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Molecular thermodynamic model for equilibria in solution

II. Statistical microscopic properties of ensembles

A. Braibanti*, E. Fisicaro, C. Compari

Pharmaceutical Department, Section of Applied Physical Chemistry, University of Parma, I-43100 Parma, Italy

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Abstract

A statistical thermodynamic model for the interpretation of the equilibria in solution is based on the principle that the representative statistical ensembles can be characterized by two types of molecular distribution, one for *non-reacting* systems and another for *reacting* ones, respectively. *Non-reacting* and *reacting* ensembles correspond at the molecular level to one or a couple of potential curves, respectively. The properties of the thermodynamic model for solutions can be set up following some rules. These concern the statistical extension of the microscopic model to the whole ensemble and the successive averaging to get a mean partition function. The mean partition function is linked to the experimental domain of concentrations, dilutions and equilibrium constants (probability space) and to that of calorimetry, chemical work, and potentiometry (thermodynamics space). The formal connection between probability and thermodynamic space and the conformity of thermal equivalent dilution with the formulations of statistical thermodynamics are also shown. © 1998 Elsevier Science B.V.

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A statistical thermodynamic model [1] has been proposed for the interpretation of the equilibria in solution. The model is based on the idea that two types of ensembles represent the systems, one for *non-reacting* and another for *reacting* systems. The former type corresponds to a molecular distribution where no outstanding enthalpy level can be identified and the latter to a molecular distribution where at least two distinct enthalpy levels are present.

We want now to show how the definitions of properties of the ensembles adopted conform to the phase space introduced by Gibbs and to the general treatments of the theory of fluids [2–8].

The fundamental problem in statistical mechanics is to use a knowledge of the interparticle interactions of a system to predict the thermodynamic properties of that system. Intermolecular potential theory is based upon the two apparently well-founded assumptions: first that the intermolecular potentials are a function of intermolecular separation alone; and, second, that the total potential energy of a system of N atoms may be written as a sum of two-body, three-body, four-body,. . ., potential functions. In general, for the study of dense fluids, the main concern is with the one-particle distribution function, the number density ρ and with a particular form of the two-body distribution

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*Corresponding author. Tel.: +39-521-905-024; fax: +39-521-905-006; e-mail: braiban@ipruniv.cce.unipr.it

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function, the radial distribution function $n(r)$. The two-body distribution function determines the second coefficient $B(T)$ of the virial equation of state for real gases

$$PV/(Nk_{BT}) = (1 + B(T)\rho + C(T)\rho^2 + \dots \quad (1)$$

The virial equation is a power series of the number density ρ each power being multiplied by a proper coefficient. The virial coefficients are related to integrals that can be solved by approximate calculations. In particular, the second virial coefficient $B(T)$ can be calculated in terms of Mayer *f*-bond. The Mayer *f*-bonds and other functions are very often visually represented by means of the graph theory which plays a prominent role in the description of the properties of fluids [9,10].

In *non-reacting* ensembles, the correlation function takes the form [3]

$$g(r) = \exp\left(-U(r)/kT\right)f(\rho) \quad (2)$$

where $U(r)$ is the potential of mean force between one particle and the many adjacent particles and $f(\rho)$ a function of the number density ρ

$$f(\rho) = (1 + \rho x_1(r) + \rho^2 s x_2(r) + \dots) \quad (3)$$

The functions $x_1(r)$, $x_2(r)$,..., which represent discontinuous distributions of entropy, are integrals that must be approximated. The main methods of approximation have been proposed by Yvon [11] and, independently, by Born and Green [12] and Kirkwood [13].

In solution thermodynamics, the distribution of the species over different levels of free energy [14–18] is represented by a binding polynomial or partition function. This system is represented by a *reacting* ensemble. For a receptor M with three sites, a typical partition function, Z_M, for reacting ensemble is given by

$$Z_M = 1 + \beta_1[A] + \beta_2[A]^2 + \beta_2[A]^3 \quad (4)$$

where β_1, β_2, and β_3 are operative cumulative formation constants or phenomenological coefficients. Eq. (4) is a series expansion in powers of [A], similar to Eqs. (1) and (3). Each term of Eq. (4) corresponds to one-body, two-body, ..., (i+1)-body interaction, respectively.

The operative cumulative constant or phenomenological coefficient β_i is approximately equal to $\beta_i \approx [MA_i]/([M][A]^i)$. The thermodynamic cumulative constants β_i^0, as functions of activity are pure numbers and are defined in Appendix A, where the approximations assumed to define β_i are also given. According to the relationships in the Appendix A, the cumulative constants β_i have dimensions of $conc^{-i}$. Each term of Eq. (4) is a pure number that can be obtained as the ratio between two dilutions, namely between β_i and (1/[A]), i.e. $\beta_i[A]^i = \beta_i/[A]^{-i}$. The same dimensions are associated with the products of activity coefficients as those for the cumulative constants.

The description of the state of the solution depends on the level of definition needed to interpret the experimental data. The Born–Oppenheimer level of description of ionic solution considers the particles Na^+, Cl^- and water molecules. The MacMillan–Mayer level of description of the ionic solutions considers the particles Na^+, Cl^- with water as a continuum. Our level of description is concerned with the concentration of species of order 10^{-3} mol dm^{-3} or less, where the species are bases and acids, protonated species and complexes, dimers, trimers, macromolecules, etc. The solvent is considered as an inert background unless it takes part in a reaction in which case it is considered as a ligand. We want to show how these distributions of species conform to the general framework outlined by Gibbs for thermodynamic statistical distributions. Some further rules will be added to help define the behaviour of the systems.

