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Molecular thermodynamic model for equilibria in solution

III. Equilibrium constants and correlation functions in probability, thermodynamic, and kinetic energy space

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Abstract

The partition functions of solution thermodynamics at the macroscopic level of description correspond to typical distributions of particles at the microscopic molecular level. The partition functions can be represented in probability space which is the domain of formation constants, dilution, concentrations, probability correlation function, free-energy probability, enthalpy probability, and entropy probability. Types of ensembles, either *reacting* or *non-reacting*, yield characteristic probability diagrams. The first moment of the probability distribution belongs to thermodynamic space which is the domain of the extensive thermodynamic variables. The ratios of heat, free energy, enthalpy, entropy to thermal energy RT, as well as logarithm of activity coefficient, logarithm of probability correlation function, and logarithm of equilibrium constant can be measured in affinity thermodynamic space. The properties of the ensembles can be also represented in kinetic energy probability space which corresponds to the experimental domain of thermal dilutions, with variable $\{(1/[\mathrm{A}])^T\}$ and in kinetic energy thermodynamic space which is the domain of absolute free energy, enthalpy and entropy, of $-RT\ln[\mathrm{A}]$, and of heat and work. © 1998 Elsevier Science B.V.

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The molecular thermodynamic description of equilibria in solution is possible [1,2] with reference to ensembles of cells, which are classified as *reacting* or *non-reacting*. The *reacting* ensemble is characterized by the existence in the cells of at least one outstanding enthalpy level. This condition reduces the *reacting* ensemble to a discontinuous (=quantized) distribution of enthalpy. The distribution of enthalpy levels corresponds to average values of enthalpy difference at the macroscopic level. The *non-reacting* ensemble of cells is characterized by a continuous distribution of enthalpy levels centred around a mean enthalpy value. An experimental reacting mixture is represented on the whole by a *reacting* ensemble while each single component is by itself a *non-reacting* ensemble.

The distinction between *reacting* and *non-reacting* ensembles is made on the basis of the intrinsic properties of the ensembles and is at variance with the usual convention adopted in statistical mechanics, where the distinction between *canonical* and *grand canonical* ensembles is based on the external conditions (closed or open, respectively) and not on the internal properties. Actually, canonical partition functions are suited

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to the description of *non-reacting* ensembles and grand canonical partition functions for *reacting* ensembles. For this reason, we have sometimes [3–8] considered the *non-reacting* ensembles as canonical and the *reacting* ensembles as grand canonical.

The external conditions enter to limit the variability of the partition functions and to specify the peculiarities of the ensembles under given external conditions [1]. *Non-reacting* ensembles (*nre*) can be *microcanonical* (nre_{μ}), *osmotic* ($\mathrm{nre_o}$), thermal (nre_t), *thermo-osmotic* ($nre_{t,o}$). The *reacting* ensembles can be either *osmotic* (re_o), *thermal* (re_t), *thermo-osmotic* ($re_{t,o}$), *electrochemical* (re_e), *thermo-electrochemical* ($re_{t,e}$), *osmotic-electrochemical* ($re_{e,o}$), or *thermo-electrochemical-osmotic* ($re_{t,e,o}$) depending on the types of exchanges with the surroundings.

It has been shown [2] how partition functions used in molecular thermodynamic of solutions represent average values of the properties of the ensembles of cell, each cell representing a molecular description of the chemical process on the microscopic scale. This correspondence is exactly the same as that used in the description of the properties of ensembles in statistical mechanics. The same analogy existing at the microscopic level of description, can be found also at the macroscopic scale from the analogy of the functions employed to describe the macroscopic systems.

The conformity of the functions used in solution thermodynamic [1–18] to those of statistical mechanics can be demonstrated by formal functional representations in the probability space and in the affinity thermodynamics space. The capability of the correlation function of statistical mechanics [19] to be fitted in this framework and, in particular, the equivalence between entropy change and correlation function will be shown to be a fundamental link between solution thermodynamics [20] and classical statistical mechanics [21].

1. Probability space

The equation for a *reacting* ensemble (*re*) is:

$$\exp(-\Delta G/RT) = \exp(-\Delta H/RT)\exp(\Delta S/R) \tag{1}$$

can be represented in a diagram defining the probability space.

The free energy factor in a simple equilibrium is equal to the formation function k multiplied by the concentration of the ligand A

$$k[\mathrm{A}] = \exp(-\Delta G/RT) \tag{2}$$

where k is the affinity constant, specific for one binding site. At [A]=1, the standard energy change is obtained as $k{=}\exp(-\Delta G^{\phi}/RT)$. Alternatively, the free energy factor can be put equal to the formation partition function

$$\begin{aligned} Z_{\mathrm{M}} &\equiv 1+\beta_1[\mathrm{A}]+\beta_2[\mathrm{A}]^2+\cdots\beta_i[\mathrm{A}]^i+\cdots\beta_t[\mathrm{A}]^t \\ &= \exp(-\Delta G_f/RT) \end{aligned} \tag{3}$$

which is a measure of the probability of binding the ligand A to the receptor M with t sites. The β_i's are the cumulative formation constants for the $\beta_i{=}[\mathrm{MA}_i]([\mathrm{M}][\mathrm{A}]^i)$ (see Eq. (23)).

The probability space (Fig. 1) can be better represented by displacing the origin of the representative vectors to the point $P(x,y){=}(1,1)$ which corresponds to the equilibrium state $((-\Delta G/RT){=}0)$. The abscissa is the entropy probability axis, $x(\exp(-\Delta S/R)$ and the ordinate is the enthalpy probability axis, $y(\exp(-\Delta H/RT)$. A third auxiliary coplanar axis, $z^{*}(\exp(-\Delta G/RT)$ is taken along the bisector of the angle between x and y. The asterisk indicates that, because of the geometry of the axes, the actual length along $z^{*}{=}\exp(-\Delta G/RT)$ is related to the values on x or y by hyperbolic projection $(2\exp(-\Delta G/RT))^{1/2}{=}(2xy)^{1/2}$.

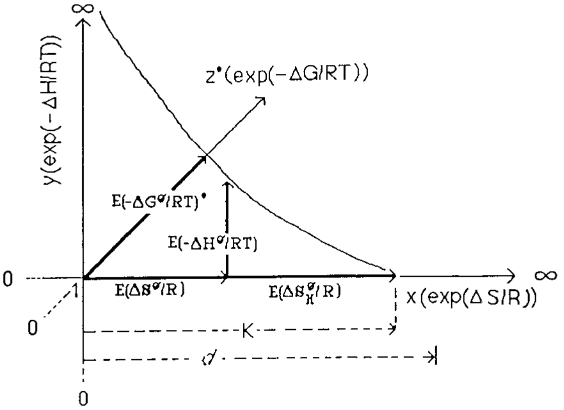

Fig. 1. Probability space: *reacting* ensemble (*re*): exothermic, exoergonic reaction. $E(-\Delta G/RT)$, $E(-\Delta H/RT)$, etc. stand for exp $(-\Delta G/RT)$, exp $(-\Delta H/RT)$, etc., respectively, for the sake of brevity.

