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Chemical Potential of the Solvent: a Crucial Player for Rationalizing Host−Guest Affinities[**]

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ABSTRACT

An access to reliable values of the thermodynamic constants $\beta_{1,1}^{H,G}$, which controls simple host-guest ([HG]) association, is crucial in medicine, biology, pharmacy and chemistry since the optimum concentration of an effector (i.e. a drug) acting on a receptor is set to $1/\beta_{1,1}^{H,G}$. Intermolecular association between charged species in polar solvents, for which water is the archetype, largely obeys this principle. Any deviation from ideality, which alters the speciation in solution, is mastered by the Debye-Hückel theory of ionic atmosphere. Much less is known for related association reactions involving neutral species in non-polar (lipophilic) media such as membranes, bilayers or organic polymers. Taking the intermolecular association between [La(hfa)$_3$dig] guest (hfa = hexafluoroacetylacetonate, dig = 2-(2-methoxyethoxy)ethane) and tridentate polyaromatic host receptors **L1-L3** in dichloromethane as a proof-of-concept, we show that the progress of the association reactions, as measured by the increase in the mole fraction of occupied sites of the

receptors, disrupt the chemical potential of the solvent to such an extent that $\beta_{1,1}^{H,G}$ may seemingly be shifted by two orders of magnitude, thus leading to erroneous dose-response prescriptions. A simple chemical model, which considers a subset of solvent molecules in surface contact with the partners of the association reaction, restores a reliable access to true and interpretable thermodynamic constants. The concomitant emergence of a concentration-dependent corrective parameter reestablishes satisfying dose-dependent response under real conditions. This 'complement' to the law of mass action offers a simple method for safely taking care of the non-predictable variations of the activity coefficients of the various partners when host-guest reactions are conducted in non-polar media.

INTRODUCTION

Beyond their indisputable contribution to the deciphering of specific host-guest interactions (H−G) operating in biological, medical and pharmaceutical media,[1] supramolecular interactions (hydrogen bond, solvation effects, dative bonds, halogen bonds, just to name a few) additionally offer some unprecedented potential for programming the free energy drift responsible for the formation of $[H_mG_n]$ assemblies (eq. 1).[2]

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

The free energy change $\Delta G_{m,n}^{H,G}$ can be partitioned between two main contributions.[3] Firstly, the change in rotational entropy between the reactants and products provides a pure entropic contribution,[4] often referred to as the statistical factor,[5] which can be safely estimated by using symmetry numbers techniques.[6] The remaining modulation of $\Delta G_{m,n}^{H,G}$ originates from chemical intercomponent interactions, host and guest (H−G), guest and guest (G−G) and host-host (H−H),[3g] among which the H−G contribution is prominent since both stability and selectivity are largely indepted to this parameter.[2a] Intermolecular[7] and intramolecular (chelate)[3] intercomponent association processes have to be treated separately and the thermodynamic corrective term 'transforming' an intermolecular H−G interaction into its intramolecular counterpart is referred to as

the effective molarity, a concept related to chelate cooperativity.[8] Its correct interpretation and modelling was subject to lively debates, which ended in 2011 with a thorough and exhaustive formulation brought by Ercolani.[9] With this in mind, any deviation of the energy change accompanying the H−G association along the operation of multiple successive binding events can be assigned to G−G and/or H−H interactions, a phenomenon known in biology as allosteric cooperativity, and for which the successive fixation of four dioxygen molecules onto hemoglobin is a famous case history.[10] Modern supramolecular chemistry[11] and material sciences[12] benefited from these pioneering developments and a detailed statistical mechanical method, referred to as the *site binding* (SB) model,[13] is now at hand for analyzing the free energy change $G(\{\boldsymbol{s}_i\}) = -\sum_{i=1}^{N} RT \ln\left(f_i^{\mathrm{G}}\right)s_i + \frac{1}{2}\sum_{i=1}^{N}\sum_{j\neq i}^{N} \Delta E_{i,j}^{\mathrm{G,G}} s_i s_j$ accompanying the formation of a {$\boldsymbol{s}_\mathbf{i}$}-[HG$_n$] microspecies characterized by its {$\boldsymbol{s}_\mathrm{i}$} state vector, for which each element s_i = 1 when a guest is bound to site *i* and s_i = 0 when no guest is coordinated (eq. 2, left). The sum runs over the *N* accessible binding sites of the host, of which *n* are occupied by guest molecules ($n \leq N$, Figure 1a).

$$\mathrm{H} + n\,\mathrm{G} \rightleftharpoons [\mathrm{HG}_n] \qquad \beta_{1,n}^{\mathrm{H,G}} = \sum_{\{\boldsymbol{s}_i\}} e^{-\left[G(\{\boldsymbol{s}_i\})/RT\right]} \qquad (2)$$

