Enthalpy–entropy correlations as chemical guides to unravel self-assembly processes

Claude Piguet*

Received 12th January 2011, Accepted 12th April 2011
DOI: 10.1039/c1dt10055f

Intermolecular connections play a crucial role in biology (recognition, signalling, binding), in physics (material cohesion) and in chemistry ((supra)molecular engineering). While a phenomenological thermodynamic free-energy approach for modelling self-assemblies is now at hand, a more satisfying description based on the chemically-intuitive enthalpic and entropic contributions remains elusive. On the other hand, the innumerable reports of empirical enthalpy/entropy correlations characterizing intermolecular interactions justify a questioning about the emergence and exploitation of an apparent ‘fourth law of thermodynamics’, which could provide a simple manipulation of intermolecular binding processes. This tutorial Perspective aims at highlighting the current level of non-quantum rationalization of enthalpy–entropy correlations and their chemical consequences on the tuning and on the programming of intermolecular interactions in pure materials, and in diluted solutions.

1. The thermodynamic free-energy model for simple intermolecular associations

The modelling of the sequential intermolecular binding of i ligands B onto a receptor A represents one of the first challenge addressed by classical thermodynamics at the turn of the 19th century. The associated cumulative stability constant $b_{A,B}^{1,i}$ can be expressed in eqn (1) within the frame of the van’t Hoff isotherm

$$ \Delta G_{i,i}^{A,B} = -RT \ln(\beta_{i,i}^{A,B}) = -RT \ln \left( \frac{[AB_i]}{[A][B]} \right)^{\mu} $$

Assuming that the receptor A has n available and identical binding sites, $\beta_{i,i}^{A,B}$ can be theoretically modelled by the combination of a binomial coefficient $C_i^n = n!/(n-i)!i!$, which represents the purely entropic statistical factor of the assembly (i.e. the number of possible arrangements of i ligands B among the n equivalent sites) with the thermodynamic microscopic affinity $k_{A,B}$ for a single intermolecular A–B connection ($\Delta G_{i,i}^{A,B} = -RT \ln(k_{A,B})$, eqn (2)).

$$ \beta_{i,i}^{A,B} = C_i^n (k_{A,B})^\mu $$

Obviously, A and B hold for any receptor/substratum pair which could be found in biology (protein/ligand, effector/receptor, etc.), in physics (cation/anion in ionic solids, micro-cohesion in material, etc.) or in chemistry (metal/ligand, host/guest, etc.). The consideration of the occupancy factor $\mu$ (eqn (3), left), followed by the introduction of the pertinent mass balances provides mathematical sums which can be easily transformed into polynomials (eqn (3), centre). Straightforward simplifications eventually yields the classical Langmuir binding isotherm (eqn (3), right).

For the sake of clarity, the well-accepted standard concentration $c^0$ for the reference state of each partner ([|A|, |B| and [|AB|]) are the molar concentrations of the incriminated species).
When some changes of sites, according that the fixation of each B ligand may affect the measured for various compositions of the mixture (|A|_{tot}/|B|_{tot}).

D straight lines and the process is said to be non-cooperative or coordinated to A, plots according to eqn (4) and (5) display term cooperativity (positive cooperativity is characterized by i.e. cooperativity) is usually assigned to the operation of a non-
i_A,B with eqn (6) and (7) may frighten the broad chemical

Any deviation of these plots from linearity can be assigned to

The origin of non-statistical behaviour provides the best free-energy parameters \( \Delta G_{\text{micro}}^\text{Ni,NH}_3 = -RT \ln(k\text{Ni,NH}_3) = -11.70(6) \text{ kJ mol}^{-1} \), \( \Delta E_{\text{desolvNi,NH}_3}^\text{desolv} = -RT \ln(u\text{Ni,NH}_3) = 1.35(2) \text{ kJ mol}^{-1} \) and \( \Delta E_{\text{entNi,NH}_3}^\text{ent} = -RT \ln(u\text{Ni,NH}_3) = 1.33(2) \text{ kJ mol}^{-1} \). The positive values found for the allosteric factors \( \Delta E_{\text{desolvNi,NH}_3} \) and \( \Delta E_{\text{entNi,NH}_3} \) indicate that the sequential replacement of water molecules with ammonia around Ni(II) follows an anti-cooperative protocol. However, its origin in term of electronic or steric effects remains elusive in absence of a reliable dissection of these free energy terms into chemically accessible enthalpoh and entropic contributions. The latter limitation is even more dramatic for the interpretation of the microscopic free energy \( G_{\text{microNi,NH}_3} \) characterizing each Ni–NH\(_3\) connection, since any intermolecular assembly in solution indeed corresponds to a two-step mechanism where the initial desolvation step is followed by a pure association process (Fig. 1). We can thus write

\[
\Delta G_{\text{micro}}^\text{Ni,NH}_3 = -RT \ln(k^{A,B}) = \Delta G_{\text{desolvNi,NH}_3}^\text{desolv} + \Delta G_{\text{entNi,NH}_3}^\text{ent}
\]

We now easily realize that the free energy change accompanying any assembly process performed in solution is indeed a balance between successive dissociation (i.e. desolvation) and association steps. This difficulty is further amplified when the enthalpic and entropic contributions are derived with the help of the Gibb–Helmholtz relationship (eqn (13)–(15) in Fig. 1). The free-energy change in each step is itself a balance between two opposite contributions (\( \Delta H_{\text{A,B}}^\text{desolv} > 0 \) while \( -T\Delta S_{\text{A,B}}^\text{desolv} < 0 \) in eqn (13) and \( \Delta H_{\text{A,B}}^\text{desolv} < 0 \) while \( -T\Delta S_{\text{A,B}}^\text{desolv} > 0 \) in eqn (14)), while the global enthalpic \( \Delta H_{\text{A,B}}^\text{desolv} + \Delta H_{\text{A,B}}^\text{ent} \) and entropic \( \Delta S_{\text{A,B}}^\text{desolv} + \Delta S_{\text{A,B}}^\text{ent} \) contributions (eqn (15)) again result from the combinations of terms with opposite signs. In order to establish some chemical correlations between the thermodynamics of intermolecular

Although eqn (6) and (7) may frighten the broad chemical audience concerned by a Perspective in Dalton Transactions, they indeed rigorously describe the very simple energetic change brought by the successive intermolecular chemical binding of i ligands B to a single receptor A possessing a maximum of n binding sites, according that the fixation of each B ligand may affect the entry of the next one by a free-energy correction term \( \Delta E_{B,B} \).

