Application of Castellano-Eggers' solvation theory to multiple association processes

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Theoretical background

According to standard thermodynamics, the formation of a [HG$_n$] assembly (eq. 1, H = host, G = guest) is associated with a global energy change $\Delta G_{1,n}^{\mathrm{H,G}} = -RT \ln\left(\beta_{1,n}^{\mathrm{H,G}}\right)$, which can be partitioned into n successive contributions (eq. 2$_n$), so that $\Delta G_{1,n}^{\mathrm{H,G}} = -RT \sum_{i=1}^{n} \ln\left(K_i^{\mathrm{G}}\right)$.[CP1]

$$\mathrm{H} \quad + \quad n\,\mathrm{G} \quad \rightleftharpoons \quad [\mathrm{HG}_n] \qquad\qquad \Delta G_{1,n}^{\mathrm{H,G}} = -RT \ln\left(\beta_{1,n}^{\mathrm{H,G}}\right) \qquad (1)$$

$$\mathrm{H} \quad + \quad \mathrm{G} \quad \rightleftharpoons \quad [\mathrm{HG}] \qquad\qquad \Delta G_{1}^{\mathrm{H,G}} = -RT \ln\left(K_1^{\mathrm{G}}\right) \qquad (2_1)$$

$$\mathrm{HG} \quad + \quad \mathrm{G} \quad \rightleftharpoons \quad [\mathrm{HG}_2] \qquad\qquad \Delta G_{2}^{\mathrm{H,G}} = -RT \ln\left(K_2^{\mathrm{G}}\right) \qquad (2_2)$$

$$\vdots$$

$$\mathrm{HG}_{n\text{-}1} \quad + \quad \mathrm{G} \quad \rightleftharpoons \quad [\mathrm{HG}_n] \qquad\qquad \Delta G_{n}^{\mathrm{H,G}} = -RT \ln\left(K_n^{\mathrm{G}}\right) \qquad (2_n)$$

For analytical, coordination and supramolecular chemists, the searched free-energy changes are deduced from the thermodynamic stability constants by using van't Hoff equation (3), in which the equilibrium constant $\beta_{1,n}^{\mathrm{H,G}}$ is deduced from the quotient of reaction $Q_{1,n}^{\mathrm{H,G}}$ expressed in concentration units (we assume that the standard concentration of the reference state is fixed at $c^{\theta} = 1$ mol·l^{-1}) and measured at equilibrium $Q_{1,n,\mathrm{eq}}^{\mathrm{H,G}}$. For ideal solution (i.e. at infinite dilution), the activity coefficients are set to $\gamma_i = 1$, and any deviations from ideal conditions can be taken into account by the application of a pertinent set of activity coefficients ($\gamma_i \neq 1$).

$$\beta_{1,n}^{\mathrm{H,G}} = \exp\left(-\Delta G_{1,n}^{\mathrm{H,G}} / RT\right) = \frac{\gamma_{\mathrm{HG}_n}}{\gamma_{\mathrm{H}} \cdot \left(\gamma_{\mathrm{G}}\right)^n} \cdot \frac{\left(\left|\mathrm{HG}_n\right|_{\mathrm{eq}} / c^{\theta}\right)}{\left(\left|\mathrm{H}\right|_{\mathrm{eq}} / c^{\theta}\right)\left(\left|\mathrm{G}\right|_{\mathrm{eq}} / c^{\theta}\right)^n} = \frac{\gamma_{\mathrm{HG}_n}}{\gamma_{\mathrm{H}} \cdot \left(\gamma_{\mathrm{G}}\right)^n} Q_{1,n,\mathrm{eq}}^{\mathrm{H,G}} \qquad (3)$$

For association reactions involving charged particles, the Debye-Hückel theory of the ionic atmosphere exploits the concept of ionic strength for fixing, rationalizing and predicting the magnitudes of the activity coefficients.[CP1] Consequently, the vast majority of association constants has been determined at large, fixed and invariant ionic strengths duly mentioned with the experimental data.[CP2] When the latter conditional approach is not followed, the quotient of reaction may vary during the titration process, thus preventing a direct link with thermodynamic constants. In this context, Castellano and Eggers[CP3] indeed noticed that the experimentally accessible conditional quotient of the simple association reaction $Q_{1,1,\text{cond}}^{\text{EDTA,Ca}} = \left(\left| \text{Ca}\left(\text{EDTA}\right) \right|_{\text{eq}} \Big/ \left| \text{Ca} \right|_{\text{eq}} \left| \text{EDTA} \right|_{\text{tot}}^{\text{unbound}} \right)$ is not constant along the titration of 2,2',2'',2'''-(ethane-1,2-diyldinitrilo)tetraacetic acid (= EDTA) with divalent calcium Ca^{2+} in buffered aqueous solution at fixed pH (eq. 4).

$$\text{EDTA} + \text{Ca}^{2+} \; \rightleftharpoons \; [\text{Ca(EDTA)}]^{2+} \qquad \beta_{1,1,\text{cond}}^{\text{EDTA,Ca}} = \frac{\gamma^{\text{CaEDTA}}}{\gamma^{\text{EDTA}}\gamma^{\text{Ca}}} \cdot \frac{\left| \text{Ca}\left(\text{EDTA}\right) \right|_{\text{eq}}}{\left| \text{Ca} \right|_{\text{eq}} \left| \text{EDTA} \right|_{\text{tot}}^{\text{unbound}}} \qquad (4)$$
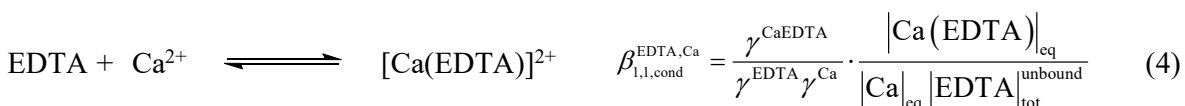
This embarassing trend can be circumvented by the selection of judicious sets of activity coefficients for each mixture considered during the titration, which restores constant reaction quotients for any total guest and host concentrations. This approach is commonly used when dealing with association processes occurring in (very) complicated media encountered in biology and biochemistry, where low concentrations of hosts and guests are dispersed within aqueous buffers containing inorganic salts for fixing the activity coefficients.[CP4] However, supramolecular chemists, who often deal with non-charged partners reacting at relatively high concentrations (millimolar or larger) for being monitored by NMR techniques, have no toolkit in hand for catching the imprevisible changes of the activity coefficients during their titration processes.[CP5] An alternative strategy has thus been proposed by Castellano and Eggers for 1:1 host-guest association processes (eq. 5). They explicitely considered the change in chemical potential produced by the subset of solvent molecules in contact with reactants (S^{solv}), which are released into the bulk (S^{bulk}),

a contribution not accounted for by the chemical potential of the pure species (including specific solvation 'spheres') and which may be at the origin of the variation of the activity coefficients.[CP3]

$$H \quad + \quad G \quad + \quad p\,S^{\text{Solv}} \quad \rightleftharpoons \quad [HG] \quad + \quad p\,S^{\text{bulk}} \tag{5}$$
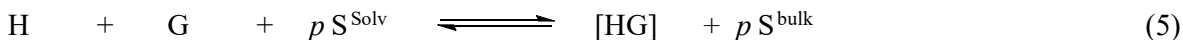
The thorough application of chemical potentials to equilibrium 5 led to eq. 6, which assigns the variation of the activity coefficients to the stepwise change in the chemical potential of the solvent accompanying the accumulation of the final [HG] complex.[CP3]

$$-RT\ln\left(Q_{1,1}^{H,G}\right) = -RT\ln\left(\beta_{1,1}^{H,G}\right) + \frac{\left|HG\right|_{eq}}{c^{\theta}}\Delta G^{S} \tag{6}$$

Assuming eq. 6, the experimentally accessible quotient of the reaction at equilibrium $Q_{1,1}^{H,G} = \dfrac{\left|HG\right|_{eq}}{\left|H\right|_{eq}\left|G\right|_{eq}}$ now depends on (i) a true thermodynamic stability constant $\beta_{1,1}^{H,G}$ extrapolated at infinite dilution (i.e. when $\left|HG\right|_{eq} \to 0$) and (ii)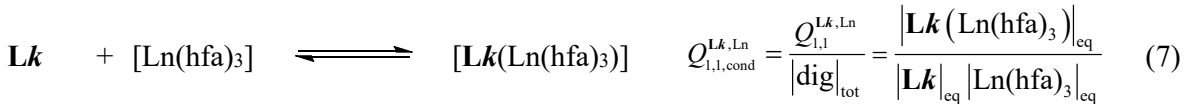 a free energy change ΔG^{S} in the surface solvation (i.e. disordered second-sphere solvation for coordination chemists) accompanying the transformation of the reactants into products. In simple words, eq. 6 restores a straightforward access to a true thermodynamic constant $\beta_{1,1}^{H,G}$, pertinent to the determination of free energy changes accompanying the 1:1 asssociation process in ideal solution.
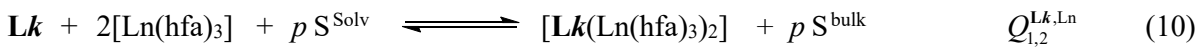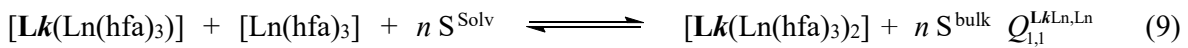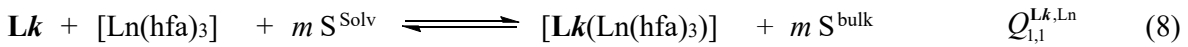