Eq. (1) is represented in the diagram by a family of hyperbolas, each of which corresponds to a constant value $z^*=\exp(-\Delta G/RT)$. Among the hyperbolas, by determining the equilibrium constant k or K, one chooses that hyperbola with coordinate $z^*=k$ or K pertaining to the reaction. Thus, one finds the standard value $\exp(-\Delta G^{\phi}/RT)$ on the diagram. Along the hyperbola of constant value $\exp(-\Delta G^{\phi}/RT)$, the point corresponding to the actual reaction can be found if the enthalpy component $\exp(-\Delta H/RT)$ is determined and, consequently, the standard entropy factor, $\exp(\Delta S^{\phi}/R)$, is fixed. The components $\exp(-\Delta H/RT)$ and $\exp(\Delta S^{\phi}/R)$ projected hyperbolically by rotation around the point $P(x,y)=(1,1)$ onto z^* axis, yields $\exp(-\Delta G^{\phi}/RT)$. The enthalpy factor, $\exp(-\Delta H/RT)$, projected hyperbolically by rotation around the point $P(x,y)=(1,1)$ onto the x axis produces the entropy component $\exp(\Delta S_{(H)}/R)$ which is measured along the entropy axis, but is exactly equal to the hyperbolic projection of the enthalpy factor, $\exp(-\Delta H/RT)$. It is clear that, if the temperature is changed, the enthalpy factor is changes proportionally to $-\Delta H/R$, but at the same time both free energy, $\exp(-\Delta G^{\phi}/RT)$, and entropy, $\exp(\Delta S_{(H)}/R)$, probability components change by the same amount, by construction.

The probability space is well suited to represent the behaviour of the different ensembles.

The *osmotic non-reacting* ensemble (nre_o) also belongs to the probability space (Fig. 2). In fact, one can write

$$\exp(-\delta\mu_{\mathrm{A}}/RT) \equiv \exp(\delta s_{\mathrm{A}}([\mathrm{A}])/R) = [\mathrm{A}]^{-1} \tag{4}$$

where $\delta\mu_{\mathrm{A}}=\mu_{\mathrm{A}}-\mu_{\mathrm{A},0}$ and dilution, $[\mathrm{A}]^{-1}$, is proportional to the partition, Γ_{A} (i.e. to the probability of state). The symbol 'δ' is used for a finite change of the function in *nre*, instead of Δ. The capital is maintained to design the change of a function in a *reacting* ensemble. In the standard state, [A]=1 for $\mu_A=\mu_{A,0}$

$$\exp(-\Delta\mu/RT) \equiv [\mathrm{A}]^{-1} = 1 \tag{5}$$

The *thermal non-reacting* ensemble (nre_t) is also representable in the probability space (Fig. 3). The *non-reacting* ensemble refers to a pure compound and its chemical potential is in the reference state and,

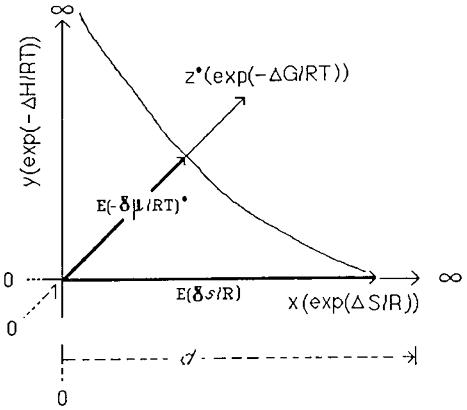

Fig. 2. Probability space: *osmotic non-reacting* ensemble (nre_o). $E(-\delta\mu/RT)$, $E(\delta s/R)$, etc. stand for $\exp(-\delta\mu/RT)$, $\exp(\delta s/R)$, etc., respectively, for the sake of brevity.

thus, the following equality holds

$$\exp(-\delta\mu/RT) \equiv \exp(-\delta h/RT)\exp(\delta s(T)/R) = 1 \tag{6}$$

where $\delta s(T)$ indicates the dependence of entropy on the temperature. Eq. (6) shows how the enthalpy and entropy probability factors are equal

$$\exp(\delta h/RT) = \exp(\delta s(T)/R) \tag{7}$$

as shown in Fig. 3.

The *thermo-osmotic non-reacting* ensemble ($nre_{\mathrm{t,o}}$) is obtained (Fig. 4) by combining the properties of the component ensembles, by introducing the dependence of entropy on both, dilution and temperature. The resulting probability is again proportional to the

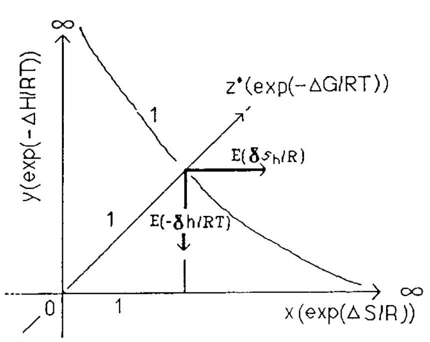

Fig. 3. Probability space: *thermal non-reacting* (nre_t) ensemble $E(-\delta h/RT)$, $E(\delta s_h/R)$, etc. stand for $\exp(-\delta h/RT)$, $\exp(\delta s_h/R)$, etc., respectively, for the sake of brevity.

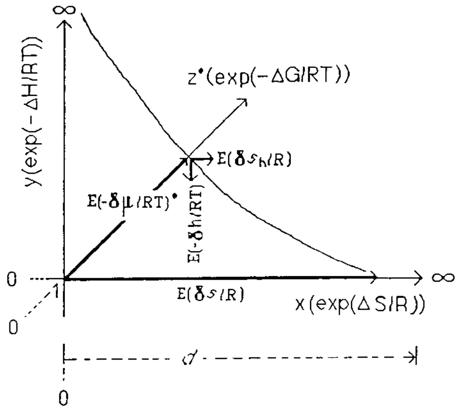

Fig. 4. Probability space: *thermo-osmotic non-reacting* ensemble ($nre_{t,o}$) $E(-\delta\mu/RT)$, $E(\delta s_h/R)$, etc. stand for $\exp(-\delta\mu/RT)$, $\exp(\delta s_h/R)$, etc., respectively, for the sake of brevity.

dilution

$$\exp(-\delta\mu/RT) \equiv \exp(-\delta h/RT) \times \exp(\delta s([\mathrm{A}],T)/R) = [\mathrm{A}]^{-1} \tag{8}$$

and can be represented in the probability diagram.