As often in chemistry, the application of apparently complicated equations to simple examples greatly facilitates their acceptance. Let’s then illustrate this approach for the replacement of two water molecules with two ammonia ligands around divalent octahedral Ni(II) in equilibrium (8).

\[
[Ni(H\text{H}_2\text{O})_6]^{2+} + 2\text{NH}_3 \rightarrow [Ni(H\text{H}_2\text{O})(\text{NH}_3)_2]^{2+} + 2\text{H}_2\text{O}: \beta_{\text{Ni,NH}_3}^{11}(8)
\]

Since there are two microstates (cis-[Ni(H\text{H}_2\text{O})(\text{NH}_3)_2])\(^2\), statistical factor \( \omega_{\text{Ni,NH}_3}^{11} = 12 \); and trans-[Ni(H\text{H}_2\text{O})(\text{NH}_3)_2])\(^2\), statistical factor \( \omega_{\text{Ni,NH}_3}^{12} = 3 \) corresponding to the macromolecules [Ni(H\text{H}_2\text{O})(\text{NH}_3)_2]\(^2\), the modelling of each micro-constant with eqn (6) gives

\[
\beta_{\text{Ni,NH}_3}^{11} = 12(k^{\text{Ni,NH}_3})^2 u_{\text{Ni,NH}_3} < (9)
\]

\[
\beta_{\text{Ni,NH}_3}^{12} = 3(k^{\text{Ni,NH}_3})^2 u_{\text{Ni,NH}_3} < (10)
\]

Their combination into a single macro-constant according to eqn (7) eventually yields

\[
\beta_{\text{Ni,NH}_3} = 12(k^{\text{Ni,NH}_3})^2 u_{\text{Ni,NH}_3} < + 3(k^{\text{Ni,NH}_3})^2 u_{\text{Ni,NH}_3} < = (k^{\text{Ni,NH}_3})^2 (12u_{\text{Ni,NH}_3} < + 3u_{\text{Ni,NH}_3} < ) < (11)
\]
interactions and the stereo-electronic structures of the molecular partners, the explicit dissection of each process into enthalpic and entropic contributions is thus crucial. Encouraged by the heading of this invited contribution as a ‘Perspective’, we propose a critical but chemically-intuitive approach to the concept of enthalpy/entropy correlation, which can be considered as a guide for a deeper interpretation of self-assembly processes occurring in pure materials (in absence of solvent) or in dilute solution (in presence of solvent).

2. Modelling the enthalpic and entropic contributions in intermolecular associations

There is a common belief in chemistry that the change in dynamics accompanying a simple intermolecular association (measured by $\Delta S_{\text{asso}} < 0$ in eqn (14) is correlated with the strength in bonding (measured by $\Delta H_{\text{asso}} < 0$ in eqn (14)). The innumerable experimental reports of such enthalpy/entropy compensations observed in biology, physics and chemistry strongly support this axiomatic statement. Moreover, the classical chelate enhancement of binding of Jencks similarly claims that the entropic cost ($T\Delta S_{\text{asso}}$) for the association of A and B is some fraction of 50–60 kJ mol$^{-1}$, and it is a sensitive function of the exothermicity of the interaction. Though there is no ‘fourth law of thermodynamics’ which could theoretically justify enthalpy/entropy compensation (later written $H/S$ compensation in the following), there were some noticeable efforts for rationalizing weak intermolecular interactions with the help of simple Lennard-Jones potentials, in which the depth of the electrostatic well, responsible for the intermolecular association would be correlated with the density of states (Fig. 2).

Simply speaking, the basic idea links a deep electrostatic well ($\Delta H_{\text{asso}} \ll 0$) with relatively little motion ($\Delta S_{\text{asso}} \ll 0$) because the density of states is too small for being populated at room temperature (Fig. 2a). The reverse situation holds for a looser association between the A and B partners (Fig. 2b). A supporting theoretical model was proposed by Düritz in 1995, which indeed strictly predicted positive $H/S$ correlations (i.e. compensation effects). However, the simulated enthalpy–entropy curve was generated by the variation of the energy parameter (i.e. the well depth) while the size parameter (i.e. the most probable bond length) was held fixed. This limitation is probably responsible for discarding negative $H/S$ correlation (i.e. anti-compensation, see next section), a phenomenon also encountered in the literature, and unambiguously established in chemistry.

In order to get rid of debatable assumptions, Ford followed the formalism of molecular association proposed by Luo and Sharp, that is traced back to Bjerrum’s model. If the receptor A is assumed...
to be fixed near the origin, the equilibrium constant $K_{asso}^{A,B}$ for the association process described in eqn (14) is given by eqn (16), whereby $r$ and $\Omega$ are the position, respectively the orientation of B, $\beta = (k_b T)^{-1}$ is the thermal factor with $k_b$ being the Boltzmann's constant and $T$ being the temperature, $\omega$ is the potential mean force between A and B, and $H(r, \Omega)$ is a bonding function that is $H(r, \Omega) = 1$ when complex [AB] exists and $H(r, \Omega) = 0$ otherwise (Fig. 3).\(^{18,19}\)

$$K_{asso}^{A,B} = \left[\frac{[AB]}{[A][B]}\right] = e^{\frac{\theta}{8\pi^2}} \int H(r, \Omega) \cdot e^{-\frac{\omega(r, \Omega)}{k_b T}} dr d\Omega$$  \hspace{1cm} (16)

Fig. 3 Schematic illustration of Bjerrum's model for the intermolecular process depicted in eqn (14).

