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Configurational Entropy in Chiral Solutions—Negative Entropy of Solvent Envelopes

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Abstract: A homogeneous solution of a chiral substance is acquired with an overall asymmetry which is expressed by a specific rotation of a linearly polarized light. Such a solution, despite being at a complete equilibrium, stores configurational entropy in a form of negative entropy which can be nullified by mixing with a solution of the opposite enantiomer. This abundant, yet quite a specific case of inherent negative entropy, resides predominantly in the chiral configuration of the solvent envelopes surrounding the chiral centers. Heat release, amounting to several cal/mol, associated with the annulment of negative entropy in aqueous solutions of D- and L-amino acids, was recently documented by Shinitzky *et al.* [1]. This heat corresponds almost exclusively to TΔS stored in the solvent envelope upon adoption of a chiral configuration. Simple fundamental expressions which combine configurational entropy and information capacity in chiral solutions have been developed and were found to comply well with the observed heat release upon intermolecular racemization.

1. Configurational Entropy in Flexible Molecules

Intramolecular configurations which are at a dynamic equilibrium between transition states store configurational entropies which take a distinct part in the free energy of the transition process. In flexible molecules, the various configurations are at equilibrium between a series of energy minima stations. For simple cases, like that of *n*-butane in the gaseous phase, the statistical weight of these stations can be mathematically evaluated [2] and then translated to a relative scale of configurational

entropy. Such a scale can be further applied for the estimation of the stored information in each of these stations [2].

In macromolecules, configurational entropy is stored in any of the equilibrium conformations. This is in particular relevant to biological macromolecules like poly peptides. Experimental evaluation of the entropy stored in a specific conformation faces the problem of resolution of the change in the free energy of transition to its enthalpy component, which in general demands elaborate procedures. At the current state of the art, this is doable in only limited simple cases [2]. This issue is elaborated on in a series of articles presented in this volume.

2. The Enthalpy-Entropy Interplay in Chiral Solutions

Spontaneous physical interactions in solution are, in general, associated with changes in free energy, ΔG, in the range of kcal/mol. The contributions of the change in enthalpy, ΔH, and the change due to entropy, $T\Delta S$, to the displayed change in free energy, are *a priori* difficult to predict, but in general appear to be of the same order of magnitude, namely in the kcal/mol range. These basic thermodynamic parameters are readily determined and their scattered values for various protein-ligand interactions in water [3], can illustrate their expected experimental range. However, translating the determined changes in enthalpy and entropy to the ensuing changes in the coordinates of the molecular assembly, is beyond the framework of classical thermodynamics. This can be achieved by employing specific technologies such as, for example, X-ray crystallography.

In the rather common processes of dilution or mixing of non reacting solutes in the same solvent, the changes in free energy are much smaller and expected to fall in the range of cal/mol, namely about 3 orders of magnitude below the range for specific interactions. Measurements of low energy processes, such as these, were neglected till recently, partially due to lack of interest but mostly because of shortage in suitable instruments. With the availability of accurate micro calorimetry set ups, in particular isothermal titration calorimetry (ITC) and related instrumentations [4,5], processes associated with changes in free energy in the range of cal/mol, or below, could be addressed. However, in such low energy processes, where no specific intermolecular interactions take place, resolution of the observed heat release or heat consumption, Q, to its thermodynamic components becomes non realistic. In this small energy region, the changes in enthalpy and entropy are actually intermingled and compensate for each other [5]. In molecular terms they can be ascribed to the interplay between the overall change in order (entropy) and the parallel net distortion in the intermolecular bonds (enthalpy).
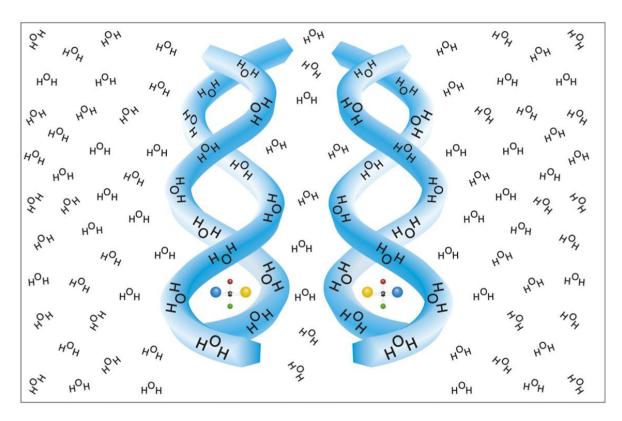
The observed heat release upon dilution of concentrated chiral solutions into water can be formally interpreted as the release of the excess chemical potential, μ_{exc}, which prevails in the concentrated solutions. This dilution process can be formulated as an increase of the activity coefficient γ ($0 < \gamma < 1$) of the solute towards 1:

$$\mu_{exc} = RT\ln\gamma \tag{1}$$

Yet, in this particular somewhat trivial case, one can attribute the increase in γ to a decrease in "communication" between the solute molecules at distances greater than their net dimensions. This can be further ascribed to the dissociation of supra molecular solvent organizations which in the case of chiral solutions may imply solvent envelopes of a specific chiral configuration (see below). Thus, simple