The representation of the properties of the *reacting* ensemble in the probability space has been shown previously in Fig. 1. In particular, in the standard state, the probability is proportional to the equilibrium constant k

$$k = \exp(-\Delta G^{\phi}/RT) \equiv \exp(-\Delta H^{\phi}/RT)\exp(\Delta S^{\phi}/R) \tag{9}$$

By hyperbolical projection on to a line parallel to the x axis (under the imposed condition $\exp(-\Delta H/RT)=1$), the equilibrium constant probability equals the total entropy probability factor

$$k = \exp(\Delta S^{\phi}_{\mathrm{tot}}/R) \equiv [\mathrm{A}]^{-1} \tag{10}$$

which can be experimentally evaluated through dilution determinations. The domains of Z_{M}, k, and dilution, $d_{\mathrm{A}}=[\mathrm{A}]^{-1}$ belong to the probability space.

2. Probability space and correlation function

The conformity of the partition functions of solution thermodynamics to classical statistical mechanics can be demonstrated by showing the relationship in the probability space representation between partition function (or its component probability factors) and correlation function.

The correlation function, $g(r)$ gives the number of particle configurations in a spherical cell of thickness $d(r)$. It is related to the radial distribution function, $dn(r)$ [20] by

$$dn(r) = \rho g(r) 4\pi r^2 dr \tag{11}$$

where ρ is the number density.

The number of particle configurations in the volume element $4\pi r^2 dr$ or radial distribution function in a *non-reacting* ensemble due to the correlation function $g(r)$ is given by Eq. (11) and the excess number of particle configurations in the volume element $4\pi r^2 dr$ is given by

$$dn(r)_{\mathrm{exc}} = \rho[g(r) - 1]4\pi r^2 dr \tag{12}$$

where $h(r)=g(r)-1$ is defined as the total correlation function.

In *non-reacting* ensembles, the correlation function assumes the form

$$g(r) = \exp(-U(r)/kT)f(\rho) \tag{13}$$

where $U(r)$ is the potential of mean force between one particle and the surroundings, and $f(\rho)=(1+\rho x_1(r)+\rho^2 x_2(r)+\cdots)$. The functions $x_1(r), x_2(r), \ldots$ are integrals that must be approximated. The main methods of approximation have been proposed by Yvon [22] and, independently, by Born and Green [23] and by Kirkwood [24]. We note that the function $f(\rho)$ can be compared with the partition function of Eq. (2) for a system containing a receptor with $i=t$ non-cooperative sites. The functions $x_1(r), x_2(r), \ldots, x_t(r)$ are, apparently, analogous to the cumulative formation constants β_i. The difference is that the constants β_i in *reacting* ensembles correspond to different quantized enthalpy levels, whereas the functions $x_t(r)$ indicate discontinuities in the concentration distributions, thus giving rise to quantization of the entropy. The discontinuities of probability can be represented at the molecular level of description by sets of cells where the concentrations are changing periodically in space (Fig. 5). The probability correlation function $g_{\mathrm{P}}(r)= g(r)^{(1/N)}$ is a (geometric) mean correlation function and can be represented on the x-axis of the probability space (Fig. 6), where the origin is taken at 0. In the same diagram, the probability total correlation function (i.e. mean total correlation function) $h_{\mathrm{P}}(r)=$

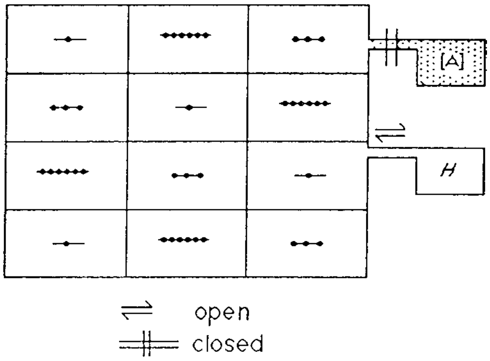

Fig. 5. Discrete (quantized) entropy distribution. [A] is a substance reservoire (closed), and H a heat reservoire (open).

($g_P(r)-1$) can be also represented by a vector starting from the point $P(x,y)=(1,1)$.

Association of discontinuities of energy can be accounted for in the probability correlation function $g_P(r)$. The three factors of Eq. (13) can be assimilated to probability functions. Specifically, a partition function $Z=g_P(r)$, or mean total entropy change, can be substituted for the correlation function $g(r)$:

$$g_P(r) = Z \equiv \exp(-\Delta F/RT) \tag{14}$$

a probability of change of internal energy, ΔE can be substituted for the potential energy $-U(r)/kT$

$$\exp(-U(r)/kT) \rightarrow \exp(-\Delta E/RT) \tag{15}$$

due to the difference in internal energy between two binary potential curves and a dilution function $Y(r)$ or mean entropy change probability assimilated to the density function $f(\rho)$:

$$(1 + \rho x_1(r) + \rho^2 x_2(r) + \cdots)^{(1/N_L)} = Y(r) \rightarrow \exp(\Delta S/R) \tag{16}$$

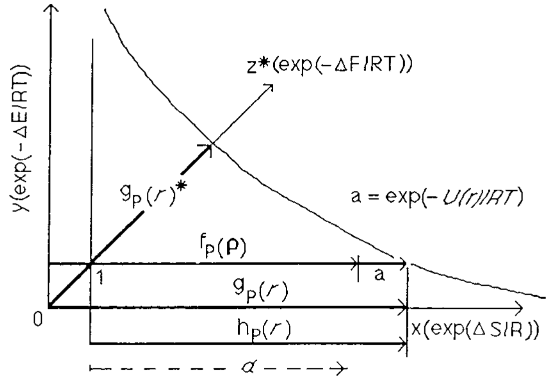

Fig. 6. Probability space mean correlation function (*non-reacting*) $g_P(r)$: $f_P(\rho) = (1 + \rho x_1 + \rho^2 x_2 + \cdots)^{(1/N_{N_L})}$, a=exp~($-U(r)/RT$), $h_P(r)=g_P(r)-1$=mean total correlation function. Quantities with asterisks are in units of the auxiliary coplanar axis z^*: $g_P(r)$ is the hyperbolic projection of $g_P(r)^*$ onto a parallel to x axis at $y=1$.

Thus, the properties of the *reaction* mean correlation function $g_P(r)$ of Eq. (14) can be expressed in terms of thermodynamic probability factors

$$\exp(-\Delta F/RT) = \exp(-\Delta E/RT)\exp(\Delta S/R) \tag{17}$$

and be represented in the probability space diagram as a *reacting* ensemble.

