

A Simple Thermodynamic Model for Quantitatively Addressing Cooperativity in Multicomponent Self-Assembly Processes—Part 1: Theoretical Concepts and Application to Monometallic Coordination Complexes and Bimetallic Helicates Possessing Identical Binding Sites

Josef Hamacek,* Michal Borkovec, and Claude Piguet*[a]

Abstract: A thermodynamic model has been developed for quantitatively estimating cooperativity in supramolecular polymetallic $[M_nL_n]$ assemblies, as the combination of two simple indexes measuring intermetallic (I_c^{MM}) and interligand (I_c^{LL}) interactions. The usual microscopic intermolecular metal–ligand affinities (f_i^{ML}) and intermetallic interaction parameters (u^{MM}), adapted to the description of successive intermolecular binding of metal ions to a preorganized receptor, are completed

with interligand interactions (u^{LL}) and effective concentrations (c^{eff}), accounting for the explicit free energy associated with the aggregation of the ligands forming the receptor. Application to standard monometallic pseudo-octahedral complexes $[M(L)_n(H_2O)_{(6-n)}]$ ($M = Co, Ni, Hf, L = ammonia, fluoride, imi-$

dazole, $n = 1–6$) systematically shows negative cooperativity ($u^{LL} < 1$), which can be modulated by the electronic structures, charges, and sizes of the entering ligands and of the metal ions. Extension to the self-assembly of more sophisticated bimetallic helicates possessing identical binding sites is discussed, together with the origin of the positively cooperative formation of $[Eu_2(L3)_3]$.

Keywords: cooperativity • helical structures • lanthanides • thermodynamics

Introduction

The implementation of predictive strategies for the design of functional multimetallic molecular assemblies displaying predetermined optical, magnetic, and catalytic properties requires a deep understanding of the specific recognition processes responsible for the introduction of different d- and/or f-block metal ions in well-defined environments.^[1] This objective can be achieved through a detailed analysis of the thermodynamic and kinetic processes leading to the final architectures; these analyses form the basis for the development and validation of theoretical models.^[2] A recent ther-

modynamic approach, proposed by Ercolani for the quantitative characterisation of multicomponent assemblies involving metals and ligands in supramolecular complexes, gives a new insight into some reliable assessments of cooperativity and repetitive statistical binding in these systems.^[3] In his model, Ercolani uses two microscopic constants (K_{inter} , K_{intra}) combined with symmetry numbers for describing macroscopic formation constants; this restrains the number of experimental thermodynamic data required for the modeling of multicomponent assembly processes.^[3] However, this model is restricted to homopolymetallic complexes, in which the metal ions occupy identical binding sites. Moreover, intermetallic and interligand interactions are not explicitly considered, and this limits the analysis to the detection of qualitative deviations from repetitive statistical binding.^[2,3]

An alternative approach, based on the classical site-binding model,^[4] has been proposed recently by Borkovec and Piguet^[5,6] in order to address the dual challenge of 1) modeling the thermodynamic formation of heteropolymetallic complexes possessing different binding sites and 2) obtaining reliable parameters for unravelling cooperativity, and its origin, in multicomponent assemblies. In the latter model, a preassembled receptor possesses p coordination sites for the

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Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author. Tables S1–S5 give experimental and fitted thermodynamic parameters for $[Co(NH_3)_n]^{2+}$, $[Hf(F)_n]^{(4-n)+}$, and $[Ni(imidazole)_n]^{2+}$.

complexation of metal ions. Each site i is characterized by a microscopic intermolecular affinity (in terms of free energy) for a given metal $\Delta g_i^M = -RT\ln(k_i^M)$, which includes desolvation, while the intramolecular intermetallic interaction between two adjacent metal ions is modeled by a single free-energy parameter ΔE^{MM} . Application to simple D_3 -symmetrical bimetallic lanthanide helicates $[M_2(L)_3]^{6+}$ leads to a specific affinity of the terminal N_6O_3 site for each metal $\Delta g_i^M = -RT\ln(k_i^M)$, and an average repulsive intermetallic parameter $\Delta E^{MM} \approx 50 \text{ kJ mol}^{-1}$, which corresponds to that calculated for pure electrostatic interactions between two trivalent metals in these complexes (Figure 1a).^[5,6] Exten-

Although the application of the site-binding model to polymetallic assemblies has improved our capacity to program the formation of specific supramolecular complexes,^[5] two limitations are still to be overcome. Firstly, this model strictly operates with a single receptor, which is eventually made up of several ligands, and the free energy associated with the preorganization step is considered as a fixed translation of the zero-level of the free-energy scale, which is arbitrarily set to zero.^[2,5] Therefore, the fitted absolute affinities $\Delta g_i^M = -RT\ln(k_i^M)$ do not correspond to physically meaningful free energies of complexation. The second drawback arises from the limited number of experimental stability

constants associated with a unique conformation of the pre-assembled ligands.^[5] To overcome these limitations, it is necessary to explicitly consider the pre-assembly of the receptor from its constituent ligands by 1) introducing a free-energy term accounting for interligand interactions and 2) separating inter/intramolecular complexation processes, which characterize the successive connection of ligands and metals in the final assembly. Evidently, the increased number of parameters requires a larger body of experimental macroscopic thermodynamic stability data, which can be obtained by a judicious combination of thermodynamic and kinetic studies. For example, the thorough kinetic data reported for the self-assembly of Eu^{III} triple-stranded bimetallic helicates^[8,9] can be combined with thermodynamic data obtained under chemical equilibrium.^[10,11]

sion to the trimetallic helicates provides Δg_i^M and ΔE^{MM} values similar to that found for the bimetallic helicates, but a different affinity is obtained for the central N_9 site $\Delta g_c^M = -RT\ln(k_c^M)$ (Figure 1b).^[5] The strongly positive value of ΔE^{MM} is diagnostic for negative cooperativity, which affects the binding of trivalent cations in adjacent metallic sites, as expected from simple electrostatic considerations.^[5,6] Finally, the site-binding model was successfully used^[2,6] for two-dimensional sandwich complexes with lanthanides (Figure 1c).^[7] The three equidistant binding sites in these triangular receptors are again characterized by standard microscopic intermolecular affinities $\Delta g^M = -RT\ln(k^M)$ and intermetallic interactions ΔE^{MM} . However, the lack of accessible macroscopic formation constants for any thermodynamic intermediate prevents the eventual separation of these two parameters.^[2,6]

In this paper, we first introduce the basic concepts of an extended thermodynamic model, which 1) holds for the formation of homopolymetallic complexes with identical or different coordination cavities, 2) explicitly takes into account the free energy associated with the preorganization of the receptor, and 3) reliably addresses cooperativity in polymetallic complexes. In the second section, the applicability of the model to experimental binding constants is illustrated for standard monometallic coordination complexes and for more sophisticated bimetallic helicates containing identical binding sites.

Results and Discussion

Thermodynamic model: In our original application of the site-binding model to homopolymetallic self-assembly pro-

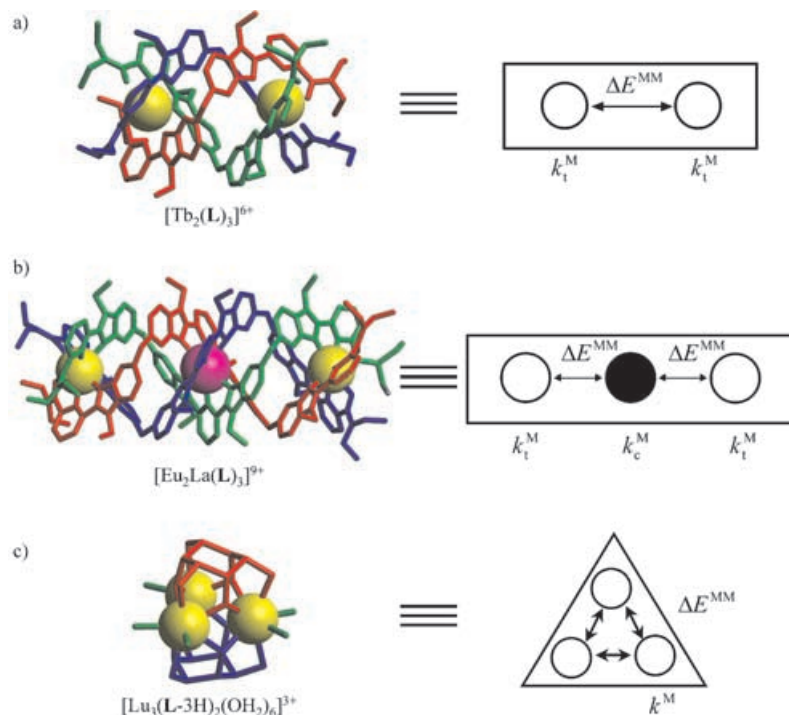
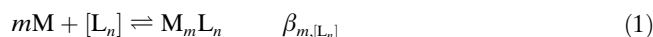