Neglecting any specific internal structure for A and B, the potential mean force simplifies to $\omega(r, \Omega) = u(r)$ and only depends on the scalar distance $r$ between the centres of mass. Moreover, we will assume that $u(r) = u_{min}^{A,B} + (k^A,B/2) r^2$ is a straightforward harmonic potential with the energy minimum $u_{min}^{A,B}$ located at $r = 0$ (Fig. 3) and with a force constant $k^{A,B}$. Following Luo and Sharp, $H(r, \Omega) = 1$ over all space since the Boltzmann's factor $e^{-\beta (u^{A,B}_{min} + (k^A,B/2) r^2)}$ in eqn (16) will vanish for high energy configurations anyway (i.e. unbound states with large $r$ distance). With these assumptions, Ford showed that the integral in eqn (16) gave\(^{18}\)

$$K_{asso}^{A,B} = e^{\frac{2\pi}{\beta k^{A,B}}} e^{-\frac{\theta}{k^{A,B}_{min}}}$$  \hspace{1cm} (17)

The use of the van’t Hoff isotherm transforms the association constant into its associated free energy.\(^3\)

$$\Delta G_{asso}^{A,B} = -k_b T \ln(K_{asso}^{A,B}) = -\frac{1}{\beta} \ln \left[ e^{\frac{2\pi}{\beta k^{A,B}}} e^{-\frac{\theta}{k^{A,B}_{min}}} \right]$$  \hspace{1cm} (18)

Taking into account the change in the number of translational degrees of freedom accompanying the association process, the application of the Gibbs–Helmholtz relationship to eqn (18) yields\(^{18}\)

$$\Delta H_{asso}^{A,B} = u_{min}^{A,B} + \frac{3}{2} k_b T$$  \hspace{1cm} (19)

$$\Delta S_{asso}^{A,B} = k_b \ln \left[ e^{\frac{2\pi e}{\beta k^{A,B}}} \right]$$  \hspace{1cm} (20)

In complete agreement with chemical intuition for an intermolecular connection controlled by a single harmonic potential,\(^{11,20}\) the enthalpic contribution $\Delta H_{asso}^{A,B}$ only depends on the well depth of the interaction ($u_{min}^{A,B}$ in eqn (19)). Obviously, the entropic contribution $\Delta S_{asso}^{A,B}$ depends on the original choice of the standard state ($e^\theta$ in eqn (20)),\(^3\) but its magnitude is further modulated by the force constant of the interaction ($k^{A,B}$ in eqn (20)). To the best of our knowledge, there is however no fundamental principle of weak interactions that dictates the relative dependence of well depth $u_{min}^{A,B}$ and force constant $k^{A,B}$, hence justifying a special thermodynamic relationship between $\Delta H_{asso}^{A,B}$ and $\Delta S_{asso}^{A,B}$. One can however deduce from eqn (19) and (20) that, if a perturbation is applied to the molecular [AB] pairs such that $u_{min}^{A,B}$ and $k^{A,B}$ move in the opposite direction, the result will be $H/S$ compensation, i.e. $\Delta H_{asso}^{A,B}$ and $\Delta S_{asso}^{A,B}$ both decrease, or both increase. When $u_{min}^{A,B}$ and $k^{A,B}$ move in the same direction, anti-compensation occurs.

3. Enthalpy–entropy compensation in intermolecular associations: a ‘hidden’ structural constraint

Following the simple (non-quantum) model catching the physical forces responsible for the formation of a molecular [AB] pair, an intermolecular interaction (equilibrium (14) can be modeled with a simple Lennard-Jones (12,6) potential $V_{LJ}$, which resorts to only two parameters: (i) the absolute minimum of the attractive well depth $\varepsilon$ and (ii) the minimum intermolecular A ... B distance $r_0$ at which the potential of the interaction is zero (eqn (21) and Fig. 4).\(^{20}\)

$$V_{LJ}(r) = 4\varepsilon \left[ \left( \frac{r_0}{r} \right)^{12} - \left( \frac{r_0}{r} \right)^6 \right]$$  \hspace{1cm} (21)

Fig. 4 Representation of a Lennard-Jones (12,6) potential (full trace) with the interpretation of $\varepsilon$ and $r_0$ parameters, and its harmonic approximation (eqn (22), dashed trace) modeling the intermolecular interactions operating in a [AB] complex.

While the correlation between the well depth and the harmonic potential used for obtaining eqn (18) is trivial and $\varepsilon = -u_{min}^{A,B}$, an analytical formulation of the force constant $k^{A,B}$ as a function of $\varepsilon$ and $r_0$ requires the development of the harmonic potential $V_{harm}$ at the minimum of the Lennard-Jones attractive well.\(^{14}\) The application of the three conditions $V_{harm}(r = r_0) = 0$, $dV_{harm}/dr = 0$ and $V_{harm}(r = 2^{1/6}r_0) = -\varepsilon$ leads to (Fig. 4).\(^{21}\)
\[ V_{\text{hhm}}(r) = \frac{\varepsilon}{\lambda} \left[ -2^{-7/6} \left( \frac{r}{r_0} \right)^2 + \left( \frac{r}{r_0} \right) + 2^{-7/6} \right] \] (22)

\[ \lambda = 2^{-7/6} - 2^{-1/6} - 2^{-7/6} + 1 \]

Since the total energy of the harmonic oscillator for the motion amplitude \( A = r_i (1 - 2^{1/6}) \) amounts to \( \varepsilon \) (Fig. 4), we can simply write

\[ \varepsilon = \frac{\kappa^{\text{AB}}}{r_i (1 - 2^{1/6})^2} \Rightarrow \kappa^{\text{AB}} = \left( \frac{2}{1 - 2^{1/6}} \right) \varepsilon \] (23)

which is eventually transformed into eqn (24) if we remind that \( \varepsilon = -4 \mu_{\text{min}}^{\text{AB}} \).

\[ \kappa^{\text{AB}} = -\frac{2}{(1 - 2^{1/6})^2} \mu_{\text{min}}^{\text{AB}} \] (24)

When the structural parameter \( r_0 \) is constant along a perturbation applied to the molecular [AB] pair (i.e. the minimum contact distance at which the interaction potential is zero is retained along the perturbation), eqn (24) predicts that the force constant \( \kappa^{\text{AB}} \) controlling the association entropy (eqn (20)), and the well depth \( \mu_{\text{min}}^{\text{AB}} \) controlling the association enthalpy (eqn (19)) are indeed correlated.\(^{18,21}\) This result, which implies a ‘hidden’ physicochemical process at the origin of \( H/S \) correlation\(^{22}\) was recently theoretically justified for isobaric–isothermal partition functions with the help of statistical thermodynamics.\(^{23}\) Assuming a minor perturbation of the system for which \( r_0 \) is fixed, eqn (24) becomes

\[ \kappa^{\text{AB}} = -f \cdot \mu_{\text{min}}^{\text{AB}} \] (25)