The first term $-\sum_{i=1}^{N} RT \ln\left(f_i^{\mathrm{G}}\right)s_i$ corresponds to the sum of free energies of intermolecular host-guest connections, each being represented by a simple intrinsic intermolecular host-guest site affinity f_i^{G}. The second quadratic sum $\frac{1}{2}\sum_{i=1}^{N}\sum_{j\neq i}^{N} \Delta E_{i,j}^{\mathrm{G,G}} s_i s_j$ estimates the contribution of guest-guest interactions to the global free energy change and it relies on single pair interactions $\Delta E_{i,j}^{\mathrm{G,G}}$ limited to nearest neighbours. The stability of the target [HG$_n$] macrospecies is measured by its thermodynamic macroconstant $\beta_{1,n}^{\mathrm{H,G}}$, which corresponds to the sum of the contributions of each microspecies (eq. 2, right).[13]

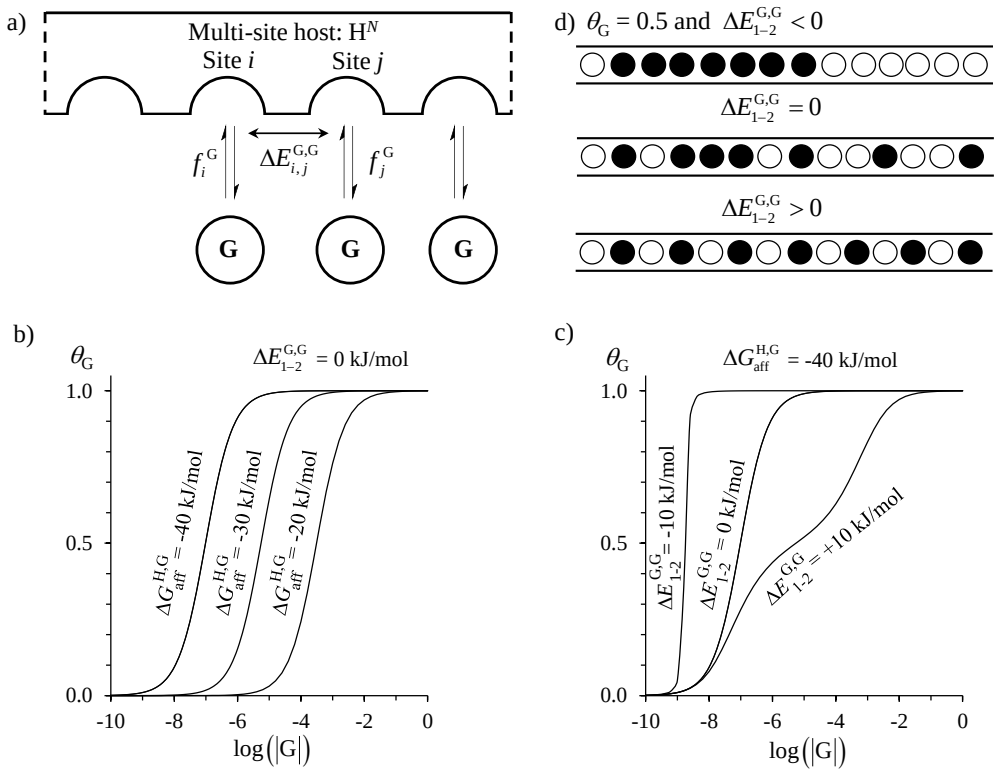


Figure 1 a) Thermodynamic model for the successive intermolecular connections of guests (G) to a one-dimensional multi-site host (H) possessing N available binding sites. $\Delta G_{\mathrm{aff},i}^{\mathrm{H,G}} = -RT\ln\left(f_i^{\mathrm{G}}\right)$ is the free energy of intermolecular host-guest affinity for a single site and $\Delta E_{1\text{-}2}^{\mathrm{G,G}}$ is the free energy of guest-guest interaction occurring when two adjacent sites are occupied. b)-c) Binding isotherms computed for the guest loading of an infinite linear host H^N ($N\rightarrow\infty$) showing the influence of b) variable H-G affinity ($\Delta E_{1\text{-}2}^{\mathrm{G,G}} = 0$) and c) variable nearest neighbor interactions ($\Delta G_{\mathrm{aff}}^{\mathrm{H,G}}$ = -40 kJ/mol).[13] d) Dominant microscospecies for the half-filled host ($\theta_{\mathrm{G}} = 0.5$) upon the operation of positive ($\Delta E_{1\text{-}2}^{\mathrm{G,G}} <0$), zero ($\Delta E_{1\text{-}2}^{\mathrm{G,G}} =0$) or negative ($\Delta E_{1\text{-}2}^{\mathrm{G,G}} >0$) cooperativity.[13]