Figure 1. X-ray crystal structures and associated thermodynamic site-binding model for a) bimetallic triple-stranded helicates $[M_2(L)_3]^{6+}$,^[5] b) trimetallic triple-stranded helicates $[M_3(L)_3]^{9+}$,^[5] and c) trimetallic sandwich complexes $[Ln_3(L-3H)_2(OH_2)_6]^{3+}$.^[6,7]

cesses, we considered preorganized rigid receptors L_n made up of n parallel ligand strands and providing a maximum of p binding sites.^[2,5,6] The associated free energy $\Delta G(\{s_i\})$ for the complexation of m metal ions ($m \leq p$) to this receptor in the microspecies $M_m L_n$ [equilibrium in Eq. (1)] is given by Equation (2), whereby s_i is defined to be unity when the metal ion is bound to the site i and zero otherwise, k_i^M represents the microscopic intermolecular association constant of the site i for the metal M (including desolvation processes) and ΔE_{ij}^{MM} is the pair interaction energy between two metal ions occupying the sites i and j .^[6]



$$\Delta G(\{s_i\}) = - \sum_{i=1}^p RT \ln(k_i^M) s_i + \frac{1}{2} \sum_{i=1}^p \sum_{j \neq i}^p \Delta E_{ij}^{MM} s_i s_j \quad (2)$$

The subsequent use of partition functions, binding isotherms and transfer matrix techniques allowed us to solve this problem for a linear receptor $[L_n]$.^[6] However, if we restrict this approach to the treatment of discrete multimetallic assemblies, for which thermodynamic formation constants are available ($p \leq 5$), the application of Equation (2) to a specific microspecies reduces to sums containing explicit expressions for the interaction parameters and for the degeneracy of each microspecies [Eq. (3)]. The microconstants $\beta_{m,[L_n]}$ can be then combined to give macroconstants whenever necessary.^[2]

$$\Delta G_{m,[L_n]} = -RT \ln(\beta_{m,[L_n]}) = - \sum_{i=1}^m {}' RT \ln(k_i^M) + \sum_{i < j} {}'' (\Delta E_{ij}^{MM}) - RT \ln(\sigma_{\text{chir}}^M \omega_{m,[L_n]}) \quad (3)$$

The first sum $\sum_{i=1}^m {}' RT \ln(k_i^M)$ refers to the free energy of complexation (including desolvation) associated with the set of binding sites occupied by the m metal ions in the $M_m L_n$ microspecies. The pair interaction ΔE_{ij}^{MM} only operates between metal ions occupying adjacent binding sites; it is defined by the second sum $\sum_{i < j} {}'' (\Delta E_{ij}^{MM})$. The term $\sigma_{\text{chir}}^M \omega_{m,[L_n]}$ represents the degeneracy of the microscopic state, whereby σ_{chir}^M accounts for the entropy of mixing of enantiomers ($\sigma_{\text{chir}}^M = 2$ when chirality is created during the complexation process, and $\sigma_{\text{chir}}^M = 1$ in other cases),^[3] and the numerical values of $\omega_{m,[L_n]}$ must be evaluated for each microspecies by using standard statistical methods.^[2] For a pre-assembled receptor $[L_n]$ containing p identical binding sites, and in absence of intermetallic interactions, $\omega_{m,[L_n]}$ corresponds to the binomial coefficient $C_m^p = p! / [(p-m)! m!]$; that is, the number of ways of picking m unordered outcomes (i.e., the number of metal ions) from p possibilities (i.e., the number of available binding sites). Although this approach has been shown to be adequate 1) for modeling the formation of linear triple-stranded helicates and two-dimensional sand-

wich complexes shown in Figure 1,^[2,5-7] and 2) for assigning negative cooperativity to the successive binding of metal ions in these complexes, it fails to give interpretable free energy of complexation (including desolvation) for each site $\Delta g_i^M = -RT \ln(k_i^M)$, because $\Delta G_{m,[L_n]}$ refers to an arbitrary zero-level of the free energy, assigned to a mixture of metal ions with the hypothetical preassembled receptor $[L_n]$ (Figure 2).

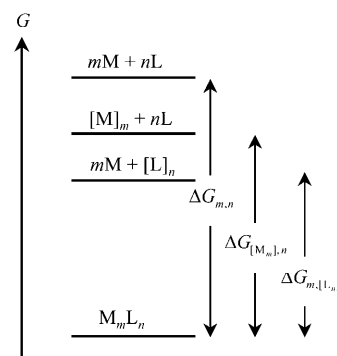
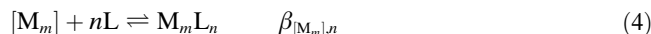


Figure 2. Illustration of the changes in free energy for the assembly of $M_m L_n$ according to the equilibria given in Equations (1) ($\Delta G_{m,[L_n]}$), (4) ($\Delta G_{[M_m],n}$), and (6) ($\Delta G_{m,n}$). The relative order of the free energies for the various starting materials is arbitrary.

Conversely, the same reasoning can be applied when the role of ligands and metal ions are reversed. The final microspecies $M_m L_n$ can be thus alternatively considered as being made up of n rigid monotopic ligands coordinated to a pre-organized array of m metal ions exhibiting a maximum of p coordination sites [$n \leq p$ equilibrium in Eq. (4)].



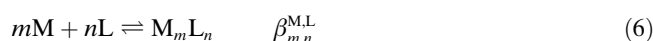
Although less intuitive than the equilibrium in Equation (1), which is reminiscent of classical coordination or ligand/protein interactions, the equilibrium in Equation (4) is strictly analogous, and the associated free energy of the microspecies $M_m L_n$ is given by Equation (5), whereby q_k^L is the microscopic intermolecular association constant of the ligand k to the array of metals, ΔE_{kl}^{LL} is the free energy of interaction between two ligands connected to the array of metal ions ($\sum_{k < l} {}''' (\Delta E_{kl}^{LL})$ indicates that the sum considers only adjacent ligands), and $\sigma_{\text{chir}}^L \omega_{[M_m],n}$ is the degeneracy of the microscopic state.

$$\Delta G_{[M_m],n} = -RT \ln(\beta_{[M_m],n}) = - \sum_{k=1}^n {}' RT \ln(q_k^L) + \sum_{k < l} {}''' (\Delta E_{kl}^{LL}) - RT \ln(\sigma_{\text{chir}}^L \omega_{[M_m],n}) \quad (5)$$

Evidently, $\Delta G_{[M_m],n} \neq \Delta G_{m,[L_n]}$ because the zero-level of the free energy is different for both models (Figure 2). Consequently, $\Delta g_i^M = -RT \ln(k_i^M)$ has no straightforward relation-

ship with $\Delta g_k^L = -RT \ln(q_k^L)$, and the thermodynamic description of the same microspecies depends on the model.

