are capable of largely affecting the obtained values of thermodynamic parameters. The work [53] discusses, both qualitatively and quantitatively, how significant are the both mentioned groups of factors in this connection. Therefore, the methods of distinguishing between the “apparent” and the “real” ΔH and ΔS values, as proposed in the work [53], could in principle be related to other types of sorption/adsorption systems, as well. In our opinion, microscopy could be of immense use here to ensure the proper interpretation of different structure-related data arrays.

Moreover, the most recent works [54,55] discuss different thermodynamic aspects of hydration in particular and solvation in general. Specifically, the work [54] considers Abraham solvation equations which find widespread use in environmental chemistry and pharmaco-chemistry, to describe the partitioning of organic compounds over two phases A and B, defined by a partition coefficient P_{AB} , can be estimated from the set of molecular descriptors for the various types of solute–solvent interactions. Conventionally, these equations are employed just as regression formulas to fit the relevant experimental data. To simplify the determination of the coefficients in Abraham solvation equations, the work [54] derives theoretical expressions for the value of the Abraham solvation equation intercept to describe various partition processes and proposes to reformulate the conventional description (by A. Ben-Naim [56,57]) of the standard state in terms of the van der Waals volume. The differences between the theoretically predicted and numerically obtained (using regression analysis) values of the Abraham solvation equation intercept for the solvation enthalpy and the solvation entropy, solvent–water partitioning, air-solvent partitioning, partitioning into micelles, partitioning into lipid membranes and lipids, and chromatographic retention indices are shown [54] to be comparable to the experimental uncertainties in these values.

Then, the most recent work [55] provides insight into the aggregation thermodynamics in connection with the hydrogel formation by molecular gelators derived from l-valine and l-iso-leucine. This work uses solubility data from NMR measurements to extract thermodynamic parameters for the aggregation in water. It is concluded that at room temperature and up to 55.8°C, these systems form self-assembled fibrillar networks in water with quite low or zero enthalpic component, whereas the entropy of the aggregation is favorable. The work [55] explains such results by assuming that the hydrophobic effect is dominant in the self-assembly. Meanwhile, the proper combination of NMR and IR-spectroscopic studies reveals that intermolecular hydrogen bonding also plays an important role in the aggregation process of these molecules in water. The work [55] ascribes the low enthalpy values measured for the self-assembly process to the result of a compensation between the favorable intermolecular hydrogen-bond formation and the unfavorable enthalpy component of the hydrophobic effect.

Additionally, the work [55] shows that by using the hydrophobic character as a design parameter, the enthalpy-controlled hydrogel formation, as opposed to the entropy-controlled hydrogel formation, can be achieved in water if the gelator is polar enough. It is noteworthy that these two types of hydrogels, enthalpy-*versus*-entropy-driven hydrogels, exhibit quite different responses to temperature changes in some of their properties such as the minimum gelator concentration (mgc) or their rheological moduli. Finally, the presence of a polymorphic transition in a hydrogel upon heating above 70.8°C is reported and ascribed to the weakening of the hydrophobic effect upon heating. The new soft polymorphic materials present dramatically different solubility and rheological properties.

To sum up, the work [55] aims at contributing to the rational design of molecular hydrogelators, which could be used for the tailored preparation of such soft materials. The results reported in this work could in principle provide the grounds for understanding the physical-chemical sense of different self-assembly processes in aqueous media. As both the EEC and the structural aspects are of great significance for the results of the works [54,55], the proper usage of microscopy might really be of definite help for continuing the studies described in these works, in our opinion.

There is also a couple of most recent works [58,59] which also make interesting contributions to the topics closely related to the ones discussed above. Specifically, the work [58] is theoretical and checks the accuracy of the free energy perturbation (FEP) model used to study the ionic liquid-type Gemini imidazolium surfactants (ILGISs) and in particular – the Enthalpy–Entropy Compensation (EEC) in the Sulfobetaine-type Zwitterionic Gemini Surfactants (SZGSs) with different number of carbon atoms in the hydrophobic groups or various spacer chain lengths, in aqueous solutions. Within the frame of the FEP model in the work [58], the Gibbs free energy contributions to the driving force for micelle formation are computed using hydration data obtained from molecular dynamics simulations. According to the pseudo-phase separation model, the thermodynamic properties of micellization in aqueous solutions for the SZGSs were discussed in the work [58]. The results clearly show that the micellization of SZGSs in aqueous solutions is a spontaneous and mostly entropy-driven process. Moreover, it is linearly Enthalpy–Entropy Compensated – and is quite different from the micelle formation of ILGIS, but similar to the behaviour of anionic surfactants. The compensation temperature was found to be equal to $(302 \pm 3)^\circ \text{K}$, which was lower than that for ILGISs. As the temperature rises, the micellization is initially facilitated, but then becomes apparently more aggravated, with quite unusual changes in the

enthalpy values: from the positive to the negative ones. The entropy contribution to the micellization tends anyway to decrease, whereas the pertinent enthalpy contribution definitely increases, instead. In particular, as the number of carbon atoms in the alkyl chains and spacer chains increases, both the thermodynamic favorability and stability of the micelles get clearly improved (this indicates an important role of the hydrophobicity in the effects under study).