In a *reacting* ensemble, Z is a dilution function because it is proportional to the total dilution of the receptor (with $t=1$, $Z \equiv Z_M = [M]^{-1}/([M]+[MA])^{-1}$). For $t=1$, the levels are two, namely the ground level 0 and the first level 1. Therefore, the total number of particles in the volume element $4\pi r^2 dr$ or level distribution function in a *reacting* ensemble can be calculated in analogy with Eq. (11) as

$$dn(r)_{tot} = \rho Z 4\pi r^2 dr \tag{18}$$

The total excess number of particles in the volume element $4\pi r^2 dr$ can be calculated by

$$dn(r)_{ex,tot} \equiv \rho[Z-1]4\pi r^2 dr = \rho[f_P(r)]4\pi r^2 dr \tag{19}$$

where $f_P(r)=k$ is the total saturation function in *reacting* ensembles or $f_P(r) = (f_{1,2}(r))^{(1/N_L)}$ is the N_L-th root of the Mayer function [21] in *non-reacting* ensembles.

The analogies and differences of distributions and functions typical of statistical mechanics of gases with quantities encountered in chemically *reacting* or *non-reacting* systems at equilibrium can be shown by considering that the reaction partition function Z is identical with the partition function for chemical equilibrium Z_M, referred to the receptor M and depending on the concentration of free ligand [A]. For one single site ($t=1$), this is

$$Z_M = 1 + k[A] = 1 + \rho f(r) \tag{20}$$

The partition function Z_M is actually an association or a formation partition function. It is a measure of the probability of binding the ligand A to form the complex MA under different concentration [A] (or activity) of free A. The probability of binding exp($-\Delta G_f$/RT) as the function of the site affinity constant k can be compared with the probability exp($-\Delta G_d$/RT) of dissociating A from MA as the function of (1/k). The comparison is given by the ratio (probability of binding)/(probability of dissociating) as follows:

$$\exp(-\Delta G_{\mathrm{sat}}/RT) = \exp(-\Delta G_{\mathrm{f}}/RT)/\exp(-\Delta G_{\mathrm{d}}/RT) \qquad (21)$$

which is calculated [10] as

$$\exp(-\Delta G_{\mathrm{sat}}/RT) = k[\mathrm{A}] \qquad (22)$$

where k is the saturation function identical with that of Eq. (2). The formation constant k refers to a *reacting* system and the Mayer function (i.e. entropy change only) to a *non-reacting* one.

When more sites are involved (class of identical interacting sites with t>1), the *reaction* partition function is expressed by

$$Z_{\mathrm{M}} \equiv (1 + k\gamma(i)[\mathrm{A}])^t = 1 + \sum m_i(k\gamma(i)[\mathrm{A}])^i \qquad (23)$$

where the summation is from i=1 to i=t, m_i is a multiplicity coefficient, and $\gamma(i)$ an appropriate cooperativity function between sites. The coefficients of the single terms of the polynomial of Eq. (23) correspond to the cumulative constants β_i of Eq. (3), which are experimentally determined by the fitting of the experimental data.

Z_{M} can be represented as a vector $\mathbf{J}_i$. If there are more classes of sites, the partition function can be represented as a tensor product $[\mathbf{J}_i]\cdot\{\mathbf{J}_j\}$ [6,7]. In case of self association, the function Z_{M} can be obtained as the tensor product $[\mathbf{J}_i]\cdot\{\mathbf{J}_j\}$, where $[\mathbf{J}_i]$ represents the probability of binding A to M, and $\{\mathbf{J}_j\}$ represents the binding of clusters of receptors M_j bound to M.

The correlation function for *non-reacting* ensembles takes a special form in very diluted gases or in very diluted solutions

$$\lim_{[\mathrm{A}]\to 0} \{g(r)/Z\} = \exp(-U_{1,2}(r)/k_{\mathrm{B}}T) \qquad (24)$$

where $U_{1,2}(r)$ is the pair potential between two particles. The entropy factor only depends on the configuration integral. It corresponds to the Ornstein–Zernike equation [25] solved by Percus–Yevick [26,27] first approximation.

Table 1
Probability space (Domains)

Probability	Symbol
Partition function	Z_{M}
Equilibrium constant	K (or k or β)
Concentration (number density)	[A]
Activity	a_{A}
Dilution	d_{A}
Probability correlation function	$g_{\mathrm{P}}(r)$
Probability total correlation function	$h_{\mathrm{P}}(r)$
Pressure	P
Temperature	T
Enthalpy probability	exp($-\Delta H$/RT)
Entropy probability	exp(ΔS/R)
Joint probability	exp(ΔG/R)
Binding probability	exp($-\Delta G_{\mathrm{f}}$/RT)
Dissociation probability	exp($-\Delta G_{\mathrm{d}}$/RT)
Saturation probability	exp($-\Delta G_{\mathrm{sat}}$/RT)
Experimental methods	
Spectrophotometry	
Volumetric analysis	

The probability space is representative of every domain whose units are proportional to probabilities (Table 1).

3. Thermodynamic space

The differential of Eq. (1) can be calculated

$$\mathrm{d}\{\exp(-\Delta G/RT)\} = \mathrm{d}\{\exp(-\Delta H/RT)\} \times \exp(\Delta S/R) + \mathrm{d}\{\exp(\Delta S/R)\} \times \exp(-\Delta H/RT) \qquad (25)$$

and then divided by exp($-\Delta G$/RT) in order to obtain the relative change of probability

$$\mathrm{d}\{\exp(-\Delta G/RT)\}/\exp(-\Delta G/RT) = \mathrm{d}\{\exp(-\Delta H/RT)\}/\exp(-\Delta H/RT) + \mathrm{d}\{\exp(\Delta S/R)\}/\exp(\Delta S/R) \qquad (26)$$

This equation yields

$$\mathrm{dln}\{\exp(-\Delta G/RT\} = \mathrm{dln}\{\exp(-\Delta H/RT)\} + \mathrm{dln}\{\exp(\Delta S/R)\} \qquad (27)$$