To reconcile both approaches in the usual microscopic thermodynamic equilibrium [Eq. (6)], we introduce a novel microscopic free energy $\Delta g_{i,inter}^{M,L} = -RT \ln(f_i^{M,L})$, in which $f_i^{M,L}$ is the microscopic affinity constant for a single intermolecular connection between one metal ion and one ligand binding site i (including desolvation). Moreover, according to the model of “effective concentration” discussed by Jacobson, Stockmayer and Jenks^[12] and used by Ercolani for modeling the formation of cyclic structures in self-assembled edifices,^[3] intramolecular metal–ligand connection, which occurs when the metal–ligand bond is part of a cycle, is obtained by correcting the related intermolecular process for the entropic change $\Delta g_{i,inter}^{M,L} = -RT \ln(f_i^{M,L}) - T(\Delta S_{i,intra}^{M,L} - \Delta S_{i,inter}^{M,L})/R$.^[13] In other words, the microscopic affinity constant for a single intramolecular connection between the metal ion and the ligand binding site i (including desolvation) is given by $f_i^{M,L} c_i^{eff}$, whereby c_i^{eff} is the effective concentration for the site i (referring to the standard molar state), mathematically related to the entropy difference according to $c_i^{eff} = e^{(\Delta S_{i,intra}^{M,L} - \Delta S_{i,inter}^{M,L})/R}$.^[12, 13] Assuming the principle of maximum site occupancy,^[14] the formation of $M_m L_n$ requires a total of mn connections, among which $m + n - 1$ are intermolecular.^[3] Consequently, a total entropic correction of $\Delta G_{corr}^{M,L} = - \sum_{i=1}^{mn-m-n+1} RT \ln(c_i^{eff})$ is introduced for modeling the $mn - (m + n - 1) = mn - m - n + 1$ intramolecular connections. The concomitant consideration of the two interaction parameters ΔE_{ij}^{MM} and ΔE_{kl}^{LL} , together with the adequate degeneracy of the microscopic state $\sigma_{chir}^{M,L} \omega_{m,n}$ results in Equation (7) for modeling the formation free energy $\Delta G_{m,n}^{M,L}$ of the $M_m L_n$ assembly, with respect to the free energy of components given by the equilibrium in Equation (6) (Figure 2).



$$\begin{aligned} \Delta G_{m,n}^{M,L} = & -RT \ln(\beta_{m,n}^{M,L}) = - \sum_{i=1}^{mn} RT \ln(f_i^{M,L}) - \sum_{i=1}^{mn-m-n+1} RT \ln(c_i^{eff}) \\ & + \sum_{i < j}'' (\Delta E_{ij}^{MM}) + \sum_{k < l}''' (\Delta E_{kl}^{LL}) - RT \ln(\sigma_{chir}^{M,L} \omega_{m,n}) \end{aligned} \quad (7)$$

Straightforward algebra transforms Equation (7) into Equation (8), which appears suitable for correlating experimentally accessible microscopic constants with the various parameters.

$$\begin{aligned} \beta_{m,n}^{M,L} = & (\sigma_{chir}^{M,L} \omega_{m,n}) \prod_{i=1}^{mn} (f_i^{M,L}) \prod_{i=1}^{mn-m-n+1} (c_i^{eff}) \\ & \prod_{i < j}'' \left(e^{-\frac{\Delta E_{ij}^{MM}}{RT}} \right) \prod_{k < l}''' \left(e^{-\frac{\Delta E_{kl}^{LL}}{RT}} \right) \end{aligned} \quad (8)$$

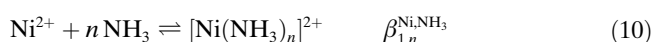
The introduction of the usual terminology for the interaction parameters as Boltzmann's factors $u_{ij}^{MM} = e^{-\frac{\Delta E_{ij}^{MM}}{RT}}$ and

$u_{kl}^{LL} = e^{-\frac{\Delta E_{kl}^{LL}}{RT}}$ leads to the final compact formulation given in Equation (9).^[4]

$$\beta_{m,n}^{M,L} = (\sigma_{chir}^{M,L} \omega_{m,n}) \prod_{i=1}^{mn} (f_i^{M,L}) \prod_{i=1}^{mn-m-n+1} (c_i^{eff}) \prod_{i < j}'' (u_{ij}^{MM}) \prod_{k < l}''' (u_{kl}^{LL}) \quad (9)$$

The three first terms of Equations (8) and (9) are closely related to the parameterization previously proposed by Ercolani,^[3] except that he used $K_{inter} = f_i^{M,L}$ and $K_{intra} = f_i^{M,L} c_i^{eff}$. However, he did not explicitly formulate possible deviations from statistical binding in terms of intermetallic and interligand interactions as described in Equation (9).

Application to monometallic coordination complexes: As a first illustration of our approach, we have used Equation (9) for unravelling the successive binding of monodentate ammonia (NH₃) to a single six-coordinate octahedral Ni^{II} ion (valency v = coordination number/denticity of the ligand binding unit = 6/1 = 6) according to the equilibrium given in Equation (10) ($n = 1-6$). Since the intermolecular microscopic affinity constant f^{Ni,NH_3} includes the desolvation process, the water molecules are not explicitly considered in these equilibria, in agreement with the common use in self-assembly processes [see, for example, equilibrium in Eq. (6)].



The formation of the achiral monometallic ($m = 1$) complexes $[Ni(NH_3)_n]^{2+}$ [equilibrium in Eq. (10)]^[15, 16] only involves virtually identical intermolecular metal–ligand connections; the number of intramolecular bonds is thus $mn - m - n + 1 = 0$ (in other words, the parameters ΔE^{MM} and c^{eff} do not affect $\beta_{1,n}^{Ni,NH_3}$). We will now consider three successive models displaying a stepwise improvement of the description of interligand interactions. In model 1, we completely neglect interligand interactions ($\Delta E^{LL} = 0$, then $u^{LL} = 1$) as is usually done in standard coordination chemistry for qualitatively investigating deviations from statistical binding,^[17] which indeed corresponds to Ercolani's model.^[3] Consequently, each $[Ni(NH_3)_n]^{2+}$ complex ($n = 1-6$) is made up of a unique achiral microspecies ($\sigma_{chir}^{Ni,NH_3} = 1$), whose degeneracy is given by the usual binomial factor $\omega_{1,n} = C_n^6$. Application of Equation (9) leads to the standard Equation (11),^[17] which generates a set of six independent Equations (13)–(18) ($u^{LL} = 1$) required for modeling the experimental macroscopic formation constants $\beta_{1,n}^{Ni,NH_3}$ collected in Table 1.^[15, 16] A multilinear least-squares fit of these last equations in their logarithmic forms gives $\log(f^{Ni,NH_3}) = 1.60$ corresponding to the free energy $\Delta g_{inter}^{Ni,NH_3} = -RT \ln(f^{Ni,NH_3}) = -9.1 \text{ kJ mol}^{-1}$, but this simple model does not satisfyingly reproduce the experimental data (Table 1, model 1).

$$\beta_{1,n}^{Ni,NH_3} = C_n^6 (f^{Ni,NH_3})^n \quad (11)$$

The second model proposes an improved description of the complexation processes by assigning a single interaction

Table 1. Experimental^[15] and fitted stability constants $\beta_{1,n}^{\text{Ni,NH}_3}$ for $[\text{Ni}(\text{NH}_3)_n]^{2+}$ ($n = 1-6$, water, 298 K).