Consequently, any change of \( \mu_{\text{min}}^{\text{AB}} \) induces a shift of \( \kappa^{\text{AB}} \) in the opposite direction and, reciprocally, any change of \( \kappa^{\text{AB}} \) induces an opposite shift of \( \mu_{\text{min}}^{\text{AB}} \), which explains the frequent occurrence of \( H/S \) compensation when molecular systems are submitted to minor electronic and/or structural perturbations compatible with a constant value of \( r_0 \). The introduction of eqn (25) into eqn (19) yields

\[ \Delta H_{\text{asso}}^{\text{AB}} = -\kappa^{\text{AB}} + \frac{3}{2} k_T \Rightarrow \Delta H_{\text{asso}}^{\text{AB}} = f \left[ \frac{3}{2} k_T (\Delta H_{\text{asso}}^{\text{AB}}) \right] \] (26)

Moreover, such minute perturbations only moderately affect the average global force constant of the interaction around its average magnitude \( \kappa_0^{\text{AB}} \). The use of the linear development \( \ln(\kappa^{\text{AB}}) = \ln(\kappa_0^{\text{AB}}) + \left( \kappa^{\text{AB}} - \kappa_0^{\text{AB}} \right) \kappa_0^{\text{AB}} / \kappa_0^{\text{AB}} \) is thus justified in eqn (20) (first-order Taylor series), and eqn (27) can be easily obtained.

\[ \Delta S_{\text{asso}}^{\text{AB}} = \kappa_0^{\text{AB}} \ln \left[ e^{2 \pi \kappa_0^{\text{AB}} / \beta} \left( \frac{4 \pi e}{\beta \kappa_0^{\text{AB}}} \right)^{3/2} \right] + \frac{3}{2} \kappa_0^{\text{AB}} \ln \left( \frac{\kappa^{\text{AB}}}{\kappa_0^{\text{AB}}} \right) \] (27)

The ultimate combination of eqn (26) into (27) followed by some simple, but tedious algebraic transformations, provides the linear correlation shown in eqn (28)–(30), sometimes referred to as ‘strict \( H/S \) correlations’ or as ‘strong forms of \( H/S \) correlation’.\(^{24}\)

\[ \Delta H_{\text{asso}}^{\text{AB}} = a \Delta S_{\text{asso}}^{\text{AB}} + b \] (28)

with

\[ a = \frac{2 \kappa_0^{\text{AB}}}{3k} f = \frac{\left( 1 - 2^{-1/6} \right)^2 \left( r_0 / \kappa_0^{\text{AB}} \right)}{3k} \] (29)

and

\[ 9k_f T f = 4\kappa_0^{\text{AB}} \left[ \ln \left( \frac{2 \kappa_0^{\text{AB}} f}{\kappa^{\text{AB}}} \right) \right]^{1/2} + \frac{3}{2} \] (30)

We immediately notice that \( a > 0 \) and linear \( H/S \) compensation ‘naturally’ results for a series of association (or dissociation) processes for which (i) the structural arrangement (measured by \( r_0 \)) is invariant and (ii) the force constant (measured by \( \kappa^{\text{AB}} \)) are not drastically affected and can be estimated by a linear expansion around its central value \( \kappa_0^{\text{AB}} \). While the first condition affecting \( r_0 \) is crucial for rationalizing \( H/S \) correlations (see the following sections), the second limitation can be relaxed by increasing the global order of the Taylor series, as experimentally evidenced for the parabolic distortions of series of intermolecular connection processes spanning large domains of association enthalpies.\(^{25}\)

4. Enthalpy–entropy compensation in the melting of pure solids

Single-step \( H/S \) compensations have been recently investigated in melting processes involving solid \( \rightarrow \) liquid or solid \( \rightarrow \) liquid crystalline phase transitions (\( \Delta G_{\text{m}}^{\text{H/S}}, \Delta H_{\text{m}}^{\text{H/S}}, \Delta S_{\text{m}}^{\text{H/S}} \)) or during the reverse physical transformations where liquids or liquid crystals condensate to give some organized solid-state materials (\( \Delta G_{\text{asso}}, \Delta H_{\text{asso}}, \Delta S_{\text{asso}} \)).\(^{17,26}\) These processes can be roughly modelled by a simple homotropic \( n \)-merization reaction (eqn (31)) for which \( \Delta G_{\text{m}} = -\Delta G_{\text{asso}}, \Delta H_{\text{m}} = -\Delta H_{\text{asso}} \) and \( \Delta S_{\text{m}} = -\Delta S_{\text{asso}} \).

\[ nA \Delta G_{\text{asso}}^{\text{m}} = \Delta nA \] (31)

The justification for the abundant thermodynamic data reported for melting processes arises from the fact that the melting enthalpy, \( \Delta H_{\text{m}} \), together with the temperature dependence of the heat capacity \( C_T \) in solids, liquid crystals and liquids, can be experimentally obtained with high precision by using standard calorimetric techniques. The associated entropy change is deduced from the melting temperature by using \( \Delta S_{\text{m}} = \Delta H_{\text{m}} / T_m \). The subsequent corrections for changes of \( \Delta H_{\text{m}} \) and \( \Delta S_{\text{m}} \) with temperature (seldom considered in the literature) eventually give the standard melting enthalpy \( \Delta H_{\text{m}}^0 \) and entropy \( \Delta S_{\text{m}}^0 \).\(^{27}\) The most famous example concerns the melting of linear saturated hydrocarbons \( \text{C}_n \text{H}_{2n+2} \) of increasing length \( n > 1 \), in which two terminal methyl tripods are separated by an increasing number \( n - 2 \) of methylene rotors.\(^{28}\) The plot of \( \Delta H_{\text{m}}^0 (\text{C}_n \text{H}_{2n+2}) \) vs. \( \Delta S_{\text{m}}^0 (\text{C}_n \text{H}_{2n+2}) \) indeed displays strict \( H/S \) compensation (Fig. 5a, eqn (32)).

