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Neutral Heteroleptic Lanthanide Complexes for Unravelling Host-Guest Assemblies in Organic Solvents: The Law of Mass Action Revisited.

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Abstract

The binding of lanthanide containers $[\text{Ln}(\beta\text{-diketonate})_3\text{dig}]$ (dig = 1-methoxy-2-(2-methoxyethoxy)ethane) to aromatic tridentate N-donor ligands (**L**) in dichloromethane produces neutral nine-coordinate heteroleptic $[\text{LLn}(\beta\text{-diketonate})_3]$ complexes, the equilibrium reaction quotients of which vary with the total concentrations of the reacting partners. This problematic drift prevents the determination of both reliable thermodynamic stability constants and intrinsic host-guest affinities. The classical solution theory assigns this behavior to changes in the activity coefficients of the various partners in non-ideal solutions and a phenomenological approach attempts to quantitatively attribute this effect to some partition of the solvent molecules between bulk-innocent and contact-non-innocent contributors to the chemical potential. This assumption eventually predicts an empirical linear dependence of the equilibrium reaction quotient on the concentration of the formed $[\text{LLn}(\beta\text{-diketonate})_3]$ complexes, a trend experimentally supported in this contribution for various ligands **L** differing in lipophilicity and nuclearity and for lanthanide containers grafted with diverse beta-diketonate co-ligands. Even if the origin of the latter linear dependence is still the subject of debate, this work demonstrates that this approach can be exploited by experimentalists for

extracting reliable thermodynamic constants suitable for analyzing and comparing host-guest affinities in organic solvents.

Introduction

Basic thermodynamics of host-guest assemblies: a non-trivial problem. Experimental coordination chemists with (or without) interest in lanthanide complexation reactions are determined to get reliable free-energies affinities $\Delta G_{\text{asso}}^{\circ}$ accompanying the association between a host ligand (**L**) and a guest metal container (**M**) occurring in a specific solvent according to eqn (1).



The thermodynamic stability constant $\beta_{1,1}^{\text{L,M}}$, often unduly mixed by experimentalists with the equilibrium reaction quotient $Q_{1,1,\text{eq}}^{\text{L,M}}$ expressed in concentration units, is defined by the van't Hoff isotherm as the ratio of the activities (a_i^{eq}) of the various partners at equilibrium (left part of eqn 2). Except for some rare cases where activities can be monitored directly by selective electrodes or by vapor pressure measurements, most experimental protocols consider the gathering of concentrations at equilibrium for the estimation of $\beta_{1,1}^{\text{L,M}}$. The introduction of activity coefficients γ , which transform mole fractions (x_i) or concentrations (c_i) into activities according to $a_i = \gamma_i x_i = \gamma_i (c_i/c^{\theta})$,¹ together with the standard concentration of the reference state c^{θ} ($c^{\theta} = 1 \text{ M}$ is used for the rest of this contribution)² ensures an adequate procedure for estimating thermodynamic stability constants by using equilibrium reaction quotients $Q_{1,1,\text{eq}}^{\text{L,M}} = c_{\text{LM}}^{\text{eq}}/c_{\text{L}}^{\text{eq}} \cdot c_{\text{M}}^{\text{eq}}$ defined by the speciation expressed in molar concentration units (right part of eqn 2).

$$\beta_{1,1}^{\text{L,M}} = e^{-(\Delta G_{\text{asso}}^{\circ}/RT)} = \frac{a_{\text{LM}}^{\text{eq}}}{a_{\text{L}}^{\text{eq}} a_{\text{M}}^{\text{eq}}} = \frac{\gamma_{\text{LM}}}{\gamma_{\text{L}} \gamma_{\text{M}}} \cdot \frac{(c_{\text{LM}}^{\text{eq}}/c^{\theta})}{(c_{\text{L}}^{\text{eq}}/c^{\theta})(c_{\text{M}}^{\text{eq}}/c^{\theta})} = \frac{\gamma_{\text{LM}}}{\gamma_{\text{L}} \gamma_{\text{M}}} \cdot Q_{1,1,\text{eq}}^{\text{L,M}} \cdot c^{\theta} \quad (2)$$

Since coordination chemists are mainly focused on the determination of the stability constants (and their associated free-energy changes) by monitoring concentrations at equilibrium, eqn (2) provides considerable difficulties because the activity coefficients are usually not accessible except for ideal

solutions ($\gamma_i=1$) where all intermolecular interactions are identical, a situation characterized by $\xi = 0$ within the frame of the classical solution model (ξ is a dimensionless parameter that estimates the energy of solute-solvent interactions relative to that of solvent-solvent and solute-solute interactions).¹ For chemical reactions involving ionic partners in solution, the Debye-Hückel limiting law provides a satisfying key since the activity coefficients of the ions only depend on their intrinsic charge and size, and on the ionic strength of the mixture, a parameter which can be fixed by the addition of a large excess of dissociated non-reacting electrolytes. Even though the ratio $\gamma_{LM}/(\gamma_L \cdot \gamma_M)$ is unknown for the charged partners at equilibrium, it corresponds to a constant for a fixed ionic strength. The equilibrium reaction quotient $Q_{1,1,eq}^{L,M} = c_{LM}^{eq}/(c_L^{eq} \cdot c_M^{eq})$ estimated in concentration units (we take for granted the original choice of $c^0 = 1$ M) is therefore proportional to the thermodynamic stability constant $\beta_{1,1}^{L,M}$ (eqn 2). For these reasons, numerous equilibrium reaction quotients have been reported for the formation of charged coordination complexes in polar solvents, for which specific ionic strengths are duly mentioned.³ The situation becomes critical when association reactions are conducted (i) in polar solvent in absence of added polyelectrolytes or in non-polar (usually organic) solvents where the ionic strength cannot be fixed and (ii) when neutral partners are considered. A very rough, but instructive approach considers the classical solution theory for mastering the free-energy changes accompanying the mixing of two non-ideal chemical components A and B, the latter one being taken as the solvent (B, mole fraction x_B) while A (mole fraction $x_A = x_M + x_L + x_{LM}$) is assigned to the sum of the solute particles controlled by equilibrium (1). According to this hypothesis, the free-energy of mixing $nRT(x_A \ln(a_A) + x_B \ln(a_B))$ deviates from that of an ideal solution $nRT(x_A \ln(x_A) + x_B \ln(x_B))$ by an excess enthalpic contribution $n\xi RT x_A x_B$, which develops for n moles of mixture when the solute-solvent (A-B) interactions differ from solvent-solvent (B-B) and solute-solute (A-A) interactions ($\xi < 0$ means exothermic mixing and the dominance of favorable solute-solvent interactions, while the reverse situation characterizes $\xi > 0$).¹ Since $a_A = \gamma_A x_A$, the activity coefficient of the solute in a non-ideal binary mixture finds a mathematical expression $\ln(\gamma_A)$

$= \xi(x_B)^2 = \xi(1-x_A)^2$ (Fig. 1a), often referred to as the Margules equation,⁴ which finally leads to the solute activity $a_A = \gamma_A x_A = e^{\xi(1-x_A)^2} x_A$ (Fig. 1b).

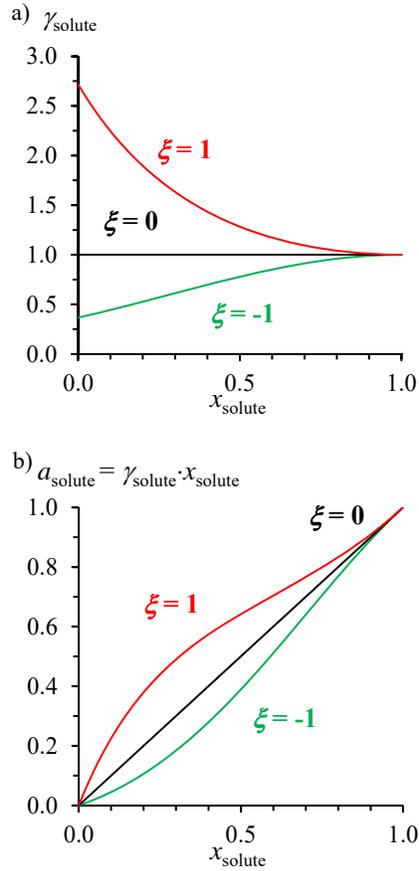


Figure 1 Plots of a) activity coefficients γ_{solute} and b) activities a_{solute} for a solute dispersed into a solvent in a binary mixture according to Margules equation.⁴ ξ is the dimensionless parameter measuring the energy of the solute-solvent interactions relative to that of the solute-solute and solvent-solvent interactions.¹

Using concentration units for diluted solutions ($x_B \geq 0.9$ and $c_B \gg c_L^{\text{eq}} + c_M^{\text{eq}} + c_{LM}^{\text{eq}}$), the mole fraction of the solute x_A in our ‘binary’ mixture at equilibrium is given in eqn (3) and its activity coefficient in eqn (4).

$$x_A = \frac{c_L^{\text{eq}} + c_M^{\text{eq}} + c_{LM}^{\text{eq}}}{c_L^{\text{eq}} + c_M^{\text{eq}} + c_{LM}^{\text{eq}} + c_B} \simeq \frac{c_L^{\text{tot}} + c_M^{\text{tot}} - c_{LM}^{\text{eq}}}{c_B} \quad (3)$$

$$\gamma_A = \gamma_{\text{solute}} = e^{\xi \left(1 - \frac{c_L^{\text{tot}} + c_M^{\text{tot}} - c_{LM}^{\text{eq}}}{c_B} \right)^2} \quad (4)$$

Introducing eqn (4) into eqn (2) yields eqn (5) where $Q_{1,1,\text{eq}}^{\text{L,M}}$ is the experimentally accessible reaction quotient, which is (very) often mistaken by coordination chemists for the thermodynamic stability constant $\beta_{1,1}^{\text{L,M}}$.

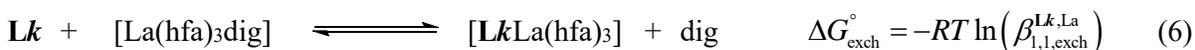
$$\beta_{1,1}^{\text{L,M}} = e^{-(\Delta G_{\text{asso}}^{\circ}/RT)} = e^{-\xi \left(1 - \frac{c_{\text{L}}^{\text{tot}} + c_{\text{M}}^{\text{tot}} - c_{\text{LM}}^{\text{eq}}}{c_{\text{B}}} \right)^2} \cdot \frac{c_{\text{LM}}^{\text{eq}}}{c_{\text{L}}^{\text{eq}} \cdot c_{\text{M}}^{\text{eq}}} \cdot c^{\theta} = e^{-\xi \left(1 - \frac{c_{\text{L}}^{\text{tot}} + c_{\text{M}}^{\text{tot}} - c_{\text{LM}}^{\text{eq}}}{c_{\text{B}}} \right)^2} \cdot Q_{1,1,\text{eq}}^{\text{L,M}} \cdot c^{\theta} \quad (5)$$

Since (i) the sum $c_{\text{L}}^{\text{tot}} + c_{\text{M}}^{\text{tot}} - c_{\text{LM}}^{\text{eq}}$ varies during the titration of a receptor **L** with an **M** guest and (ii)

$\beta_{1,1}^{\text{L,M}}$ is a constant, eqn (5) predicts that the reaction quotients recorded at equilibrium

$Q_{1,1,\text{eq}}^{\text{L,M}} = c_{\text{LM}}^{\text{eq}} / (c_{\text{L}}^{\text{eq}} \cdot c_{\text{M}}^{\text{eq}})$ will indeed change for various total concentrations of host and guest. It is

therefore not so surprising that titrations of ligands **L1-L3** with $[\text{La}(\text{hfa})_3\text{dig}]$ (eqn (6), hfa is the hexafluoroacetylacetonate anion, see Figure 2a) in dichloromethane systematically exhibit significant variations of the reaction quotients at equilibrium (Figure 2b),⁵ a trend previously noted for titrations of EDTA^{4-} with Ca^{2+} conducted in aqueous buffered solutions.⁶



Since (i) the stepwise appearance of free diglyme in solution exactly matches (stoichiometry 1:1) the complexation of **Lk** during the NMR titrations and (ii) $[\mathbf{LkLa}(\text{hfa})_3]$ is the only complex characterized in the solid state and in solution,⁷ there is no ambiguity concerning the exclusive formation of 1:1 complexes in eqn (6). In this situation, how may coordination chemists decide which one of the various reaction quotients collected in Figure 2b is pertinent for applying van't Hoff equation leading to the searched free-energy change $\Delta G_{\text{exch}}^{\circ}$ associated with equilibrium (6)? According to the classical solution theory, one expects $\gamma_{\text{solute}} \rightarrow 1$ for large concentrations of reacting partners (Figure 1), a situation impossible to reach in diluted solution. On the other hand, working at infinite dilution should also fix the activity coefficients to constant values, but their considerable sensitivities to minor changes in the composition of the mixture makes this approach also precarious (Figure 1). We conclude that the systematic measurements of concentrations instead of activities during titration

processes is a severe handicap, which finds a single acceptable key for the assembly of ionic partners in polar solvents where the ionic strength is fixed.