The two basic postulates of Gibbs are the following:

Postulate I (Gibbs microcanonical distribution). An observable thermodynamic property reflects some particular time-averaged behaviour of the system components. Gibbs' idea of statistical ensemble is a device for conceptually avoiding the time averaging process. The time-averaged value of a single system property is replaced by the instantaneous average property value taken over a large number of systems each of which is an exact microscopic replication of the original system. This large collection of systems is the ensemble. The number of ensemble elements is taken sufficiently large to represent meaningful averages. The distribution in the cells of phase space that the molecules of an ensemble can assume at any one instant of time is exactly equal to the positions that each molecule can take in successive instants of time. The postulate can be expressed, by taking enthalpy as the property under consideration, as follows: the equilibrium distribution of macroscopic states of a conservative system consists in a uniform distribution on the enthalpy surface of all the microscopic elements of the ensemble [2].

Postulate II (Gibbs canonical distribution). In an ensemble representative of a thermodynamic system coupled to a heat reservoir, the distribution of the cells of phase space over different levels is uniform.

The ultimate purpose of statistical thermodynamics is to express the interactions between components by the sum of pair potentials, starting from the properties of the element of phase space up to the properties of the macroscopic system.

The distinction between *non-reacting* and *reacting* ensembles can be referred to an appropriate type of potential. The potential for a *non-reacting* closed ensemble is drawn in Fig. 1. The curve is supposed to follow some type of Lennard–Jones potential, but this is not strictly necessary. The minimum of the curve is $-\eta_0/k_BT$ (η_0 is enthalpy per molecule and k_B the Boltzmann constant) and evaluates the total potential energy. At a distance along r axis, sufficiently large from the minimum, the potential energy has reduced to zero and all the potential energy has been transformed into kinetic energy or s_0/k_B (entropy per molecule). At any point along the r axis, the sum of potential and kinetic energy is constant

$$-\eta/(k_BT) + s/K_B = S_0/k_B \tag{5}$$

By differentiating Eq. (5), one obtains

$$\mathrm{d}\{-\eta/(k_BT)\} + \mathrm{d}\{s/k_B\} = 0 \tag{6}$$

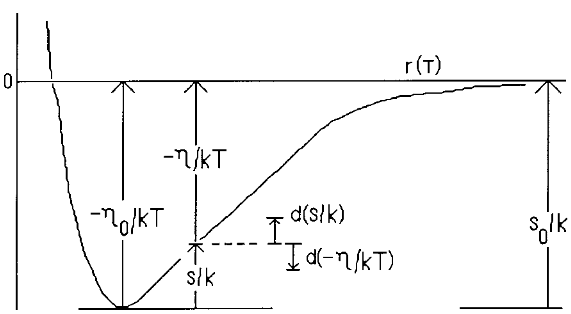

Fig. 1. Pair-potential function for a *non-reacting* ensemble (k_B, Boltzmann constant).

and, hence,

$$\mathrm{d}\{\eta/k_B\} = T\mathrm{d}\{s/k_B\} \tag{7}$$

(see Appendix B). By dividing both sides of Eq. (7) by dln T, one obtains

$$(1/T)\partial\{-\eta/k_B\}/\partial \ln T = \partial\{s/k_B\}/\partial \ln T \tag{8}$$

Both sides of Eq. (8) can be multiplied by (N_L/N_L), where N_L is Avogadro number. From the RHS of Eq. (8), one obtains C_p which is the isobaric heat capacity

$$\partial\{S/R\}/\partial \ln T = C_p/R \tag{9}$$

with S=(sN_L) as molar entropy. The LHS of Eq. (8), with H=(∂N_L) as molar enthalpy, can be transformed as follows into the derivative with respect to T

$$\partial\{H/R\}/T\partial \ln T \equiv \partial\{H/R\}/\partial T = C_p/R \tag{10}$$

whereby it is shown that, in *non-reacting* ensembles, the isobaric heat capacity C_p is a measure of a change, either of entropy (Eq. (9)) or of enthalpy (Eq. (10)), without any possibility of distinguishing between them by thermodynamic means.

The reference molecular potential of a *reacting* ensemble is a couple of potential functions (Fig. 2).

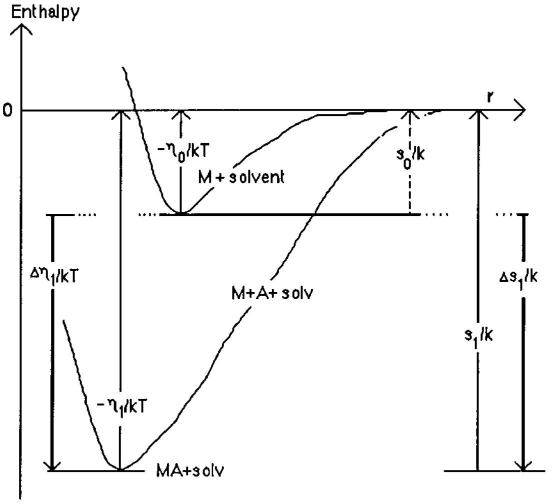

Fig. 2. Couple of pair-potential functions in a reacting ensmble (re). The existence of the enthapy difference $\Delta\eta$ is a necessary condition for an equilibrium reaction and, hence, for having a reaction ensemble. (k_B, Boltzmann constant). Note that the formation of the complex in this example is an exothermic process and is analogous to an emission spectroscopic process.