\[ \Delta H_{\text{m}}^0 (\text{C}_n \text{H}_{2n+2}) = 295(19) \Delta S_{\text{m}}^0 (\text{C}_n \text{H}_{2n+2}) - 7327(1400) \text{ J mol}^{-1} \] (32)

The replacement of \( \Delta H_{\text{asso}}^{\text{H/S}} (\text{C}_n \text{H}_{2n+2}) \) and \( \Delta S_{\text{asso}}^{\text{H/S}} (\text{C}_n \text{H}_{2n+2}) \) with their opposite associative counterparts \( \Delta H_{\text{asso}}^{\text{H/S}} (\text{C}_n \text{H}_{2n+2}) \) and \( \Delta S_{\text{asso}}^{\text{H/S}} (\text{C}_n \text{H}_{2n+2}) \) leads to a mathematical formulation (eqn (33)), which is compatible with eqn (28).

\[ \Delta H_{\text{asso}}^{\text{H/S}} (\text{C}_n \text{H}_{2n+2}) = 295(19) \Delta S_{\text{asso}}^{\text{H/S}} (\text{C}_n \text{H}_{2n+2}) + 7327(1400) \text{ J mol}^{-1} \] (33)
\[ \Delta H_m = \Delta H^0_m - T_m \Delta S^0_m = 0 \implies T_m = \frac{\Delta H^0_m}{\Delta S^0_m} \]  
\[ \Delta G_m = \Delta H_m - T_m \Delta S_m = 0 \implies T_m = \frac{\Delta H^0_m}{\Delta S^0_m} \]  
\[ T_m = T_m^{\text{comp}} \left( 1 + \frac{\Delta G_m^{\text{comp}}}{\Delta H^0_m} \right) = T_m^{\text{comp}} \left( 1 - \frac{\Delta G^0_m}{\Delta H^0_m} \right) \]  
A rapid inspection of eqn (36) and (37) shows that the sign of the compensation free energy change, \( \Delta G^\text{comp}_\text{asso} \), is crucial for the evolution of the melting temperature with the entropic (eqn (36)) or with the enthalpic (eqn (37)) contributions. Three different situations can be envisioned. (1) When \( \Delta G^\text{comp}_\text{asso} \gg 0 \), a weak cohesion regime operates and \( T_m \) increases with \( \Delta S^0_m \) (eqn (36)) or with \( \Delta H^0_m \) (eqn (37)), a situation encountered for the melting of linear saturated hydrocarbons containing increasing amounts of methylene rotors (Fig. 5b). (2) When \( \Delta G^\text{comp}_\text{asso} = 0 \), the operation of an intermediate cohesion regime de-correlates \( T_m \) from \( \Delta S^0_m \) and \( \Delta G^0_m \), and the melting temperature remains invariant upon the imposed perturbation. This trend is observed in silver alkanethiolates complexes Ag(SC\( \text{H}_{2n+1} \)) possessing chains of increasing lengths (Fig. 6).  

![Graph showing compensation free energy change](image-url)
significant deviations from linear contact distances and/or in force constants with the emergence of structural perturbations are expected to induce larger changes in potential with a specific contact distance eqn (28)–(30), the linear decrease).

According to a synthetic point of view, $H/S$ compensation can be exploited for the rational tuning of melting temperatures, and liquid crystal engineering is particularly eager for such developments. However, the minor evolution of the melting temperatures ($i.e.$ $\Delta G_{\text{comp}}^{\text{mol}} = 0$) with the increasing length of grafted peripheral alkyl chains beyond a critical size, as found in (i) Ag(SC$_2$H$_{4n+1}$) (Fig. 6), critical length $n \geq 9$), (ii) in the polycatenar series L$_2$ (critical length $n \geq 8$), L$_3$ (critical length $n \geq 6$) or L$_4$ (critical length $n \geq 8$, Fig. 8 and 9)$^{22}$ and (iii) in planar neutral Pt(II) hexacatenar complexes, suggests that the classical construction of phase diagrams with alkyl chains of stepwise increasing lengths has only a limited potential for designing room-temperature mesophases. We however notice that the slope of the rough linear $H/S$ correlations estimated for the hexacatenar ligands L$_4$ is significantly smaller than those found for L$_2^{0,6}$ and L$_3^{0,4}$ (Fig. 8a), a trend suggesting different intermolecular interactions (as measured by the $r_0$ parameter in eqn (29)) in polycatenar systems possessing a large number of diverging alkyl chains. This empirical polycatenar effect, systematically exploited for its beneficial consequences on the lowering of melting temperatures,$^{23,24}$ indeed finds its thermodynamic origin in the significant changes of these structural characteristics. Since ($r_0$)$^2 \kappa_0$ varies along the series L$_2^{0,6}$ $\rightarrow$ L$_3^{0,4}$ $\rightarrow$ L$_4^{0,4}$ for a fixed value of $n = 8$, or of $n = 12$, we predict (and indeed observe) significant deviation from linear $H/S$ correlations for $\Delta H_m^0$ vs. $\Delta S_m^0$ plots measuring the polycatenar effect (Fig. 10a). It is worth stressing here that the polycatenar perturbations analyzed in Fig. 7 and 10, are both characterized by a strong cohesion regime ($\Delta G_{\text{comp}}^{\text{mol}} \ll 0$), and thus the melting temperatures decrease with increasing molecular weights.

5. Enthalpy–entropy compensation in intermolecular complexation processes occurring in solution

According to Choppin’s model for standard intermolecular connections operating in solution (Fig. 1),$^{14}$ a desolvation step should precede the target association step. The $n$-merization process of eqn (31) must be adapted for solvation effects, and eqn (38) holds for a simple dimerization occurring in solution ($n = 2$, S is a solvent molecule).

$$2\text{A(S)}_m \rightleftharpoons [\text{A}_2]_p + 2(m-p)S; \Delta G_{\text{comp}}^{\text{dim}} = \Delta H_{\text{dim}}^{\text{dim}} - T\Delta S_{\text{dim}}^{\text{dim}}$$

(38)

The separation of the global intermolecular dimerization into two successive steps yields

$$2\text{A(S)}_m \rightleftharpoons 2\text{A(S)}_p + 2(m-p)S; \Delta G_{\text{desolv}}^{\text{dim}} = \Delta H_{\text{desolv}}^{\text{dim}} - T\Delta S_{\text{desolv}}^{\text{dim}}$$