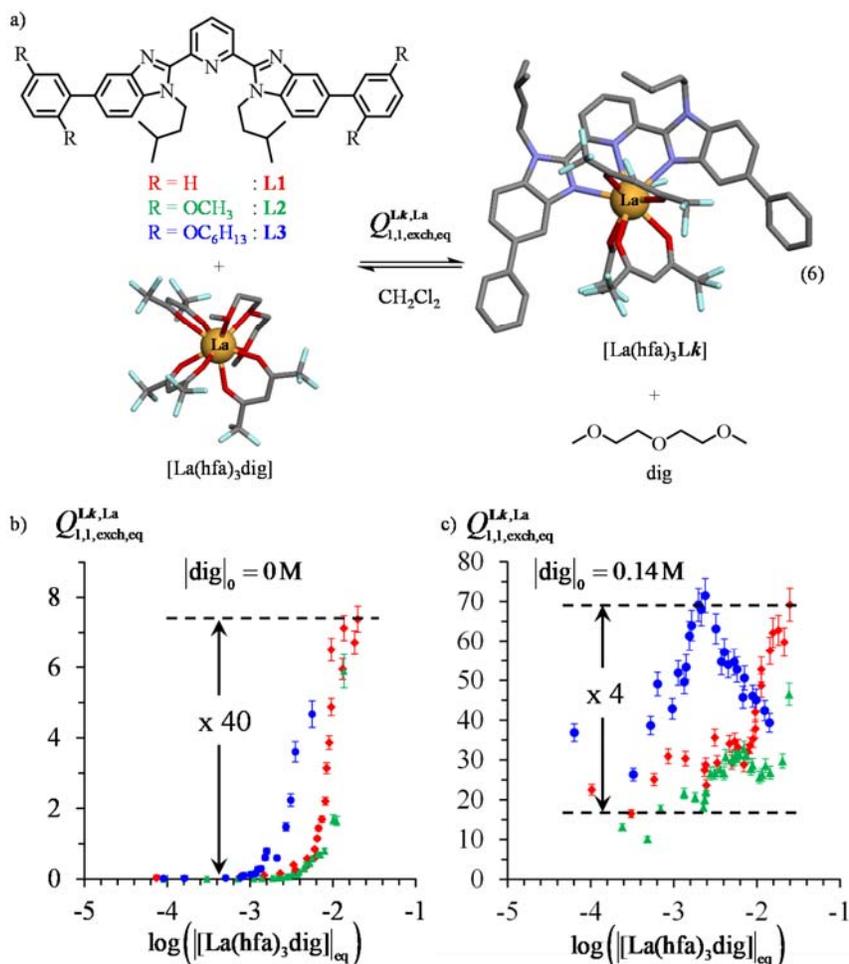


Figure 2 (a) Graphical illustration of the host-guest association involving the exchange of diglyme (dig) with tridentate ligand **L1-L3** around $[La(hfa)_3]$ according to eqn (6) (Color code: C = grey, O = red, N = blue, F = light blue, La = orange, hydrogen atoms are omitted for clarity) and (b,c) reaction quotients $Q_{1,1,exch,eq}^{Lk,La} = \left(\frac{[LkLa(hfa)_3]_{eq} \cdot [dig]_{eq}}{[La(hfa)_3]_{eq} \cdot [Lk]_{eq}}\right)$ estimated during 1H -NMR titrations performed at total 10 millimolar host concentrations (b) in absence and (c) in presence of an excess (0.14 M) of diglyme (Color code: **L1** = red, **L2** = green, **L3** = blue).⁵

Results and Discussions

Some practical attempts to unravel the thermodynamics of host-guest assemblies in solution.

Whereas host-guest assemblies involving charged species can be satisfyingly modeled and understood thanks to the theory of the ionic atmosphere,¹ we are not aware of comparable

rationalization for related reactions conducted between neutral partners in poorly polar solvents. However, a simple look at Margules equation plotted in Figure 1a suggests that γ_{solute} varies less when at least one member of the chemical entities under equilibrium can be fixed at high concentration, thus leveling out the change in composition accompanying the complexation reaction. With this in mind, the titrations summarized in eqn (6) were repeated, still using 10 millimolar concentration of ligand receptors **L1-L3**, but in presence of a constant total concentration of 0.14 M diglyme, which is one of the products of the reaction. As anticipated, the variation of the novel equilibrium reaction quotients $Q_{1,1,\text{asso,eq}}^{\text{Lk,La}} = \left(\frac{|\mathbf{LkLa(hfa)}_3|_{\text{eq}} \cdot |\text{dig}|_{\text{tot}}}{|\text{La(hfa)}_3|_{\text{eq}} \cdot |\mathbf{Lk}|_{\text{eq}}} \right)$ during the titration is reduced by one order of magnitude (Figure 2c).⁵ For a fixed concentration of diglyme, eqn (6) transforms into the conditional association process summarized in eqn (7), which is reminiscent of equilibrium (1).



The plots of the occupancy factors $\theta_{\text{Lk}}^{\text{La}} = \frac{|\text{La(hfa)}_3|_{\text{eq}}^{\text{bound}}}{|\mathbf{Lk}|_{\text{tot}}}$ as a function of the free concentration of $[\text{La(hfa)}_3]$ guest (left part of eqn 8) for the titrations of **L1-L3** conducted in $\text{CD}_2\text{Cl}_2 + 0.14 \text{ M}$ diglyme (diamonds in Figure 3a) indeed highlights only some minor shifts with respect to the theoretical binding isotherms (right part of eqn 8) built by using a single thermodynamic constant

$\beta_{1,1,\text{asso}}^{\text{Lk,La}} = (1/N) \sum_{i=1}^N (Q_{1,1,\text{asso,eq}}^{\text{Lk,La}})_i$ taken as the average of the N equilibrium reaction quotients determined along the titrations (dotted green traces in Figure 3a).⁵

$$\theta_{\text{Lk}}^{\text{La}} = \frac{|\text{La(hfa)}_3|_{\text{eq}}^{\text{bound}}}{|\mathbf{Lk}|_{\text{tot}}} = \frac{|\text{La}|_{\text{tot}} - |\text{La(hfa)}_3|_{\text{eq}}}{|\mathbf{Lk}|_{\text{tot}}} = \frac{\beta_{1,1,\text{asso}}^{\text{Lk,La}} |\text{La(hfa)}_3|_{\text{eq}}}{1 + \beta_{1,1,\text{asso}}^{\text{Lk,La}} |\text{La(hfa)}_3|_{\text{eq}}} \quad (8)$$

Interestingly, Castellano and Eggers⁶ attempted to assign the change in the activity coefficients occurring during the titrations to some desolvation processes involving the solvent molecules in contact with the reactants and products. Their simple derivation postulates that a p subset of solvent molecules in second-sphere contact with the partners of the reactions ($\text{S}^{\text{contact}}$) possesses a specific chemical potential, which is different from that of the bulk solvent (S^{bulk}). In these conditions, the conditional association reaction (eqn 7) transforms into equilibrium (9).

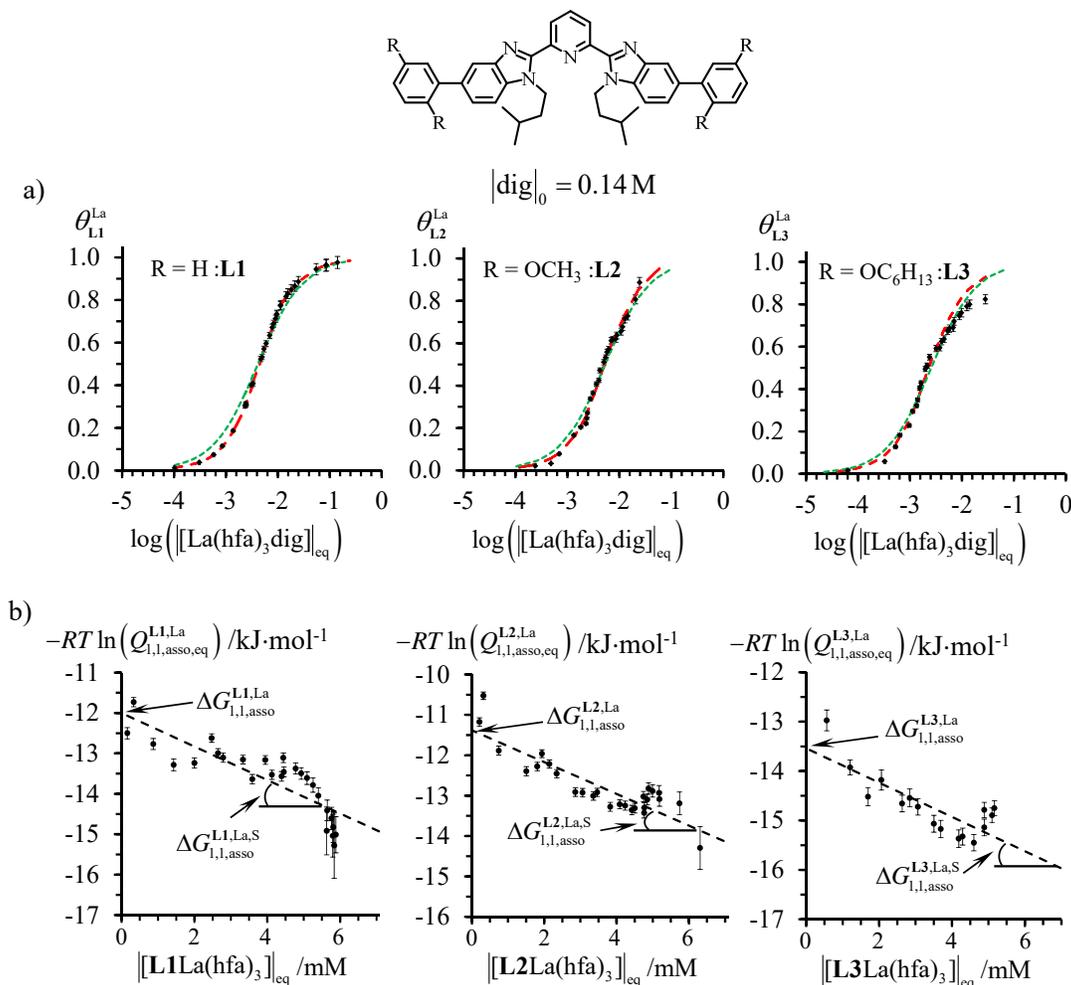


Figure 3 a) Experimental (diamonds) and fitted (dotted green traces using eqn 8; dashed red traces using eqn 11) binding isotherms for the titration of \mathbf{Lk} with $[\text{La}(\text{hfa})_3]\text{dig}$ in $\text{CD}_2\text{Cl}_2 + 0.14 \text{ M diglyme}$ at 298 K. b) Dependences of the equilibrium reaction quotients $-RT \ln(Q_{1,1,\text{asso},\text{eq}}^{\text{L}k,\text{La}})$ on the progress of the association reactions highlighting $\Delta G_{1,1,\text{asso}}^{\text{L}k,\text{La}}$ and $\Delta G_{1,1,\text{asso}}^{\text{L}k,\text{La},\text{S}}$ according to eqn (10).⁵