ITC dilution experiments of chiral solutions can lead to an estimated solvent configuration and its extension [6]. The most plausible chiral configuration of a solvent envelope is that of a spiral, either right or left handed. As implied experimentally, such a putative spiral (or helix) can occupy a large number of solvent molecules and at high solute concentration can presumably form supra molecular chiral configurations, like double or triple helices, of solvent shells of adjacent solutes [6]. A model for such chiral hydration envelopes, is presented in Figure 1.

Figure 1. A helical model for chiral hydration envelopes surrounding opposite enantiomers in an isotropic water environment [6].

Homogeneous solutions of chiral substances are characterized by rotation of the optical axis of polarized light, a unique property which was already implemented by the great Louis Pasteur in 1848 [7]. Thus, despite being fully isotropic, such solutions retain an overall asymmetry which can be readily evaluated by simple spectral tests. The quantitative parameter which corresponds to the degree of order which prevails in chiral solutions is the angle of rotation, α, of linearly polarized light recorded upon passage through the solution. It is linear with respect to concentration and optical path and could thus provide a quantitative scale for the overall asymmetry which prevails in the solution. This unique feature can provide an experimental quantitative bridging between entropy and order in chiral solutions [1]. Furthermore, correlation between optical rotation and entropy can be extended to information capacity, expressed in energy units [1], yet unprecedented achievement.

The recorded α in the common case of a homogeneous solution of a chiral substance, termed here as "chiral solution", is the resultant of two levels of chiral asymmetries. The first is the overall asymmetry of the homogeneously distributed molecules of the chiral solute itself which, in principle, can be roughly evaluated by the optical activity of the same concentration in the vapor phase [8,9]. Its contribution to

the displayed α is considerably smaller than that contributed by the chiral organization of the solvent molecules around the chiral centers of the solute [1,6,9]. At high solute concentration such chiral envelopes can aggregate to supra molecular chiral assemblies which are dissociated upon dilution [6]. Heat release, in the range of several cal/mol, ensuing such a dilution, was recently recorded in D and L alanine solutions and could be attributed to TΔS stored in the supra molecular chiral configuration of the intermolecular conjunctions of the chiral envelopes surrounding the individual chiral solutes [6]. The negative entropy and its corresponding thermal energy, TΔS, stored in the individual chiral configuration of solvent envelopes, in addition to the solute overall asymmetry, is readily achieved by intermolecular racemization upon mixing [1]. Specific values obtained by this procedure are presented in Table 1.

3. Entropy and Order

In assemblies of macroscopic objects deviations from homogeneous distribution can be qualitatively presented in terms of "increased order". Quantitative scales for the acquired "degree of order", W, in such cases, can be inferred from statistical algorithms, initiated by Shannon and his associates and later by Brillouin [10,11]. It is of fundamental importance that under such statistical evaluation, W apparently correlates inversely with a term analogous to entropy, S, in statistical thermodynamics. In a homogeneous chiral solution the situation is quite unique. Despite being isotropic it stores an inherent degree of order expressed in reduction of entropy, S, which can be presented in terms of "negative entropy" or "configurational entropy". The correlation between the degree of order, W, and the entropy in such systems is analogous to the macroscopic anisotropy [10,11] and is fundamentally formulated in the well-known Boltzmann equation:

$$S = R\ln W \tag{2}$$

where R is the gas constant.

At a complete hypothetical isotropy, where the system reaches its maximal degree of homogeneity or minimal order of W_0, the corresponding maximal entropy, S_0 provides the base line for evaluation of corresponding "negative entropy" ΔS stored in the homogeneous chiral solution:

$$\Delta S = S - S_0 = R\ln W/W_0 \tag{3}$$

The term TΔS represents the chemical potential stored in the ordered system which is released as thermal energy upon annulment.

4. Information Capacity of Chiral Solutions

Information is a complex physical measure which correlates with order and entropy, as discussed extensively already half a century ago [10-13]. In the macroscopic realm, order and information capacity confer to statistical matrices which are not confined to thermodynamics. However, under a thermodynamic equilibrium of molecular assemblies, like solutions, information can be regarded as a thermodynamic parameter since creation of information involves energy investment while in the converse direction information can save energy. For such systems one can in principle ascribe to information a potential energy scale expressed in thermodynamic terms which awaits theoretical

developments. For the specific case of chiral solutions a quantitative energy scale for information has been suggested by Shinitzky *et al.* [1], as outlined below.