Species	$\log(\beta_{1,n}^{\text{Ni,NH}_3})$ (exptl)	$\log(\beta_{1,n}^{\text{Ni,NH}_3})$ (model 1) ^[a]	$\log(\beta_{1,n}^{\text{Ni,NH}_3})$ (model 2) ^[b]	$\log(\beta_{1,n}^{\text{Ni,NH}_3})$ (model 3) ^[c]
$[\text{Ni}(\text{NH}_3)]^{2+}$	2.79	2.38	2.83	2.83
$[\text{Ni}(\text{NH}_3)_2]^{2+}$	5.05	4.38	5.05	5.05
$[\text{Ni}(\text{NH}_3)_3]^{2+}$	6.74	6.10	6.75	6.75
$[\text{Ni}(\text{NH}_3)_4]^{2+}$	7.99	7.58	7.98	7.98
$[\text{Ni}(\text{NH}_3)_5]^{2+}$	8.73	8.78	8.69	8.69
$[\text{Ni}(\text{NH}_3)_6]^{2+}$	8.76	9.60	8.79	8.79

[a] Model 1: Computed by using Equation (11). [b] Model 2: Computed by using Equations (13)–(18). [c] Model 3: Computed by using Equations (13) and (20)–(24).

parameter $\Delta E^{\text{LL}} \neq 0$ (i.e., $u^{\text{LL}} \neq 1$) to any pair of ammonia moieties bound to Ni^{2+} , whatever their relative *cis* or *trans* orientation in the final pseudo-octahedral complexes. The free energies for the formation of *trans*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$ and *cis*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$ are identical in these conditions, as is the case for the *mer*- $[\text{Ni}(\text{NH}_3)_3]^{2+}$ /*fac*- $[\text{Ni}(\text{NH}_3)_3]^{2+}$ and *cis*- $[\text{Ni}(\text{NH}_3)_4]^{2+}$ /*trans*- $[\text{Ni}(\text{NH}_3)_4]^{2+}$ pairs, respectively. At this level of approximation, each complex $[\text{Ni}(\text{NH}_3)_n]^{2+}$ ($n = 1-6$) still corresponds to a unique microspecies, whose degeneracy is given by $\omega_{1,n} = C_n^6$. Application of Equation (9) provides Equation (12), together with the final set of six independent equations [Eqs. (13)–(18)] required for modeling the experimental macroscopic formation constants $\beta_{1,n}^{\text{Ni,NH}_3}$ collected in Table 1.^[15,16]

$$\beta_{1,n}^{\text{Ni,NH}_3} = C_n^6 (f^{\text{Ni,NH}_3})^n (u^{\text{LL}})^{n(n-1)/2} \quad (12)$$

$$\beta_{1,1}^{\text{Ni,NH}_3} = 6(f^{\text{Ni,NH}_3}) \quad (13)$$

$$\beta_{1,2}^{\text{Ni,NH}_3} = 15(f^{\text{Ni,NH}_3})^2 (u^{\text{LL}}) \quad (14)$$

$$\beta_{1,3}^{\text{Ni,NH}_3} = 20(f^{\text{Ni,NH}_3})^3 (u^{\text{LL}})^3 \quad (15)$$

$$\beta_{1,4}^{\text{Ni,NH}_3} = 15(f^{\text{Ni,NH}_3})^4 (u^{\text{LL}})^6 \quad (16)$$

$$\beta_{1,5}^{\text{Ni,NH}_3} = 6(f^{\text{Ni,NH}_3})^5 (u^{\text{LL}})^{10} \quad (17)$$

$$\beta_{1,6}^{\text{Ni,NH}_3} = (f^{\text{Ni,NH}_3})^6 (u^{\text{LL}})^{15} \quad (18)$$

The ratio of two successive binding constants $K_{n+1}^{\text{Ni,NH}_3}/K_n^{\text{Ni,NH}_3}$ can be calculated with Equation (12), and one obtains Equation (19).

$$\begin{aligned} \frac{K_{n+1}^{\text{Ni,NH}_3}}{K_n^{\text{Ni,NH}_3}} &= \frac{(\beta_{1,n+1}^{\text{Ni,NH}_3})(\beta_{1,n-1}^{\text{Ni,NH}_3})}{(\beta_{1,n}^{\text{Ni,NH}_3})^2} = \frac{(C_{n+1}^6)(C_{n-1}^6)}{(C_n^6)^2} (u^{\text{LL}}) \\ &= \frac{(6-n)n}{(6-n+1)(n+1)} (u^{\text{LL}}) \end{aligned} \quad (19)$$

This relation is well-known in coordination chemistry, when interligand interactions are neglected (i.e., $u^{\text{LL}} = 1$).^[17] In other words, u^{LL} is a quantitative measure of the deviation from the statistical binding, when ligands are fixed to a

single receptor, as similarly considered in the classical protein–ligand model.^[18] When $u^{\text{LL}} = 1$, statistical binding operates, but $u^{\text{LL}} > 1$ or $u^{\text{LL}} < 1$ correspond to positive and negative cooperativity, respectively.

A multilinear least-squares fit of Equations (13)–(18) in their logarithmic forms gives $\log(f^{\text{Ni,NH}_3}) = 2.05$ and $\Delta E^{\text{LL}} = 1.34 \text{ kJ mol}^{-1}$, in agreement with the well-established negative cooperativity reported for the equilibrium in Equation (10), which is commonly assigned to the electronic change affecting the metal upon successive binding of ammonia.^[17b] Therefore, ΔE^{LL} is mainly of electronic origin and $\Delta G_{\text{inter}}^{\text{Ni,NH}_3} = -RT \ln(f^{\text{Ni,NH}_3}) = -11.7 \text{ kJ mol}^{-1}$ refers to the free energy balance between the desolvation of both metallic and ligand binding sites, and the formation of the metal–ligand bond. The computed formation constants $\beta_{1,n}^{\text{Ni,NH}_3}$ closely match the experimental data (Table 1, model 2), but a more detailed model eventually requires two different parameters associated with pairs of ammonia moieties coordinated to Ni^{2+} in *cis* ($u_{\text{cis}}^{\text{LL}}$) and *trans* ($u_{\text{trans}}^{\text{LL}}$) positions (model 3). In these conditions, each isomer in the pairs *trans*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$ /*cis*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$, *mer*- $[\text{Ni}(\text{NH}_3)_3]^{2+}$ /*fac*- $[\text{Ni}(\text{NH}_3)_3]^{2+}$ and *cis*- $[\text{Ni}(\text{NH}_3)_4]^{2+}$ /*trans*- $[\text{Ni}(\text{NH}_3)_4]^{2+}$ possesses its own energy, and the associated macrospecies must take into account two different microspecies. This is illustrated below for the case of *trans*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$ and *cis*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$. Among the fifteen possible arrangements of two ammonia units about an octahedral Ni^{2+} ion [Eq. (14)], twelve correspond to *cis*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$ with a single *cis* interaction $u_{\text{cis}}^{\text{LL}}$, while three arrangements correspond to *trans*- $[\text{Ni}(\text{NH}_3)_2]^{2+}$ with a *trans* interaction $u_{\text{trans}}^{\text{LL}}$. The resulting macroscopic constant is the sum of two microconstants [Eq. (20)], a reasoning which can be repeated for the other complexes $[\text{Ni}(\text{NH}_3)_n]^{2+}$ [Eqs (21)–(24)].

$$\beta_{1,2}^{\text{Ni,NH}_3} = 3(f^{\text{Ni,NH}_3})^2 [4(u_{\text{cis}}^{\text{LL}}) + (u_{\text{trans}}^{\text{LL}})] \quad (20)$$

$$\beta_{1,3}^{\text{Ni,NH}_3} = 4(f^{\text{Ni,NH}_3})^3 [2(u_{\text{cis}}^{\text{LL}})^3 + 3(u_{\text{cis}}^{\text{LL}})^2 (u_{\text{trans}}^{\text{LL}})] \quad (21)$$

$$\beta_{1,4}^{\text{Ni,NH}_3} = 3(f^{\text{Ni,NH}_3})^4 [4(u_{\text{cis}}^{\text{LL}})^5 (u_{\text{trans}}^{\text{LL}}) + (u_{\text{cis}}^{\text{LL}})^4 (u_{\text{trans}}^{\text{LL}})^2] \quad (22)$$

$$\beta_{1,5}^{\text{Ni,NH}_3} = 6(f^{\text{Ni,NH}_3})^5 (u_{\text{cis}}^{\text{LL}})^8 (u_{\text{trans}}^{\text{LL}})^2 \quad (23)$$

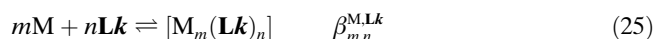
$$\beta_{1,6}^{\text{Ni,NH}_3} = (f^{\text{Ni,NH}_3})^6 (u_{\text{cis}}^{\text{LL}})^{12} (u_{\text{trans}}^{\text{LL}})^3 \quad (24)$$

A nonlinear least-squares fit of Equations (13) and (20)–(24) gives $\log(f^{\text{Ni,NH}_3}) = 2.05$, $\Delta E_{\text{cis}}^{\text{LL}} = 1.35 \text{ kJ mol}^{-1}$ and $\Delta E_{\text{trans}}^{\text{LL}} = 1.33 \text{ kJ mol}^{-1}$. The computed $\beta_{1,n}^{\text{Ni,NH}_3}$ constants again closely match the experimental data (Table 1, model 3), but they do not bring significant improvement with respect to the previous model (Table 1, model 2). We indeed find that $|\Delta E_{\text{cis}}^{\text{LL}}| \cong |\Delta E_{\text{trans}}^{\text{LL}}|$ in agreement with the absence of reliable thermodynamic *trans* influence of ammonia in octahedral complexes, a well-established fact in coordination chemistry.^[19] We thus conclude that our simplistic model catches the main phenomenological parameters responsible for the successive binding of ligands (i.e., substrate) to a single metal (i.e., receptor).