This approach has been rebutted recently with the support of sophisticated and probably irrefutable statistical thermodynamic arguments.⁸ In order to avoid any controversy, it is fair to mention here that an intuitive and simple balance of chemical potentials pertinent to equilibrium (9) led Castellano and Eggers to propose eqn (10),⁶ which catches the variation of the activity coefficients with the progress of the reaction measured by the equilibrium concentration of the formed final $[\mathbf{LkLa}(\text{hfa})_3]$ complex ($c_{\text{LM}}^{\text{eq}}$). The factor of proportionality is written as a free-energy change $\Delta G_{1,1,\text{asso}}^{\text{L},\text{M},\text{S}}$ assigned to

some solvation effects accompanying the association reaction, which is not taken into account by the standard chemical potentials of the various species at equilibrium (for a detailed derivation, see Appendix 1 in the Supporting Information and reference 6).

$$-RT \ln(Q_{1,1,asso,eq}^{L,M}) = \Delta G_{1,1,asso}^{L,M} + (c_{LM}^{eq}/c^\theta) \Delta G_{1,1,asso}^{L,M,S} \quad (10)$$

Empirical plots of $-RT \ln(Q_{1,1,asso,eq}^{Lk,La})$ as a function of $|\mathbf{LkLa(hfa)}_3|_{eq}$ for titrations of **L1-L3** in presence of a constant excess of diglyme (0.14 M) indeed support approximate linear dependences predicted by eqn (10) (Figure 3b), from which the thermodynamics free-energy changes $\Delta G_{1,1,asso}^{Lk,La}$ and correction factors $\Delta G_{1,1,asso}^{Lk,La,S}$ can be extracted (Table 1, columns 2-4).⁵ The re-built binding isotherms using the latter two fitted parameters in eqn (11) slightly improve the matching with the experimental data (Figure 3a, dashed red traces).

$$\theta_{Lk}^{La} = \frac{|\mathbf{La(hfa)}_3|_{eq}^{bound}}{|\mathbf{Lk}|_{tot}} = \frac{Q_{1,1,asso,eq}^{Lk,La} |\mathbf{La(hfa)}_3|_{eq}}{1 + Q_{1,1,asso,eq}^{Lk,La} |\mathbf{La(hfa)}_3|_{eq}} = \frac{e^{-[(\Delta G_{1,1,asso}^{Lk,La} + |\mathbf{LkLa(hfa)}_3|_{eq} \Delta G_{1,1,asso}^{Lk,La,S})/RT]} |\mathbf{La(hfa)}_3|_{eq}}{1 + e^{-[(\Delta G_{1,1,asso}^{Lk,La} + |\mathbf{LkLa(hfa)}_3|_{eq} \Delta G_{1,1,asso}^{Lk,La,S})/RT]} |\mathbf{La(hfa)}_3|_{eq}} \quad (11)$$

Related linear correlations between $-RT \ln(Q_{1,1,exch,eq}^{Lk,La})$ and $|\mathbf{LkLa(hfa)}_3|_{eq}$ were observed for the ligand exchange reaction (eqn 6) conducted in pure deuterated dichloromethane in absence of fixed concentration of diglyme (Figure 4a). Since the activity coefficients vary much more dramatically during the exchange process (compare Figure 2b for the exchange reaction with Figure 2c for the association reaction), the pseudo-binding isotherms re-built with eqn (12) and using a single average thermodynamic constant $\beta_{1,1,exch}^{Lk,La} = (1/N) \sum_{i=1}^N (Q_{1,1,exch,eq}^{Lk,La})_i$ (Table 1, column 5) are clearly not adapted (green traces in Figure 4b).

$$\theta_{Lk}^{La} = \frac{|\mathbf{La}|_{tot} - |\mathbf{La(hfa)}_3 \mathbf{dig}|_{eq}}{|\mathbf{Lk}|_{tot}} = \frac{\beta_{1,1,exch}^{Lk,La} (|\mathbf{La(hfa)}_3 \mathbf{dig}|_{eq} / |\mathbf{dig}|_{eq})}{1 + \beta_{1,1,exch}^{Lk,La} (|\mathbf{La(hfa)}_3 \mathbf{dig}|_{eq} / |\mathbf{dig}|_{eq})} \quad (12)$$

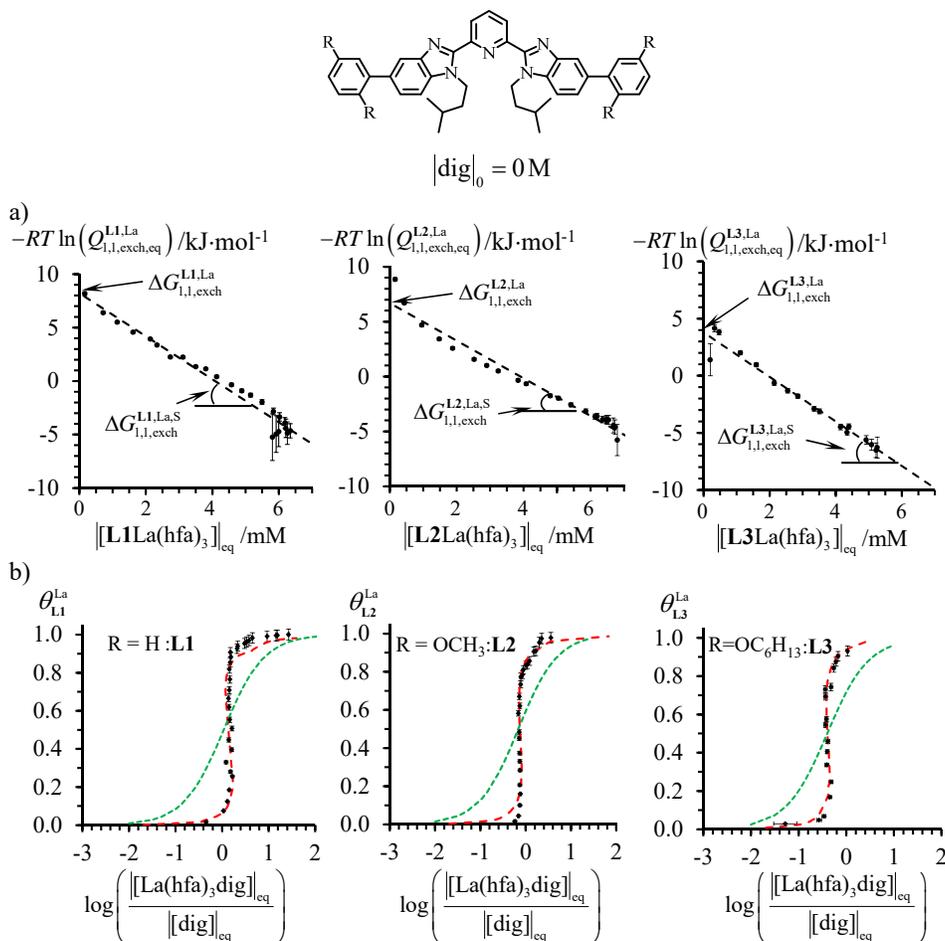


Figure 4 a) Dependences of the equilibrium quotient reactions $-RT \ln(Q_{1,1,\text{exch,eq}}^{\text{Lk,La}})$ on the progress of the association reactions highlighting $\Delta G_{1,1,\text{exch}}^{\text{Lk,La}}$ and $\Delta G_{1,1,\text{exch}}^{\text{Lk,La,S}}$ according to eqn (10) and b) experimental (diamonds) and fitted (dashed green traces using eqn 12; dashed red traces using eqn 13) pseudo-binding isotherms for the titration of Lk with $[\text{La}(\text{hfa})_3 \text{dig}]$ in CD_2Cl_2 at 298 K.⁵

On the contrary, Castellano-Eggers' approach summarized in eqn (10), where $\beta_{1,1,\text{asso}}^{\text{Lk,La}}$ is now replaced with $\beta_{1,1,\text{exch}}^{\text{Lk,La}}$, provides thermodynamic free-energy changes $\Delta G_{1,1,\text{exch}}^{\text{Lk,La}}$ and $\Delta G_{1,1,\text{exch}}^{\text{Lk,La,S}}$ (Table 1, columns 6-7) adapted to the satisfying reproduction of the experimental pseudo-binding isotherms using eqn (13) (Figure 4b, red traces).

$$\theta_{\text{Lk}}^{\text{La}} = \frac{Q_{1,1,\text{exch,eq}}^{\text{Lk,La}} [\text{La}(\text{hfa})_3 \text{dig}]_{\text{eq}}}{1 + Q_{1,1,\text{exch,eq}}^{\text{Lk,La}} [\text{La}(\text{hfa})_3 \text{dig}]_{\text{eq}}} = \frac{e^{-\left[\left(\Delta G_{1,1,\text{exch}}^{\text{Lk,La}} + [\text{LkLa}(\text{hfa})_3]_{\text{eq}} \Delta G_{1,1,\text{exch}}^{\text{Lk,La,S}}\right) / RT\right]} \left([\text{La}(\text{hfa})_3 \text{dig}]_{\text{eq}} / [\text{dig}]_{\text{eq}}\right)}{1 + e^{-\left[\left(\Delta G_{1,1,\text{exch}}^{\text{Lk,La}} + [\text{LkLa}(\text{hfa})_3]_{\text{eq}} \Delta G_{1,1,\text{exch}}^{\text{Lk,La,S}}\right) / RT\right]} \left([\text{La}(\text{hfa})_3 \text{dig}]_{\text{eq}} / [\text{dig}]_{\text{eq}}\right)} \quad (13)$$

Please note that the occupancy factors θ_{Lk}^{La} associated with the exchange reactions are plotted as a function of the ratio $|\text{La(hfa)}_3\text{dig}|_{\text{eq}}/|\text{dig}|_{\text{eq}}$ in eqns (12)-(13), because the concentration of diglyme is no longer constant.⁵

Table 1 Average Free Energies $-RT \ln(\beta_{1,1}^{Lk,La})$ (eqns 8 and 12, Ideal Solutions) and Thermodynamic Parameters $\Delta G_{1,1}^{Lk,La}$ and $\Delta G_{1,1}^{Lk,La,S}$ (eqn 10, Non-Ideal Solutions), Determined for the Titrations of Lk with $[\text{La(hfa)}_3\text{dig}]$ in $\text{CD}_2\text{Cl}_2 + 0.14 \text{ M Diglyme}$ (eqn 7, columns 2-4) or in Pure CD_2Cl_2 (eqn 6, 5-7).^a

Hosts	$-RT \ln(\beta_{1,1}^{Lk,La})$	$\Delta G_{1,1}^{Lk,La}$	$\Delta G_{1,1}^{Lk,La,S}$	$-RT \ln(\beta_{1,1}^{Lk,La})$	$\Delta G_{1,1}^{Lk,La}$	$\Delta G_{1,1}^{Lk,La,S}$
	/kJ·mol ⁻¹	/kJ·mol ⁻¹	/kJ·mol ⁻¹	/kJ·mol ⁻¹	/kJ·mol ⁻¹	/kJ·mol ⁻¹
L1	-13.2(6)	-12.2(1)	-305(22)	-4.6(2.1)	5.9(3)	-1615(50)
L2	-9.8(6)	-8.8(1)	-254(24)	-3.4(2.7)	5.6(3)	-1503(71)
L3	-9.5(8)	-9.0(1)	-285(36)	-3.9(2.4)	4.0(3)	-2020(92)
L7	-11.5(2)	-11.6(1)	16(9)	-7.8(2.1)	-1.7(2)	-729(27)

^aUncertainties are those obtained by least-square fits using eqns (8) and (10).