Even at this level of description, the existence of a definite enthalpy difference between the minima of a couple of potential curves is the necessary condition to distinguish a *reacting* from a *non-reacting* ensemble. The definite enthalpy difference is necessary to have an equilibrium between species in the experimental system.

In order to get a better definition of the properties of the statistical model for solutions, the two postulates can be integrated by the four following rules.

Rule I (Probability space). The probability of the states of any cell or cluster of cells of the phase space is described in the probability space. Any intensive variable or weighting coefficient is independent of the size of the system. Possible probability functions satisfying this condition are the Boltzmann functions

$$\begin{aligned}\exp(-\Delta\eta/k_\mathrm{B}T) &= \exp(-2\Delta\eta/2k_\mathrm{B}T)\\ &= \ldots\exp(-n\Delta\eta k_\mathrm{B}T) = \ldots\exp(-\Delta H/RT)\end{aligned} \tag{11}$$

where $\Delta\eta$ is the enthalpy per molecule, k_B the Boltzmann constant, ΔH the enthalpy per mole and R the gas constant. In *reacting* ensembles, sums of Boltzmann functions can form probability functions, such as the molecular partition function

$$a_\mathrm{M} = 1 + \exp(-\Delta g/k_\mathrm{B}T) \equiv 1 + k[\mathrm{a}] \tag{12}$$

where Δg is the free energy per molecule, k a specific site binding constant and $[\mathrm{a}]=n_\mathrm{A}/\phi_0$ the number of molecules per unit volume with $\phi_0=V_0/N_\mathrm{L}$, where V_0 is $1000\ \mathrm{cm}^3$. Alternatively, the probability can be represented by the molar partition function

$$A_\mathrm{M} = 1 + \exp(-\Delta G/RT) \equiv 1 + k[A] \tag{13}$$

where ΔG is free energy per mole and [A] the number of moles per unit volume V_0. Note that $z_\mathrm{M}=Z_\mathrm{M}$, the molecular partition function of Eq. (12) and the molar partition function of Eq. (13) are numerically equal. The equality is valid in the thermodynamic limit "which simply means that the thermodynamic quantities as entropy, heat capacity, free energy, etc. are asymptotically proportional to the size of the system" [2].

The justification of the equality of Eqs. (12) and (13) is that z_M and Z_M are actually weighting factors of the unit cell ϕ_0 of phase space (z_M) and of the unit volume V_0 of the real space (Z_M), respectively. The weighting factors of probability space are independent from the size of the system. In fact, if in each j part of the total J parts of the whole ensemble, clusters l_j of size t_l are formed, then one can calculate the partition function as

$$z_\mathrm{M}(1/J)\sum_{j=1}^{j=J}\left\{\prod_{l_j=1}^{l_j}(z_{lj})^{t_l}\right\}^{\left(1/\sum t_l\right)} \tag{14}$$

where the product $\prod$ refers to all clusters l of one group j and the summation $\sum$ refers to all J parts of the ensemble.

If $J=1$ and $t_\mathrm{l}=\sum t_\mathrm{l}=N$, i.e. there is a unique cluster of size N, then by substituting into Eq. (14), one obtains

$$z_\mathrm{M} \equiv (x_1)^{N(1/N)} = \langle\langle z_1\rangle\rangle \tag{15}$$

where $\langle\langle\ \rangle\rangle$ indicates a geometric average. If $J=N$ and $t_\mathrm{l}=\sum t_\mathrm{l}=N$ (i.e. N parts each with a unique cluster of size N) then the following partition function is obtained (cf. Eq. (26) below)

$$Z_\mathrm{M} = (1/N)\sum_{j=1}^{j=N}\langle\langle z_i\rangle\rangle = \langle(\langle\langle z_i\rangle\rangle)\rangle \tag{16}$$

which becomes the molar partition function, when $N=N_\mathrm{L}$. The function z_M is geometrically averaged ($\langle\langle z_\mathrm{i}\rangle\rangle$) over the size of cluster N, whereas Z_M is further arithmetically averaged ($\langle\ \rangle$) over N or N_L replicas. Both z_M and Z_M are referred to one cell of the phase space and then the approximate equality holds $z_\mathrm{M}\approx Z_\mathrm{M}$. In the thermodynamic limit $z_\mathrm{M}=A_\mathrm{M}$, as for Eqs. (12) and (13) above.

Fermi–Dirac statistics is applicable to the probability space for *reacting* ensembles (*gce*). In fact, chemical combinations of reactants in *gce* are represented in the probability space by products of probability factors or products of partition functions which is on the scale of molecules

$$z_\mathrm{M} = (1 + \exp(-\Delta g/RT))^{i_t} \equiv (1 + k[\mathrm{a}])^{i_t} \tag{17}$$

and the scale of moles

$$Z_\mathrm{M} = (1 + \exp(-\Delta\mu/RT))^{i_t} \equiv (1 + k[\mathrm{A}])^{i_t} \tag{18}$$

The total probability polynomials of Eqs. (17) and (18) contain coefficients that are obtained from the rules of the Fermi–Dirac statistics, e.g. for $i_t = 3$, on the macroscopic molar scale

$$Z_{\mathrm{M}} = (1 + k[\mathrm{A}])^3 \equiv 1 + 3k[\mathrm{A}] + 3(k[\mathrm{A}])^2 + (k[\mathrm{A}])^3 \qquad (19)$$

Each term of the polynomial in Eq. (19) is related to the occupation probability of two enthalpy levels. The occupation probability is proportional to the number of molecules occupying that level. On the contrary, the probability of the state is inversely proportional to the occupation probability and is proportional to dilution.