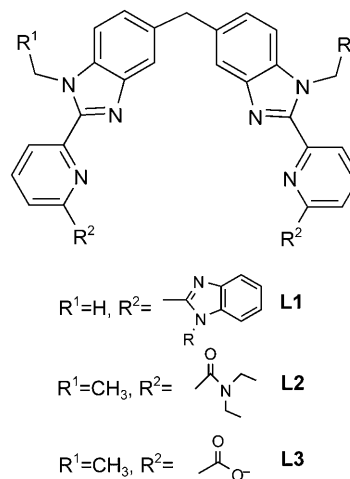
Evidently, similar data analyses can be performed for any monometallic coordination complexes, provided a sufficient number of experimental thermodynamic formation constants are available. The quantitative analysis of some well-known factors affecting the stability of coordination complexes is illustrated with the consideration of the formation constants of $[\text{Co}(\text{NH}_3)_n]^{2+}$, $[\text{Hf}(\text{F})_n]^{(4-n)+}$, and $[\text{Ni}(\text{imidazole})_n]^{2+}$ ($n=1-6$) in water,^[16] and their modeling with Equations (13)–(18) (model 2) and Equations (13) and (20)–(24) (model 3, Tables S1–S5 in the Supporting Information). For $[\text{Co}(\text{NH}_3)_n]^{2+}$, the microscopic affinity $\log(f^{\text{Co},\text{NH}_3})=1.38$ is smaller than that found for $[\text{Ni}(\text{NH}_3)_n]^{2+}$, in agreement with the well-established Irving–Williams series,^[17b] while $\Delta E^{\text{LL}}=1.1 \text{ kJ mol}^{-1}$ remains essentially unchanged (Tables S1 and S2 in the Supporting Information). For $[\text{Hf}(\text{F})_n]^{(4-n)+}$, both the microscopic affinity ($\log(f^{\text{Hf},\text{F}})=7.93$) and the interligand interaction ($\Delta E^{\text{LL}}=3.7 \text{ kJ mol}^{-1}$) are larger and reflect the increased electrostatic interactions between 1) the highly charged Hf^{4+} ion and the fluoride anion ($f^{\text{Hf},\text{F}}$) and 2) two negatively charged anions bound to Hf^{4+} (ΔE^{LL} , Tables S3 and S4 in the Supporting Information). Finally, for $[\text{Ni}(\text{imidazole})_n]^{2+}$, the microscopic affinity ($\log(f^{\text{Ni},\text{imidazole}})=2.25$) is somewhat larger than the value found for $[\text{Ni}(\text{NH}_3)_n]^{2+}$ ($\log(f^{\text{Ni},\text{NH}_3})=2.05$). This fact combined with standard interligand repulsion ($\Delta E^{\text{LL}}=1.1 \text{ kJ mol}^{-1}$) suggest the occurrence of some additional stabilizing π -back-bonding with the electron-deficient imidazole ligand (Table S3 and S5 in the Supporting Information). However, the balance between desolvation and complexation processes contributing to $f^{\text{M,L}}$ prevents a definitive interpretation of such small differences. For all investigated complexes, the successive replacement of water molecules by entering ligands is negatively cooperative ($\Delta E^{\text{LL}} > 0$), and its partition between *cis* ($\Delta E_{\text{cis}}^{\text{LL}}$) and *trans* ($\Delta E_{\text{trans}}^{\text{LL}}$) interactions (model 3) is not justified. Extension toward other geometries (e.g., tetrahedral, square planar, pentagonal bipyramidal) is straightforward, provided the application of Equation (9) carefully considers 1) the exact number of involved dative bonds and 2) a judicious statistical treatment of the degeneracy of each microspecies.

Application to homobimetallic triple-stranded helicates:

Each segmental ligand **Lk** ($k=1-3$) possesses two identical tridentate binding sites ($p=2$), and reacts with nine-coordinate lanthanide metal ions (valency v =coordination number/denticity of the ligand binding unit $=9/3=3$) to give the D_3 -symmetrical bimetallic triple-stranded helicates $[\text{M}_2(\text{Lk})_3]^{6+}$ ($k=1, 2$, Figure 1a) and $[\text{M}_2(\text{L3})_3]$.^[5,8-11] Combined kinetic and thermodynamic studies show the formation of stable intermediates displaying various stoichiometries summarized in the equilibrium given in Equation (25) ($m=1, 2$ and $n=1-3$, the charges are omitted for clarity).



To minimize the number of parameters required for modeling complicated assembly processes, we assign, whatever the stoichiometry m,n of the microspecies, 1) a single inter-



metallic interaction u^{MM} , when two metals occupy adjacent tridentate binding sites of the same ligand; 2) a single interligand interactions u^{LL} , when two binding sites of different ligands are bound to the same metal; 3) a unique intermolecular microscopic affinity constant $f^{\text{M,Lk}}$ assigned to a single connection between a metal and a tridentate binding site; and 4) a single effective concentration c^{eff} rationalizing intramolecular binding processes, when a cyclic structure is formed. Since no theoretical values are available for c^{eff} with semirigid ligands, the latter parameter is considered as a fitting parameter. Moreover, c^{eff} is expected to vary with the different levels of preorganization exhibited in the different complexes undergoing an intramolecular binding process, but the limited amount of thermodynamic data forces us to consider a single and invariant value. Finally, 5) the rigid spacer connecting the tridentate binding units in **Lk** ($k=1-3$) prevents the coordination of both sites of the same ligand to a single metal ion, thus excluding hairpin arrangements and 6) we assume that the principle of maximum site occupancy is obeyed;^[14] in other words, any metal ion is bound to n different ligands in each $[\text{M}_m(\text{Lk})_n]$ microspecies (Figure 3a). We demonstrate in the next section that point 6 is fully justified, and that it follows from our model. According to these reasonable assumptions, application of Equation (9) to the equilibrium in Equation (25) leads to the formation constant $\beta_{m,n}^{\text{M,Lk}}$ given in Equation (26).

$$\beta_{m,n}^{\text{M,Lk}} = \sigma_{\text{chir}}^{\text{M,Lk}} \omega_{\text{chir}}^{\text{M,Lk}} (f^{\text{M,Lk}})^{mn} (c^{\text{eff}})^{(mn-m-n+1)} (u^{\text{LL}})^{\frac{m}{2}(n-1)} (u^{\text{MM}})^{(m-1)} \quad (26)$$

$\sigma_{\text{chir}}^{\text{M,Lk}}=1$, except when the point group of the microspecies does not contain symmetry element of the second kind, then $\sigma_{\text{chir}}^{\text{M,Lk}}=2$ (i.e., the achiral C_{2v} -symmetrical ligand **Lk** is transformed into a chiral complex, Figure 3). The degeneracy of each $[\text{M}_m(\text{Lk})_n]$ microspecies is given by the product of two binomial coefficients $\omega_{m,n}^{\text{M,Lk}}=(C_n^v)^m (C_m^p)^n$, whereby C_n^v stands for the number of ways of putting n ligands to v positions available around one metal ion ($n \leq v$), and C_m^p refers to the