The positive free-energy changes $\Delta G_{1,1}^{Lk,La} > 0$ (Table 1, column 6) imply logically that the replacement of a tridentate O-donor ligand (diglyme) with a less electronegative tridentate N-donor ligand Lk around oxophilic trivalent lanthanides is thermodynamically unfavorable.⁹ The trend $\Delta G_{1,1}^{L1,La} > \Delta G_{1,1}^{L2,La} > \Delta G_{1,1}^{L3,La}$ points to some minor, but specific effects of the peripheral lipophilic chains on the energetic balance pertinent to the ligand exchange process. In presence of a constant and large excess of the leaving diglyme ligands, the energetic profiles $\Delta G_{1,1}^{Lk,La} < 0$ (Table 1, column 3) reflect the affinity of the neutral lanthanide carrier $[\text{La(hfa)}_3]$ for the entering tridentate Lk ligand. The associated trend $\Delta G_{1,1}^{L1,La} < \Delta G_{1,1}^{L2,La} \approx \Delta G_{1,1}^{L3,La}$ is surprisingly reversed compared with that found for $\Delta G_{1,1}^{Lk,La}$, which suggests some delicate balances in solvation processes affecting the lipophilic N-donor ligand upon changing the nature of the solvent (pure dichloromethane for $\Delta G_{1,1}^{Lk,La}$ and

dichloromethane with 0.14 M diglyme for $\Delta G_{1,1,asso}^{Lk,La}$). Castellano-Eggers' approach (eqn 10) provides a second parameter $\Delta G_{1,1,exch}^{Lk,La,S}$ or $\Delta G_{1,1,asso}^{Lk,La,S}$, which is supposed to estimate the effect of the change in contact solvation. The data collected in Table 1 (columns 4 and 7) show huge negative values with no relationship with standard solvation energies produced by dipole molecules immersed into a dielectric (1-30 kJ·mol⁻¹).¹⁰ We conclude that $\Delta G_{1,1,exch}^{Lk,La,S}$ or $\Delta G_{1,1,asso}^{Lk,La,S}$ cannot be interpreted in terms of simple contact solvation, but that they mainly reflect the change in activity coefficients, a phenomenon which becomes crucial at high concentration since the $(c_{eq}^{LM}/c^0)\Delta G_{1,1}^{L,M,S}$ terms in eqn (10) become dominant and drive the quantitative replacement of diglyme with **Lk** at decimolar concentrations. Attempts to separate some pertinent enthalpic and entropic contributions using low-temperature NMR proved to be very delicate because of the technical limitations of our setup, which required to return to room temperature for opening the NMR tube and adding one more crop of metal prior to restore the working temperature. The resulting scattered data are too imprecise for being exploited for the exchange process (equilibrium 6; see Figure S1 and Table S1 in the Supporting Information). For the conditional association reaction (eqn 7), the trends are more precise and probably reliable for $\Delta G_{1,1,asso}^{Lk,La}$ (see Figure S2 and Table S2 in the Supporting Information), which are characterized by slightly unfavorable enthalpy changes ($\Delta H_{1,1,asso}^{Lk,La} \geq 0$). The opposite entropic contributions ($-T\Delta S_{1,1,asso}^{Lk,La} \ll 0$) are responsible for the driving force leading to non-negligible lanthanide-ligand association ($\Delta G_{1,1,asso}^{Lk,La} < 0$) at room temperature, a mechanism in line with the compensation model popularized during the early eighties by Choppin for rationalizing lanthanide complexation in aqueous solution.¹¹

Applying the 'contact solvent-correction' patch to the binding of non-symmetrical [La(β -diketonate)₃] guests to tridentate receptors L1-L3. After having explored systematic lipophilic changes in the ligands **L1-L3**, the nature of the lanthanide containers was varied by using the non-symmetrical [La(tta)₃dig] (Htta = 2-thenoyltrifluoroacetone, Figure 5a) and [La(pbta)₃dig] (Hpbta =

perfluorophenyltrifluoroacetone, Figure 6a) complexes, the structure of the latter being isostructural with that recently reported for [Eu(pbta)dig] (Figure S3 and Tables S3-S7 in the Supporting Information).¹² Again, a simple look at the experimental binding isotherms extracted from the ¹H-NMR titrations of **L1-L3** with these non-symmetrical lanthanide containers in pure dichloromethane (equilibrium 6; Figures 5b-6b and Figures S4-S5) or in dichloromethane containing 0.14 M of diglyme (equilibrium 7; Figure S6) unambiguously shows that they obey eqn (10), thus leading to approximate linear dependences of the logarithms of the equilibrium reaction quotients on the concentrations of the [**Lk**LaX₃] adducts (X = tta, pbta, Figure 5c-6c). The associated thermodynamic free-energy changes $\Delta G_{1,1,\text{exch}}^{\text{Lk},\text{LaX}_3}$ and $\Delta G_{1,1,\text{exch}}^{\text{Lk},\text{LaX}_3,\text{S}}$ for the exchange reaction (CH₂Cl₂ + 0 M diglyme) and $\Delta G_{1,1,\text{asso}}^{\text{Lk},\text{LaX}_3}$ and $\Delta G_{1,1,\text{asso}}^{\text{Lk},\text{LaX}_3,\text{S}}$ for the conditional association reactions (CH₂Cl₂ + 0.14 M diglyme) are gathered in Table 2 and can be directly compared with those previously reported for the symmetrical [Ln(hfa)₃dig] container (Table 1).

Table 2 Average Free Energies $-RT \ln(\beta_{1,1}^{\text{Lk},\text{LaX}_3})$ (eqns 8 and 12) and Thermodynamic Parameters $\Delta G_{1,1}^{\text{Lk},\text{LaX}_3}$ and $\Delta G_{1,1}^{\text{Lk},\text{LaX}_3,\text{S}}$ (eqn 10), Determined for the Titrations of **Lk** with [La(X)₃dig] (X = tta, pbta) in CD₂Cl₂ + 0.14 M Diglyme.

Host/ guest	$-RT \ln(\beta_{1,1,\text{asso}}^{\text{Lk},\text{La}})$ /kJ·mol ⁻¹	$\Delta G_{1,1,\text{asso}}^{\text{Lk},\text{La}}$ /kJ·mol ⁻¹	$\Delta G_{1,1,\text{asso}}^{\text{Lk},\text{La},\text{S}}$ /kJ·mol ⁻¹	$-RT \ln(\beta_{1,1,\text{exch}}^{\text{Lk},\text{La}})$ /kJ·mol ⁻¹	$\Delta G_{1,1,\text{exch}}^{\text{Lk},\text{La}}$ /kJ·mol ⁻¹	$\Delta G_{1,1,\text{exch}}^{\text{Lk},\text{La},\text{S}}$ /kJ·mol ⁻¹
L1 /tta	-10.4(6)	-8.8(1)	-463(16)	-2.5(1)	3.0(2)	-848(30)
L2 /tta	<i>b</i>	<i>b</i>	<i>b</i>	-0.2(2)	4.6(1)	-973(15)
L3 /tta	<i>b</i>	<i>b</i>	<i>b</i>	3.0(1)	7.0(3)	-1510(122)
L1 /pbta	-12.8(2)	-12.3(1)	-100(24)	0.6(2)	6.2(1)	-1197(24)
L2 /pbta	-9.3(9)	-8.4(2)	-524(69)	-0.3(2)	6.0(1)	-1368(18)
L3 /pbta	<i>b</i>	<i>b</i>	<i>b</i>	-1.8(2)	4.6(2)	-2080(80)

^aUncertainties are those obtained by least-square fit of eqns 8 and 10. ^b Too small affinities for being analyzed by NMR at 10 mM concentrations.

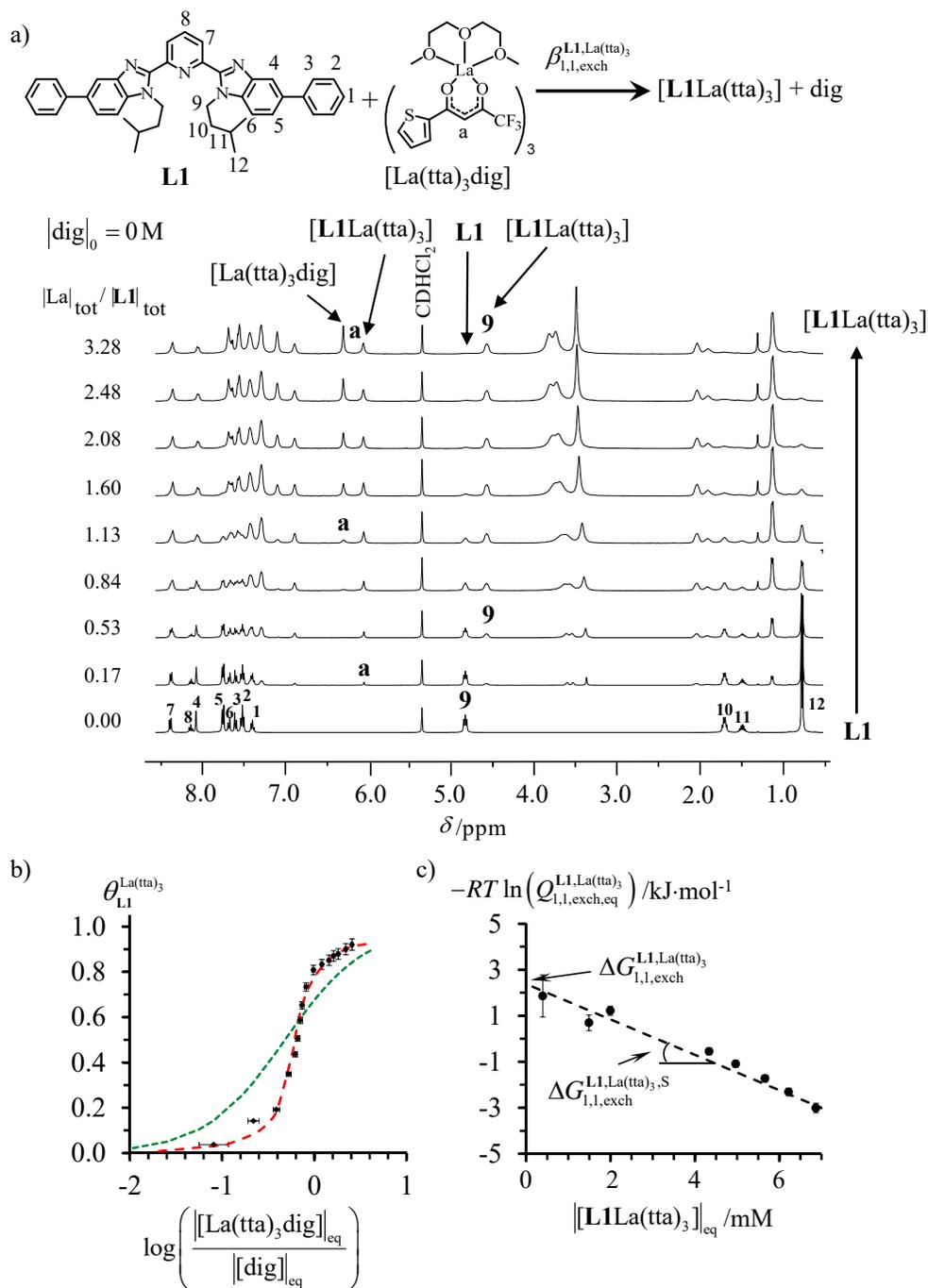


Figure 5 a) ^1H -NMR titration of **L1** with $[\text{La(tta)}_3\text{dig}]$ in CD_2Cl_2 at 298 K with numbering scheme ($8.3 \cdot 10^{-3} \leq [\text{L1}]_{\text{tot}} \leq 1.1 \cdot 10^{-2} \text{M}$ and $4.3 \cdot 10^{-4} \text{M} \leq [\text{La}]_{\text{tot}} \leq 2.7 \cdot 10^{-2} \text{M}$), b) experimental (diamonds) and fitted (dotted green traces using eqn 12; dashed red traces using eqn 13) pseudo-binding isotherms and c) dependence of the equilibrium reaction quotients $-RT \ln(Q_{1,1,\text{exch,eq}}^{\text{L1,La(tta)}_3})$ on the progress of the association reaction highlighting $\Delta G_{1,1,\text{exch}}^{\text{L1,La(tta)}_3}$ and $\Delta G_{1,1,\text{exch}}^{\text{L1,La(tta)}_3,\text{S}}$ according to eqn (10).