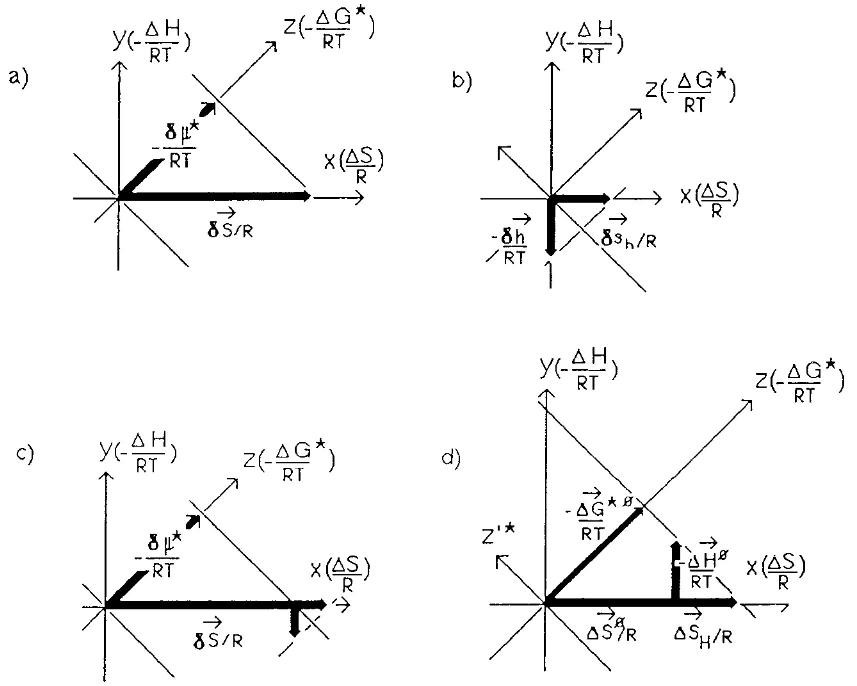

Fig. 7. Representation of (a) *osmotic non-reacting* (nre_o), (b) *thermal non-reacting* (nre_t), (c) *thermo-osmotic non-reacting* ($nre_{t,o}$), and (d) *reacting* (*re*) ensembles in affinity thermodynamic space.

and, therefore,

$$d(-\Delta G/RT) = d(-\Delta H/RT) + d(\Delta S/R) \tag{28}$$

Thus, the general relation between probabilities of Eq. (1) can be transformed into the thermodynamic relation between the exponents. The terms of the general thermodynamic relation

$$-\Delta G/RT = -\Delta H/RT + \Delta S/R \tag{29}$$

are the first moments of the probability distribution.

If these quantities are considered as vectors, they can be represented in a plane (Fig. 7). The abscissa represents the entropy and $x(\Delta S/R)$, the ordinate the enthalpy, $y(-\Delta H/RT)$. A third auxiliary coplanar axis $z^*(-\Delta G/RT)$, bisecting the other two, is used to represent the joined probability (i.e. free energy). The asterisk indicates that any vector or composition of vectors on either x or y axis can be projected onto the z^* coplanar axis on multiplication by 0.707= cos 45°. This axis system defines the affinity thermodynamic space (or plane).

The relations between enthalpy, entropy and free energy of non-reacting and reacting ensembles, respectively, can be represented in this space.

The *osmotic non-reacting* ensemble, nre_o (Fig. 7(a)) depends on the dilution alone. The change observed is along the abscissa (or entropy). Projection onto the z^* axis yields the chemical potential of the solute A.

The *thermal non-reacting* ensemble, nre_t (Fig. 7(b)) shows how the enthalpy and entropy components along the x- and y-axes, respectively, are equal. The vector composition drawn in the diagram corresponds to heating the system. An analogous combination of reversed vectors indicates the cooling of the solution.

The *thermo-osmotic non-reacting* ensemble, $nre_{t,o}$ (Fig. 7(c)) is the combination of the properties of nre_o (dependence on dilution) with those of nre_t (dependence on temperature).

The *reacting* ensemble, *re* (Fig. 7(d)) shows how the free-energy vector can be projected onto the x-axis. This corresponds to the determination of the standard free energy from the equilibrium constant. The equilibrium constant is a completely entropic function. In

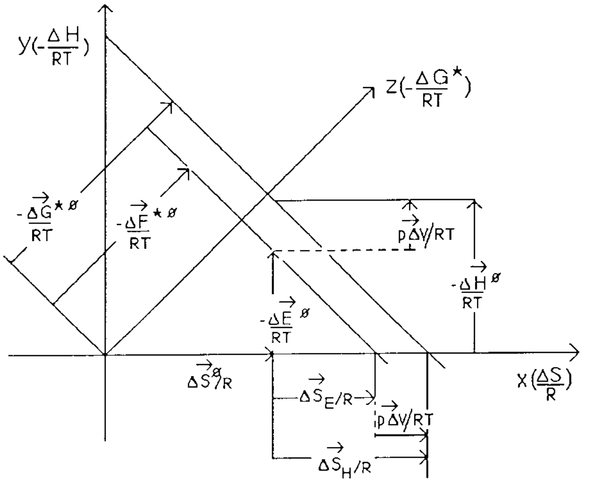

Fig. 8. Relationship between Gibbs and Helmohltz free energy in affinity thermodynamic space.

fact, it is a ratio of experimentally determined dilutions. The total entropy, corresponding to free energy, $\Delta S_{\rm tot}/R$, is comprehensive of an intrinsic standard entropy component, $\Delta S^{\phi}/R$ and of an entropy component, $\Delta S_H/R$ corresponding exactly to the enthalpy change, $\Delta H^{\phi}/RT$. The equivalence is shown geometrically in the affinity thermodynamic diagram. The equivalence of enthalpy and entropy is the fundamental relation on which the differential van't Hoff equation is based. Any change in $\Delta H^{\phi}/RT$, obtained by changing T, is paralleled by an equal change in $\Delta S_H/R$ and a proportional displacement of $\Delta G^{\phi}/RT$.

The affinity thermodynamic space is also suited to the demonstration of the relationship between Helmohltz free energy, ΔF, and Gibbs free energy, ΔG, and between the internal energy, E, and enthalpy, H (Fig. 8). Substitution of enthalpy, $\Delta H^{\phi}/RT$ for energy, $\Delta E^{\phi}/RT$ in the characterization of the levels is justified by the equivalence between entropy and enthalpy and between entropy and energy, respectively. The term $P\Delta V/RT$ at constant P can be summed up to $\Delta E_i/RT$ without any loss of generality. The entropy (equivalent to ΔE) component, $\Delta S_E/R$ is increased by the compressibility coefficient, $P\Delta V/RT$ to give the entropy equivalent, $\Delta S_H/R$ in the same amount as the energy term, $\Delta E^{\phi}/RT$ is increased to give the enthalpy term $\Delta H^{\phi}/RT$. The compressibility term is constant for ideal gases and rather small in solution. Corrections for its variability must be introduced for real solutions at different temperatures. In the model, we consider that this term is constant, for the sake of simplicity.