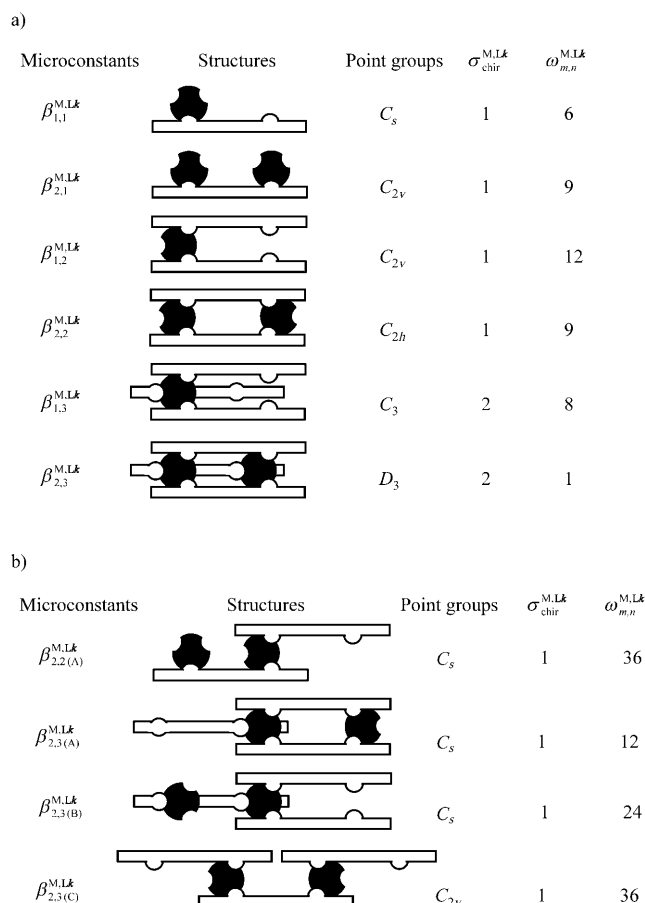


Figure 3. Schematic structures, symmetries, and degeneracies of $[M_m(\text{Lk})_n]$ microspecies described in the equilibrium given in Equation (25) ($k=1-3$). The point groups are those established in solution ($^1\text{H NMR}$, 298 K).^[5,8-11] Arrangement of microspecies a) obeying and b) deviating from the principle of maximum site occupancy.

number of ways of connecting m metal atoms to the available p binding sites of one ligand ($m \leq p$). For $[M_m(\text{Lk})_n]$ with $v=3$ and $p=2$, $\omega_{m,n}^{\text{M,Lk}} = (C_n^3)^m (C_m^2)^n$, the numerical values for which are collected for each microspecies in Figure 3a.

Application of Equation (26) for the saturated $[M_m(\text{Lk})_n]$ microspecies shown in Figure 3a provides the microscopic constants in Equations (27)–(32).

$$\beta_{1,1}^{\text{M,Lk}} = 6(f^{\text{M,Lk}}) \quad (27)$$

$$\beta_{2,1}^{\text{M,Lk}} = 9(f^{\text{M,Lk}})^2(u^{\text{MM}}) \quad (28)$$

$$\beta_{1,2}^{\text{M,Lk}} = 12(f^{\text{M,Lk}})^2(u^{\text{LL}}) \quad (29)$$

$$\beta_{2,2}^{\text{M,Lk}} = 9(f^{\text{M,Lk}})^4(u^{\text{LL}})^2(u^{\text{MM}})(c^{\text{eff}}) \quad (30)$$

$$\beta_{1,3}^{\text{M,Lk}} = 16(f^{\text{M,Lk}})^3(u^{\text{LL}})^3 \quad (31)$$

$$\beta_{2,3}^{\text{M,Lk}} = 2(f^{\text{M,Lk}})^6(u^{\text{LL}})^6(u^{\text{MM}})(c^{\text{eff}})^2 \quad (32)$$

Since the four parameters $f^{\text{M,Lk}}$, c^{eff} , u^{LL} , and u^{MM} must be extracted by using least-squares techniques, a minimum set

of five experimental macroscopic constants $\beta_{m,n}^{\text{M,Lk}}$ is required to obtain an overdetermined set of equations. For **L1**, only four stability constants ($\beta_{1,1}^{\text{M,L1}}$, $\beta_{1,2}^{\text{M,L1}}$, $\beta_{2,2}^{\text{M,L1}}$, and $\beta_{2,3}^{\text{M,L1}}$)^[8] are available. Moreover, comparison with monometallic complexes possessing analogous monotopic N_3 ligands^[20] shows that the low experimental stability constant estimated for $[\text{Eu}(\text{L1})]^{3+}$ from the kinetic data indeed refers to only partial binding of one ligand site to Eu^{III} .^[8] Therefore, $\beta_{1,1}^{\text{M,L1}}$ does not reflect a complete Eu-L1 connection, and it cannot be further considered in the modeling process. Consequently, the three remaining experimental macroscopic constants prevent an estimation of thermodynamic parameters, as is the case for **L2**, for which only three constants are available ($\beta_{2,2}^{\text{M,L2}}$, $\beta_{1,3}^{\text{M,L2}}$, and $\beta_{2,3}^{\text{M,L2}}$).^[5] For the Eu-L3 system, the combination of kinetic and thermodynamic data leads to five experimental macroscopic constants ($\beta_{1,1}^{\text{M,L3}}$, $\beta_{1,2}^{\text{M,L3}}$, $\beta_{2,1}^{\text{M,L3}}$, $\beta_{2,2}^{\text{M,L3}}$, and $\beta_{2,3}^{\text{M,L3}}$, Table 2),^[9] which are amenable to theoretical model-

Table 2. Experimental and fitted^[a] stability constants for $[\text{Eu}_m(\text{L3})_n]^{(3m-2n)+}$ complexes (water, 298 K, pH 6.15).

Species	$\log(\beta_{m,n}^{\text{Eu,L3}})$ (exptl)	$\log(\beta_{m,n}^{\text{Eu,L3}})$ (calcd)
EuL3	4.3(2)	4.4
$\text{Eu}_2\text{L3}$	6.4(2)	6.4
$\text{Eu}(\text{L3})_2$	9.3(2)	9.2
$\text{Eu}_2(\text{L3})_2$	16.1(3)	16.0
$\text{Eu}(\text{L3})_3$	–	14.7
$\text{Eu}_2(\text{L3})_3$	26.1(4)	26.1

[a] Computed by using the fitted parameters in Table 3 and Equations (27)–(32). The quoted errors correspond to those reported in reference [9].

ing using Equations (27)–(32), providing that a degeneracy of 18 is used in Equation (30) (instead of 9) because the complex $[\text{Eu}_2(\text{L3})_2]^{2+}$ adopts a helical D_2 -symmetrical structure in solution (i.e., $\sigma_{\text{chir}}=2$).^[9] Multilinear least-squares fit of Equations (27)–(30) and (32) in their logarithmic forms gives $f^{\text{M,L}}$, c^{eff} , u^{LL} , and u^{MM} collected in Table 3.

Table 3. Fitted thermodynamic parameters for $[\text{Eu}_m(\text{L3})_n]^{(3m-2n)+}$ complexes (water, 298 K, pH 6.15).^[a]

Fitted parameters	$[\text{Eu}_m(\text{L3})_n]^{(3m-2n)+}$
$\log(f^{\text{Eu,L3}})/\Delta g_{\text{inter}}^{\text{Eu,L3}}$ [kJ mol^{-1}]	3.6(1)/–20.8(6)
$\log(u^{\text{LL}})/\Delta E^{\text{LL}}$ [kJ mol^{-1}]	0.9(2)/–5(1)
$\log(u^{\text{MM}})/\Delta E^{\text{MM}}$ [kJ mol^{-1}]	–1.8(3)/10(2)
$\log(c^{\text{eff}})/\Delta g_{\text{corr}}^{\text{Eu,L3}}$ [kJ mol^{-1}]	0.3(4)/–2(2)

[a] Standard errors estimated by the least-squares fits are given between parentheses.