R = H : **L1**
R = OCH$_3$: **L2**
R = OC$_6$H$_{13}$: **L3**

+

[Ln(hfa)$_3$dig]

$$\xrightarrow[\text{CH}_2\text{Cl}_2]{\beta_{1,1,\text{exch}}^{\textbf{L}k,\text{Ln}}}$$

(7)

[Ln(hfa)$_3$**L**k]

+

dig
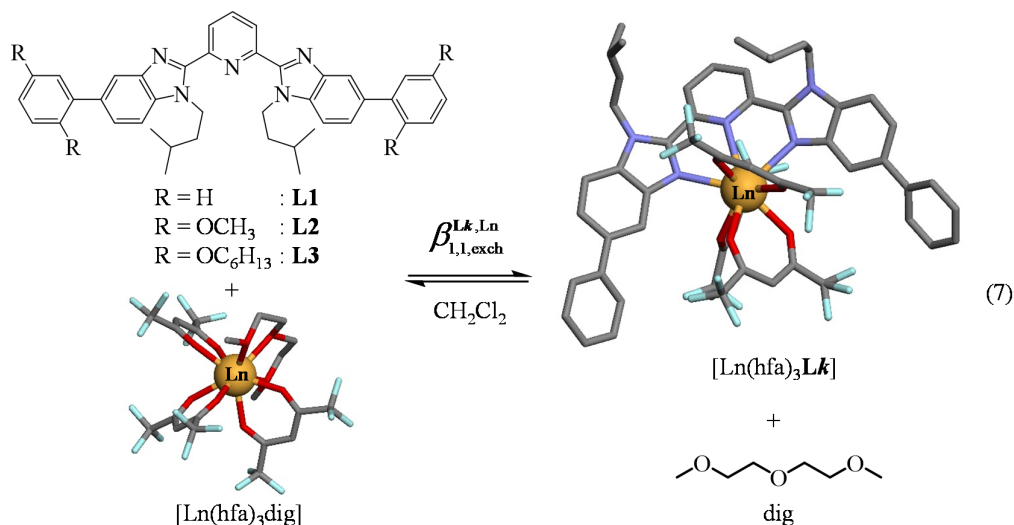
Scheme 1 Host−guest association involving the exchange of diglyme (dig) with tridentate ligand **L1-L3** around [Ln(hfa)₃] (Ln = trivalent lanthanide).

The recent titrations of tridentate ligands **L1**-**L3** (*i.e.* the host H) with neutral lanthanide containers [Ln(hfa)$_3$(dig)] (*i.e.* the guest where hfa = hexafluoroacetylacetonate and dig = 2-(2-methoxyethoxy)ethane)) in non-polar dichloromethane indeed gave 1:1 adducts [**Lk**(Ln(hfa)$_3$)] obeying eq. 6 (Scheme 1).[CP6] Interestingly, the contribution of contact solvation ΔG^S is maximum for titrations displaying large relative variations in the concentrations of the various partners. When the concentration of one partner is largely dominant and thus considered as invariant during the titration process, the effect of ΔG^S is reduced by orders of magnitude. This conditional approach restores nearly constant activity coefficients. Consequently, the conditional association shown in eq. 7 can be satisfyingly fitted with the usual approximation $Q_{1,1}^{H,G} = \dfrac{\left|HG\right|_{eq}}{\left|H\right|_{eq}\left|G\right|_{eq}} \simeq \beta_{1,1}^{H,G}$ at millimolar concentrations according that the total diglyme concentration $\left|dig\right|_{tot}$ is in large excess.[CP6]

$$\mathbf{L}k \quad + \quad [Ln(hfa)_3] \quad \rightleftharpoons \quad [\mathbf{L}k(Ln(hfa)_3)] \qquad Q_{1,1,cond}^{\mathbf{L}k,Ln} = \frac{Q_{1,1}^{\mathbf{L}k,Ln}}{\left|dig\right|_{tot}} = \frac{\left|\mathbf{L}k\left(Ln(hfa)_3\right)\right|_{eq}}{\left|\mathbf{L}k\right|_{eq}\left|Ln(hfa)_3\right|_{eq}} \qquad (7)$$
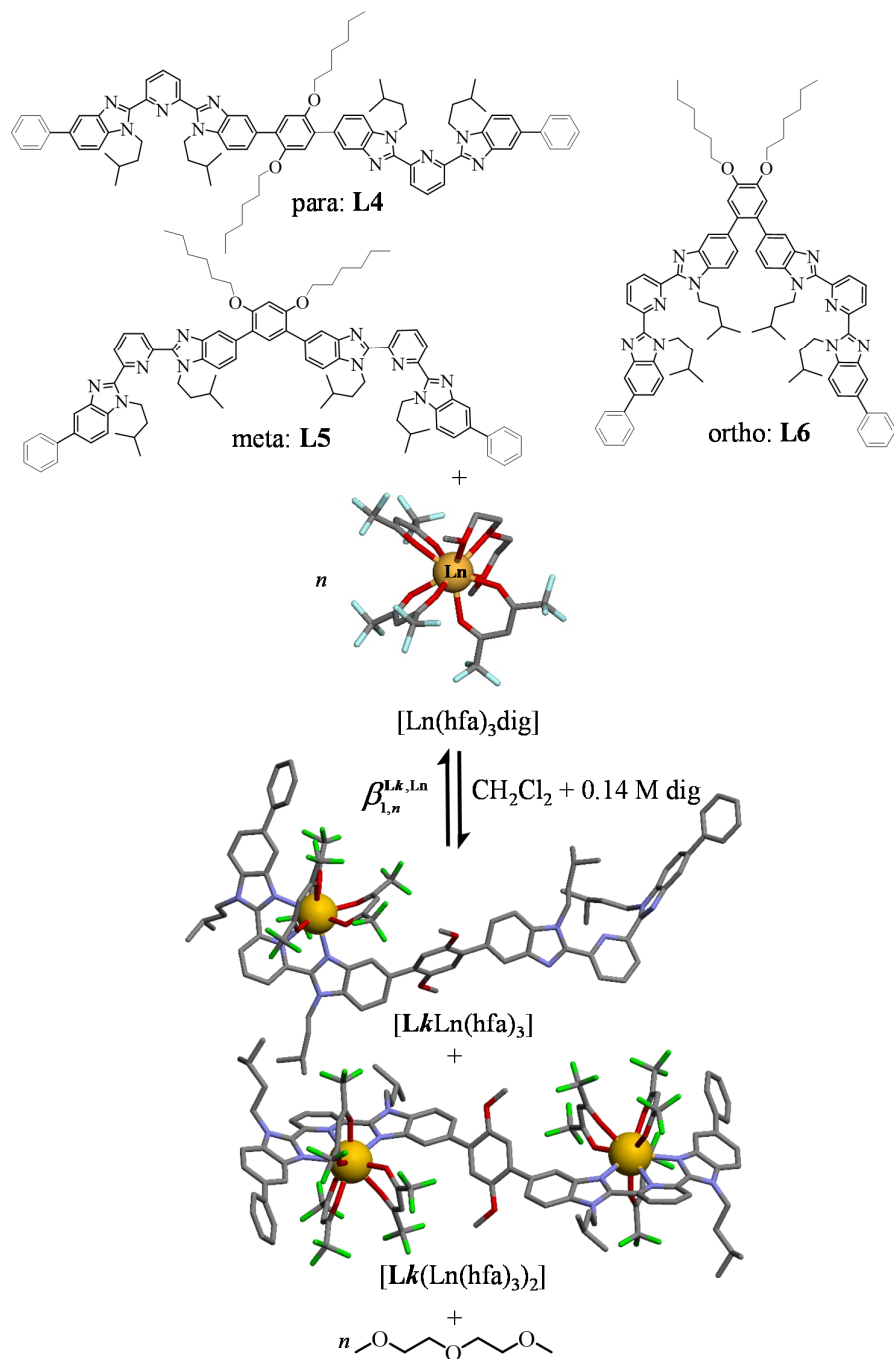
However, in coordination and supramolecular chemistry, the consideration of a single equilibria is rare and the Castellano and Eggers strategy illustrated in Eqs 5-6 lead to major inconsistencies when the successive binding processes shown in eqs 2$_n$ are considered. Let's illustrate this point with the successive fixation, at large and constant concentration of diglyme, of two [Ln(hfa)$_3$] guests to the di-tridentate host ligands **L4**-**L6**, the latter differing only by the geometries of the phenyl spacers (eqs 8-10 and Scheme 2).

$$\mathbf{L}k + [Ln(hfa)_3] + m\,S^{Solv} \rightleftharpoons [\mathbf{L}k(Ln(hfa)_3)] + m\,S^{bulk} \qquad Q_{1,1}^{\mathbf{L}k,Ln} \qquad (8)$$

$$[\mathbf{L}k(Ln(hfa)_3)] + [Ln(hfa)_3] + n\,S^{Solv} \rightleftharpoons [\mathbf{L}k(Ln(hfa)_3)_2] + n\,S^{bulk} \quad Q_{1,1}^{\mathbf{L}kLn,Ln} \qquad (9)$$

$$\mathbf{L}k + 2[Ln(hfa)_3] + p\,S^{Solv} \rightleftharpoons [\mathbf{L}k(Ln(hfa)_3)_2] + p\,S^{bulk} \qquad Q_{1,2}^{\mathbf{L}k,Ln} \qquad (10)$$