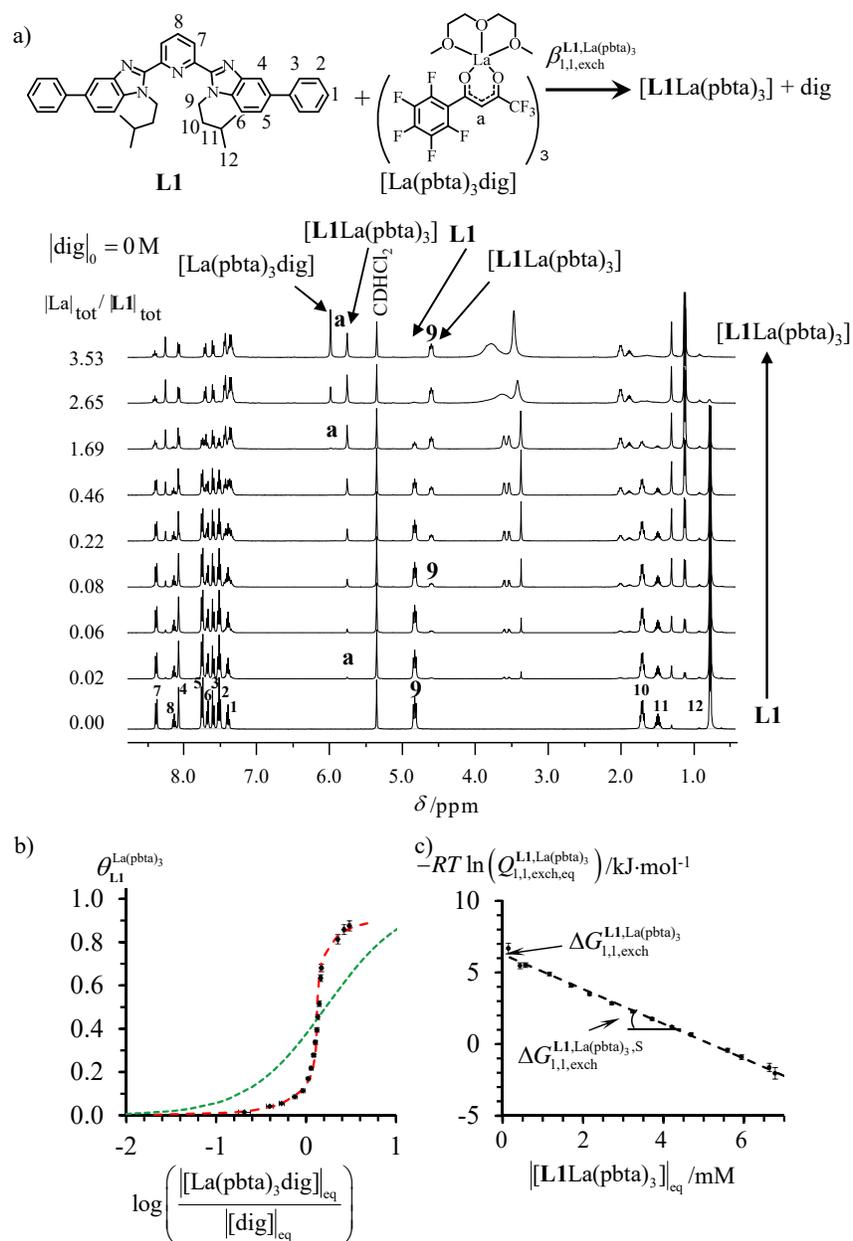


Figure 6 a) $^1\text{H-NMR}$ titration of **L1** with $[\text{La}(\text{pbta})_3\text{dig}]$ in CD_2Cl_2 at 298 K with numbering Scheme ($7.7 \cdot 10^{-3} \leq |\text{L1}|_{\text{tot}} \leq 1.1 \cdot 10^{-2} \text{M}$ and $1.8 \cdot 10^{-4} \text{M} \leq |\text{La}|_{\text{tot}} \leq 2.7 \cdot 10^{-2} \text{M}$), b) experimental (diamonds) and fitted (dotted green traces using eqn 12; dashed red traces using eqn 13) pseudo-binding isotherms and c) dependence of the equilibrium reaction quotients $-RT \ln(Q_{1,1,\text{exch},\text{eq}}^{\text{L1,La}(\text{pbta})_3})$ on the progress of the association reaction highlighting $\Delta G_{1,1,\text{exch}}^{\text{L1,La}(\text{pbta})_3}$ and $\Delta G_{1,1,\text{exch}}^{\text{L1,La}(\text{pbta})_3,\text{S}}$ according to eqn (10).

While the magnitude of the contact-solvent corrections, which take into account the change in activity coefficients, are difficult to rationalize (columns 7 in Tables 1-2), the exchange free energies

extrapolated at infinite dilutions (columns 6 in Tables 1-2) are all positive and do not largely vary ($3.0 \leq \Delta G_{1,1,\text{exch}}^{\text{Lk},\text{LaX}_3} \leq 7.0$ kJ/mol), this whatever the choice of ligands or of lanthanum containers. The Born-Haber thermodynamic cycle built in Figure 7 and summarized in eqn (14) is well-suited for clarifying this observation.

$$\Delta G_{1,1,\text{exch},\text{sol}}^{\text{Lk},\text{LaX}_3} = \Delta G_{1,1,\text{exch},\text{gas}}^{\text{Lk},\text{LaX}_3} + \Delta_{\text{solv}} G_{\text{dig}}^0 - \Delta_{\text{solv}} G_{[\text{LaX}_3\text{dig}]}^0 + \Delta_{\text{solv}} G_{[\text{LkLaX}_3]}^0 - \Delta_{\text{solv}} G_{\text{Lk}}^0 \quad (14)$$

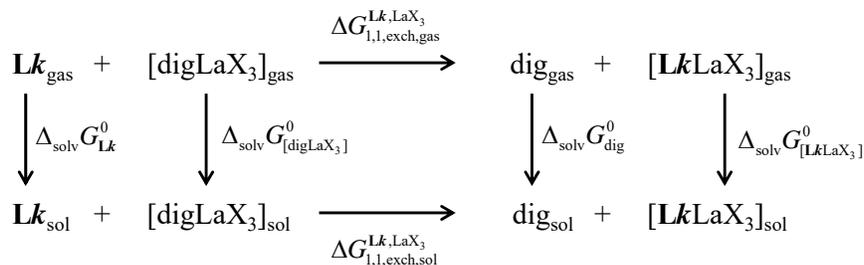


Figure 7 Thermodynamic cycle for ligand exchanges around $[\text{La}(\text{X})_3]$ containers ($\text{X} = \text{hfa}, \text{tta}, \text{pbta}$).

For a given lanthanide container $[\text{LaX}_3]$, the gas-phase contribution $\Delta G_{1,1,\text{exch},\text{gas}}^{\text{Lk},\text{LaX}_3}$ is not expected to vary significantly because peripheral substitution in going from **L1** to **L3** has little, if any, inductive effect on the basicity of the N-donor atoms of the entering tridentate ligands. The contribution $\Delta_{\text{solv}} G_{\text{dig}}^0 - \Delta_{\text{solv}} G_{[\text{LaX}_3\text{dig}]}^0$ being independent of the nature of the ligands, the Born-Haber cycle summarized in eqn (14) can be abridged to give eqn (15)

$$\Delta G_{1,1,\text{exch},\text{sol}}^{\text{Lk},\text{LaX}_3} = \Delta_{\text{solv}} G_{[\text{LkLaX}_3]}^0 - \Delta_{\text{solv}} G_{\text{Lk}}^0 + \text{constant} \quad (15)$$

The variable solvation energies of the neutral dipolar molecules **Lk** and $[\text{LkLaX}_3]$ can be estimated with the help of Onsager equation which predicts a μ^2/R_H^3 dependence (μ is the dipole moment of the particle and R_H is the radius of a spherical cavity cut from the dielectric when a spherical solute is immersed into the solvent).¹³ Due to the much larger dipole moments calculated for the $[\text{LkLaX}_3]$ complexes ($13.1 \leq \mu \leq 14.9$ D) compared with those of the free **Lk** ligands ($1.5 \leq \mu \leq 3.4$ D),^{10,12} $\Delta_{\text{solv}} G_{[\text{LkLaX}_3]}^0$ (-10 to -20 kJ/mol) dominates $\Delta_{\text{solv}} G_{\text{Lk}}^0$ (-1 to -2 kJ/mol) by one order of magnitude.

With this in mind, eqn (15) predicts that the changes in $\Delta_{\text{solv}} G_{[\text{LkLaX}_3]}^0$ controls those of $\Delta G_{1,1,\text{exch},\text{sol}}^{\text{Lk},\text{LaX}_3}$

along the ligand series for a given lanthanide container. Consequently, the only minor changes computed recently¹⁰ for the total pseudo-spherical volumes and electric dipoles accompanying specific ligand substitution in going from **L1** to **L3** fully justify the limited variation of $\Delta G_{1,1,\text{exch},\text{sol}}^{\text{Lk},\text{LaX}_3}$ observed in solution (columns 6 in Tables 1-2).

When considering the alternative situation, for which different lanthanide containers are connected to the same tridentate ligand **Lk**, the situation is more complicated since the Born-Haber cycle in eqn (14) translates into eqn (16), which contains three variable contributions.

$$\Delta G_{1,1,\text{exch},\text{sol}}^{\text{Lk},\text{LaX}_3} = \Delta G_{1,1,\text{exch},\text{gas}}^{\text{Lk},\text{LaX}_3} + \Delta_{\text{solv}} G_{[\text{LkLaX}_3]}^0 - \Delta_{\text{solv}} G_{[\text{LaX}_3\text{dig}]}^0 + \text{constant} \quad (16)$$

The dipole moments of the lanthanide containers [La(hfa)₃dig], [La(pbta)₃dig] and [La(tta)₃dig] decrease in the order: hfa (7.7 D) > pbta (6.7 D) > tta (4.6 D), whereas those of [L1La(hfa)₃], [L1La(pbta)₃] and [L1La(tta)₃] are more scattered (hfa: 13.8 D, pbta: 13.1 D, tta: 14.9 D).¹² With these numbers in hand, the pertinent difference $\Delta_{\text{solv}} G_{[\text{LkLaX}_3]}^0 - \Delta_{\text{solv}} G_{[\text{LaX}_3\text{dig}]}^0$ found in eqn (16) is systematically negative and maximizes its favorable contribution according to the order tta << hfa ≈ pbta if we reasonably assume similar sizes for [L1La(X)₃]. We therefore expect more favorable free energies of exchange for the [La(tta)₃] container, a trend roughly obeyed in Tables 1-2 (columns 6).

Extending the ‘contact solvent-correction’ patch to successive host-guest assemblies in solution.