The conditional intermolecular binding free energy related to the N_2O sites in Eu-L3 amounts to $\Delta g_{\text{inter}}^{\text{Eu,L3}} = -21 \text{ kJ mol}^{-1}$ (water, pH 6.15), and the fitted intermetallic parameter ΔE^{MM} between two europium cations in $[\text{Eu}_2(\text{L3})_n]^{(6-2n)+}$ amounts to 10 kJ mol^{-1} (Table 3), a value close to $\Delta E^{\text{MM}} = 9 \text{ kJ mol}^{-1}$ previously obtained by using the site-binding model for the successive complexation of two Eu^{3+} to a single **L3** strand.^[2] Interestingly, the latter repul-

sion is smaller than $\Delta E^{\text{MM}} = 17.7 \text{ kJ mol}^{-1}$ estimated for the electrostatic work required for approaching two triply charged cations in water ($R_{\text{EuEu}} = 8.85 \text{ \AA}$, $\epsilon_r(\text{H}_2\text{O}) = 80$).^[5] This indicates that the successive connection of cations to the negative **L3** strands produces considerable charge compensation and/or charge redistribution, which eventually reduces intermetallic repulsion. A positive interligand cooperativity ($\Delta E^{\text{LL}} = -5 \text{ kJ mol}^{-1}$) is detected despite the electrostatic repulsion expected between negatively charged strands in $[\text{Eu}_m(\text{L3})_n]^{(3m-2n)+}$ ($n \geq 2$). This paradox can be tentatively resolved by considering the crystal structure of $[\text{Eu}_2(\text{L3})_3]$, which shows sophisticated intra- and intermolecular networks of hydrogen bonds involving the carboxylate groups of **L3**, and a huge number of surrounding water molecules.^[11] This stabilizing effect, which is expected to be partially maintained in aqueous solution, may contribute to overcome the destabilizing electrostatic interligand interactions. Finally, the effective concentration $c^{\text{eff}} = 2 (\Delta g_{\text{corr}}^{\text{Eu,L3}} = \Delta G_{\text{corr}}^{\text{Eu,L3}} / \text{intramolecular connections} = \Delta G_{\text{corr}}^{\text{Eu,L3}} / (mn - m - n + 1) = -2 \text{ kJ mol}^{-1}$, Table 3) is larger than $c^{\text{eff}} = 0.34$ estimated for a flexible polymer, in which the binding sites are separated by 9 Å, as in $[\text{Eu}_2(\text{L3})_n]^{(6-2n)+}$ ($n = 2, 3$).^[12d] Since $\Delta g_{\text{corr}}^{\text{Eu,L3}} = T\Delta S_{\text{inter}}^{\text{Eu,L3}} - T\Delta S_{\text{intra}}^{\text{Eu,L3}} < 0$, we conclude that the intramolecular process is strongly favored for the ligand **L3**, despite the considerable separation between the sites. This can be tentatively assigned to the rigid link offered by the methylene spacer, which prevents the usual relationship $c^{\text{eff}} \propto r^{-3}$, occurring when the second binding site may access to the whole volume of a sphere.^[12] Recalculation of the thermodynamic constants for the Eu–**L3** complexes almost perfectly matches the experimental data (Table 2).

Assuming the accepted concept in coordination chemistry that cooperativity for the formation of the $[\text{M}_m(\text{L})_n]$ complex corresponds to the free-energy deviation from that expected for the repetitive statistical binding of the $m + n$ components described by the three first terms of Equation (9),^[2,3,5,6,17] we introduce a global cooperativity index I_c^{tot} for each microspecies [Eq. (33)], which combines all intermetallic (u^{MM}) and interligand (u^{LL}) interactions described by the two last terms of Equation (9).

$$I_c^{\text{tot}} = \prod_{i < j}'' (u_{ij}^{\text{MM}}) \prod_{k < l}''' (u_{kl}^{\text{LL}}) \quad (33)$$

Application to the Eu–**L3** system [Eq. (26)] leads to Equations (34) and (35), which show that $I_c^{\text{tot}} > 1$ corresponds to $\Delta E_c^{\text{tot}} < 0$ and global positive cooperativity, while $I_c^{\text{tot}} < 1$ corresponds to $\Delta E_c^{\text{tot}} > 0$, which is diagnostic for global negative cooperativity. The calculated values of intermetallic (I_c^{MM}) and interligand (I_c^{LL}) contributions together with the overall cooperativity indexes I_c^{tot} are summarized in Table 4.

$$I_c^{\text{tot}} = I_c^{\text{LL}} I_c^{\text{MM}} = (u^{\text{LL}})^{\frac{m(m-1)}{2}} (u^{\text{MM}})^{(m-1)} \quad (34)$$

Table 4. Index of cooperativity (I_c) for the formation of the saturated microspecies $[\text{Eu}_m(\text{L3})_n]^{(3m-2n)+}$.

Microspecies	$\log(I_c^{\text{LL}})$ (ΔE_c^{LL}) ^[a]	$\log(I_c^{\text{MM}})$ (ΔE_c^{MM}) ^[a]	$\log(I_c^{\text{tot}})$ (ΔE_c^{tot}) ^[a]	Cooperativity
$[\text{Eu}(\text{L3})_2]^-$	0.9 (−5.1)	–	0.9 (−5.1)	positive
$[\text{Eu}_2(\text{L3})_4]^{2+}$	–	−1.8 (10.3)	−1.8 (10.3)	negative
$[\text{Eu}_2(\text{L3})_2]^{2+}$	1.7 (−9.7)	−1.8 (10.3)	−0.1 (0.6)	negative ($\approx$ none)
$[\text{Eu}_2(\text{L3})_3]$	5.2 (−29.7)	−1.8 (10.3)	3.4 (−19.4)	positive

[a] Cooperativity indexes [see text and Eqs. (33)–(35)]. Values in kJ mol^{-1} are given between parentheses.

$$\begin{aligned} \Delta E_c^{\text{tot}} &= \Delta E_c^{\text{LL}} + \Delta E_c^{\text{MM}} \\ &= -RT \left[\frac{mn}{2} (n-1) \ln(u^{\text{LL}}) + (m-1) \ln(u^{\text{MM}}) \right] \end{aligned} \quad (35)$$

With this simple index, global positive cooperativity is clearly demonstrated for the formation of $[\text{Eu}(\text{L3})_2]^-$ and $[\text{Eu}_2(\text{L3})_3]$, while that for $[\text{Eu}_2(\text{L3})_2]^{2+}$ is roughly non-cooperative (Table 4). For $[\text{Eu}_2(\text{L3})_4]^{2+}$, a negatively cooperative process is evidenced, because the intermetallic repulsion is not balanced by favorable interstrand interactions. Interestingly, the stability constant for the $[\text{Eu}(\text{L3})_3]^{3-}$ complex, which is not experimentally accessible, can be estimated, a posteriori, from the fitted parameters given in Table 3. We predict that $[\text{Eu}(\text{L3})_3]^{3-}$ is fairly stable ($\beta_{1,3}^{\text{Eu,L3}} = 14.7$) and its formation is driven by positive cooperativity ($\Delta E_c^{\text{tot}} = -15 \text{ kJ mol}^{-1}$). However, this complex was not detected by kinetic investigations probably due to its lability.^[9]

Testing the principle of maximum site occupancy: The restricted set of microspecies considered in Figure 3a for modeling the self-assembly process results from the assumption that only saturated complexes, (i.e., those for which each metal ion is connected to n ligands), contribute significantly to the macrospecies $[\text{M}_m(\text{L})_n]$. The validity of this hypothesis, known as the principle of maximum site occupancy,^[14] can be verified for bimetallic $[\text{M}_2(\text{Lk})_2]$ and $[\text{M}_2(\text{Lk})_3]$ macrospecies, because the stability of the unsaturated microspecies not obeying this principle (Figure 3b) can be, a posteriori, estimated with Equations (36)–(39).