Meanwhile, the work [59] demonstrates how microscopy can be used to characterize the formation of nanoparticles. Nanoparticles are well-known to differ in their optical, electrical and magnetic properties from the bulk phase, and by triggering the self-assembly of nanoparticles into some ordered structures, various new materials might be prepared with their properties deduced from those of the original nanoparticles. Fundamental aspects of the self-assembly process are of great current interest, in particular the effect of interactions between the nanoparticles, but often even the basic quantitative information is missing. Contributions to the interactions between nanoparticles might include van der Waals dispersion interactions, electrostatic interactions between the net nanoparticle charges, interactions between the permanent electrical or magnetic dipoles, as well as, occasionally, even sterical interactions due to some adsorbed organic capping layers.

The proper theories are in principle available to calculate the effects of those interactions, but experimental data for the magnitude of the interactions between the nanoparticles are rather scarce [59]. The work [59] proposes to determine the contact interaction of nanoparticles dispersed in a liquid environment from the image analysis of equilibrium association structures. The size of such structures depends not only on the coupling energy of the interacting nanoparticles, but also on the interconnection between the nanoparticle coupling and their rotational and translational entropy. This is why, the work [59] suggests to perform temperature-dependent analysis of equilibrium assemblies, to separate the enthalpic and entropic effects of the pairwise nanoparticles coupling.

As is well known [59], quantum dots ought to form equilibrium structures in liquid dispersions, owing to some forces that are often hard to quantify thermodynamically. Analysis of these structures, visualized using cryogenic electron microscopy, yields, *inter alia*, their formation free energy, as well. The work [59] clearly demonstrates that the nanoparticle interaction free energy can be further separated into the enthalpic and entropic contributions, using the temperature dependence of the assembled structures. Monodisperse oleic acid-capped PbSe nanoparticles dispersed in decalin were used in the work [59] as a model system, and the temperature-dependent equilibrium structures were imaged by cryo-TEM, after quenching from various initial temperatures. In the work [59], the interaction enthalpy and entropy follow from the van 't Hoff's exact equation for the temperature dependence of the pertinent thermodynamic equilibria, now applied to the nanoparticles' association. Interestingly, according to the work [59], the enthalpic component reaches the magnitude of the contact interaction, which is a crucial information for understanding the energetics of the nanoparticles' self-assembly into ordered structures, but it is not yet clear what happens to the relevant entropy contribution. Still, as we have already pointed out in the above chapters, if using only the 'van't-Hoff'-type of reasoning, it is senseless to look for the physically-chemically valid ratios between the enthalpic and entropic effects in the free energy. This is why, the interesting direction of experimental studies proposed in the work [59] would surely need an addition of some independent methods, like, e. g., microcalorimetry, to obtain a reasonable separation of the enthalpic and entropic contributions to the free energy of the nanoparticles' self-associated structures and gain much more insight into the fine mechanisms of the nanoparticles' self-association.

To conclude with our minireview, we would like to make mention of another two interesting and most recent papers on the theme, namely [60,61]. The topic of the work [60] is in fact closely related to that of the [59], for the paper [60] is devoted to analysing the thermodynamic signatures of the intermolecular interactions in protein monomer – dimer systems with a tendency to form tighter dimers at higher temperatures. Moreover, the authors [60] mention that the self-association in such protein systems, characterized by positive enthalpy and entropy changes, is entropically driven – and mediated by hydrophobic interactions. More specifically, these endothermic associations appear to be dominated by hydrophobic effects entropically driven by water. So that, the nonpolar regions of such proteins, previously accessible to solvent in the isolated subunits, become buried upon dimer formation [60].

There are also proteins whose self-association energetically differs from that of other types under study [60] in that the pertinent dimers are destabilized at higher temperatures. The relevant thermodynamic profile indicates that both the dimerization of such a type of protein and the formation of the complexes with the proteins of other types are exothermic processes. Meanwhile, during the heterogeneous tetrameric formation, lower absolute values of the negative Gibbs free energy clearly confirm that the resulting complexes are less stable at higher temperatures. Furthermore, the large exothermic enthalpy change and the negative entropy are accompanied with a negative heat capacity change (in the specific heat capacity – constant pressure). Thus, the whole profile in question suggests that such a tetramer formation is controlled mainly by the enthalpy, whereas the interactions between the subunits are mediated by van der Waals interactions, hydrogen bonds, and salt bridges [60].