Whereas standard thermodynamic requires $\Delta G_{1,2}^{\mathbf{L}k,Ln} = \Delta G_{1,1}^{\mathbf{L}k,Ln} + \Delta G_{1,1}^{\mathbf{L}kLn,Ln}$, it is obvious that the application of eq. 6 to equilibria (8)-(10) introduces an innaceptable drift, which can be expressed as:

$$\Delta G_{1,2}^{\mathbf{L}k,\mathrm{Ln},0} = -RT\ln\left(Q_{1,2}^{\mathbf{L}k,\mathrm{Ln}}\right) - \left|\mathbf{L}k\mathrm{Ln}_2\right|\Delta G_{2,1}^{\mathbf{L}k,\mathrm{Ln},S}$$

$$\neq -RT\ln\left(Q_{1,1}^{\mathbf{L}k,\mathrm{Ln}}\cdot Q_{1,1}^{\mathbf{L}k\mathrm{Ln},\mathrm{Ln}}\right) - \left|\mathbf{L}k\mathrm{Ln}_2\right|\Delta G_{1,1}^{\mathbf{L}k\mathrm{Ln},\mathrm{Ln},S} - \left|\mathbf{L}k\mathrm{Ln}\right|\Delta G_{1,1}^{\mathbf{L}k,\mathrm{Ln},S} = \Delta G_{1,1}^{\mathbf{L}k,\mathrm{Ln},0} + \Delta G_{1,1}^{\mathbf{L}k\mathrm{Ln},\mathrm{Ln},0}$$

para: **L4**

meta: **L5**

ortho: **L6**

+

n

[Ln(hfa)$_3$dig]

$\beta_{1,n}^{\mathbf{L}k,\mathrm{Ln}}$ ⇅ CH$_2$Cl$_2$ + 0.14 M dig

[**L**kLn(hfa)$_3$]

+

[**L**k(Ln(hfa)$_3$)$_2$]

+

n

Scheme 2. Host−guest association involving the exchange of diglyme (dig) with di-tridentate ligand **L4-L6** around [Ln(hfa)$_3$] (Ln = trivalent lanthanide).

This discrepancy originates from the controbution of contact solvation, which considers different corrections for the formation of [**L**k(Ln(hfa)$_3$)$_2$] and [**L**k(Ln(hfa)$_3$)$_2$] complexes. In other words, for

our simple case, $[\mathbf{L}k(\mathrm{Ln(hfa)_3})_2]$ formed by the successive complexation equilibrium (9) is accompanied by a contact solvation correction transforming $[\mathbf{L}k(\mathrm{Ln(hfa)_3})_2]$ and $[\mathrm{Ln(hfa)_3}]$ which is different from that considered in equilibrium (10) for the formation of the same complex, but from two $[\mathrm{Ln(hfa)_3}]$ metal contained and one $\mathbf{L}k$ ligands. This limitation can be overcome by considering the sum of the two successive complexation reactions (eq. 11).

$$2\,\mathbf{L}k \;+\; 3[\mathrm{Ln(hfa)_3}] + r\,\mathrm{S}^{\,\mathrm{Solv}} \;\rightleftharpoons\; [\mathbf{L}k(\mathrm{Ln(hfa)_3})] + [\mathbf{L}k(\mathrm{Ln(hfa)_3})_2] + r\,\mathrm{S}^{\,\mathrm{bulk}} \qquad Q_{2,3}^{\mathbf{L}k,\mathrm{La}} \quad (11)$$
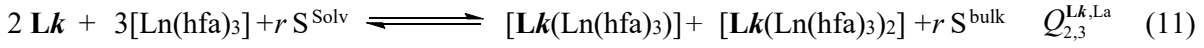
Eq. 6 is restored and yields

$$-RT\ln\left(Q_{2,3}^{\mathbf{L}k,\mathrm{Ln}}\right) = \Delta G_{2,3}^{\mathbf{L}k,\mathrm{Ln},0} + \left|\mathbf{L}k\mathrm{Ln}\right|\Delta G_{1,1}^{\mathbf{L}k,\mathrm{Ln},\mathrm{S}} + \left|\mathbf{L}k\mathrm{Ln}_2\right|\Delta G_{2,1}^{\mathbf{L}k,\mathrm{Ln},\mathrm{S}} \qquad (12)$$

from which only the true thermodynamic constant corresponding to the sum of the two cumulative association reactions is accessible. In this chapter, we will explore three different models (eqs (13)-(17)) for analyzing the experimental speciation previously reported for the ^{1}H NMR titration of the di-tridentate ligands **L4-L6** (i.e. the host H) with the neutral lanthanide container $[\mathrm{La(hfa)_3}]$ in presence of a large excess of diglyme in dichloromethane at room temperature.[CP7]

Model 1: No disruption of the chemical potential of the solvent

$$-RT\ln\left(Q_{1,1}^{\mathbf{L}k,\mathrm{La}}\right) = \Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},0} \qquad (13)$$

$$-RT\ln\left(Q_{1,2}^{\mathbf{L}k,\mathrm{La}}\right) = \Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},0} \qquad (14)$$

Model 2: Disruption of the chemical potential of the solvent with no mixture of successive complexes

$$-RT\ln\left(Q_{1,1}^{\mathbf{L}k,\mathrm{La}}\right) = \Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},0} + \left|\mathbf{L}k\mathrm{Ln}\right|\Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},\mathrm{S}} \qquad (15)$$

$$-RT\ln\left(Q_{1,2}^{\mathbf{L}k,\mathrm{La}}\right) = \Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},0} + \left|\mathbf{L}k\mathrm{Ln}_2\right|\Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},\mathrm{S}} \qquad (16)$$

Model 3: Disruption of the chemical potential of the solvent including mixture of successive complexes

$$-RT\ln\left(Q_{2,3}^{\mathbf{L}k,\mathrm{La}}\right) = \Delta G_{2,3}^{\mathbf{L}k,\mathrm{La},0} + \left|\mathbf{L}k\mathrm{Ln}\right|\Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},\mathrm{S}} + \left|\mathbf{L}k\mathrm{Ln}_2\right|\Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},\mathrm{S}} \qquad (17)$$

Results and Discussions

Model 1: No disruption of the chemical potential of the solvent. The free energy changes are completely explained by the balance of the chemical potentials between the products and reactants, this including solvent reorganization as it can be identified within each partner of the reaction taken as pure compounds. The quotients of the cumulative complexation reactions (8) and (10), calculated along the titration procedure, are considered as constant and assigned to the thermodynamic constants $\beta_{1,1}^{\mathbf{L}k,\mathrm{La}} = Q_{1,1}^{\mathbf{L}k,\mathrm{La}}$ and $\beta_{1,2}^{\mathbf{L}k,\mathrm{La}} = Q_{1,2}^{\mathbf{L}k,\mathrm{La}}$ (Table 1, entries 1-2). The integration of the signals obtained in the ^{1}H NMR spectra for $\mathbf{L}k$ ($I_{\mathbf{L}k}^{\mathrm{H}}$), [$\mathbf{L}k$Ln(hfa)$_3$] ($I_{\mathbf{L}k\mathrm{Ln}}^{\mathrm{H}}$ taken as the sum of two non-equivalent protons located on the two binding sites) and [$\mathbf{L}k$(Ln(hfa)$_3$)$_2$] ($I_{\mathbf{L}k\mathrm{Ln}_2}^{\mathrm{H}}$) provides the occupancy factors $\theta_{\mathbf{L}k}^{\mathrm{Ln}}$ (eq 18)[CP7] together with the concentration of free host $\left|\mathrm{Ln(hfac)}_3\right| = \left|\mathrm{Ln}\right| = \left|\mathrm{Ln}\right|_{\mathrm{tot}} - \theta_{\mathbf{L}k}^{\mathrm{Ln}} \cdot N \cdot \left|\mathbf{L}k\right|_{\mathrm{tot}}$, from which the well-known binding isotherms are built in Figure 1 (red dots).

$$\theta_{\mathbf{L}k}^{\mathrm{Ln}} = \frac{1}{2}\frac{\left|\mathrm{Ln}\right|_{\mathrm{bound}}}{\left|\mathbf{L}k\right|_{\mathrm{tot}}} = \frac{\left|\mathrm{Ln}\right|_{\mathrm{tot}} - \left|\mathrm{Ln}\right|}{2\left|\mathbf{L}k\right|_{\mathrm{tot}}} = \frac{1}{2}\cdot\frac{I_{\mathbf{L}k\mathrm{Ln}}^{\mathrm{H}} + 2\left(I_{\mathbf{L}k\mathrm{Ln}_2}^{\mathrm{H}}\right)}{I_{\mathbf{L}k}^{\mathrm{H}} + I_{\mathbf{L}k\mathrm{Ln}}^{\mathrm{H}} + I_{\mathbf{L}k\mathrm{Ln}_2}^{\mathrm{H}}} = \frac{\beta_{1,1}^{\mathbf{L}k,\mathrm{Ln}}\left|\mathrm{Ln}\right| + 2\beta_{1,2}^{\mathbf{L}k,\mathrm{Ln}}\left|\mathrm{Ln}\right|^2}{2\left(1 + \beta_{1,1}^{\mathbf{L}k,\mathrm{Ln}}\left|\mathrm{Ln}\right| + \beta_{1,2}^{\mathbf{L}k,\mathrm{Ln}}\left|\mathrm{Ln}\right|^2\right)} \qquad (18)$$