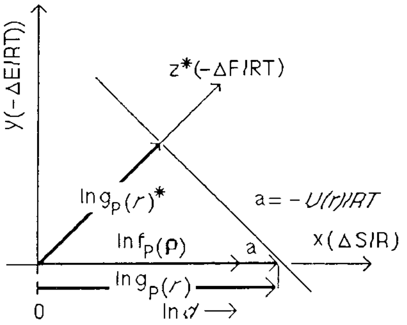

Fig. 9. The logarithm of the *non-reacting* mean correlation function, $g_{\rm P}(r)$ and its components in the affinity thermodynamic space. $f_{\rm P}(\rho)=(1+\rho x_1+\rho^2 x_2+\cdots)^{(1/N_{\rm L})}$, a=exp$(-U(r)/RT)$, Quantities with asterisks are in units of the auxiliary coplanar axis z^*: ln $g_{\rm P}(r)^*$ being the orthogonal projection of ln $g_{\rm P}(r)$ onto z^*.

The affinity thermodynamic space is also suited to describe the properties of the mean correlation function. By taking the logarithms of Eqs. (14)–(16)

$$\ln g_{\rm P}(r) = -\,U(r)/RT + \ln\,(1+\rho x_1(r) + \rho^2 x_2(r) + \cdots)^{1/N_{\rm L}} \qquad (30)$$

one obtains the first moments of the probability distributions that can be represented in the affinity thermodynamic diagram as a *non-reacting* ensemble (Fig. 9).

The thermodynamic space is, in general, suited to represent the properties of all those domains whose units are proportional to energies and logarithms of probabilities either relative to *thermal energy*, *RT*, or in absolute units (Table 2).

4. Relationships between probability and thermodynamic space

The probability space and the thermodynamic space are related to one another by means of hyperbolic functions. In fact, the binding of A to form a complex MA is given by the exponential

$$k[\mathrm{A}] = \exp(-i\Delta G/RT) \qquad (31)$$

where k is the affinity constant specific for one binding site, $\Delta G/RT$ is the free energy of formation of a complex MA, and $-i=\sqrt{-1}$. By recalling the

Table 2
Thermodynamic space (domains)

	Relative to thermal energy/(number)	Absolute energy [a]/(J/mol)
logarithm of partition function	$\ln Z_M$	$RT \ln Z_M$
logarithm of equilibrium const	$\ln K$	$RT \ln K$
logarithm of dilution	$\ln d_A$	$RT \ln d_A$
logarithm of concentration	$\ln[A]$	$-RT \ln[A]$
logarithm of activity	$\ln a_A$	$-RT \ln a_A$
Chemical potential	$\mu/RT = \ln a_A$	$\mu = RT \ln a_A$
Free energy (Gibbs/Helmholtz)	$-\Delta G/RT$	$-\Delta G$
Affinity	$\Delta A/RT$	ΔA
Enthalpy	$-\Delta H/RT$	$-\Delta H$
Heat	Q/RT	Q
Work (mechanical)	$P\Delta V/RT$	$P\Delta V$
Work (chemical)	$\ln[A]$	$-RT \ln[A]$
emf times Faraday const	$nFE/(RT)$	nFE
Entropy	S/R	TS
Formation function	$\bar{n}$	$RT\bar{n}$
Mole fraction	α	$RT\alpha$
Thermal dilution	$(C_p/R)\mathrm{d}\ln T$	$C_p\mathrm{d}T$
Experimental methods		
Potentiometry		
Calorimetry		

[a] For relations between affinity (relative) and kinetic energy (absolute) thermodynamic space, see Eqs. (48)–(55).

relation between exponentials and hyperbolic functions

$$\exp(-ix) = \cosh x - i \sinh x \tag{32}$$

and by putting $x = (\Delta G/RT)$, the Eq. (31) becomes

$$k[\mathrm{A}] = \cosh(\Delta G/RT) - i \sinh(\Delta G/RT) \tag{33}$$

Therefore, the free energy change, $\Delta G/RT$, of the thermodynamic space is the argument (angle) of the hyperbolic function whose transform in the probability space is k[A], the product of the affinity constant specific for one binding site times the concentration of the ligand. Analogous relationships can be found for enthalpy and entropy factors, by substituting $x = (\Delta H/RT)$ in the Eq. (32)

$$\exp(-i\Delta H/RT) = \cosh(\Delta H/RT) - i \sinh(\Delta H/RT) \tag{34}$$

and by substituting $x = (\Delta S/R)$ in the Eq. (32)

$$\exp(i\Delta S/R) = \cosh(-\Delta S/R) - i \sinh(-\Delta S/R) \tag{35}$$

respectively. By multiplying the Eq. (34) by Eq. (35) and on rearranging the RHS, the following equality can be obtained

$$\begin{aligned}\exp(-i\Delta H/RT)\exp(i\Delta S/R) &= \cosh((\Delta H/RT) - (\Delta S/R) \\ &\quad - i\sinh((\Delta H/RT) - (\Delta S/R))\end{aligned} \tag{36}$$

which by comparison with Eq. (33) shows how the argument $\Delta G/RT$ is the difference

$$(\Delta G/RT) = (\Delta H/RT) - (\Delta S/R) \tag{37}$$

between two argument $\Delta H/RT$ and $\Delta S/R$, respectively.

Another relationship can be obtained by recalling that

$$\tanh x = (1 - 2x)/(1 + 2x) \tag{38}$$

and by putting

$$\exp(-2x) = k[\mathrm{A}] \tag{39}$$

One obtains that the molar fraction

$$\alpha_1 = k[\mathrm{A}]/(1 + k[\mathrm{A}]) \tag{40}$$

becomes

$$\alpha_1 = \exp(-2x)/(1+\exp(-2x)) \tag{41}$$

and the molar fraction of free receptor becomes

$$\alpha_0 = 1/(1+\exp(-2x)) \tag{42}$$

Thus, the foregoing expressions are related to Eq. (38) by

$$-\tanh x = \alpha_1 - \alpha_0 \tag{43}$$

Therefore, by putting $x=(1/2)(\Delta G/RT)$ from Eqs. (41)–(43), one obtains the molar fraction expressed as hyperbolic function whose argument is the free energy of formation of the thermodynamic space

$$\alpha_1 = 1/2 - (1/2)\tanh(\Delta G/RT) \tag{44}$$

which is the well-known logistic formula.

In one considers that the free energy of the reaction can be obtained as

$$-\Delta G^{\phi}/RT = \int_0^1 \ln[\mathrm{A}]\mathrm{d}\alpha_1 \tag{45}$$

the differential of Eq. (44) can be substituted for $\mathrm{d}\alpha_1$ in Eq. (45), thus, giving

$$-\Delta G^{\phi} = RT\int_0^1 \ln[\mathrm{A}]\{-2\tanh(\Delta G/RT)\} \tag{46}$$

The analytical expressions of probability and thermodynamic space by means of hyperbolic functions confirms the relationships shown in the diagrams. The former, however, come out to be much less manageable than the diagrammatic representations.