In this way, in *reacting* ensembles, the probability for each level i corresponding to one species $\mathrm{MA_i}$ relative to the ground state represented by the species M is expressed on the macroscopic scale by the molar dilution ratio

$$[\mathrm{M}]^{-1}/[\mathrm{MA}_j]^{-1} = \beta_i[\mathrm{A}]^i \qquad (20)$$

Both sides of Eq. (20) are pure numbers, although each factor has the dimension of dilution or $(\text{concentration})^{-1}$. The constant β_{i} indicates how much the free ligand [A] has been diluted when bound to M.

Rule II (Thermodynamics space). The microscopic element, or a cluster of elements of a statistical ensemble, is related to the macroscopic system by a transformation (subdivision) in the thermodynamic space of extensive variables and functions. Any extensive variable, e.g. volume, free energy, enthalpy, etc. undergoes the same transformation. The extensive variable is given as the ratio between the energy (or volume, or entropy, etc.) of a group of elements with the energy content, $\varepsilon_{\mathrm{id}}=k_{\mathrm{B}}T$ (or entropy content, $s_{\mathrm{id}}=k_{\mathrm{B}}$) of an equal number of elements of an ideal gas, $(n\varepsilon_{\mathrm{id}}=nk_{\mathrm{B}}T)$. Therefore,

$$\varepsilon/\varepsilon_{\mathrm{id}} = \varepsilon/k_{\mathrm{B}}T = 2\varepsilon/2k_{\mathrm{B}}T = 3\varepsilon/3k_{\mathrm{B}}T \ldots = n\varepsilon/nk_{\mathrm{B}}T \ldots = N_{\mathrm{L}}\varepsilon/RT \qquad (21)$$

where k_{B} is the Boltzmann constant, $R=k_{\mathrm{B}}N_{\mathrm{L}}$ the gas constant.

The ratios of Eq. (21) are consistent with the general principles of statistical thermodynamics. In fact, the molecular partition function is set in statistical thermodynamics [3] as

$$z = V_0/\phi_{\mathrm{m}} \equiv (1/\phi_{\mathrm{m}})/(1/V_0) \qquad (22)$$

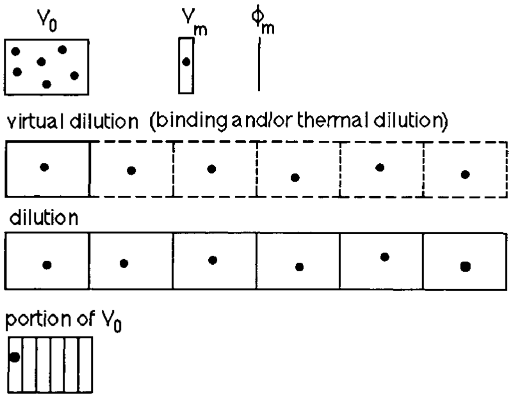

Fig. 3. Accessible volume and probability of state. V_{m}, portion of the original standard volume V_0 that, *before* dilution, contains the same number of *moles* as the whole volume V_0 *after* dilution. ϕ_{m}, an infinitesimal portion of V_0 that contains *before* dilution the same number of *molecules* as the whole volume V_0 *after* dilution. Probability of state (molecular): $z=(1/\phi_{\mathrm{m}})/(1/V_0)$, Probability of state (molar): $Z_{\mathrm{M}}=(1/V_{\mathrm{m}})/(1/V_0)$, Probability of state (molecular): $z_{\mathrm{M}}=(1/\phi_{\mathrm{m}})/(1/\phi_0)$; $\phi_0=\mathrm{V}_0/N_{\mathrm{L}}$; $z_{\mathrm{M}}=Z_{\mathrm{M}}=z/N_{\mathrm{L}}$.

which is, for a gas, equal to the ratio between the volume V_0 accessible by one mole of ideal gas at STP (22 414 cm^3) and the volume ϕ_{m} accessible by one real molecule (Fig. 3). The accessible volume is inversely proportional to dilution, $1/\phi_{\mathrm{m}}$, which, in turn, is proportional to the probability of the state; $(1/V_0)$ is, therefore, proportional to the probability of unitary standard state. The volume ϕ_{m} is related to molecular momentum λ by

$$\phi_{\mathrm{m}} = \lambda f(\eta) \qquad (23)$$

if $\lambda=\Lambda^3$, where $\Lambda=h(2\pi mkT)^{-1/2}$ is the De Broglie thermal wavelength, and $f(\eta)$ is a probability weighting function depending on the enthalpy of the reaction, then ϕ_{m} has the dimension of volume. $f(\eta)$ is a function of the reciprocal of the configuration integral Z_{c} and represents in ϕ_{m} the factor of virtual dilution.

The molecular partition function z is an extremely large number (e.g. $z=\exp(67.2)=1.53\times10^{29}$ for gaseous helium), representing the dilution combined with the virtual dilution due to bindings as given by $f(\eta)$ of the volume ϕ_{m} (accessible by one molecule) from one to all the cells $(=N_{\mathrm{L}})$ contained in one volume of gas at STP. Alternatively, the molecular partition function z can be interpreted as the dilution of one molecule from ϕ_{m} to the corresponding standard volume ϕ_0 by repeating the dilution N times. For a solution, the volume V_0 is set equal to 1000 cm^3.