(39)

Consequently, we can write

$$\Delta G_{\text{dim}}^{\text{dim}} = \Delta G_{\text{desolv}}^{\text{dim}} + \Delta G_{\text{asso}}^{\text{dim}}$$

(41)

$$\Delta H_{\text{dim}}^{\text{dim}} = \Delta H_{\text{desolv}}^{\text{dim}} + \Delta H_{\text{asso}}^{\text{dim}}$$

(42)

$$\Delta S_{\text{dim}}^{\text{dim}} = \Delta S_{\text{desolv}}^{\text{dim}} + \Delta S_{\text{asso}}^{\text{dim}}$$

(43)
Let’s now assume that a minor perturbation is applied to A, so that each intermolecular step (i.e. dissociation in eqn (39) and association in eqn (40)) can be modelled with a specific Lennard-Jones potential relying on constant values for $r^\text{desolv}_0$ and $r^\text{asso}_0$ within the frame of Ford’s model (eqn (28)–(30)). Strict H/S compensation depicted in eqn (34) operates twice and we can write

\begin{equation}
\Delta H^\text{A,S}_{\text{desolv}} = T^\text{comp}\Delta S^\text{A,S}_{\text{desolv}} + \Delta G^\text{comp}_{\text{desolv}}
\end{equation}

\begin{equation}
\Delta H^\text{A,S}_{\text{asso}} = T^\text{comp}\Delta S^\text{A,S}_{\text{asso}} + \Delta G^\text{comp}_{\text{asso}}
\end{equation}

The introduction of eqn (44), (45) into eqn (42) yields

\begin{equation}
\Delta H^\text{A,S}_{\text{dim}} = T^\text{comp}\Delta S^\text{A,S}_{\text{asso}} + \Delta G^\text{comp}_{\text{asso}} - \Delta S^\text{A,S}_{\text{desolv}} (T^\text{comp}_{\text{desolv}} - T^\text{comp}_{\text{asso}}) + (\Delta G^\text{comp}_{\text{desolv}} + \Delta G^\text{comp}_{\text{asso}})
\end{equation}

A close scrutiny at eqn (46) indicates that, beyond the original structural requirements $r^\text{desolv}_0 = \text{constant}$ and $r^\text{asso}_0 = \text{constant}$ which must be obeyed along the perturbation, the operation of a linear $H/S$ correlation for intermolecular dimerization in solution only results when at least one of the additional criteria collected in eqn (47)–(49) is fulfilled.

\begin{equation}
\Delta S^\text{A,S}_{\text{desolv}} = \text{constant}
\end{equation}

\begin{equation}
T^\text{comp}_{\text{desolv}} = T^\text{comp}_{\text{asso}}
\end{equation}

\begin{equation}
\Delta S^\text{A,S}_{\text{asso}} = \gamma \Delta S^\text{A,S}_{\text{desolv}} + \delta
\end{equation}

The first condition, i.e. $\Delta S^\text{A,S}_{\text{desolv}} = \text{constant}$ (eqn (47)) has deep chemical roots, and it is matched when the perturbation applied to the complexation process does not significantly affect the entropy changes accompanying the desolvation process. The second condition $T^\text{comp}_{\text{desolv}} = T^\text{comp}_{\text{asso}}$ (eqn (48)) is purely mathematical and it cannot be a priori correlated with obvious molecular parameters. However, eqn (48) automatically applies when an empirical linear correlation is detected between $\Delta H^\text{A,S}_{\text{dim}}$ and $\Delta S^\text{A,S}_{\text{dim}}$.\footnote{\textit{Dalton Trans.}, 2011, 40, 8059–8071 This journal is \textcopyright 2011 The Royal Society of Chemistry}
(vide supra, eqn (52)). The last alternative depicted in eqn (49) is clearly the less constraining condition, but, to the best of our knowledge, we cannot foresee any specific chemical behaviour inducing this linear correlation. The introduction of eqn (49) into eqn (46) yields the linear correlation shown in eqn (50) after some algebraic transformations.

\[
\Delta H_{\text{dimer}}^{\text{AS}} = \Delta S_{\text{dimer}}^{\text{AS}} \left( \frac{\chi T_{\text{asso}}^{\text{comp}} + T_{\text{desolv}}^{\text{comp}}}{\gamma + 1} \right) + \delta \left( \frac{T_{\text{asso}}^{\text{comp}} - T_{\text{desolv}}^{\text{comp}}}{\gamma + 1} \right) + \left( \Delta G_{\text{comp}}^{\text{desolv}} + \Delta G_{\text{asso}}^{\text{comp}} \right)
\]  

(50)

Depending on the sign and magnitude of \( \gamma \), both \( H/S \) compensation ((\( \chi T_{\text{asso}}^{\text{comp}} + T_{\text{desolv}}^{\text{comp}} \))/(\( \gamma + 1 \)) > 0) and anti-compensation ((\( \chi T_{\text{asso}}^{\text{comp}} + T_{\text{desolv}}^{\text{comp}} \))/(\( \gamma + 1 \)) < 0) can be predicted when eqn (49) is obeyed.

An intentional test for eqn (46) was recently designed with the thorough thermodynamic investigation of the dimerization of a series of large semi-dendrimeric complexes \([\text{Ln(L6}^\text{L6}^\text{+NO}_3\text{)}_3]\) in dichloromethane (eqn (51), \( \text{Ln} = \text{Pr, Eu} \); Fig. 11 and 12).\(^{21}\)

\[ 2[\text{Ln(L6}^\text{L6}^\text{+NO}_3\text{)}_3] = [\text{Ln}_2(\text{L6}^\text{L6}^\text{+NO}_3\text{)}_3]; \Delta G_{\text{dimer}}^{\text{AS}} = 202(5) \text{kJ mol}^{-1} \]  

(51)

The classical Onsager’s approach,\(^{35}\) further substantiated by modern quantum computing techniques,\(^{36}\) predicts that the solvation free energy change produced by a neutral globular dipolar molecule in a dielectric depends on its molecular volume according to \( \Delta G_{\text{solv}}^{\text{m}} \propto (V_m)^{1/3} \). So, the larger the molecules, the smaller variations of \( \Delta \Delta G_{\text{solv}} \) along the series, and eqn (47) is obeyed.\(^{14,37}\)