5. Kinetic energy space

We can also analyse the effect of raising a probability factor to the power T (absolute temperature).

By assuming, in the probability space, a reaction partition function Z_M

$$Z_\mathrm{M} = (1+\kappa[\mathrm{A}])^t \equiv \exp(-\Delta G/RT) \tag{47}$$

for a receptor M with t binding sites, we obtain the power

$$(Z_\mathrm{M})^T = (a+\kappa[\mathrm{A}])^{tT} \equiv \exp(-\Delta G/R) \tag{48}$$

and, hence,

$$\begin{aligned}\exp(-\Delta G/R) &\equiv (1+\kappa[A])^{tT}\\ &= \exp(-\Delta H/R)\exp(T\Delta S/R)\end{aligned} \tag{49}$$

By recalling that the dilution of the ligand upon binding is proportional to the number of sites, we can conclude that the raising of the partition function to the power T (the absolute temperature) is equivalent to raising the number of sites of the receptor to the power T and, hence, to dilute the solution T orders of magnitude (Fig. 10).

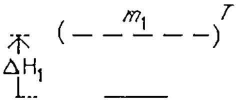

Fig. 10. Effect of the temperature on the multiplicity of sites in kinetic energy space.

This raising to a power transforms the probability space into the kinetic energy probability space. The experimental domain corresponding to this space is that of thermal dilutions $(\exp(T\Delta S/R))\rightarrow 1/[\mathrm{A}]^T$. The kinetic energy probability space conforms to a different kind of molecular mechanism. In fact, whereas in the probability space every change of temperature is associated to a change of populations of the levels, in the kinetic energy space every change of temperature produces a change of multiplicity or dilution of the levels. The representation of this space is on a plane where the axes are $x(\exp(T\ \Delta S/R))$, $y(\exp(-\mathrm{i}\Delta H/R))$ with z^* $(\exp(-\mathrm{i}\Delta G/R))$ as the coplanar axis.

In the hyperbolic representation in the imaginary plane of the kinetic energy probability space, we can write, from Eq. (49) by introducing $-\mathrm{i}=\sqrt{-1}$, the following:

$$\exp(-\mathrm{i}\Delta G/R) = \cosh(\Delta G/R) - \mathrm{i}\sinh(\Delta G/R) \tag{50}$$

By substituting Eq. (49) into Eq. (50), and recalling Eqs. (34)–(36), we can transform the free energy probability into the product of two factors

$$\exp(-i\Delta G/R) = \{\cosh(\Delta H/R) - i\sinh(\Delta H/R)\}\{\cosh(T\Delta S/R) - i\sinh(T\Delta S/R)\} \tag{51}$$

where

$$\exp(-i\Delta H/R) = \{\cosh(\Delta H/R) - i\sinh(\Delta H/R)\} \tag{52}$$

is the potential energy probability factor and

$$\exp(-iT\Delta S/R) = \{\cosh(T\Delta S/R) + i\sinh(T\Delta S/R)\} \tag{53}$$

is the kinetic-energy probability factor.

The kinetic-energy probability space can be transformed into the kinetic energy thermodynamic space

$$\Delta G/R = (-\Delta H/R) + (T\Delta S/R) \tag{54}$$

From Eq. (54), by assuming that we are dealing with molar thermodynamic quantities, one obtains

$$-\Delta G = -\Delta H + T\Delta S \tag{55}$$

which is the usual thermodynamic definition of free energy.

The potential-energy factor of the kinetic-energy probability space depends on the argument of the kinetic-energy thermodynamic space

The kinetic-energy probability space can be transformed into the kinetic energy thermodynamic

$$\omega_{\mathrm{H}} = -\Delta H/R \tag{56}$$

the kinetic-energy probability factor depends on the argument

$$\omega_{\mathrm{S}} = T\Delta S/R \tag{57}$$

and the joint probability factor depends on the argument

$$\omega_{\mathrm{G}} = \omega_{\mathrm{H}} - \omega_{\mathrm{S}} \equiv -\Delta G/R \tag{58}$$

thus, showing that the factorability of the probability space corresponds to the separability of the arguments in the kinetic-energy thermodynamic space as shown in the general Eq. (55). In analogy with the relationship between $\Delta S_{\mathrm{H}}/R$ and $\Delta H^{\phi}/RT$, even the argument ω_{H} has an entropic counterpart

$$\omega_{\mathrm{H}} = -\omega_{\mathrm{SH}} \tag{59}$$

The analytical expressions of kinetic-energy thermodynamic space of hyperbolic functions confirms to be much less manageable than usual probability and thermodynamic functions with corresponding diagramatic representations.

In order to illustrate the relationship between kinetic-energy probability functions and the experimental domain in a *non-reacting* ensemble (*nre*), we can consider an example given by a solution containing free hydrogen ions in concentration [H^+]. By determining the electromotive force of such a solution against a hydrogen electrode, the following equality holds.

$$\exp\{(E - E_0)/RT\} = [\mathrm{H}^+] \tag{60}$$

where the solution is assumed to be at constant activity coefficient. Raising both sides of Eq. (60) to the power *T* yields

$$(\exp\{(F(E - E_0)/R)\} = [\mathrm{H}^+]^T \tag{61}$$

where the ‘active thermal concentration’ of the RHS is dramatically changed under constant emf, ($E-E_0$). For instance, if the solution is 10^{-2} M, then the active concentration becomes 10^{-2} M, an extremely diluted solution at T=300 K with a very high entropy content. On the other hand, the ratio F/R in Eq. (61) guarantees that the amount of electric charge transferred in the electric circuit (96498 Coulomb=$N_{\mathrm{L}}\times 1.6\times$ $10-19$ Coulomb) is paralleled by a transfer of one mole of ions (N_{L}=6.02×10^{23} ions) throughout the electrolytic portion of the chain under constant potential difference ($E-E_0$).

6. Solute activity and role of the solvent

The dilution of a compound has been expressed so far in these papers by means of concentration or number density, [A] and [M], thus assuming an ideal behaviour of the ligand or receptor, typical of a microcanonical ensemble. The interaction with the solvent, however, implies an interaction energy even in a microcanonical ensemble, where the binding is not expressed by the mass action law but rather by some other type of attraction or repulsion, e.g. by electrostatic interaction depending on the ionic strength in ionic solution.