The molar partition function is set [3] as

$$\mathrm{Z} = z^{\mathrm{N}}/\mathrm{N}! \tag{24}$$

which according to the Stirling approximation ($\ln N! = N \ln N - N$) yields

$$\ln Z = N \ln (ze/N) \tag{25}$$

Z is an inconceivably large number. We can, however, reduce it to a reasonable size if we consider some mean similar to the geometric mean, calculated for clusters in Eq. (16). If we take the geometric mean $Z^{(1/N)}$, we consider a statistical average of N events concerning the dilution or reaction (1 : 1) of one molecule with one cell of volume $\phi_0 = V_0/N$. This means that we remove the effect of dilution from ϕ_0 to V_0 and we are left with virtual dilution from ϕ_m to ϕ_0 only due to binding. In fact, by rearranging Eq. (25) one obtains

$$\begin{aligned} Z^{(1/N)}/e = z/N = (V_0/N)\phi_{\mathrm{m}} = \phi_0/\phi_{\mathrm{m}} \\ = (1/\phi_{\mathrm{m}})/(1/\phi_0) \end{aligned} \tag{26}$$

If $N = N_{\mathrm{L}}$, then the ratio is between the accessible cell volume ϕ_0 at STP by one molecule of ideal gas and the volume ϕ_{m} accessible by one molecule of a real gas. In a solution ($V_0 = 1000$ cm^3) the ratio of Eq. (26) is between the unit volume $\phi_0 = 1000/N_{\mathrm{L}}$ and the statistical average accessible volume ϕ_{m} of one solute molecule. The probability of the average event is related to the free energy of the reaction by

$$Z^{(1/N)}/c = \exp(-\Delta g/k_{\mathrm{B}}T) \tag{27}$$

where $Z^{(1/N)} = 1$ if $\Delta g = k_{\mathrm{B}}T$. This indicates that the ratio of the LHS of Eq. (27) is the mean probability ratio with respect to the system presenting the distribution of the ideal gas ($k_{\mathrm{B}}T$).

On comparing Eqs. (26) and (27), one concludes that (i) on the scale of molecules it is possible to compare the probability of reaction with a ratio of accessible molecular volumes (i.e. dilutions)

$$\exp(-\Delta g/k_{\mathrm{B}}T) = (1/\phi_{\mathrm{m}})/(1/\phi_0) \tag{28}$$

and (ii) on the molar scale the probability of reaction with a ratio of molar accessible volumes

$$\begin{aligned} \exp(-\Delta G/RT) = \phi_0 N/(\phi_{\mathrm{m}} N) \\ \equiv (1/V_{\mathrm{m}})/(1/V_0) \end{aligned} \tag{29}$$

where V_{m} is the statistical average accessible volume of 1 mole. It can be stressed the point that the ratio of accessible volumes is a ratio between probabilities of states which are typical intensive variables of the probability space.

The couples (V_0, ϕ_0), (V_{m}, ϕ_{m}), and ($-\Delta G$, $-\Delta g$) are proportional to the ratios $R/K_{\mathrm{B}}/N_{\mathrm{L}}$. Therefore, the ratios

$$V_{\mathrm{m}}/R = \phi_{\mathrm{m}}/k_{\mathrm{B}} \tag{30}$$

and

$$V_0/R = \phi_0/k_{\mathrm{B}} \tag{31}$$

are comparable with the first and last ratios of Eq. (21). Their equality is again valid on the assumption of the existence of the thermodynamic limit [2].

The same arguments can be used to explain how the molar reaction partition function Z_{M} conforms to general statistical thermodynamics. In fact, Z_{M} is proportional to dilution of the receptor. With reference to a simple reaction M+A=MA, the partition function or binding polynomial is

$$Z_{\mathrm{M}} = [\mathrm{M}]^{-1}/\{[\mathrm{M}] + [\mathrm{MA}]\}^{-1} \tag{32}$$

and

$$Z_{\mathrm{M}} = \exp(\Delta G/RT) \tag{33}$$

From Eq. (29) one obtains

$$Z_{\mathrm{M}} = V_0/V_{\mathrm{m}} = (1/V_{\mathrm{m}})/(1/V_0) \tag{34}$$

and from Eqs. (26) and (28)

$$Z_{\mathrm{M}} = z/\mathrm{N} \tag{35}$$

which shows how the binding polynomial obtained from the experiment is actually a mean molar partition function coincident with the geometric mean of classical partition function of Eq. (24).

Finally, by recalling Eqs. (28)–(31), the molecular partition function comes out to represent a ratio of probabilities of states on the molecular scale

$$z_{\mathrm{M}} = \exp(-\Delta g/k_{\mathrm{B}}T) = (1/\phi_{\mathrm{m}})/(1/\phi_0) \tag{36}$$

which is a mean molecular partition function related to the classical statistical molecular partition function z by

$$z = z_{\mathrm{M}} N \tag{37}$$

Therefore, z_{M} of Eq. (36) represents the probability of dilution or reaction (1 : 1) of one molecule with accessible volume ϕ_m with one cell of volume ϕ_0. By analogy, Z_M of Eq. (35) represents the probability of dilution or reaction (1 : 1) of N molecules (1 mole if $N=N_\mathrm{L}$) with accessible volume V_m and with solution volume $N\phi_0=V_0$. The partition functions z_M and Z_M are numerically equal as are $\exp(-\Delta g/k_\mathrm{B}T)$ and $\exp(-\Delta G/\mathrm{RT})$, again on the assumption of the validity of the thermodynamic limit.