After application of the standard criteria for removing artificial correlations resulting from inadequate dissections of the free energy changes \( \Delta G_{\text{dimer}}^{\text{AS}} \) into enthalpic and entropic contributions by using van’t Hoff plots,\(^{38}\) the residual non-artificial thermodynamic data collected for the dimerization of \([\text{Ln(L6}^\text{L6}^\text{+NO}_3\text{)}_3]\) (eqn (51)) indeed display exact \( H/S \) compensations along the complete series of ligand in agreement with eqn (46), but with different slopes for each specific metal (\( \text{Ln} = \text{Pr, Eu} \); Fig. 13).\(^{21}\) Since the slopes of the \( \Delta H_{\text{dimer}}^{\text{AS}} \) vs. \( \Delta S_{\text{dimer}}^{\text{AS}} \) correlation plots correspond to the compensation temperature \( T_{\text{asso}}^{\text{comp}} \) (eqn (46)), a parameter which can be theoretically rationalized by using Ford’s model as \( T_{\text{asso}}^{\text{comp}} = (1 - 2^{1/2})^2(r_0)^2/k_b \) (eqn (29)), we deduce that the observed trend 

\[ T_{\text{asso}}^{\text{comp}}(\text{Pr}) = 329(17) \text{K} > T_{\text{asso}}^{\text{comp}}(\text{Eu}) = 278(7) \text{K} \]  

is a consequence of the decrease of the minimum intermolecular contact distance \( r_0 \).

Fig. 10  (a) \( \Delta H_{\text{dimer}}^{\text{AS}} \) vs. \( \Delta S_{\text{dimer}}^{\text{AS}} \) and (b) \( T_{\text{asso}}^{\text{comp}} \) vs. \( \Delta S_{\text{asso}}^{\text{comp}} \) correlation plots for the melting of the ligands \( \text{L}^{\text{L6}^\text{+}} \) (black) and \( \text{L}^{\text{L6}^\text{+}} \) (red, \( k = 2–4 \)) highlighting the polycatenar effect.\(^{22}\)

Fig. 11 Chemical structures of the semi-dendrimeric complexes \([\text{Ln(L6}^\text{L6}^\text{+NO}_3\text{)}_3]\).\(^{14}\)

Fig. 12 Schematic dimerization of \([\text{Ln(L6}^\text{L6}^\text{+NO}_3\text{)}_3]\) occurring in dichloromethane (eqn (51)). The molecular structures correspond to crystal structures obtained by X-ray diffraction techniques.\(^{21}\)

This journal is © The Royal Society of Chemistry 2011

Dalton Trans., 2011, 40, 8059–8071 | 8067
for the smaller europium(III) cation, combined with a decrease of the force constant \( k_3 \) resulting from the reluctance of Eu\(^{3+} \) to extend its coordination number (CN) beyond CN = 9 in the dimer \([\text{Ln}_2(\text{L}^{6+})_2(\text{NO}_3)_6]\), which requires CN = 10 (Fig. 12).\(^{21} \)

It is worth noting here that, as soon as a linear \( H/S \) compensation effect is empirically observed for any intermolecular complexion process occurring in solution, the simultaneous consideration of eqn (46) and of its twin form in which \( \Delta S_{\text{desolv}}^\text{comp} \) is replaced with \( \Delta S_{\text{desolv}}^\text{asso} \) (eqn (52)), implies that \( T_{\text{assolv}} = T_{\text{comp}}^\text{asso} \) (eqn (48)), a simple inference which justifies the interpretation of \( T_{\text{asso}}^\text{comp} \) as the crucial structural factor for the dimerization of \([\text{Ln}(\text{L}^{6+})_2(\text{NO}_3)_3]\) in dichloromethane.

\[
\Delta H_{\text{dim}}^\text{comp} = T_{\text{asso}}^\text{comp} \Delta S_{\text{asso}}^{\text{comp}} + \Delta S_{\text{asso}}^{\text{comp}} (T_{\text{asso}}^\text{comp} - T_{\text{assolv}}) + (\Delta G_{\text{asso}}^\text{comp} + \Delta G_{\text{asso}}^\text{desolv})
\]  

(52)

Raymond, Bergman and co-workers recently reported on a remarkable \( H/S \) compensation process characterizing the encapsulation of various cationic iridium guests (the choice of the \( R \) groups attached to the iridium atom represents the perturbation applied to the system) by an anionic \([\text{Ga}_n(\text{L}_5)_6]\) host in various solvents (Fig. 14).\(^{14e} \) After checking for non-artificial dissection of the free energy changes \( \Delta G_{\text{complex}} \) into enthalpic \( \Delta H_{\text{complex}} \) and entropic \( \Delta S_{\text{complex}} \) contributions,\(^{18} \) the Berkeley’s groups established that exact linear \( \Delta H_{\text{complex}} \) vs. \( \Delta S_{\text{complex}} \) compensations occur in water and in methanol. Without referring to eqn (46), these authors used related, but qualitative arguments for analyzing their data, and concluded that the desolvation of the iridium guests in polar aprotic solvents is crucial for observing \( H/S \) compensation, in full agreement with a system obeying eqn (46).

The latter observations, which are in line with a wealth of empirical thermodynamic observations previously collected for association processes occurring in biologic media, indicate that eqn (46) obviously extends beyond strict dimerization processes, and thus holds for any hetero-component intermolecular \([AB]\) interactions according that \( \Delta S_{\text{desolv}}^\text{asso} \) and \( \Delta H_{\text{desolv}}^\text{asso} \) (eqn (39)) are replaced with \( \Delta S_{\text{desolv}}^{\text{entropic}} \) and \( \Delta H_{\text{desolv}}^{\text{entropic}} \) (eqn (13)), as illustrated in Fig. 1.