Table 1. Cumulative formation constants ($\beta_{1,1}^{\mathbf{L}k,\mathrm{La}}$ and $\beta_{1,2}^{\mathbf{L}k,\mathrm{La}}$; eqs 13-14), associated free energy changes $\Delta G_{1,1}^{\mathbf{L}k,\mathrm{La}}$ and $\Delta G_{1,2}^{\mathbf{L}k,\mathrm{La}}$, binding affinities $f_{\mathbf{L}k}^{\mathrm{La}}$ (eq 19) and cooperativity factors $u_{\mathbf{L}k}^{\mathrm{La\text{-}La}}$ (eq 20) for the titration of $\mathbf{L}k$ with [La(hfa)$_3$(dig)] in CH$_2$Cl$_2$ + 0.14 M diglyme (298 K).[CP7]

Ligand	L4	L5	L6
$\log\left(\beta_{1,1}^{\mathbf{L}k,\mathrm{La}}\right)$	2.34(1)	2.09(1)	2.53(1)
$\log\left(\beta_{1,2}^{\mathbf{L}k,\mathrm{La}}\right)$	4.07(3)	3.38(1)	4.59(3)
$\Delta G_{1,1}^{\mathbf{L}k,\mathrm{La}}$ /kJ·mol^{-1}	-13.4(1)	-11.92(4)	-14.4(1)
$\Delta G_{1,2}^{\mathbf{L}k,\mathrm{La}}$ /kJ·mol^{-1}	-23.2(2)	-19.25(7)	-26.2(2)
$f_{\mathbf{L}k}^{\mathrm{La}}$	110(2)	61(1)	167(2)
$u_{\mathbf{L}k}^{\mathrm{La\text{-}La}}$	0.97(6)	0.63(1)	1.4(1)
$\Delta G_{\mathbf{L}k,\mathrm{aff}}^{\mathrm{La}}$ /kJ·mol^{-1}	-11.7(1)	-10.20(4)	-12.7(1)
$\Delta E_{\mathbf{L}k}^{\mathrm{La\text{-}La}}$ /kJ·mol^{-1}	0.1(2)	1.15(5)	-0.8(2)
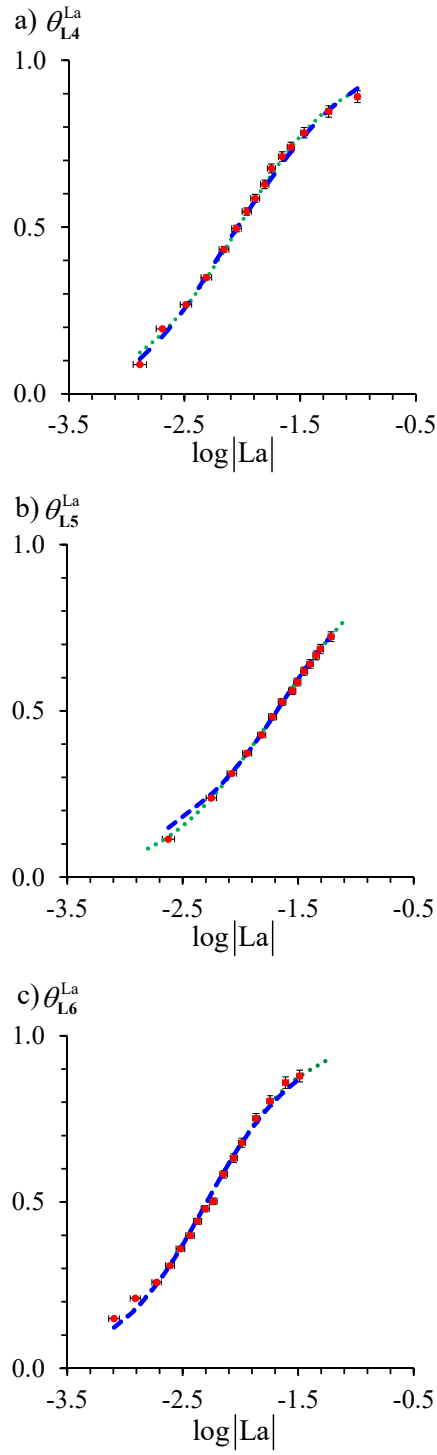
Figure 1. Binding isotherms (red dots) for the titrations of a) **L4**, b) **L5** and c) **L6** with [La(hfa)₃dig)] in CH_2Cl_2 + 0.14 M dig (298 K).[CP7] The dotted green traces correspond to the best fits using eqs (13)-(14) and $\beta_{1,1}^{Lk,Ln}$ and $\beta_{1,2}^{Lk,Ln}$ collected in Table 1 (model 1). The dashed blue traces correspond to the best fits obtained with eqs (15)-(16) and the thermodynamic parameters gathered in Table 2 (model 2).

Non-linear least-square fits of the binding isotherm with eq. (18) (right part) give the thermodynamic constants $\beta_{1,1}^{\mathbf{L}k,\mathrm{Ln}}$ and $\beta_{1,2}^{\mathbf{L}k,\mathrm{Ln}}$ from which the free energy changes $\Delta G_{1,1}^{\mathbf{L}k,\mathrm{Ln}} = -RT\ln\left(\beta_{1,1}^{\mathbf{L}k,\mathrm{Ln}}\right)$ and $\Delta G_{1,2}^{\mathbf{L}k,\mathrm{Ln}} = -RT\ln\left(\beta_{1,2}^{\mathbf{L}k,\mathrm{Ln}}\right)$, and the binding affinities $\Delta G_{\mathbf{L}k,\mathrm{aff}}^{\mathrm{Ln}} = -RT\ln\left(f_{\mathbf{L}k}^{\mathrm{Ln}}\right)$ (eq 19)[CP7] and cooperativity factors $\Delta E_{\mathbf{L}k}^{\mathrm{Ln\text{-}Ln}} = -RT\ln\left(u_{\mathbf{L}k}^{\mathrm{Ln\text{-}Ln}}\right)$ (eq 20)[CP7] are collected in Table 1.

$$\Delta G_{1,1}^{\mathbf{L}k,\mathrm{Ln}} = -RT\ln\left(2f_{\mathbf{L}k}^{\mathrm{Ln}}\right) = \Delta G_{\mathbf{L}k,\mathrm{aff}}^{\mathrm{Ln}} - RT\ln(2) \tag{19}$$

$$\Delta G_{1,2}^{\mathbf{L}k,\mathrm{Ln}} = -RT\ln\left(\left(f_{\mathbf{L}k}^{\mathrm{Ln}}\right)^2 u_{\mathbf{L}k}^{\mathrm{Ln\text{-}Ln}}\right) = 2\Delta G_{\mathbf{L}k,\mathrm{aff}}^{\mathrm{Ln}} + \Delta E_{\mathbf{L}k}^{\mathrm{Ln\text{-}Ln}} \tag{20}$$

According that the tridentate binding units are identical in the three ligands **L4**-**L6** (Scheme 2), the minor decrease in intrinsic affinities $\left|\Delta G_{\mathbf{L6},\mathrm{aff}}^{\mathrm{La}}\right| > \left|\Delta G_{\mathbf{L4},\mathrm{aff}}^{\mathrm{La}}\right| > \left|\Delta G_{\mathbf{L5},\mathrm{aff}}^{\mathrm{La}}\right|$ (Table 1, entry 7) can be tentatively assigned to minor change in primary sphere solvation/desolvation processes controlled by the various sizes and shapes of the free ligands and of the final complexes.[CP7] Interestingly, one notes that the (very) minor cooperative effects $\Delta E_{\mathbf{L}k}^{\mathrm{Ln\text{-}Ln}}$, all much below thermal energy of 2.5 kJ·mol^{-1} at room temperature, follow the same trend with favorable successive metallic binding for ortho-ligand **L6** ($\Delta E_{\mathbf{L6}}^{\mathrm{La\text{-}La}}$ = -0.8(2) kJ/mol), essentially no effect for para-ligand **L4** ($\Delta E_{\mathbf{L4}}^{\mathrm{La\text{-}La}}$ = 0.1(2) kJ/mol) and weak anti-cooperativity for **L5** ($\Delta E_{\mathbf{L5}}^{\mathrm{La\text{-}La}}$ = 1.15(5) kJ/mol). With this model, the experimental binding isotherms (red dots in Figure 1) are satisfyingly reproduced (green doted traces in Figure 1).[CP7]