The relative variables of the thermodynamic space can be transformed into absolute thermodynamic values. The units are different if they are obtained by multiplying the relative variables by R ($\mathrm{J\,mol^{-1}\,K^{-1}}$) or by k_B ($\mathrm{J\,molecule^{-1}\,K^{-1}}$). It is obvious that the experimental size is obtained by reference to R rather than k_B.

Rule III (Distribution moments). If the probability of states is statistically distributed, then the thermodynamics space functions are the first moments of the probability space distributions. In this respect, the Boltzmann function in the probability space is an eligible function to obtain the extensive variable of the thermodynamics space. In fact, if we search for a function, for which $\mathrm{d}f(x)/f(x)=\mathrm{d}x$, we find that the Boltzmann function satisfies this condition

$$\begin{aligned}&(\exp(-\Delta G/RT))^{-1}\mathrm{d}(\exp(-\Delta G/RT)\\&\quad=\mathrm{dln}(\exp(-\Delta G/RT))=\mathrm{d}(-\Delta G/RT)\end{aligned}\qquad(38)$$

Analogous equations can be written on the molecular scale, e.g $\mathrm{d}(-\Delta G/RT)=\mathrm{d}(-\Delta g/k_\mathrm{B}T)$.

Other intensive variables as pressure, concentration, dilution or partition functions find their extensive counterpart in the logarithm of the intensive variable or function, respectively. The logarithmic function is the explicit form of the relationship $S_\mathrm{A}/R=f(d_\mathrm{A})$ or $s_\mathrm{a}/k_\mathrm{B}=f(d_\mathrm{a})$ between the dilution of the probability space and the entropy S_A/R or $s_\mathrm{a}/k_\mathrm{B}$ of the thermodynamic space

$$\mathrm{d}S_\mathrm{A}/R=-\mathrm{dln}\,[\mathrm{A}]\qquad(39)$$

For the entropy also, as for any other extensive variable, there is the possibility to write equations like Eq. (21). For instance, the mixing entropy can be defined on the microscopic scale [8] by

$$S/k_\mathrm{B}=-\sum f_i\ln f_i\qquad(40)$$

and on the macroscopic scale [10] by

$$S/R=-\sum x\ln x_i\qquad(41)$$

Eqs. (40) and (41) correspond to equal numbers because they can be transformed into one another by the relation

$$s/k_\mathrm{B}\equiv(\mathrm{N_L}s)/\mathrm{N_L}k_\mathrm{B})=S/R\qquad(42)$$

This relation for entropy is analogous to Eq. (21) for energy and to Eqs. (30) and (31) for dilution.

Note how the Eqs. (40) and (41) are not equivalent to $s/k_\mathrm{B}=-\sum\ln f_l^{f_i}$ and $S/R=-\sum\ln x_l^{x_i}$, respectively, because the coefficients of the thermodynamic space do not commute with the exponents of the probability space. The two classes of numbers have different properties. The coefficients of the thermodynamic space are indicative of extensive amounts of substance and can assume any rational value, either integer or not. The coefficients of the probability space refer to molecular reactions in the probability space and can assume only integer values indicating interactions between a finite number of particles.

In probability space, the equality Eq. (42) becomes

$$\exp(s/k_\mathrm{B})=\exp(S/R)\qquad(43)$$

The second moments of the intensive distribution functions or variables, can be calculated as second derivatives with respect to either variable. *Reacting* ensembles, *re*, also admit mixed derivatives with respect to temperature and concentrations.

Rule IV (Thermal equivalent dilution). The intensive variables, temperature T and dilution $\mathrm{d_A}=1/[\mathrm{A}]$, produce equivalent entropic changes

$$(\mathrm{d}S_\mathrm{A})_T=-R\mathrm{dln}\,[\mathrm{A}]\qquad(44)$$

$$(\mathrm{d}S_T)_\mathrm{A}=-C_\mathrm{p}\mathrm{dln}\,T\qquad(45)$$

and obvious analogous expressions for the microscopic molecular scale. If the dilution of A is kept constant but the temperature is changed, a virtual change of dilution or thermal equivalent dilution (TED) is effective

$$(\mathrm{d}S_\mathrm{A,virt})_T=(\mathrm{d}S_T)_\mathrm{A}\qquad(46)$$

Being the change of the temperature obtained by exchanging heat with the system, there is a correspondence between a change of energy and a change of entropy.

A demonstration is the following. By recalling Eq. (29) applied to n molecules of solute, one can write

$$\begin{aligned}-\Delta G/RT &= \ln\{\phi_0 N/(\phi_{\mathrm{m}} N n)\}\\ &= \ln(1/V_{\mathrm{m}})/(n/V_0) \qquad (47)\end{aligned}$$

where $V_{\mathrm{m}}{=}N\Lambda^3{\equiv}N(h^2/2\pi mkT)^{3/2}$ is the statistical average volume of one mole of ideal gas at any temperature. The free energy of mixing is equivalent to an entropy of mixing

$$\begin{aligned}\Delta S/R &= \ln\{(V_0/n)/(\phi_{\mathrm{m}} N)\}\\ &= \ln\{(1/N\Lambda^3)/[\mathrm{A}]\} \qquad (48)\end{aligned}$$

where 1/[A] has been substituted for (V_0/n). By taking the logarithm of $1/V_{\mathrm{m}}$, one obtains

$$\begin{aligned}\ln(N^{-1}\Lambda-3) &= \ln\{(h^2/2\pi mkN)^{-3/2}\}\\ &\quad+(3/2)\ln T \qquad (49)\end{aligned}$$

and then

$$\begin{aligned}\Delta S/R &= \ln\{(1/[\mathrm{A}])+\ln\{(h^2/2\pi mR)^{-3/2}\}\\ &\quad+(3/2)\ln T \qquad (50)\end{aligned}$$

which is the Sakur–Tetrode equation. By differentiating Eq. (50) and remembering that $C_{\mathrm{v,id}}{=}(3/2)R$ for an ideal gas, one obtains

$$\mathrm{d}(\Delta S)=R\,\mathrm{dln}\,(1/[\mathrm{A}])+C_{\mathrm{v,id}}\mathrm{dln}\,T \qquad (51)$$