In the homo- and hetero-associations of the proteins studied in detail in the work [60], there are protein types that mediate protein interactions using van der Waals' contacts and hydrogen bonds, which suggests that the inter-protein contacts most probably involve complementary shapes of protein surfaces with a higher biological specificity. Still, for the other protein types the formation of homo-dimeric complexes ought to be driven by hydrophobic forces which are usually less specific. In these associations, hydrophobic residues at the surface interfaces become excluded from the direct contact with surrounding water molecules.

The work [60] does not pretend to completely rule out the possibility that heterotetramers are formed by the association of homodimers rather than heterodimers but in either case the analyses and conclusions of the work [60] should not be somehow affected. Still, the precise association mechanism sometimes appears to involve the association of heterodimers. This is why, the kinetics, equilibrium position and balance of the so-called “close” and “open” conformational isomers could be affected by interactions of core domains or with the N-terminal extensions of the proteins involved. The dimerization of some protein types might in principle ‘induce’ a conformational shift which favors interaction with the protein of the other type. In principle, such a representation ought to explain, why both homo- and heteroassociation of the particular proteins under study in [60] could be driven by enthalpy.

The experimental approaches conventionally employed during the studies of the type described in [60] involve, for example, the dynamic light scattering and the proteomic analysis. But if in the complexes under study there are some exchangeable components, like the so-called ‘weak’ dimers which have relatively high equilibrium binding constants. Then, the protein interfaces in ‘weak’ dimers are loosely packed and are definitely more hydrophobic than in average protein transient complexes. To this end, there are some protein types which could have a propensity to be components of a peripheral protein network, so that the less specific and more transient nature of their interactions would give these protein oligomers more flexibility for binding. But, on the other hand, much more specific and much stronger exothermic interactions involving such oligopeptides do render the latter rather suitable for the formation of the stable cores in the proteins serving as building blocks for some sturdy bodies (like lens, for example) [60]. Thus, in our opinion, some pertinent microscopic studies of such systems, in addition to the conventional methods set, would be of great help and significance for the detailed understanding of the relevant mechanisms.

Although the interactions of the proteins could in principle be mediated by either the weaker hydrophobic or the more specific van der Waals interactions – and in effect these both may occur, but, on average, only one of them dominates energetically. It is known, for example, from the antibody – antigen interactions, that initial contacts may involve hydrophobic interactions *via* interface aromatic residues followed by more specific and tighter H-bonding, as well as by salt bridges (cf. the work [60] and the references therein). To sum up, the global thermodynamics of the protein interactions clearly indicates that the latter contribute in more stable protein complexes *via* specific van der Waals contacts, hydrogen bonds and salt bridges, whereas there are also some definite protein types which associate by predominately hydrophobic forces, and thus, they are more likely to participate in some weaker protein associations.

Finally, there is another interesting example of a biophysical study [61] dealing not primarily with the structural aspects of the protein physical chemistry, but with the thermodynamic issues of the protein functioning. Specifically, the topic of relevance to the plants’ photosynthesis is discussed. Indeed, the oxygenic photosynthesis conventionally involves the cooperation of two photosystems (PS), PS I and PS II in cyanobacteria, algae, and higher plants [62,63]. PS II is an integral membrane protein complex located in the thylakoid membrane and utilizes the energy of sunlight to split water into protons, electrons, and molecular oxygen. In the past years the three-dimensional structure of PS II was determined at 3.8 Å from *Synechococcus elongates* [64] and 3.0–3.7 Å from *Thermosynechococcus elongates* [65]. The crystallographic model provides complete arrangement of 70 cofactors and protein matrix of 20 protein subunits in the structure of PS II. These cofactors include the primary electron donor (P680), primary electron acceptor pheophytin (Pheo), quinone secondary acceptors (Q_A and Q_B), and tyrosine electron donor (Y_Z). The oxygen evolution Mn_4Ca center is composed of a Mn_3CaO_4 cuboid with the fourth manganese cation attached to a corner of the cuboid. The so-called “dangler” Mn cation and Ca cation may be the active site for water oxidation [61].