$$\rho_{2,2(\text{A})}^{\text{M,Lk}} = 36(f^{\text{M,Lk}})^3 (u^{\text{LL}}) (u^{\text{MM}}) \quad (36)$$

$$\rho_{2,3(\text{A})}^{\text{M,Lk}} = 12(f^{\text{M,Lk}})^5 (u^{\text{LL}})^4 (u^{\text{MM}}) (c^{\text{eff}}) \quad (37)$$

$$\rho_{2,3(\text{B})}^{\text{M,Lk}} = 24(f^{\text{M,Lk}})^4 (u^{\text{LL}})^3 (u^{\text{MM}}) \quad (38)$$

$$\rho_{2,3(\text{C})}^{\text{M,Lk}} = 36(f^{\text{M,Lk}})^4 (u^{\text{LL}})^2 (u^{\text{MM}}) \quad (39)$$

The degeneracy of each unsaturated microspecies is obtained by $\omega_{m,n}^{\text{M,Lk}} = s \prod_{i=1}^m (C_{n_{\text{bound}}}^v) \prod_{j=1}^n (C_{m_{\text{bound}}}^p)$, whereby n_{bound} (m_{bound}) is the number of ligands (metal atoms) bound to the metal i (ligand j), and s is the number of nonequivalent metals. For example, we deduce for the $[\text{Eu}_2(\text{L3})_2]^{2+}$ microspecies A shown in Figure 3b, that $\omega_{2,2(\text{A})}^{\text{Eu,L3}} = (C_1^3)(C_2^3)(C_2^2)(C_1^2)2 = 36$ [Eq. (36)]. Taking $f^{\text{Eu,L3}}$, c^{eff} , u^{LL} , and

u^{MM} fitted previously for saturated species, we can calculate the stability constants $\beta_{2,2(\text{A})}^{\text{Eu,L3}}$, $\beta_{2,3(\text{A})}^{\text{Eu,L3}}$, $\beta_{2,3(\text{B})}^{\text{Eu,L3}}$, and $\beta_{2,3(\text{C})}^{\text{Eu,L3}}$, which are collected in Table 5. The predicted constants for all unsaturated complexes shown in Figure 3b are at least four

Table 5. Predicted^[a] stability constants for unsaturated $[\text{Eu}_2(\text{L3})_n]^{(6-2n)+}$ complexes.

Species	Type	$\log(\beta_{m,n}^{\text{Eu,L3}})$	Equation	$x_i^{[b]}$
$[\text{Eu}_2(\text{L3})_2]^{2+}$	saturated	16.0	30	>0.999
$[\text{Eu}_2(\text{L3})_2]^{2+} (\text{A})$	unsaturated	11.6	36	4.0×10^{-5}
$[\text{Eu}_2(\text{L3})_3]$	saturated	26.1	32	>0.999
$[\text{Eu}_2(\text{L3})_3] (\text{A})$	unsaturated	21.3	37	1.6×10^{-5}
$[\text{Eu}_2(\text{L3})_3] (\text{B})$	unsaturated	16.8	38	5.0×10^{-10}
$[\text{Eu}_2(\text{L3})_3] (\text{C})$	unsaturated	16.1	39	1.0×10^{-10}

[a] Computed by using the fitted parameters in Table 3. [b] Moles fractions calculated with $x_i = \beta_i / \sum \beta_j$ (see text).

orders of magnitude smaller than that found for the corresponding saturated analogues. This translates into a mole fraction of the saturated species $x^{\text{saturated}} = \beta_{m,n}^{\text{saturated}} / (\sum \beta_{m,n}^{\text{unsaturated}} + \beta_{m,n}^{\text{saturated}}) \geq 0.999$ (Table 5), which implies that the concentration of any unsaturated species in solution during the self-assembly process is negligible. This observation leads to the conclusion that the principle of maximum site occupancy is fully justified.

Conclusion

Compared with the original site-binding model, which considers the existence of a single virtual preassembled receptor that is taken as an arbitrary zero-level of the free energy and to which metal ions are connected, this novel approach explicitly accounts for any aggregation of ligands and metal ions observed during the assembly process (Figure 2). Two supplementary parameters are required for reliably modeling the formation of a $[\text{M}_m\text{L}_n]$ complex: 1) the effective concentration c^{eff} , which accounts for the entropic correction accompanying intramolecular metal–ligand connections,^[3,12] and 2) the interligand interaction, which occurs when two ligand-binding units are connected to the same metal ion (u^{LL}). Application to the formation of pseudo-octahedral monometallic $[\text{M}(\text{L})_n(\text{H}_2\text{O})_{6-n}]^{x+}$ complexes ($n=1-6$) is straightforward, and it provides a quantitative estimate of the cooperativity responsible for any deviation from successive statistical binding [Eq. (19)]. Extension to the assembly of the bimetallic triple-stranded helicate $[\text{Eu}_2(\text{L3})_3]$, for which a sufficient number of experimental stability constants is available, leads to values of $f_i^{\text{M,L}}$, c^{eff} , u^{MM} , and u^{LL} parameters that are in fair agreement with theoretical predictions based on standard electrostatic (u^{MM}) and entropic (c^{eff}) considerations. Evidently, the conclusions derived from our analysis only hold under the specific assumptions and simplifications used in our thermodynamic model.

In this context, three important issues must be highlighted.

- 1) According to the substantial numbers of independent microscopic parameters, which must be extracted simultaneously from the thermodynamic data, a detailed knowledge of the self-assembly mechanism is required in order to maximize the number of characterized intermediates. Therefore, the set of thermodynamic constants obtained under equilibrium conditions is often too limited, and a thorough kinetic study must be undertaken.
- 2) Due to the considerable rigidity of the strands in helicates, the effective concentration is large ($c^{\text{eff}} \approx 2$), which implies that intermolecular polymerization could become an efficient alternative pathway only for concentrations higher than c^{eff} .^[3,12]
- 3) The assignment of a reliable degeneracy to each microspecies partially relies on the chemist's capacity to address the chirality of each intermediate in solution (by means of σ_{chir}). The unambiguous determination of this structural characteristic is rarely accessible for elusive intermediates, and reasonable choices have to be made.

Nevertheless, the combination of intermetallic and interligand interactions in the complete thermodynamic model provides a quantitative estimation of the global cooperativity assigned to the formation of each species, which is not accessible with Ercolani's model.^[3] For monometallic octahedral complexes, in which water molecules are replaced by standard monodentate ligands, negative cooperativity is systematically observed. However, positive cooperativity is unambiguously evidenced for the Eu–L3 system, because of 1) the operation of charge compensation and/or redistribution, which reduce intermetallic repulsion, and 2) the existence of secondary interstrand hydrogen bonding. This result is reminiscent of the reported cooperative complexation of Fe^{III} to anionic preorganized polyhydroxamate receptors displaying strong peripheral $\text{NH}\cdots\text{OC}$ bonds.^[21] The recognition of such deviations suggests that programming positive cooperativity in multimetallic assemblies requires a judicious design of secondary interactions, in order to overcome unavoidable intermetallic repulsions. It is worth noting here that the original site-binding model considers only ΔE^{MM} , and that the global positive cooperativity evidenced for the formation of $[\text{Eu}_2(\text{L3})_3]$ from its components, escapes detection with this rough approach.

Finally, the weak stabilities predicted for unsaturated microspecies (i.e., those not obeying the principle of maximum occupancy) justify their neglect in the modeling process, and their absence in self-assembly processes, in complete agreement with Lehn's intuition.^[14] This situation also holds for polymers, and the recent observation of unusually low degrees of cross-linking for coordination polymers, obtained from the mixing of Nd^{III} with bifunctional pyridine–dicarboxylate ligands in water, is closely related to a similar enthalpic competition between saturated and unsaturated structures, modulated by interligand interactions.^[22] The ultimate use of $f_i^{\text{M,L}}$, c^{eff} , ΔE_c^{M} , and $\Delta E_{ij}^{\text{LL}}$ parameters, extracted from “simple” systems, for rationalizing sophisticated assem-

bly processes involving different metallic environments is treated in the second part of this contribution.^[23]

Experimental Section

Computational details: Computing of thermodynamic parameters were performed by using linear and nonlinear regression methods with least-squares minimization included in the Excel© and Mathematica®5 programs.

Acknowledgements

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