At constant pressure, by considering that, in Eq. (48) dln V_0=dln T, one can write

$$\mathrm{d}(\Delta S)=R\{\mathrm{dln}\,(1/[\mathrm{A}])+(3/2+1)\mathrm{dln}\,T\} \qquad (52)$$

Then, by remembering that $C_{\mathrm{p}}{=}(5/2)R$ for an ideal gas, one obtains for real solution

$$\mathrm{d}(\Delta S)=R\,\mathrm{dln}\,(1/[\mathrm{A}])+C_{\mathrm{p}}\mathrm{dln}\,T \qquad (53)$$

which is the sum of the two changes of entropy in Eqs. (45) and (46), respectively.

A corollary to the Rule IV is that any enthalpy change can be associated to an equivalent change of dilution, but not vice versa.

1. Conclusions

An analysis of the statistical thermodynamics model for solutions has shown how the types of ensembles, namely *non-reacting* or *reacting* are consistent with the basic principles of statistical thermodynamics. The distinction into the two classes on the basis of absence or existence of separated enthalpy levels finds its correspondence in the different types of pair-potential functions in the element of the phase space. The rules given to build-up the whole thermodynamic model complete the framework into which the properties of the thermodynamic system can be properly understood in terms of molecular processes.

2. List of symbols

ρ	number density
$n(r)$	radial distribution function
$g(r)$	correlation function
$B(T)$, $C(T)$,...	coefficients of the virial equation
p	pressure
V	volume
N	large number
N_{L}	Avogadro number
$U(r)$	potential of mean force
$f(\rho)$	function of the number density ρ
β_1, β_2, ...β^{i}...	operational formation constants, β_{i}=[MA$_{\mathrm{i}}$]/([M][A]$^{\mathrm{i}}$)
β_1^0, β_2^0,...β_i^0	thermodynamic formation constants $\beta_i^0=\mathrm{a}_{\mathrm{MA}_i}/(\mathrm{a}_{\mathrm{M}}\mathrm{a}_{\mathrm{A}}^i)$
$x_1(r)$,$x_2(r)$...	integrals
$\Delta\eta$	enthalpy difference at molecular scale
ΔH	enthalpy difference at molar scale
Δg	free energy difference at molecular scale
Δs	entropy difference at molecular scale
ΔS	entropy difference at molar scale
ΔS_{H}	entropy equivalent of the reaction enthalpy $\Delta H/T$
k	specific site binding constant
M	receptor
A	ligand
a_{A}, a_{M}...	activity of A, M, etc.

d_A, d_M...	dilution of A, M, etc.
ε_{id}	energy difference at molecular scale in ideal gas
V_0	volume of solvent accessible by one mole
V_m	volume (virtual) of solvent accessible by bound moles
ϕ_0	volume of solvent accessible by one ideal molecule
ϕ_m	volume (virtual) of solvent accessible by bound molecules
Λ	De Broglie wavelength
h	Plank constant
m	molecular mass
z	molecular partition function
Z	molar partition function
Z_M	mean molar partition function or binding polynomial
z_M	mean molecular partition function
f_i	molecular fractions
x_i	molar fractions
C_v	isochoric molar heat capacity
TED	thermal equivalent dilution
η_0	enthalpy per molecule (ground level)
$r(T)$	average radius (function of T)
s_0	molecular entropy (ground level)
n	integer number
j	jth portion of ensemble
J	maximum j
l_j	index of cluster in jth portion
t_l	size of cluster l
$\Delta\mu$	chemical potential
i_t	maximum index i
λ	molecular momentum
$f(\eta)$	function of enthalpy
Z_c	configuration integral
e	base of natural logarithm
T	absolute temperature
k_B	Boltzmann constant
C_P	isobaric heat capacity
S	entropy
R	gas constant
H	enthalpy
ΔG	free energy difference at molar scale
α	reacted molar fraction
d	dilution

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Appendix A

Activity and activity coefficients

The thermodynamic cumulative formation constant β_i^0 of the species MA_i, which is a pure number, is expressed as the function of activities of the species

$$\beta_i^0 = a_{MA_i}/(a_M a_A^i) \tag{A.1}$$

where the activity of species A is related to the concentration [A] by the activity coefficient f_A

$$a_A = [A]f_A \tag{A.2}$$

the activity of species MA_i is related by the activity coefficient f_{MA_i}

$$a_{MA_i} = [MA_i]f_{MA_i}, \tag{A.3}$$

the activity of species M is related by the activity coefficient f_M

$$a_M = [M]f_M \tag{A.4}$$

where

$$f_M = \beta_0^0 \tag{A.5}$$

The relationship between the thermodynamic constant β_i^0 and the phenomenological coefficient β_i of Eq. (4) is given by

$$\beta_i = \beta_i^0 f_A^i \tag{A.6}$$

which by recalling Eq. (A.1) can be transformed into

$$\beta_i = (a_{MA_i}/a_M)(f_{MA_i}/f_M)/[A]^i \tag{A.7}$$

From Eq. (7), one can calculate that the dimensions of β_i are the same as those of concentration [A] raised to the power $-i$. For example, if the concentrations are expressed in mol dm^{-3}, then the cumulative constants β_i have dimensions $(mol\ dm^{-3})^{-i}=mol^{-i}\ dm^{3i}$ which are the dimensions of products of the solution volume associated to one mole of ligand. These are dimensions of the dilution which, in probability space, is directly proportional to the entropy probability factor.