The kinetics of the electron transfer reactions in PS II has been thoroughly investigated over the complete timescale of femtosecond to seconds (for details, see the work [61] and the references therein). The early processes occurring in PS II, as revealed by the ultrafast spectroscopy, can be divided into several steps: (a) absorption of light quanta by antenna to form excited states of pigments; (b) trapping of excitation energy by the primary electron donor P680 in the reaction center on the picosecond time scale; (c) primary charge separation from the singlet excited state of P680 to the primary acceptor Pheo, in about 3–20 ps; (d) stabilization of the separated charges from the radical pair $P^{\bullet}680 - Pheo$ on the acceptor side by electron transfer to Q_A , in about 200 ps, and to Q_B , on the hundreds-of-ps time scale; and (e) on the donor side, an electron is supplied to reduce $P^{\bullet}680$ from a tyrosine residue (Y_Z) on the ns–ls time scale. It has been reported that the electron transfer from Y_Z to $P^{\bullet}680$ is dependent on the ambient pH of the PS II preparations (for details, see the work [61] and the references therein).

In contrast to the kinetics of electron transfer mechanisms, thermodynamic information is less accessible, so that the work [61] aims at bridging this gap. Indeed, the detailed mechanisms of the electron transfers and oxygen evolution in PS II including the structure of the protein and rates of the S-state cycle have already been extensively investigated and substantial progress has been made. However, the thermodynamics of PS II electron transfer and of the oxygen cycle are really poorly understood. Recent progress in thermodynamic measurements in photosynthesis provides novel insights into the enthalpic and entropic contributions to electron transfer in proteins. The thermodynamic parameters, including quantum yield, enthalpy, entropy, and volume changes of PS II photochemistry determined by photoacoustics and other laser techniques are summarized and evaluated in the work [61]. Light-driven volume changes *via* electrostriction are directly related to the photoreaction in PS II, and thus can be a useful measurement of PS II activity and function. The enthalpy changes of the reactions observed can be directly measured by photoacoustics. The apparent reaction entropy can also be reliably estimated when the free energy is known from some independent experimental

results. Dissecting the free energy of a photoreaction into enthalpic and entropic components provides critical information about the fine mechanisms of PS II function. Potential limitations and future direction of studying the thermodynamics of PS II electron transfer and oxygen evolution consist in the following problems [61]. Specifically, some of the relevant thermodynamic parameters have been determined using pulsed photoacoustics. However, there is a noticeable inconsistency among the parameters obtained using different organisms. Besides, there is a significant difference between the results of *in vitro* measurements and their *in vivo* counterparts.

In contrast to the volume changes in PS I and bacterial reaction centers, which agree within the error, the volume change during PS II charge separation is really enormously high – from one organism to another, as well as owing to the changes in the environmental conditions of the relevant experiments (for details, see the work [61] and the references therein). Meanwhile, reliable knowledge of both the thermodynamics and the kinetics of a reaction are required for its detailed understanding. However, in contrast to the kinetics of electron transfer in PS II, thermodynamic information is still limited. Pulsed photoacoustic methodology enables one to extract directly thermodynamic parameters, which include the molecular volume change *via* conformational change or electrostriction and energy levels of charge separation, electron transfer, and S-state cycle in PS II. Recent results show that some electron transport steps seem to be enthalpy-driven in PS II electron transfer. Surprisingly, but the S-state cycle in PS II OCE is likely entropy-driven, as are the pertinent steps in PS I (for details, see the work [61] and the references therein). In our opinion, any further work on these interesting systems ought to involve some appropriate microscopic investigations, especially in the cases where volume changes due to the conformational transitions and/or electrostriction play important roles.

The work [61] very clearly shows that the recent progress in thermodynamic measurements of the macromolecules related to the photosynthesis provides interesting novel insights into the enthalpic and entropic contribution to electron transfer in proteins in terms of a broadly thermodynamic view. These unique features provide the potential for a deeper understanding of the mechanisms of electron transfer and proton-coupled electron transfer in chemical and biological systems. The thermodynamic knowledge may have profound impact on the bioenergetics of electron transfer mechanisms in chemistry and biology in general (for details, see the work [61] and the references therein).

4. Conclusions

Our minireview aims at demonstrating that a description of enthalpy-entropy compensation in a general format (general EEC) is in no way in conflict with conventional thermodynamics and can be derived in an exact way using statistical thermodynamics. Taken together with the work of other authors, our analysis constitutes a proof of a general theorem that connects a valid, nontrivial EEC with thermodynamic (Carnot) or kinetical cycles of similar kind. The latter approach can be of great mechanistic diagnostic value, for example, useful in nanoscience when considering working efficiencies of molecular motors, ratchets, heat pumps, and refrigerators at micro- and mesoscopic level. More specifically, appropriately used microscopy supplemented with other well-established experimental methods might be of help in detection and characterization of the microscopic structures and processes underlying EEC, such as our proposed microscopic phase transitions (MPT). In this way a mechanistic interpretation of EEC might be revealed which in turn may assist in further resolution of thermodynamic and kinetical parameters in complex systems under study.

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