Information capacity of chiral solutions, I, can range from I_0 which corresponds to complete isotropy (defined here as the case of racemic solution) and I_{max} which corresponds to saturated isotropic solution. The range of I, which is defined as being linear, can be combined to the degree of optical rotation, α, which is the most fundamental linear scale for the anisotropy in chiral solutions. Accordingly:

$$I/I_{max} = \alpha/\alpha_{max} \tag{4}$$

where α_{max} corresponds to saturated solution.

The relation between information and entropy has been a long standing subject of discussion by scientists and philosophers based on the concept that entropy and order are interrelated [10-13]. According to Equation 3 a linear correlation between order and information will lead to:

$$-\Delta S = R \ln I/I_0 \tag{5}$$

where I_0 is the information capacity at complete isotropy. Insertion of ordered regions in the solution, i.e., induction of anisotropy, negative entropy is acquired due to $I > I_0$ as expressed in Equation 5 and energy amounting to $-T\Delta S$ is then accumulated:

$$-T\Delta S = RT\ln I/I_0 \tag{6}$$

Alternative presentation can be based on the other edge of the scale:

$$-T\Delta S = RT\ln I_{max}/(I_{max} - I) \tag{7}$$

which by insertion of Equation 4 becomes:

$$-T\Delta S = RT \ln \alpha_{max}/(\alpha_{max} - \alpha) \tag{8}$$

Under conditions where $I_{max} \gg I$ or $\alpha_{max} \gg \alpha$, Equations 7 and 8 are reduced by a simple exponential approximation to the linear forms:

$$-T\Delta S = RT \, I/I_{max} = RT \, \alpha/\alpha_{max} \tag{9}$$

As such, verification of information capacity in chiral solutions remains dependent only on $-T\Delta S$, the energy corresponding to the loss of order in the system. Furthermore, $-T\Delta S$ is expected to increase linearly with α, namely with concentration, a key point in its experimental verification, which is discussed below. It should be noted that Equation 9 is valid only for substantial levels of α and α_{max} at not too diluted solution, where I approaches zero.

The term RT α/α_{max}, which represents the information capacity of chiral solutions in absolute energy units, is readily measurable. Experimental values for information capacity of amino acids in water [1] are presented in Table 1.

Table 1. Information capacity values of D and L proline and alanine in water at 30 °C derived from the heat release, Q, ensuing intermolecular racemization and estimated from Equation 9. Data taken from Reference [1].

Resident solute		Heat liberation upon point racemization, (cal·mole^{-1})	Information capacity, RT α/α_{max}, estimated (cal·mole^{-1})
L-Proline	1M	4.6	70
	0.6M	1.0	40
D-Proline	1M	6.3	70
	0.6M	1.2	40
L-Alanine	1M	0.59	300
D-Alanine	1M	0.61	300

5. Reflection Symmetry in the Macroscopic Realm

Asymmetrical objects with mirror reflection symmetry prevail in the macroscopic realm as well. Common examples are right handed vs left handed spiral screws. A random assembly of such asymmetrical objects also preserves an overall asymmetry, analogous to that of a homogeneous solution of chiral molecules and is therefore endowed with information capacity. Yet, a tool for translation of the overall order in such assemblies to a measurable parameter, similar to α in chiral solutions, is not yet in hand, an issue which has been recently discussed [14].

6. Experimental Verification

A series of indirect evidence strongly suggest that the hydration layer surrounding chiral solutes, like amino acids, acquires a chiral configuration induced by their chiral centers [1,6]. The energy invested in the induction of the chiral twist in the hydration layer can predominantly be attributed to TΔS, the energy associated with "configurational entropy" [2,6]. This entropic energy amounts to only several cal/mol, about a thousandth of the enthalpy associated with the prevailing intermolecular interactions, like the hydrogen bonds. Thermal energies of this scale can be accurately monitored by microcalorimetry [3-5].

TΔS of configurational entropy in chiral solution can be determined by heat release of two independent processes; heat of dilution and heat of intermaolecular racemization. The observed heat release upon dilution of concentrated chiral solutions into water can be formally interpreted as the release of the excess chemical potential, $\mu_{exc,}$ which prevails in the concentrated solutions. This dilution process can be formulated as an increase of the activity coefficient γ ($0 < \gamma < 1$) of the solute towards 1, formulated in Equation 1. In molecular terms, the solute molecules in such "ideal" solutions are

separated by the bulk solvent beyond the level that permits static or dynamic correspondence between neighboring hydration layers. In line with this approach, all water molecules in the bulk are at a state which responds to the ordered hydration layers by adopting an overall ordered network which deviates from the isotropy prevailing in pure water. Furthermore, this putative overall degree of order increases with the solute concentration [1,6]. The hydration assemblies of the individual solutes at high concentrations presumably integrate to combined intermolecular assemblies which are tighter and more ordered than the hydration layer in dilute solutions. It has been thus shown, that heat release upon dilution of concentrated D or L-alanine in water has a TΔS component attributed to the disintegration of supramolecular chiral hydration assemblies [6].

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