If one assumes that

$$(f_{\mathrm{MA}i}/f_{\mathrm{M}}) \approx 1 \tag{A.8}$$

then the operational cumulative constant can be calculated

$$\beta_i \approx [\mathrm{MA}_i]/([\mathrm{M}][\mathrm{A}]^i) \tag{A.9}$$

For the sake of simplicity, we assume that the activity coefficient f_{A} is unitary and, thus, preserves the dimensionality of the constant.

Appendix B

Differentials of enthalpy

The differential of enthalpy H/R on the molar scale or the differential of molecular enthalpy η/k_{B} have different expressions in *reacting* and in *non-reacting* ensembles, respectively. We develop here the relationships for the molar ensembles. The transformation from molar to molecular relationships is obtained by division by N_{L}.

In an open reacting ensemble, the enthalpy change $-\Delta_{\mathrm{r}}H$ obtained from the van't Hoff equation as derivative of ln K with respect to $1/T$, is equal to an entropy change $T\Delta S_{\mathrm{H}}$. The entropy change $\Delta S_{\mathrm{H}}/R$ is obtained in the thermodynamics space [15,16] diagram as the orthogonal projection of $-\Delta_{\mathrm{r}}H/RT$ onto the entropy axis. The two quantities $\Delta S_{\mathrm{H}}/R$ and $-\Delta_{\mathrm{r}}H/RT$ are necessarily equal, by construction.

$$-\Delta^{\phi}_{rH} = T\Delta S_H \tag{B.1}$$

which can be differentiated

$$\mathrm{d}(-\Delta_r H^{\phi}) = T\mathrm{d}(\Delta S_H) \tag{B.2}$$

with partial derivative

$$\partial(-\Delta_r H^{\phi})/\partial(\Delta S_H) = T \tag{B.3}$$

The function ΔS_{H} is the projection onto the entropy axis of the thermodynamics space [15,16] of the reaction enthalpy. Alternatively, by considering that

$$-\Delta_r H^{\phi} = -\Delta_r G^{\phi} - T\Delta_r S^{\phi} \tag{B.4}$$

one obtains the differential

$$\mathrm{d}(-\Delta_r H^{\phi}) = \mathrm{d}(-\Delta_r G^{\phi} - T\Delta_r S^{\phi}) \tag{B.5}$$

with partial derivative

$$\partial(-\Delta_r G^{\phi})/\partial T = (-\Delta_r G^{\phi}/T) + (1/T) \times \partial(-\Delta_r G^{\phi}/T)/\partial(1/T) \tag{B.6}$$

which is related to the standard entropy by

$$\partial(-\Delta_r G^{\phi})/\partial T = \Delta_r S^{\phi} \tag{B.7}$$

Eq. (B.6) becomes the Gibbs–Helmholtz equation by considering that $\partial(-\Delta_{\mathrm{r}}G^{\Phi}/T)/\partial(1/T)=-\Delta_{\mathrm{r}}H^{\Phi}$

$$\partial(-\Delta_r G^{\phi})/\partial T = (-\Delta_r G^{\phi}/T) + (1/T)(-\Delta_r H^{\phi}) \tag{B.8}$$

The difference between ΔS_{H} and $\Delta_{\mathrm{r}}S^{\Phi}$ must be stressed upon. The difference is even more evident from further derivation

$$\partial(-\Delta_r H^{\phi})/\partial T = \Delta_r C_{\mathrm{p}} \tag{B.9}$$

and

$$\partial(\Delta S_H)/\partial \ln T = \Delta_r C_{\mathrm{p}} \tag{B.10}$$

For the reaction entropy, however, one has [18]

$$\partial(\Delta S/S)/\partial \ln T \equiv \partial\alpha/\partial \ln T = \Delta_r C_{\mathrm{p,app}}/R \tag{B.11}$$

with

$$\Delta_r C_{\mathrm{p,app}} = -\{\alpha(1-\alpha)(-\Delta_r H^{\phi}/T + C_{\mathrm{p,A}}\} \tag{B.12}$$

In closed *non-reacting* ensembles, the relationship between the differentials of enthalpy and entropy is

$$\mathrm{d}H = T\,\mathrm{d}S \tag{B.13}$$

where the enthalpy change is directly proportional to the entropy change with the absolute temperature T as the proportionality factor. This leads to the partial derivative

$$\partial H/\partial S = T \tag{B.14}$$

By further derivation with respect to the temperature, one obtains the isobaric heat capacity C_{p} either from entropy (Eq. (9)) or from enthalpy (Eq. (10)). On the other hand, a relationship like Eq. (B.12) does not exist for *non-reacting* systems.

The validity of Eq. (B.14) for all systems has been questioned by Weber [19,20] who puts forward some warning in the application of van't Hoff equation to all systems. While studying the interactions between protein subunits, he speaks of thermally activated motions, brought about by the increased probability of bond breakage with temperature. These thermally activated motions form a *non-reacting* subset in the biochemical system.

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