Model 2: Disruption of the chemical potential of the solvent with no mixture of successive complexes. The straightforward consideration of eqs (15)-(16) predicts a linear dependence of the quotients of the cumulative complexation reactions with the concentrations of the complexes [**L**kLa(hfa)₃] and [**L**k(La(hfa)₃)₂] formed in solution. The pertinent plots are depicted in Figures 2-3 and they confirm the existence of some rough linear correlations, but with considerable statistical errors and scatering. The associated thermodynamic parameters are collected in Table 2.
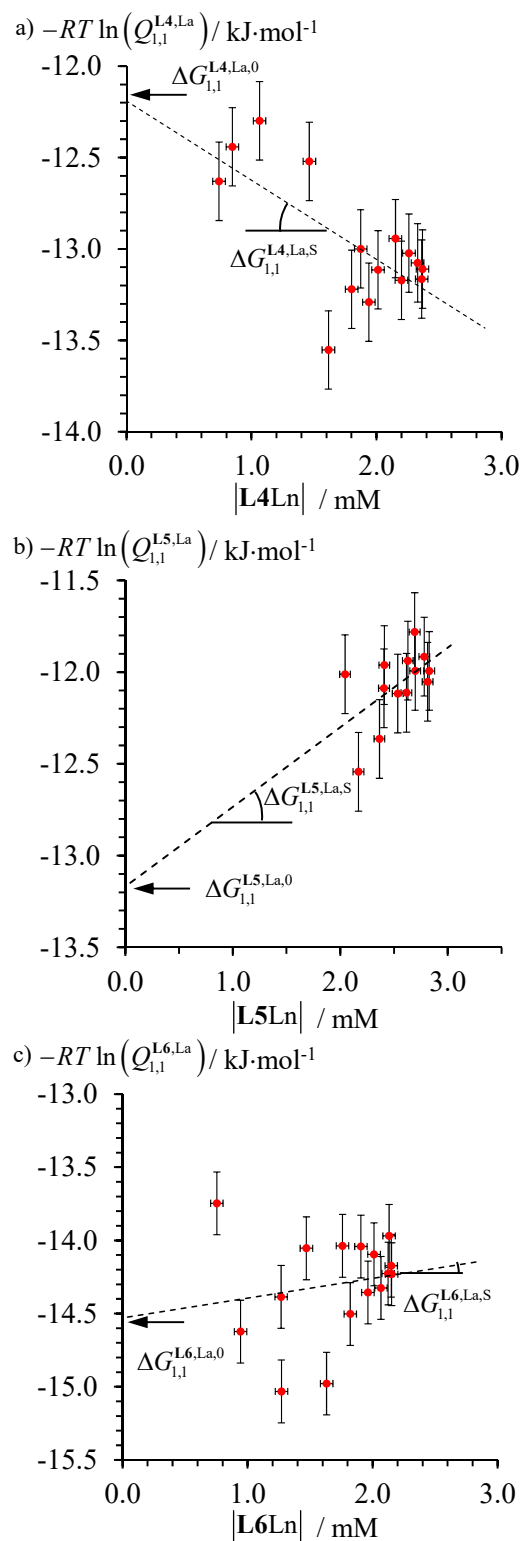
Figure 2. Plots of $-RT \ln\left(Q_{1,1}^{\mathbf{L}k,\mathrm{La}}\right)$ as a function of $\left|\mathbf{L}k\mathrm{Ln}\right|$ according to eq. (15) for the titrations of a) **L4**, b) **L5** and c) **L6** with [La(hfa)$_3$dig)] in CH_2Cl_2 + 0.14 M dig (298 K).[CP7] The dotted black traces correspond to the linear fits, from which $\Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},0}$ and $\Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},S}$ are estimated and collected in Table 2.
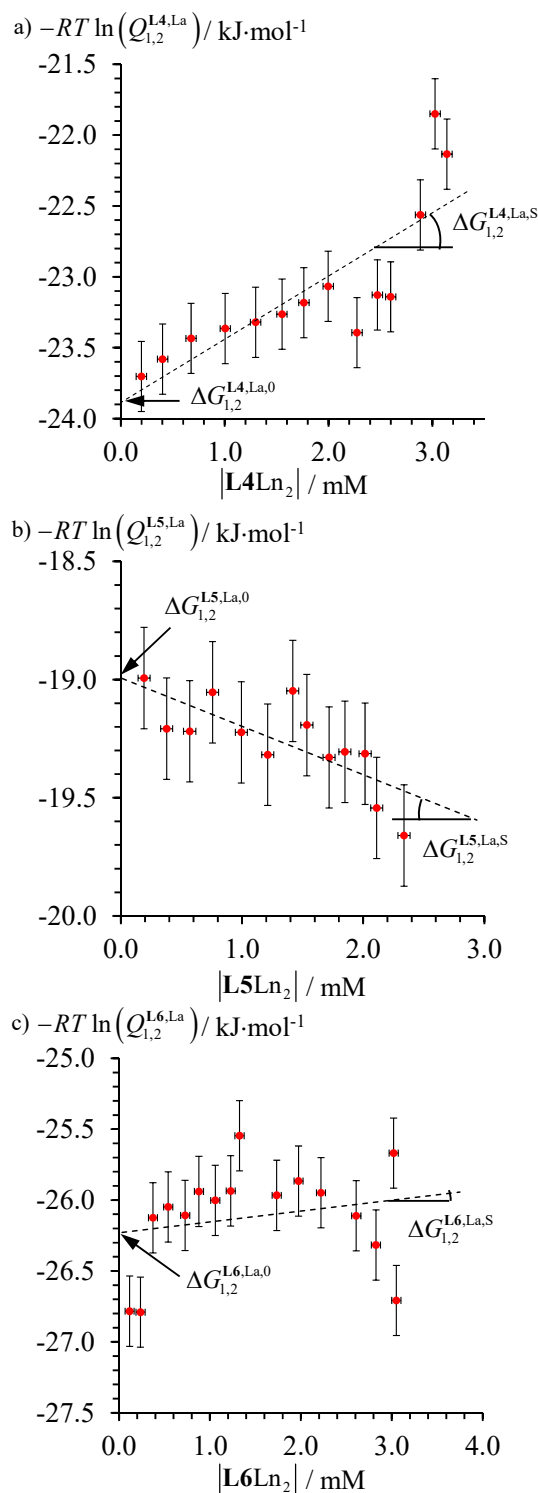
Figure 3. Plots of $-RT \ln\left(Q_{1,2}^{\mathbf{L}k,\mathrm{La}}\right)$ as a function of $\left|\mathbf{L}k\mathrm{Ln}_2\right|$ according to eq. (16) for the titrations of a) **L4**, b) **L5** and c) **L6** with [La(hfa)₃dig)] in CH₂Cl₂ + 0.14 M dig (298 K).[CP7] The dotted black traces correspond to the linear fits, from which $\Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},0}$ and $\Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},S}$ are estimated and collected in Table 2.
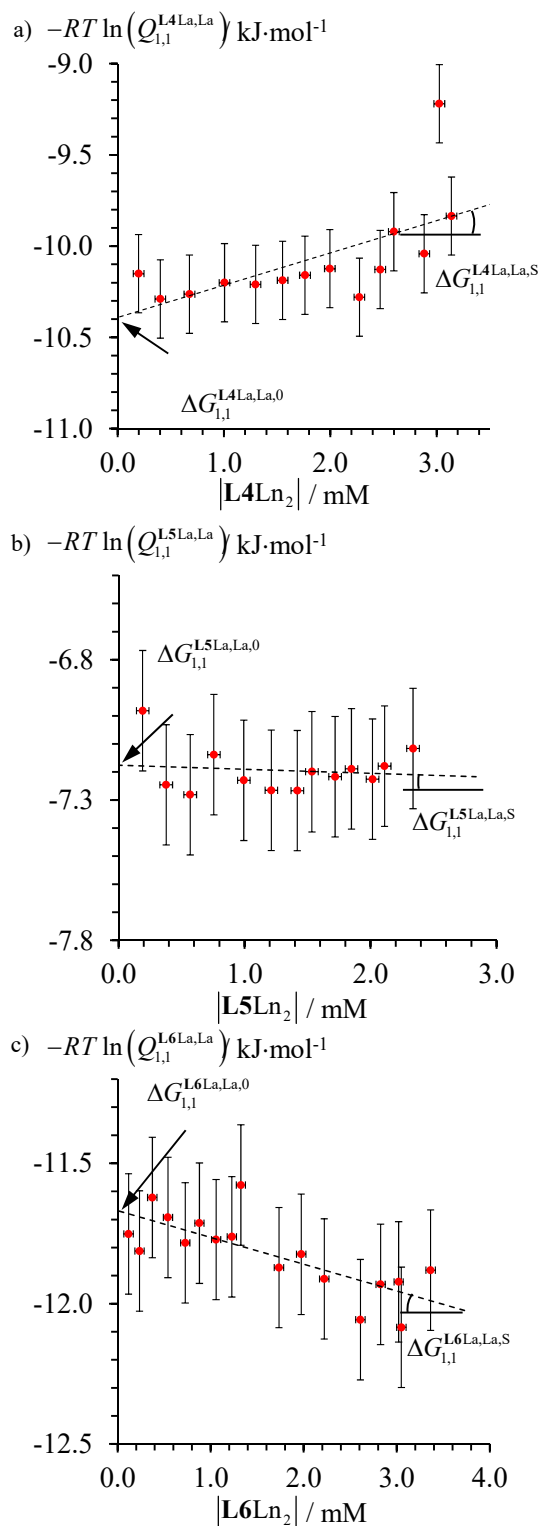
Figure 4. Plots of $-RT\ln\left(Q_{1,1}^{\mathbf{L}k\text{La,La}}\right)$ as a function of $\left|\mathbf{L}k\text{Ln}_2\right|$ according to eq. (9) for the titrations of a) **L4**, b) **L5** and c) **L6** with [La(hfa)$_3$dig)] in CH$_2$Cl$_2$ + 0.14 M dig (298 K).[CP7] The dotted black traces correspond to the linear fits, from which $\Delta G_{1,1}^{\mathbf{L}k\text{Ln,La,0}}$ and $\Delta G_{1,1}^{\mathbf{L}k\text{La,La,S}}$ are estimated and collected in Table 2.