The detailed thermodynamic investigation of the association of mono-tridentate ligands **L1-L3** with [La(X₃)dig] container in dichloromethane demonstrated that the equilibrium quotient reaction $Q_{1,1,\text{asso},\text{eq}}^{\text{L},\text{M}}$ may be an ambiguous reporter of the thermodynamic stability constants $\beta_{1,1,\text{asso}}^{\text{L},\text{M}}$. Irrespective of the chemical origin of the dependence of the equilibrium reaction quotients on the advance of the association reactions (change in activity coefficients according to the classical solution theory and/or consequences of contact solvent molecules on the chemical potential of the solvent), the empirical eqn (10) $-RT \ln(Q_{1,1,\text{asso},\text{eq}}^{\text{L},\text{M}}) = -RT \ln(\beta_{1,1,\text{asso}}^{\text{L},\text{M}}) + (c_{\text{eq}}^{\text{LM}}/c^\theta) \Delta G_{1,1,\text{asso}}^{\text{L},\text{M},\text{S}}$ proposed by Castellano and Eggers⁶

satisfyingly correlates these two parameters thus leading to a specific free-energy change at infinite

$$\text{dilution } \Delta G_{1,1,\text{asso}}^{\text{L,M}} = -RT \ln(\beta_{1,1,\text{asso}}^{\text{L,M}}).$$

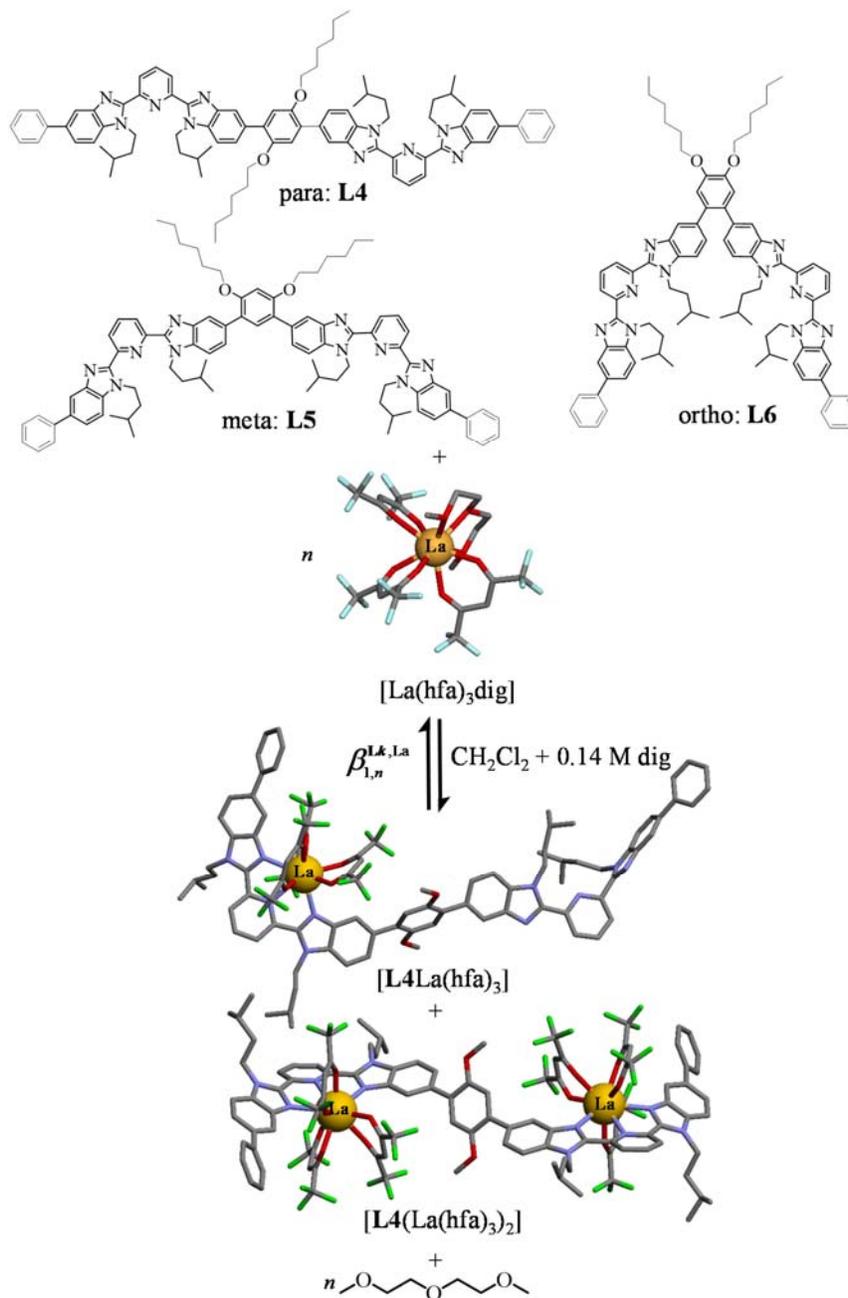
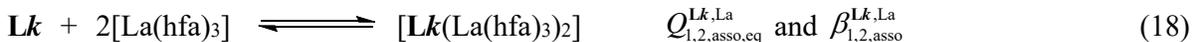


Figure 8. Host-guest association for the connection of di-tridentate ligands **L4-L6** to $[\text{La}(\text{hfa})_3]$ containers.

However, in coordination and supramolecular chemistry, the consideration of a single equilibria is rare and eqn (10) leads to major inconsistencies when, for instance, the di-tridentate ligands **L4-L6**

successively fix two [La(hfa)₃] guests in CH₂Cl₂ + 0.14 M diglyme to give [LkLa(hfa)₃] or [Lk(La(hfa)₃)₂] (eqns 17-18 and Figure 8).¹⁰



Application of eqn (10) to equilibria (17)-(18) provides

$$\Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La}} = -RT \ln(\beta_{1,1,\text{asso}}^{\mathbf{Lk},\text{La}}) = -RT \ln(Q_{1,1,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) - \left([\mathbf{LkLa}(\text{hfa})_3]_{\text{eq}} / c^\theta \right) \Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La,S}} \quad (19)$$

$$\Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La}} = -RT \ln(\beta_{1,2,\text{asso}}^{\mathbf{Lk},\text{La}}) = -RT \ln(Q_{1,2,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) - \left([\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]_{\text{eq}} / c^\theta \right) \Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La,S}} \quad (20)$$

Since G is a state function, standard thermodynamic requires that the free-energy change

$\Delta G_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}} = -RT \ln(K_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}})$ associated with the fixation of the second [La(hfa)₃] container to

[LkLa(hfa)₃] (eqn 21) is given by the difference between the two cumulative processes

$$\Delta G_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}} = \Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La}} - \Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La}} .$$



In ideal solutions, the equilibrium reaction quotients strictly mirror the thermodynamic stability constants and eqn (22) holds.

$$\Delta G_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}} = -RT \ln(K_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}}) = -RT \ln(Q_{1,1,\text{asso,eq}}^{\mathbf{LkLa},\text{La}}) = -RT \ln(Q_{1,2,\text{asso,eq}}^{\mathbf{Lk},\text{La}} / Q_{1,1,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) \quad (22)$$

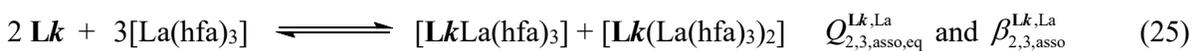
For non-ideal solutions, the use of eqns (19)-(20) gives eqn (23)

$$\begin{aligned} \Delta G_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}} &= -RT \ln(K_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}}) = \\ &-RT \ln(Q_{1,2,\text{asso,eq}}^{\mathbf{Lk},\text{La}} / Q_{1,1,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) - \left([\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]_{\text{eq}} / c^\theta \right) \Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La,S}} + \left([\mathbf{LkLa}(\text{hfa})_3]_{\text{eq}} / c^\theta \right) \Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La,S}} \end{aligned} \quad (23)$$

which is close, *but not equal* to the application of Castellano-Eggers' approach (eqn 10) to equilibrium (21) summarized in eqn (24).

$$\begin{aligned} \Delta G_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}} &= -RT \ln(K_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La}}) = \\ &-RT \ln(Q_{1,2,\text{asso,eq}}^{\mathbf{Lk},\text{La}} / Q_{1,1,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) - \left([\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]_{\text{eq}} / c^\theta \right) \Delta G_{1,1,\text{asso}}^{\mathbf{LkLa},\text{La,S}} \end{aligned} \quad (24)$$

The unacceptable discrepancy between eqns (23) and (24) originates from the contribution of contact solvation, which considers different corrections for the formation of $[\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]$ depending on the ‘mechanism’ of its formation, either from \mathbf{Lk} and two $[\text{La}(\text{hfa})_3]$ containers (equilibrium 18 and eqn 20) or from $[\mathbf{LkLa}(\text{hfa})_3]$ and one $[\text{La}(\text{hfa})_3]$ container (equilibrium 21 and eqn 24). This limitation can be overcome by considering the sum of the two cumulative complexation reactions in equilibrium (25) because the relative fractions of each formed complex $[\mathbf{LkLa}(\text{hfa})_3]$ and $[\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]$ during the titration procedure are now associated with their specific contact solvation correction in eqn (26). Now, the Born-Haber cycle $\Delta G_{2,3,\text{asso}}^{\mathbf{Lk},\text{La}} = \Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La}} + \Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La}}$ is obeyed (see eqns (19), (20) and (26)).



$$\begin{aligned} \Delta G_{2,3,\text{asso}}^{\mathbf{Lk},\text{La}} &= -RT \ln(\beta_{2,3,\text{asso}}^{\mathbf{Lk},\text{La}}) = \\ &-RT \ln(Q_{2,3,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) - \left([\mathbf{LkLa}(\text{hfa})_3]_{\text{eq}} / c^0 \right) \Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La,S}} - \left([\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]_{\text{eq}} / c^0 \right) \Delta G_{2,1,\text{asso}}^{\mathbf{Lk},\text{La,S}} \end{aligned} \quad (26)$$

Mathematically speaking, eqn (26) corresponds to the equation of a plane in a three dimensional $\langle [\mathbf{LkLa}(\text{hfa})_3]_{\text{eq}} ; [\mathbf{Lk}(\text{La}(\text{hfa})_3)_2]_{\text{eq}} ; -RT \ln(Q_{2,3,\text{asso,eq}}^{\mathbf{Lk},\text{La}}) \rangle$ cartesian frame (Figure 9 and Figures S7-S8 in the Supporting Information). Bi-linear least-square fits of the titration data collected¹⁰ for the titration of **L4-L6** with $[\text{La}(\text{hfa})_3(\text{dig})]$ in $\text{CH}_2\text{Cl}_2 + 0.14 \text{ M diglyme}$ provide total free-energy changes $\Delta G_{2,3,\text{asso}}^{\mathbf{Lk},\text{La}}$ and ‘solvation’ corrections $\Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La,S}}$ and $\Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La,S}}$ gathered in Table 3.

Table 3 Free-energy changes $\Delta G_{2,3,\text{asso}}^{\mathbf{Lk},\text{La},0}$ and associated contact solvation variations $\Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La,S}}$ and $\Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La,S}}$ (eq. 17) for the titration of \mathbf{Lk} with $[\text{La}(\text{hfa})_3(\text{dig})]$ in $\text{CH}_2\text{Cl}_2 + 0.14 \text{ M diglyme}$ (298 K).