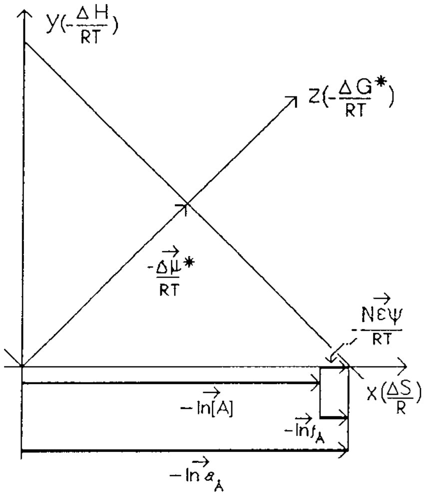

Fig. 11. Logarithm of activity and of activity coefficient in the affinity thermodynamic space. $\ln f$ is symbolically represented $N\varepsilon\psi/RT$ as integral entropy change.

The dilution ratio between two entropy states is the activity coefficient

$$f_A = a_A/[A] \tag{62}$$

where a_A is the activity and [A] the concentration in the reference state. In the limit that the ionic strength $I \to 0$, the real and ideal dilutions tend to be equal

$$\lim_{I\to 0} f_A \equiv \lim_{I\to 0} (a_A/[A]) = 1 \tag{63}$$

The relationship between concentration and activity can be represented in the thermodynamic space where Ψ represents the electrostatic potential and ε the charge (Fig. 11). If high concentrations of ionic medium are employed, the actual concentration of the solvent is no longer constant and this effect can be considered as a further entropic effect, complementary to the electrostatic effect.

The solvent, however, can also play the role of a ligand and many compounds or complexes are actually hydrated molecules or complexes. The system becomes *reacting* with affinity constant. If the solution is diluted, the concentration of the solvent-ligand can be considered as constant. Upon changing the temperature, however, an equivalent dilution can be produced, and this behaviour can be analysed by considering the change of the equilibrium constant with the temperature [12,13].

7. Conclusion

The properties of molecular ensembles and their representation in the probability space, affinity thermodynamic space, and in kinetic-energy thermodynamic space can be profitably used to put in evidence intensive and extensive properties of the chemical solutions. The intensive properties are connected with the experimental domain of concentrations and affinity constants, whereas the affinity thermodynamic space is linked to the experimental domain of heat, free energy, and logarithm of concentration. The corresponding spatial representations permit to show that the distinction into *reacting* and *non-reacting* ensembles corresponds to definite characteristic probability distributions, appropriately representable in the diagrams. The probability and affinity thermodynamic space, are also suited to show the links of the stability constants in solution thermodynamic with the functions of statistical mechanics. The kinetic thermodynamic space is suited to show the effects on the system of changes of temperature and dilution (entropic factors) under a constant potential energy factor.

8. List of symbols

nre	*non-reacting* ensemble
re	*reacting* ensemble
nre_μ	*microcanonical non-reacting* ensemble
nre_o	*osmotic non-reacting* ensemble
nre_t	*thermal non-reacting* ensemble
$nre_{t,o}$	*thermo-osmotic non-reacting* ensemble
e_o	osmotic reacting ensemble
e_t	*thermal reacting* ensemble
$re_{t,o}$	*thermo-osmotic reacting* ensemble
re_e	*electrochemical reacting* ensemble
$re_{t,e}$	*thermo-electrochemical reacting* ensemble
$re_{e,o}$	*electro-osmotic reacting* ensemble
$re_{t,e,o}$	*thermo-electro-osmotic reacting* ensemble
[A], [M],...	concentration or number density of species A, M,...
$x\exp(\Delta S/R)$	entropy probability axis

$y=\exp(-\Delta H/RT)$	enthalpy probability axis
$z^{*}\exp(-\Delta G/RT)$	auxiliary probability axis (* special scale)
$x\exp(T\Delta S/R)$	kinetic-energy probability entropy axis
$y\exp(-\Delta H/T)$	kinetic-energy probability enthalpy axis
$z\exp(-\Delta H/T)$	kinetic-energy probability auxiliary axis (* special scale)
K (or k or β)	equilibrium constant
$x(\Delta S/R)$	affinity thermodynamic entropy axis
$y(-\Delta H/RT)$	affinity thermodynamic enthalpy axis
$z^{*}(-\Delta G/RT)$	affinity thermodynamic auxiliary axis (* special scale)
$x(T\Delta S/R)$	kinetic-energy thermodynamic entropy axis
$y(-\Delta H/R)$	kinetic-energy thermodynamic enthalpy axis
$z^{*}(-\Delta G/R)$	kinetic-energy thermodynamic auxiliary axis (* special scale)
ΔG^{ϕ}	standard free energy
ΔG_{f}	formation free energy
ΔG_{d}	dissociation free energy
ΔG_{sat}	saturation free energy
ΔS^{ϕ}	standard entropy
ΔS_{H}	entropy equivalent to enthalpy
$\delta\mu_{A}$	chemical potential
$[\mathrm{A}]^{-1}$	dilution of free A
a_{A}	activity of free A
Γ_{A}	partition function
δh	finite molar enthalpy in nre_{t}
$\delta s(T)$	finite molar entropy in nre_{t}
$\gamma(i)$	cooperativity function between sites
$\Delta S^{\phi}_{\mathrm{tot}}$	total standard entropy
dr	thickness
ρ	number density
$n(r)_{\mathrm{exc}}$	excess radial distribution
$n(r)_{\mathrm{tot,exc}}$	total excess radial distribution
$g(r)$	correlation function
$h(r)$	total correlation function
$g_{\mathrm{P}}(r)$	probability space (mean) correlation function
$h_{\mathrm{P}}(r)$	probability space (mean) total correlation function
$U(r)$	potential of mean force
$U_{1,2}(r)$	pair potential between two particles
Z	partition function
Z_{M}	partition function for receptor M
ΔF	Helmholtz free energy
ΔE	internal energy
$Y(r)$	dilution function or entropy change probability
$f_{1,2}(r)$	Mayer function
ΔG_{f}	binding free energy
ΔG_{d}	dissociation free energy
ΔG_{sat}	saturation free energy
$\mathbf{J}_{i}$	vector, representing the probability of binding A to M
$[\mathbf{J}_{i}]\cdot\{\mathbf{J}_{j}\}$	tensor product
$[\mathbf{J}_{i}]$	row vector
$\{\mathbf{J}_{j}\}$	column vector
Q	heat
ψ	electrostatic potential
ε	electric charge
nFE	emf E times n Faraday constant
$\bar{n}$	formation function
α	mole fraction
f_{A}	activity coefficient
I	ionic strength
$-i$	$\sqrt{-i}$
cos hx, sin hx	hyperbolic functions

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