Table 2. Cumulative free energy changes $\Delta G_{1,1}^{\mathbf{L}k,\text{La},0}$, $\Delta G_{1,2}^{\mathbf{L}k,\text{La},0}$ and associated contact solvation variations $\Delta G_{1,1}^{\mathbf{L}k,\text{La},S}$, $\Delta G_{1,2}^{\mathbf{L}k,\text{La},S}$ (eqs 15-16), binding affinities $f_{\mathbf{L}k}^{\text{La}}$ (eq 19) and cooperativity factors $u_{\mathbf{L}k}^{\text{La-La}}$ (eq 20) for the titration of **L**k with [La(hfa)₃(dig)] in CH₂Cl₂ + 0.14 M diglyme (298 K).

Ligand	L4	L5	L6
$\Delta G_{1,1}^{\mathbf{L}k,\text{La},0}$ /kJ·mol⁻¹	-12.2(2)	-13.2(5)	-14.5(4)
$\Delta G_{1,2}^{\mathbf{L}k,\text{La},0}$ /kJ·mol⁻¹	-23.9(2)	-19.0(1)	-26.2(2)
$f_{\mathbf{L}k}^{\text{La}}$	69(5)	102(19)	176(23)
$u_{\mathbf{L}k}^{\text{La-La}}$	1.8(3)	0.5(1)	1.1(2)
$\Delta G_{\mathbf{L}k,\text{aff}}^{\text{La}}$ /kJ·mol⁻¹	-10.5(2)	-11.5(5)	-12.8(3)
$\Delta E_{\mathbf{L}k}^{\text{La-La}}$ /kJ·mol⁻¹	-1.5(4)	2.0(6)	-0.3(5)
$\Delta G_{1,1}^{\mathbf{L}k,\text{La},S}$ /kJ·mol⁻¹	-433(128)	434(203)	135(205)
$\Delta G_{1,2}^{\mathbf{L}k,\text{La},S}$ /kJ·mol⁻¹	446(90)	-205(53)	76(94)
$\Delta G_{1,1}^{\mathbf{L}k\text{La},\text{La},0}$ /kJ·mol⁻¹	-10.4(1)	-7.4(1)	-11.67(4)
$\Delta G_{1,1}^{\mathbf{L}k\text{La},\text{La},S}$ /kJ·mol⁻¹	177(64)	208(77)	-95(21)
$\Delta G_{1,1}^{\mathbf{L}k,\text{La},0} + \Delta G_{1,1}^{\mathbf{L}k\text{La},\text{La},0}$ /kJ·mol⁻¹	-22.6(3)	-20.6(5)	-26.2(4)

At total millimolar concentrations of metal containers and of ligands in CH₂Cl₂ + 0.14 M diglyme, the correction of the true thermodynamic constants $\Delta G_{1,1}^{\mathbf{L}k,\text{La},0}$ and $\Delta G_{1,2}^{\mathbf{L}k,\text{La},0}$ for contact solvation ($|\mathbf{L}k\text{Ln}|\Delta G_{1,1}^{\mathbf{L}k,\text{La},S}$ or $|\mathbf{L}k\text{Ln}_2|\Delta G_{1,2}^{\mathbf{L}k,\text{La},S}$) never exceeds 1 kJ/mol (Table 2, entries 7-8), which corresponds to less than 10% of the metal-binding-site affinity (Table 2, entries 5). In these conditions the analysis of the titrations with model 1 (eqs 13-14 in Table 1) or with model 2 (eqs 15-16 in Table 2) are comparable, thus leading to reconstructed binding isotherms of the same quality (Figure 1, green and blue traces). With this in mind, it is not so surprising that the combination of the successive complexation reactions (eqs 8 and 9) analyzed within the frame of model 2 (Figure 2 illustrates eq. 8, while Figure 4 illustrates eq. 9) roughly converge to give the expected thermodynamic identity $\Delta G_{1,2}^{\mathbf{L}k,\text{La},0} \simeq \Delta G_{1,1}^{\mathbf{L}k,\text{La},0} + \Delta G_{1,1}^{\mathbf{L}k\text{Ln},\text{La},0}$ (Table 2, compare entries 2 and 11). Obviously, the situation completely changes at larger concentration, let's say centi-to-
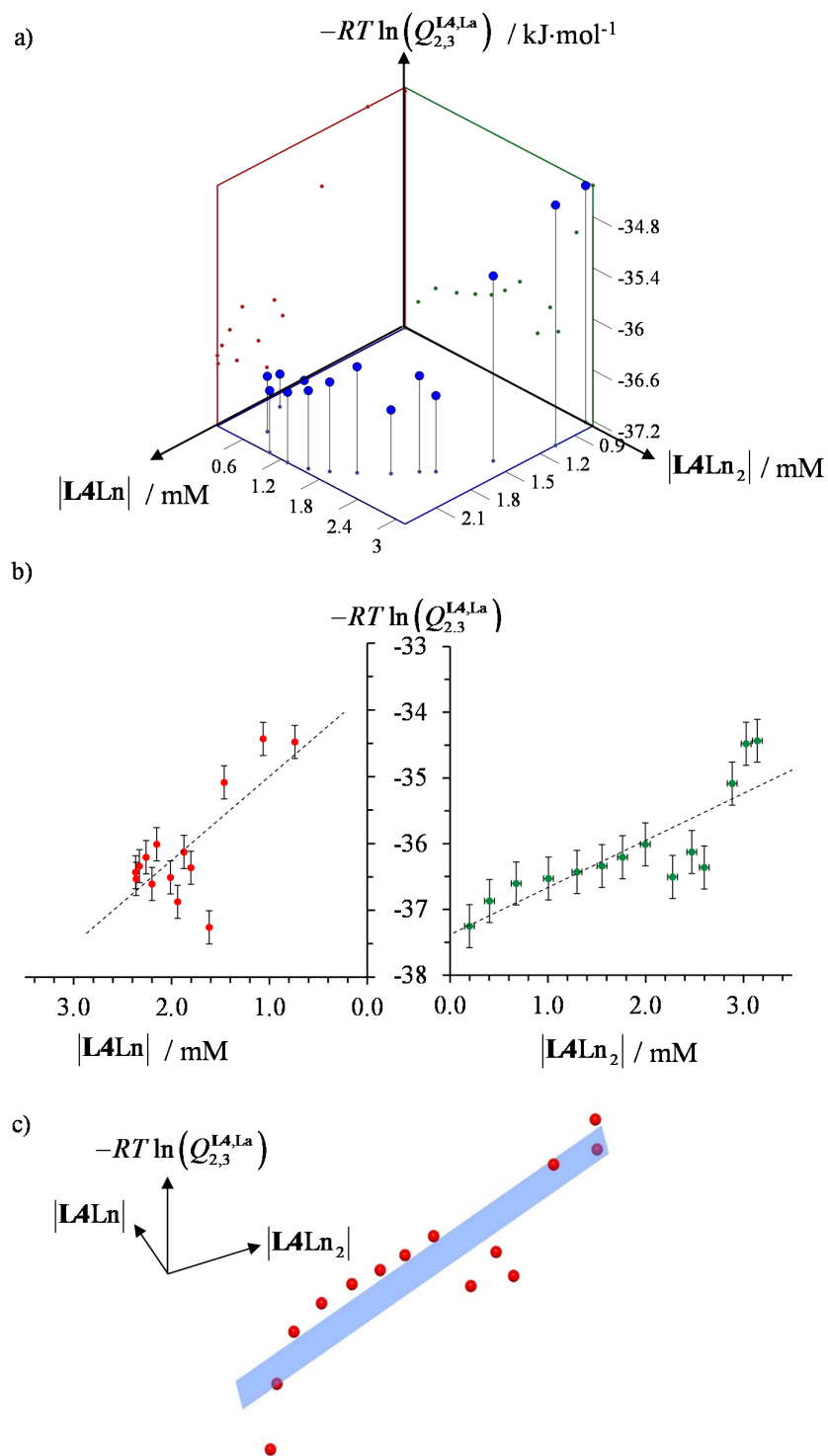
decimolar concentrations, where the solvation contribution exceeds ligand-metal affinities by one to two orders of magnitudes. Compared with model 1, which assumes ideal solution behavior, eqs (15)-(16) in model 2 open some perspectives for predictions of complexation reactions occurring at common experimental synthetic concentrations, but the consequent disparity $\Delta G_{1,2}^{\mathbf{L}k,\text{La},0} \neq \Delta G_{1,1}^{\mathbf{L}k,\text{La},0} + \Delta G_{1,1}^{\mathbf{L}k\text{Ln},\text{La},0}$ becomes a major issue for further rationalization.

Model 3: Disruption of the chemical potential of the solvent with mixture of successive complexes. In line with Castellano and Egger's approach, eq. (17) considers that the formation of a mixture of complexes [$\mathbf{L}k$La(hfa)$_3$] and [$\mathbf{L}k$(La(hfa)$_3$)$_2$] (equilibrium 11) is accompanied by the sum of two contact solvation changes, each of one being proportional to the amount of specific complex formed in solution. Mathematically speaking, eq. (17) corresponds to the equation of a plane in a three dimensional $<\left|\mathbf{L}k\text{Ln}\right| ; \left|\mathbf{L}k\text{Ln}_2\right| ;$ free energy> cartesian frame (Figures 5-7). Bi-linear least-square fits of the data collected for the titration of **L4**-**L6** with [La(hfa)$_3$dig)] in CH$_2$Cl$_2$ + 0.14 M dig provide total free energy changes $\Delta G_{2,3}^{\mathbf{L}k,\text{La},0}$ and solvation corrections $\Delta G_{1,1}^{\mathbf{L}k,\text{La},S}$ and $\Delta G_{1,2}^{\mathbf{L}k,\text{La},S}$ gathered in Table 3 (entries 1-3).