Ligand	L4	L5	L6
$\Delta G_{2,3,\text{asso}}^{\mathbf{Lk},\text{La},0} / \text{kJ}\cdot\text{mol}^{-1}$	-36.1(8)	-32.2(7)	-43.3(8)
$\Delta G_{1,1,\text{asso}}^{\mathbf{Lk},\text{La,S}} / \text{kJ}\cdot\text{mol}^{-1}$	-514(351)	552(282)	1190(357)
$\Delta G_{1,2,\text{asso}}^{\mathbf{Lk},\text{La,S}} / \text{kJ}\cdot\text{mol}^{-1}$	525(144)	-378(100)	559(158)

The fitted binding isotherms re-built using eqn (27) are shown as red traces in Figure 10 and do not display major improvements compared with previously reported fits¹⁰ taking constant activity coefficients for granted (green dotted traces in Figure 10).

$$\theta_{Lk}^{La} = \frac{|\mathbf{LkLa(hfa)}_3|_{\text{eq}} + 2|\mathbf{Lk(La(hfa)}_3)_2|_{\text{eq}}}{2|\mathbf{Lk}|_{\text{tot}}} \quad (27)$$

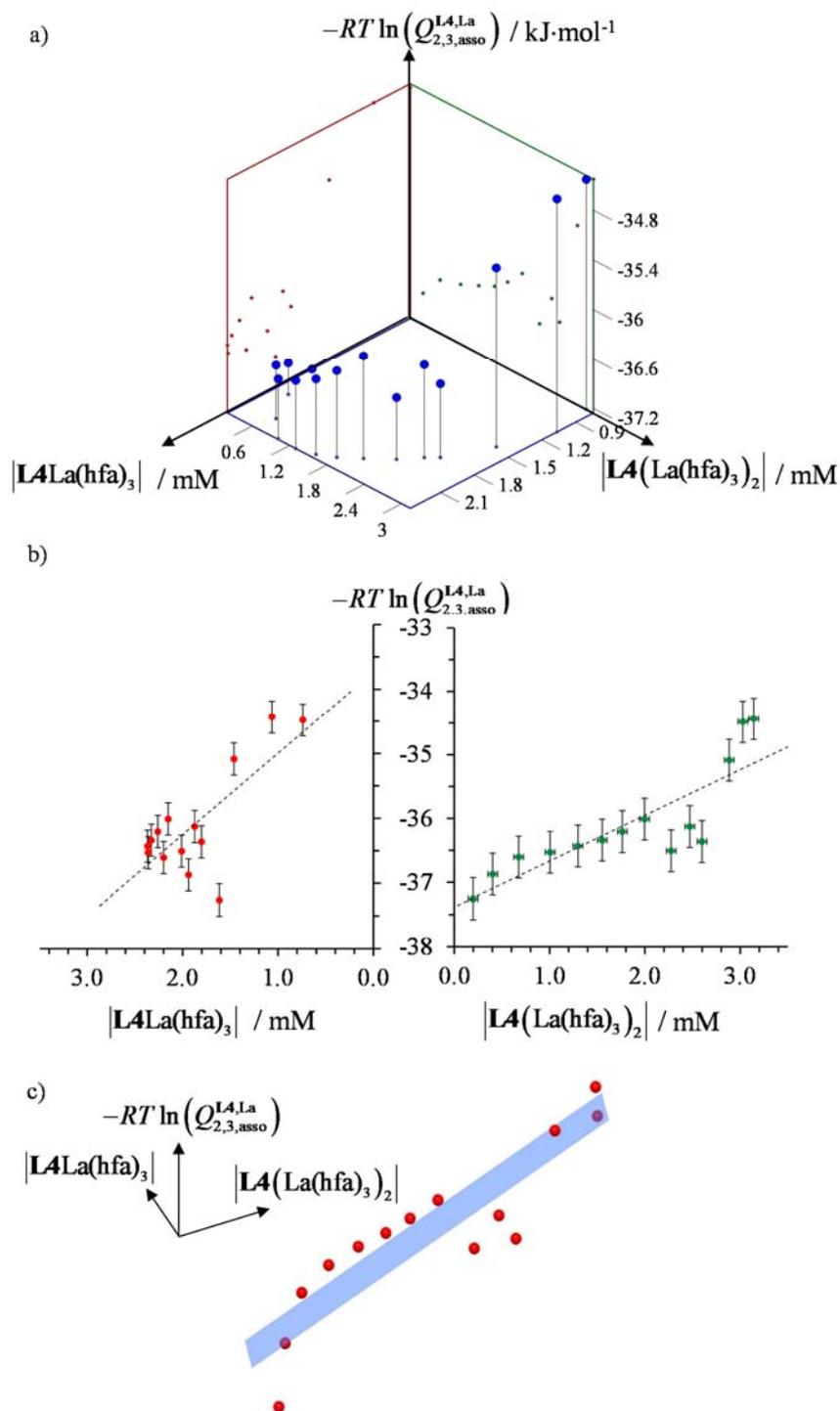


Figure 9 Plots of a) $-RT \ln(Q_{2,3,asso,eq}^{L4,La})$ as a function of $|\mathbf{L4La(hfa)}_3|_{eq}$ and $|\mathbf{L4(La(hfa)}_3)_2|_{eq}$ according to eqn (26), b) projections onto the $|\mathbf{L4(La(hfa)}_3)_2|_{eq} = \text{constant}$ plane (left) and $|\mathbf{L4La(hfa)}_3|_{eq} = \text{constant}$ plane (right) and c) projection roughly orthogonal to the best least-square plane (shown in blue) for the titrations of **L4** with $[\text{La(hfa)}_3\text{dig}]$ in $\text{CH}_2\text{Cl}_2 + 0.14 \text{ M dig}$ (298 K).

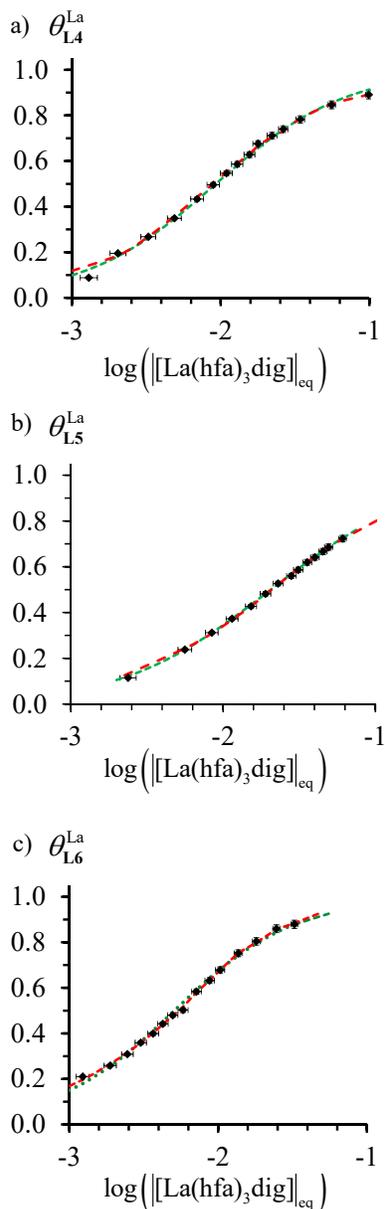
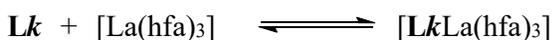


Figure 10 Experimental (diamonds) and fitted (dashed red traces using eqn 27) binding isotherms for the titrations of a) **L4**, b) **L5** and c) **L6** with $[\text{La(hfa)}_3\text{dig}]$ in $\text{CH}_2\text{Cl}_2 + 0.14 \text{ M diglyme}$ (298 K). The green dotted traces correspond to previous fits assuming fixed activity coefficients as reported in reference 10.

When standard thermodynamics is followed (i.e. $\Delta G_{2,3,asso}^{Lk,La} = \Delta G_{1,2,asso}^{Lk,La} + \Delta G_{1,1,asso}^{Lk,La}$), the introduction of contact-solvent corrections for multiple successive complexation processes (eqns 17-18) performed in excess of diglyme does not improve significantly the thermodynamic analysis (Figure 10). Consequently, the cooperativity factors for the successive binding of two $[La(hfa)_3]$ to **L4** ($\Delta E^{La-La} = 0.1(2)$ kJ/mol), **L5** ($\Delta E^{La-La} = 1.15(5)$ kJ/mol) and **L6** ($\Delta E^{La-La} = -0.8(2)$ kJ/mol)¹⁰ deduced from the simple site-binding model applied in absence of contact-solvent corrections (eqns 28-29) are reliable ($f_{asso}^{Lk,La}$ is the intrinsic affinity and ΔE^{La-La} is the closest-neighbor intersite interaction).¹⁰



$$\Delta G_{1,1,asso}^{Lk,La} = -RT \ln(\beta_{1,1,asso}^{Lk,La}) = -RT \ln(f_{asso}^{Lk,La}) - RT \ln(2) \quad (28)$$



$$\Delta G_{1,2,asso}^{Lk,La} = -RT \ln(\beta_{1,2,asso}^{Lk,La}) = -2RT \ln(f_{asso}^{Lk,La}) + \Delta E^{La-La} \quad (29)$$

Deciphering lipophilicity as a major issue for programming host-guest assemblies in solution.

Having now in hand a safe procedure for analysing the intrinsic affinities of lanthanide containers for tridentate binding sites, it is worth questioning the unsolved stepwise decrease of the latter parameter with the length of the oligomeric host (Figure 11).^{10,14} The logarithmic dependence of $-RT \ln(f_{asso}^{Lk,La})$ on the increasing size (N) of the multi-tridentate oligomers (Figure 11b) was tentatively assigned in reference 10 to the balance of solvation energies, which is controlled by the systematic freezing of rotational degrees of freedom accompanying the complexation of the entering metals to the receptors to give the target metallopolymers $\{PN[La(hfa)_3]_n\}$ ($1 \leq n \leq N$). However, a simple look at **PN** shows that the amount of lipophilic chains also linearly grows with the number of binding sites N and may therefore offer an alternative explanation, which is supported by the decrease of the affinities of the tridentate binding site for $[La(hfa)_3]$ in going from **L1** (no lipophilic hexyloxy chains,

$$\Delta G_{asso}^{L1,La} = -RT \ln(f_{asso}^{L1,La}) = -12.2 \text{ (1) kJ/mol) to } \mathbf{L3} \text{ (four lipophilic hexyloxy chains,$$

$$\Delta G_{asso}^{L3,La} - RT \ln(f_{asso}^{L3,La}) = -9.0(1) \text{ kJ/mol). Interestingly, the intrinsic affinity}$$

$\Delta G_{\text{asso}}^{\text{L4,La}} = -RT \ln(f_{\text{asso}}^{\text{L4,La}}) = -11.6(1) \text{ kJ/mol}$ of the dimeric ligand **L4**, which possesses two binding sites separated by a phenyl spacer bearing two hexyloxy chains, lies in between those of **L1** and **L3**.

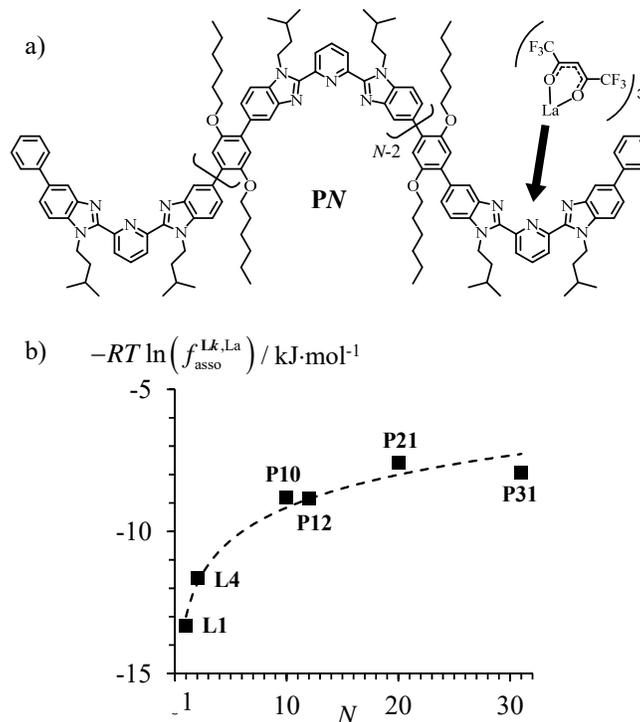


Figure 11 a) Chemical structures and b) Intrinsic association free energies $-RT \ln(f_{\text{asso}}^{\text{Lk,La}})$ for equilibrium (7) using monomeric ligand **L1** ($N = 1$), dimer **L4** ($N = 2$) and polymers **PN** ($N = 10, 12, 20, 31$) with $[\text{La}(\text{hfa})_3]$ (N is the number of available tridentate binding sites, $\text{CD}_2\text{Cl}_2 + 0.14 \text{ M diglyme}$, 298 K).^{10,14}

The non-symmetrical monomeric ligand **L7** (Figure 12a and Scheme 1) with two lipophilic hexyloxy chains thus represents the missing link for assigning the thermodynamic trend depicted in Figure 11 either to the larger size of the molecular receptor, or to the larger amount of lipophilic hexyloxy chains brought by the para-disubstituted phenylene spacers as N increases. The tricky synthesis of **L7** is reported in Appendix 2. $^1\text{H-NMR}$ titrations of **L7** with $[\text{La}(\text{hfa})_3(\text{dig})]$ conducted in absence of diglyme (Figure S9) and in presence of an excess (0.14 M) of diglyme (Figure 12 and Figure S10) indeed gave $\Delta G_{\text{asso}}^{\text{L7,La}} = -RT \ln(f_{\text{asso}}^{\text{L7,La}}) = -11.5(2) \text{ kJ/mol}$ (Table 1), a value intermediate between those found for the related monomeric ligands without lipophilic chain (**L1**) and that with four chains

(L3). Moreover, $\Delta G_{\text{asso}}^{\text{L7,La}}$ found for the non-symmetrical monomeric ligand **L7** exactly fits $\Delta G_{\text{asso}}^{\text{L4,La}} = -11.6(1)$ kJ/mol where two related tridentate sites are connected in the dimeric ligand **L4**.