**Conclusion and outlook**

Despite the statistical scepticism\(^{24,18} \) created by the report for decades of countless \( H/S \) compensation effects for simple intermolecular associations operating in solution, some recent unambiguous separations of enthalpic and entropic contributions firmly established that \( H/S \) correlation was indeed a common issue of intermolecular interactions upon the application of minor electronic and/or structural perturbations.\(^{12,14,17,18,21} \) However, one can be struck by that, contrary to the express ethical recommendations of the well-respected 17th century scientists Descartes (Discours de la M´ethode, 1637) and Newton (Philosophae Naturalis Principa Mathematica, 1686), who claimed that scientific models in experimental sciences should find their essence in some intellectual construction for which all accessible consequences should be derived and checked, experimental \( H/S \) correlations are usually deciphered with the help of purely inductive considerations. In 2005, Ford pointed out this weakness for a large part of \( H/S \) correlations regularly reported in biology and chemistry, and put the bases for an alternative deductive approach using some accessible physical concepts modelling intermolecular interactions.\(^{18} \) Modelling any standard intermolecular interaction with a simple harmonic potential developed at the minimum of a standard Lennard-Jones (12,6) curve, Ford demonstrated that positive enthalpy–entropy correlations (i.e. \( H/S \) compensations) occur as soon as the minimum intermolecular contact distance \( r_0 \) is invariant upon minor perturbations applied to the \([AB]\) pairs (eqn (19), (20) and (24)). When this ‘hidden’ structural condition...
is combined with a limited variation of the magnitude of the force constant $k_{0,A,B}$ characterizing the intermolecular cohesion, strict linear $H/S$ compensations are expected (eqn (28)-(30)). Apparently, this non-sophisticated approach catches the main aspects of a wealth of experimental systems, as exemplified by the evolution of the melting temperatures of saturated hydrocarbons discussed in section 4. It is worth stressing here that, for a single-step association or dissociation process, as that found in the melting of pure solids, linear $H/S$ compensation brings three different trends for the melting temperatures with respect to increasing melting entropies (eqn (36)) or enthalpies (eqn (37)).

Since $T_m = T_{m,comp}^\text{asso} - \Delta G_{m,comp} / \Delta S_{m,comp}^\text{asso}$ (eqn (36)), the sign of the compensation free energy change is crucial and it results in an increase ($\Delta G_{m,comp} > 0$, weak cohesion regime), a stagnation ($\Delta G_{m,comp} = 0$, intermediate cohesion regime) or a decrease ($\Delta G_{m,comp} < 0$, strong cohesion regime) of the melting temperatures for increasing melting entropies. As soon as some chemically-intuitive control of $\Delta G_{asso}$ is at hand for a given perturbation, these predictions can be exploited for the rational tuning of thermal properties in selected materials. For instance, an increase in the number of methylenic rotors within linear saturated hydrocarbons brings a weak cohesion regime and larger melting temperatures are found for the heaviest members of the series (Fig. 5). Alternatively, an intermediate cohesion regime results from the connection of linear alkyl chains of increasing length to a rigid and polarizable aromatic and/or metallic calamitic cores, and the melting temperatures only slightly vary (Fig. 6 and 8). Finally, the dispersion of several alkyl chains at the periphery of aromatic spacers (i.e. the polycatenar effect) corresponds to a strong cohesion regime displaying lower melting temperatures for the heavier members of the series (Fig. 7 and 10). Since linear $H/S$ correlations are a simple deduction of some physico-chemical concepts in Ford’s model, their slopes $T_{m,comp}^\text{asso}$ (eqn (29)) and intercepts $\Delta G_{m,comp}^\text{asso}$ (eqn (30)) are related to specific and accessible parameters, thus paving the way for some rough (because of the non-sophisticated description of intermolecular interactions in this model), but rational thermodynamic design of intermolecular interactions operating in materials. Despite the above-mentioned appealing consequences brought by $H/S$ compensation for optimizing melting temperatures of solid materials or of liquid crystalline phases, we should keep in mind that these predictions are strictly limited to systems for which the minimum contact distance is fixed (Fig. 15a). As soon as $r_0$ varies, there is no reason for obtaining any specific $H/S$ correlations and the origin for the reports of several total lack of unambiguous correlations (Fig. 15b) or of anti-compensation (Fig. 15c) can be understood with the consideration of variable compensation temperatures $T_{m,comp}^\text{asso}$ and free energies $\Delta G_{m,comp}^\text{asso}$ characterizing the different members of the series under investigation. 

![Fig. 15](image)

Finally, for a simple intermolecular connection forming a [AB] pair in solution, which represents the elementary building block of innumerable chemical or biological processes, the overall two-step mechanism requires two successive $H/S$ compensation phenomena; the first one controlling the initial desolvation step and the second one mastering the subsequent association step (eqn (44) and (45)). Since these two intermolecular processes are ‘structurally’ comparable, it is not surprising that, for a given perturbation, the invariance of $r_{0,asso}^2$ (eqn (44)) is combined with that of $\Delta S_{asso}$ (eqn (45)), thus favouring the emergence of $H/S$ compensations for connection processes occurring in solution.

Though less obvious, the additional condition requiring that $\Delta S_{asso} = \text{constant}$, stated in eqn (46) and (47), is also common for systems undergoing minor perturbations compatible with the above-mentioned invariance of the minimum contact distance. In this context, and within the frame of Ford’s model, the slope of linear $H/S$ plots unravelled in solution, provides a direct estimation of the compensation temperature for the pure association step (eqn (46)). This consequence provides a powerful

This journal is © The Royal Society of Chemistry 2011
tool for structurally investigating weak intermolecular cohesion occurring in solution as illustrated in section 5. We are now equipped for considering some extensions of the free-energy thermodynamic self-assembly model discussed in section 1. Let’s thus return to the microscopic thermodynamic parameters depicted in eqn (9) and (10) for the replacement of water molecules with ammonia molecules around Ni(II) (eqn (8)). The statistical factors correspond to purely entropic contributions and are not subject to controlling (i) the exact role played by the so-called steric bulk to the recognition and manipulation of stereo-electronic criteria into their enthalpic and entropic contributions should contribute energy change steps. For a series of amine NX3 of increasing size and/or H expect charges borne by the nitrogen donor atoms onto the Ni–N bond, |8070| gratefully acknowledged.

References

11 G. R. Choppin in Lanthanide Probes in Life, Chemical and Earth Sciences, ed. J.-C. G. Bünzli and G. R. Choppin, Elsevier, Amsterdam, 1984, pp. 18–25. Please note that, in Choppin’s model, the specific interactions between the liberated solvent molecules with bulk solvent are included within the desolvation step.
24 A. Cornelis-Bowden, J. Biosci., 2002, 27, 121.