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

Ligand	L4	L5	L6
$\Delta G_{2,3}^{\mathbf{L}k,\text{La},0}$ /kJ·mol^{-1}	-36.1(8)	-32.2(7)	-43.3(8)
$\Delta G_{1,1}^{\mathbf{L}k,\text{La},S}$ /kJ·mol^{-1}	-514(351)	552(282)	1190(357)
$\Delta G_{1,2}^{\mathbf{L}k,\text{La},S}$ /kJ·mol^{-1}	525(144)	-378(100)	559(158)
$\Delta G_{1,1}^{\mathbf{L}k,\text{La},0} + \Delta G_{1,2}^{\mathbf{L}k,\text{La},0}$ /kJ·mol^{-1} [a]	-36.6(3)	-31.2(1)	-40.6(3)
$\Delta G_{1,1}^{\mathbf{L}k,\text{La},S}$ /kJ·mol^{-1} [a]	-433(128)	434(203)	135(205)
$\Delta G_{1,2}^{\mathbf{L}k,\text{La},S}$ /kJ·mol^{-1} [a]	446(90)	-205(53)	76(94)

[a] Taken from Table 2 for comparison purpose.

a)

$-RT \ln\left(Q_{2,3}^{\mathbf{L4,La}}\right)$ / kJ·mol⁻¹ (axis label)

-34.8
-35.4
-36
-36.6
-37.2
0.9
1.2
1.5
1.8
2.1
$\left|\mathbf{L4Ln}_2\right|$ / mM

0.6
1.2
1.8
2.4
3
$\left|\mathbf{L4Ln}\right|$ / mM

b)

$-RT \ln\left(Q_{2,3}^{\mathbf{L4,La}}\right)$

-33
-34
-35
-36
-37
-38

3.0   2.0   1.0   0.0
$\left|\mathbf{L4Ln}\right|$ / mM

0.0   1.0   2.0   3.0
$\left|\mathbf{L4Ln}_2\right|$ / mM

c)

$-RT \ln\left(Q_{2,3}^{\mathbf{L4,La}}\right)$

$\left|\mathbf{L4Ln}\right|$

$\left|\mathbf{L4Ln}_2\right|$

Figure 5. Plots of a) $-RT \ln\left(Q_{2,3}^{\mathbf{L4,La}}\right)$ as a function of $\left|\mathbf{L4Ln}\right|$ and $\left|\mathbf{L4Ln}_2\right|$ according to eq. (17), b) projections onto the $\left|\mathbf{L4Ln}_2\right| = \mathrm{cte}$ plane (left) and $\left|\mathbf{L4Ln}\right| = \mathrm{cte}$ plane (right) and c) projection roughly orthogonal to the best least-square plane (shown in blue) for the titrations of **L4** with [La(hfa)₃dig)] in CH₂Cl₂ + 0.14 M dig (298 K).[CP7]
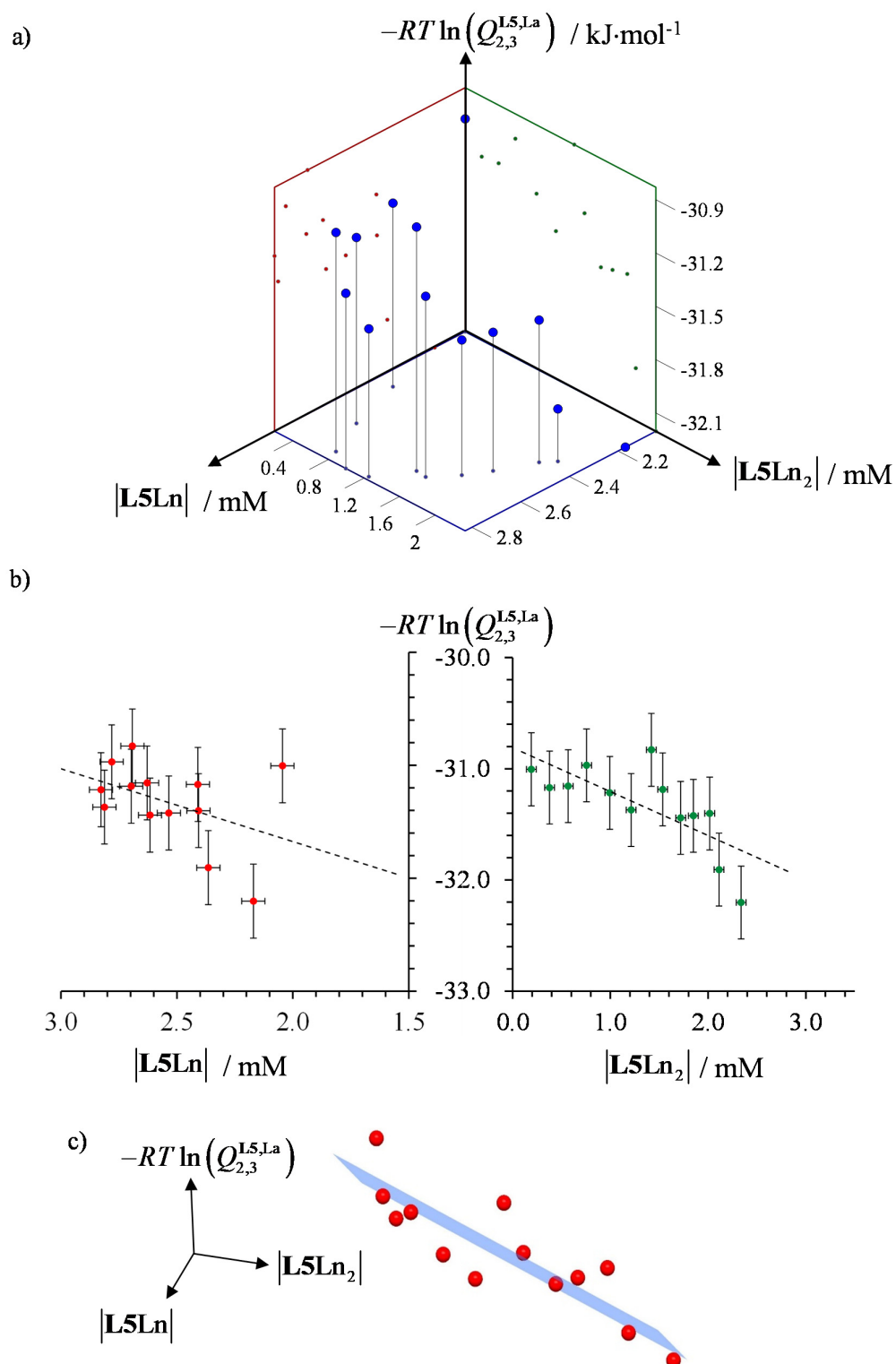
Figure 6. Plots of a) $-RT\ln\left(Q_{2,3}^{\text{L5,La}}\right)$ as a function of $\left|\textbf{L5Ln}\right|$ and $\left|\textbf{L5Ln}_2\right|$ according to eq. (17), b) projections onto the $\left|\textbf{L5Ln}_2\right| = \text{cte}$ plane (left) and $\left|\textbf{L5Ln}\right| = \text{cte}$ plane (right) and d) projection roughly orthogonal to the best least-square plane (shown in blue) for the titrations of **L5** with [La(hfa)$_3$dig)] in CH$_2$Cl$_2$ + 0.14 M dig (298 K).[CP7]

a)

b)