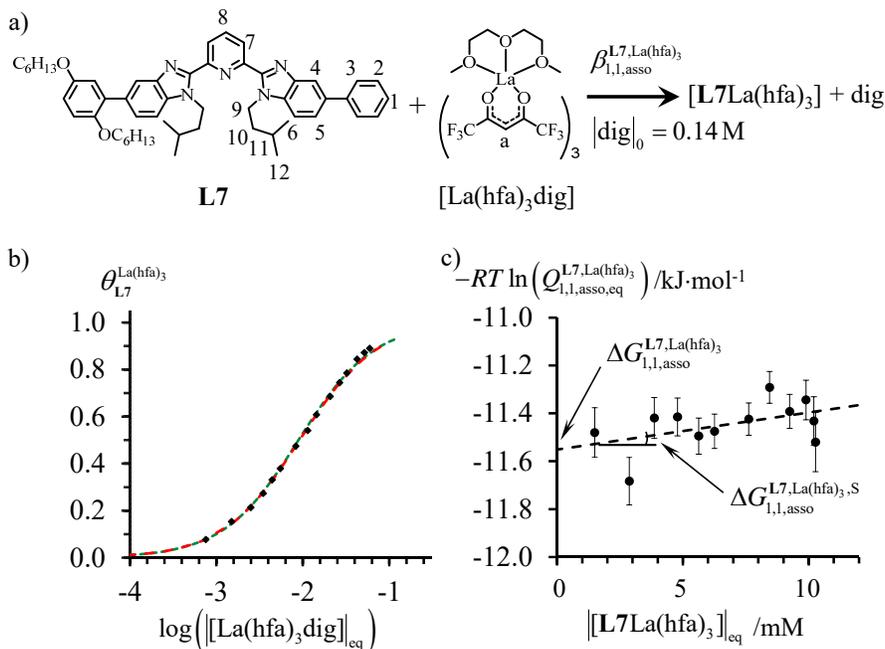
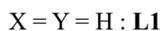
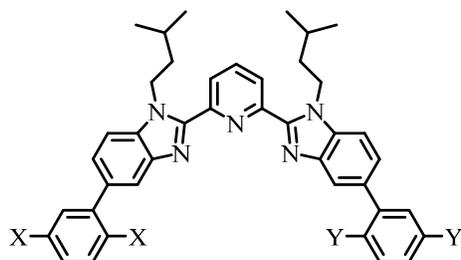


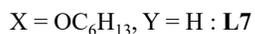
Figure 12 a) Association reaction between non-symmetrical ligand **L7** and $[\text{La}(\text{hfa})_3]\text{dig}$, b) experimental (diamonds) and fitted (dotted green traces using eqn 8; dashed red traces using eqn 11) binding isotherms for the titration of **L7** with $[\text{La}(\text{hfa})_3]\text{dig}$ in $\text{CD}_2\text{Cl}_2 + 0.14$ M diglyme at 298 K. c) Dependence of the equilibrium reaction quotients $-RT \ln(Q_{1,1,\text{asso,eq}}^{\text{L7,La}})$ on the progress of the association reaction highlighting $\Delta G_{1,1,\text{asso}}^{\text{L7,La}}$ and $\Delta G_{1,1,\text{asso}}^{\text{L7,La,S}}$ according to eqn (10).

We conclude that the surprising logarithmic dependence observed for the intrinsic affinity on the length of the polymer (Figure 11b) does not originate from the increasing number of connected binding sites as originally thought,¹⁰ but it is the result of the reduced intrinsic affinities of the tridentate binding units for $\text{La}(\text{hfa})_3$ when peripheral lipophilic 1,4-dihexyloxy-phenyl substituents are connected to the distal benzimidazole rings (Scheme 1). In other words, the lipophilic ligand **L3** may be considered as a valuable model of the binding sites in the bulk of the linear polymers **PN**, whereas **L7** is well-suited for modelling the terminal sites of these polymers. However, ligand **L1** is not pertinent for modelling any of the binding sites in polymer **PN**.



$$\Delta G_{\text{asso}}^{\mathbf{L7,La}} = -RT \ln(f_{\text{asso}}^{\mathbf{L1,La}}) = -13.2(6) \text{ kJ/mol}$$

$$f_{\text{asso}}^{\mathbf{L1,La}} = 242(12)$$



$$\Delta G_{\text{asso}}^{\mathbf{L7,La}} = -RT \ln(f_{\text{asso}}^{\mathbf{L7,La}}) = -11.5(2) \text{ kJ/mol}$$

$$f_{\text{asso}}^{\mathbf{L7,La}} = 108(4)$$



$$\Delta G_{\text{asso}}^{\mathbf{L3,La}} = -RT \ln(f_{\text{asso}}^{\mathbf{L3,La}}) = -9.5(8) \text{ kJ/mol}$$

$$f_{\text{asso}}^{\mathbf{L3,La}} = 46(4)$$

Scheme 1 Intrinsic binding affinities of monomeric ligands **L1**, **L3** and **L7** for $\text{La}(\text{hfa})_3$ in CD_2Cl_2 + 0.14 M diglyme at 298 K.

Conclusions

The host-guest assemblies between the neutral lanthanum carriers $[\text{La}(\beta\text{-diketonate})_3]$ and the tridentate N-donor binding sites found in ligands **L1-L7** unambiguously rely to non-ideal solute-solution mixtures in dichloromethane. The additional non-elusive enthalpic contribution to the mixing entropy modeled by the classical solution theory predicts that the equilibrium reaction quotients Q_{eq} deduced from molar speciation in solution (i) significantly deviate from the thermodynamic equilibrium constants β and (ii) depend on the total concentrations of hosts and guests (eqn 5). These previsions were experimentally confirmed by systematic NMR titrations (Figure 2). For an analytical chemist, this behavior is usually assigned to some changes in the activity coefficients γ_i and only setting them to a fixed value during the complete titrations is acceptable for restoring standard binding isotherms reminiscent to those observed in ideal solution ($\gamma_i = 1$). This situation is common for reactions involving ionic partners in polar solvents and the Debye-Hückel approach demonstrates that a large and constant ionic strength ensures constant activity coefficients. For host-guest associations

involving neutral partners, the rough consideration of the classical solution theory limited to binary mixtures combined with Margules equation (summarized in eqn 5) suggests that setting one of the partner of the reaction at large and constant concentration should restore a proportionality between thermodynamic stability constant β and equilibrium reaction quotients Q_{eq} . We therefore decided to set the concentration of diglyme (dig) at 0.14 M for our association reactions summarized in eqn (6), which corresponds to a sufficient excess for considering the concentration of this partner of the reaction as dominant and constant during the NMR titrations of ligands **L1-L7** with $[\text{La}(\beta\text{-diketonate})_3\text{dig}]$ containers. In these conditions, only minor drift could be detected between the ideal binding isotherms (dashed green traces in Figures 3a, 10 and 12) and the experimental occupancy factors (black diamonds in these Figures). We therefore recommend this approach for the easy collection of conditional stability constants pertinent to association processes involving neutral partners in non-ideal solution. When working with pure solvents with no excess of a given partner of the reaction in solution, the fluctuation of the activity coefficients with the evolution of the non-ideal mixtures prevents the extraction of pertinent stability constants from the various equilibrium reaction quotients (see for instance the green traces in Figures 4b, 5b and 6b). Based on some interesting and chemically-intuitive considerations of the solvent reorganization processes which accompany the host-guest assembly depicted in eqn (9), Castellano and Eggers⁶ proposed that the deviation from ideality estimated by $RT\xi\left[1 - \left(c_{\text{L}}^{\text{tot}} + c_{\text{M}}^{\text{tot}} - c_{\text{LM}}^{\text{eq}}/c_{\text{B}}\right)\right]^2$ in eqn (5) in terms of free-energy, could be modeled using a simple linear correction $\Delta G^{\text{S}} \cdot c_{\text{LM}}^{\text{eq}}$ in Eq. (10) (Appendix 1). ΔG^{S} thus stands for some additional changes in solvent-solute contact interactions, which are not taken into account by the chemical potential of the pure solvent and of the pure partners. The empirical application of eqn (10) to the NMR titrations of monomeric ligands **L1-L3** and **L7** indeed show roughly linear plots between $-RT\ln(Q_{\text{eq}})$ and $c_{\text{LM}}^{\text{eq}}$ (see Figures 4a, 5c, 6c and 12), a behaviour paralleled in two dimensions when using di-tridentate ligands **L4-L6** with two available binding sites (Figure 9). This gives access to the the free-energy change $\Delta G_{\text{I},\text{I}}^{\text{L},\text{M}}$ at infinite dilution ($c_{\text{LM}}^{\text{eq}} \rightarrow 0$), which is related to

a thermodynamic equilibrium constant $\beta_{1,1}^{L,M} = e^{-\Delta G_{1,1}^{L,M}/RT}$, together with a second parameter ΔG^S , which measures the sensitivity of the activity coefficients to the exact composition of the non-ideal mixture. The often huge experimental values estimated for ΔG^S (hundreds to thousands of $\text{kJ}\cdot\text{mol}^{-1}$ in Tables 1-2) prevent its interpretation as a straightforward balance of solvation energies brought by the replacement of the reactants with products during the chemical reaction because the Onsager equation returns maximum few tens of $\text{kJ}\cdot\text{mol}^{-1}$ for the solvation energies of these complexes and ligands in dichloromethane.¹⁰ Whatever its theoretical justification, ΔG^S can be considered by experimental coordination chemists as a constant specific to a given solvent and a specific reaction which transforms the equilibrium reaction quotients $Q_{1,1,\text{eq}}^{L,M}$ obtained by speciation at equilibrium into a single thermodynamic constant at infinite dilution $\beta_{1,1}^{L,M}$. This approach restores some pertinent comparisons between intrinsic affinities recorded for various ligands (Scheme 1) and different lanthanide containers (Table 2) in a given solvent. It is probably worth mentioning here that the addition of external chemical species, not involved in the chemical reaction, is expected to change the magnitude of $\Delta G_{1,1}^{L,M}$ and ΔG^S because the nature of the solvent has changed. However, there is no reason for inducing any significant reduction of the fluctuation of the activity coefficients during the titrations. This statement was confirmed by repeating the ^1H -NMR titrations of **L1-L3** in dichloromethane by adding 0.2 M of either benzene (Figure S11) or NBu_4PF_6 (Figure S12), which indeed show no smoothing in the change of the activity coefficients of the reacting partners (Tables S8-S9).

ASSOCIATED CONTENT

Supporting Information

Derivation of eqn (10) (Appendix 1), synthesis of ligand **L7** (Appendix 2), tables of crystal data, geometric parameters and thermodynamic data. Figures showing molecular structures, ^1H NMR titrations and thermodynamic binding isotherms. This material is available free of charge *via* the

internet at <http://pubs.acs.org>. CCDC 1902650 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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TOC

The straightforward 1:1 associations between neutral partners occurring in organic solvents (black dots) dramatically deviate from standard thermodynamics pertinent to ideal solutions (green trace). Some alternative approaches are explored for restoring simple procedures for extracting reliable stability constants in real solutions (red trace).