c)
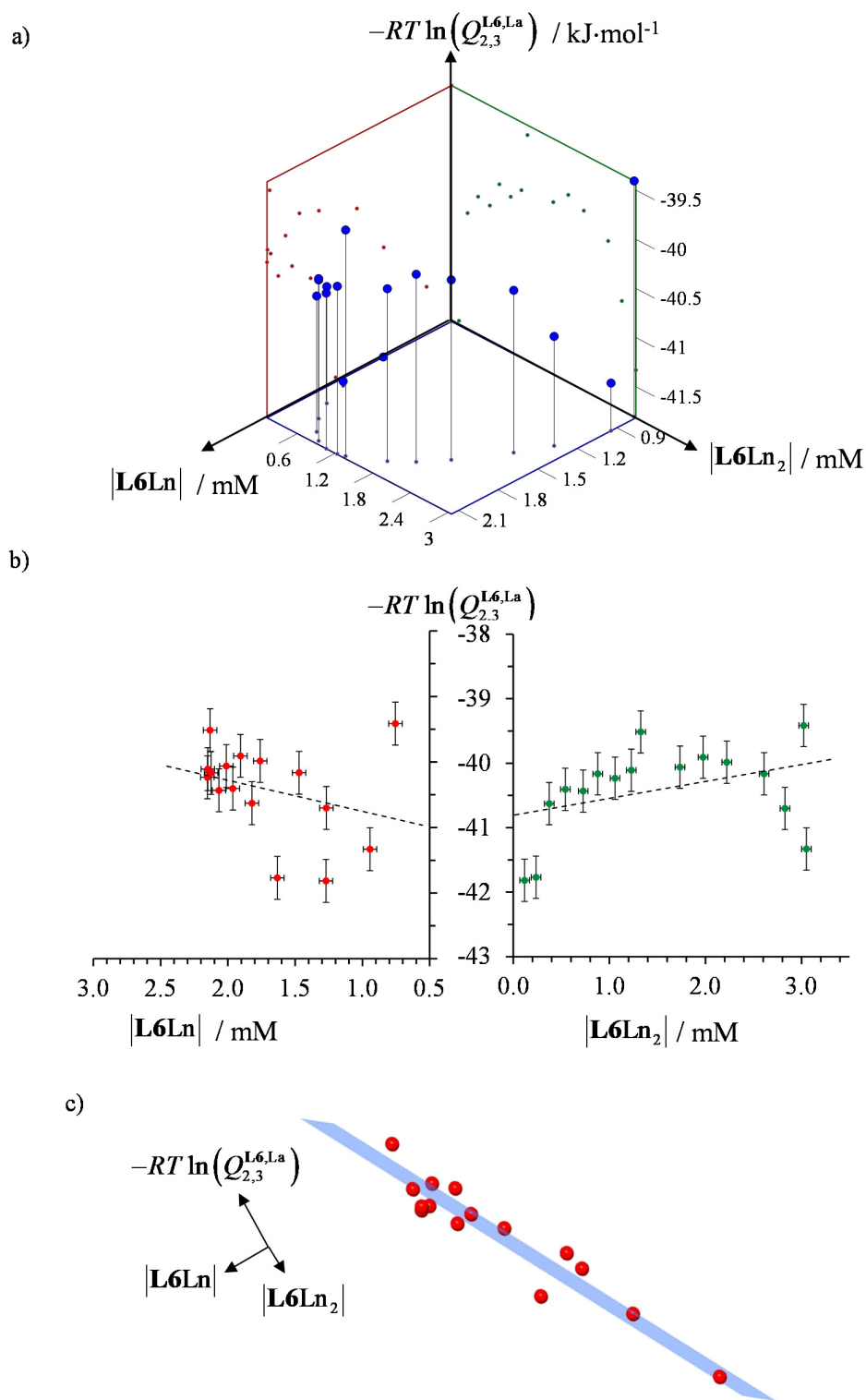
Figure 7. Plots of a) $-RT\ln\left(Q_{2,3}^{\mathbf{L6,La}}\right)$ as a function of $\left|\mathbf{L6Ln}\right|$ and $\left|\mathbf{L6Ln_2}\right|$ according to eq. (17), b) projections onto the $\left|\mathbf{L6Ln_2}\right| = \text{cte}$ plane (left) and $\left|\mathbf{L6Ln}\right| = \text{cte}$ plane (right) and c) projection roughly orthogonal to the best least-square plane (shown in blue) for the titrations of **L6** with [La(hfa)₃dig)] in CH₂Cl₂ + 0.14 M dig (298 K).[CP7]

A careful look at Figures 5c-7c show that the experimental data are roughly distributed within approximate planes, this in agreement with eq. (17). Moreover, the rough linear correlations found in the xz ($\left|\mathbf{L}k\mathrm{Ln}_2\right| = \mathrm{cte}$, Figures 5b-7b left) and yz ($\left|\mathbf{L}k\mathrm{Ln}\right| = \mathrm{cte}$, Figures 5b-7b right) projections support the complete decorrelation of the contact solvation corrections solvation mathematically expressed in eq. (17). Again, at millimolar concentration, the solvation correction in CH$_2$Cl$_2$ + 0.14 M diglyme are largely dominated by the ligand-metal binding affinities and $\Delta G_{2,3}^{\mathbf{L}k,\mathrm{La},0} \simeq \Delta G_{1,1}^{\mathbf{L}k,\mathrm{La},0} + \Delta G_{1,2}^{\mathbf{L}k,\mathrm{La},0}$ (Table 3).

Conclusions

In agreement with the titrations of the simple tridentate ligands **L1-L3** with [La(hfa)$_3$(dig)], the related complexation reactions of the di-tridentate receptors **L4-L6** demonstrate that the introduction of an excess of one of the partner (here 0.14 M diglyme in CH$_2$Cl$_2$) transforms exchange processes, which proved to be highly sensitive to contact solvation corrections,[CP6] into conditional quotient of reactions with significantly reduced dependence on contact solvation. Comparison of model 1 (eqs 13-14, Table 1), which neglects solvation contributions beyond individual and identified coordination spheres, with model 2 (eqs 15-16, Table 2), which introduces some debatable individual contact solvent corrections not fully compatible with Born-Haber cycles, indeed shows (i) no improvement in term of the quality of the data analysis (Figure 1) and (ii) the preservation of similar intrinsic affinities $\Delta G_{\mathbf{L}k,\mathrm{aff}}^{\mathrm{La}}$ and intermetallic interactions $\Delta E_{\mathbf{L}k}^{\mathrm{La\text{-}La}}$. If there is no doubt that the quotients of reactions $Q_{m,n}^{\mathbf{L}k,\mathrm{Ln}}$ display some roughly linear dependence (in term of energy change $-RT\ln(Q_{m,n}^{\mathbf{L}k,\mathrm{Ln}})$) on the advance of the chemical reaction measured by the amount of products accumulating in the solution (Figures 2-4), our analytical NMR data collected at millimolar contrations (maximum precision 2-3%) in CH$_2$Cl$_2$ + 0.14 M dig are too scattered for providing accurate enough contact solvent corrections, which could be safely used for predicting pertinent quotients of reactions at higher concentrations. The third model (eq 17) restores the original concept of Castellano and Eggers via the simultaneous consideration of different contact

solvent contributions for the simultaneous formation of the two different complexes along a single chemical equilibrium. In other words, eq. (17) simply tests a standard result of thermodynamics, i.e. $\Delta G_{2,3}^{\mathbf{Lk},\mathbf{La},0} = \Delta G_{1,1}^{\mathbf{Lk},\mathbf{La},0} + \Delta G_{1,2}^{\mathbf{Lk},\mathbf{La},0}$ but within the frame of contact solvent correction introduced by Castellano and Eggers. Our results confirm that this hypothesis is satisfied, which ultimately allows the prediction of binding isotherms for multiple-binding sites systems using eq. (21).

$$\theta_{\mathbf{Lk}}^{\mathbf{Ln}} = \frac{1}{2}\frac{|\mathrm{Ln}|_{\text{bound}}}{|\mathbf{Lk}|_{\text{tot}}} = \frac{Q_{1,1}^{\mathbf{Lk},\mathbf{Ln}}|\mathrm{Ln}| + 2Q_{1,2}^{\mathbf{Lk},\mathbf{Ln}}|\mathrm{Ln}|^2}{2\left(1 + Q_{1,1}^{\mathbf{Lk},\mathbf{Ln}}|\mathrm{Ln}| + Q_{1,2}^{\mathbf{Lk},\mathbf{Ln}}|\mathrm{Ln}|^2\right)} \tag{21}$$

Since the quotients of the reactions $Q_{1,1}^{\mathbf{Lk},\mathbf{Ln}}$ and $Q_{1,2}^{\mathbf{Lk},\mathbf{Ln}}$ are concentration dependent, eqs (15)-(16) yield

$$Q_{1,1}^{\mathbf{Lk},\mathbf{La}} = \frac{|\mathbf{Lk}\mathrm{Ln}|}{|\mathbf{Lk}||\mathrm{Ln}|} = \exp\left(-\frac{\left(\Delta G_{1,1}^{\mathbf{Lk},\mathbf{La},0} + |\mathbf{Lk}\mathrm{Ln}|\Delta G_{1,1}^{\mathbf{Lk},\mathbf{La},S}\right)}{RT}\right) \tag{22}$$

$$Q_{1,2}^{\mathbf{Lk},\mathbf{La}} = \frac{|\mathbf{Lk}\mathrm{Ln}_2|}{|\mathbf{Lk}||\mathrm{Ln}|^2} = \exp\left(-\frac{\left(\Delta G_{1,2}^{\mathbf{Lk},\mathbf{La},0} + |\mathbf{Lk}\mathrm{Ln}_2|\Delta G_{1,2}^{\mathbf{Lk},\mathbf{La},S}\right)}{RT}\right) \tag{22}$$

Which can be combined with the fixed total concetrations $|\mathbf{Lk}|_{\text{tot}}$ (eq. 23) and $|\mathrm{Ln}|_{\text{tot}}$ (eq 24)

$$|\mathbf{Lk}|_{\text{tot}} = |\mathbf{Lk}| + |\mathbf{Lk}\mathrm{Ln}| + |\mathbf{Lk}\mathrm{Ln}_2| \tag{23}$$

$$|\mathrm{Ln}|_{\text{tot}} = |\mathrm{Ln}| + |\mathbf{Lk}\mathrm{Ln}| + 2|\mathbf{Lk}\mathrm{Ln}_2| \tag{24}$$

The isolation of the concentration of complexes gives

$$|\mathbf{Lk}\mathrm{Ln}| = 2|\mathbf{Lk}|_{\text{tot}} - |\mathrm{Ln}|_{\text{tot}} + |\mathrm{Ln}| - 2|\mathbf{Lk}| \tag{25}$$

$$|\mathbf{Lk}\mathrm{Ln}_2| = |\mathrm{Ln}|_{\text{tot}} - |\mathbf{Lk}|_{\text{tot}} - |\mathrm{Ln}| + |\mathbf{Lk}| \tag{26}$$

Introduction of eqs (25)-(26) into eqs (22)-(23) follwowed by non-linear least square fit provide the four unknown free concentrations, from which $Q_{1,1}^{\mathbf{Lk},\mathbf{Ln}}$ and $Q_{1,2}^{\mathbf{Lk},\mathbf{Ln}}$ cand be deduced and the occupancy factor computed with eq. (21). On the contrary, the only resort of eq. (17) with eqs (23)-(24) is insufficient for predicting binding isotherms.

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