Once the stability constant $\beta_{1,n}^{\mathrm{H,G}}$ controlling the formation of each [HG$_n$] assembly is at hand, the occupancy factor θ_{G} (eq. 3), which corresponds to the mole fraction of occupied host binding sites under a set of experimental conditions, is the key parameter for estimating the efficiency of the host-guest interaction.[3],[13]

$$\theta_{\mathrm{G}} = \frac{\langle n\rangle}{N} = \frac{1}{N}\frac{|\mathrm{G}|_{\mathrm{bound}}}{|\mathrm{H}|_{\mathrm{tot}}} = \frac{1}{N}\frac{|\mathrm{G}|_{\mathrm{tot}} - |\mathrm{G}|}{|\mathrm{H}|_{\mathrm{tot}}} = \frac{1}{N}\frac{\sum_{n=1}^{N} n\beta_{1,n}^{\mathrm{H,G}}|\mathrm{G}|^n}{1+\sum_{n=1}^{N}\beta_{1,n}^{\mathrm{H,G}}|\mathrm{G}|^n} \qquad (3)$$

Plots of θ_G as a fonction of the activity of the guest (usually taken as its free concentration $|G|$ or as $\log(|G|)$, Figs 1b-c) are known as binding isotherms (or Langmuir isotherms when $N = 1$) and provide a simple access to the 'useful dynamic range', which is the range of guest concentration over which a receptor is sensitive and specific.[1f] Applying this method for rationalizing the guest loading of an infinite linear host $H^{N\to\infty}$ is a classical problem solved by statistical mechanics,[13] which leads to the conclusion that (i) the location of the binding isotherm along the abscissa reflects the magnitude of the intrinsic host-guest affinity $\Delta G_{\text{aff},i}^{\text{H,G}} = -RT\ln\left(f_i^{\text{G}}\right)$ (Fig. 1b) while (ii) guest−guest interaction $\Delta E_{1\text{-}2}^{\text{G,G}}$ affects its slope and shape (Fig. 1c). The latter so-called 'tyrrany'[1f] of the binding isotherm arises from the invariance of the global stability constants $\beta_{1,n}^{\text{H,G}}$, in other words of $\Delta G_{\text{aff},i}^{\text{H,G}}$ and $\Delta E_{1\text{-}2}^{\text{G,G}}$ along the complete range of concentrations spanned by the target guest.[1f] With this in mind, the programming of guest clustering ($\Delta E_{1\text{-}2}^{\text{G,G}} < 0$), statistical distribution ($\Delta E_{1\text{-}2}^{\text{G,G}} = 0$) or guest alternance ($\Delta E_{1\text{-}2}^{\text{G,G}} > 0$) for half-filled multisite receptors ($\theta_G = 0.5$, Fig. 1d) becomes an obvious target for optimizing the properties of (supra)molecular sensors,[14] electronic wires,[15] magnetic chains[16] and optical materials[17] when G corresponds to an (open-shell) metallic cation and H is a segmental multisite ligand. Following this strategy, Castellano and Eggers[18] first monitored the straightforward 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).

$$\text{EDTA} + \text{Ca}^{2+} \rightleftharpoons [\text{Ca(EDTA)}]^{2+} \qquad \beta_{1,1,\text{cond}}^{\text{EDTA,Ca}} = \frac{\gamma^{\text{CaEDTA}}}{\gamma^{\text{EDTA}}\gamma^{\text{Ca}}} \cdot \frac{\left|\text{Ca}\left(\text{EDTA}\right)\right|_{\text{eq}}}{\left|\text{Ca}\right|_{\text{eq}}\left|\text{EDTA}\right|_{\text{tot}}^{\text{unbound}}} \qquad (4)$$

They realized that the experimentally accessible conditional quotient of the association reaction $Q_{1,1,\text{cond}}^{\text{EDTA,Ca}} = \dfrac{\left|\text{Ca}\left(\text{EDTA}\right)\right|_{\text{eq}}}{\left|\text{Ca}\right|_{\text{eq}}\left|\text{EDTA}\right|_{\text{tot}}^{\text{unbound}}}$ is not constant along the titration procedure and varies with $|\text{Ca}|_{\text{total}}$ and $|\text{EDTA}|_{\text{tot}}$, that is with the occupancy factor θ_{Ca} and the free concentration of the guest (Fig. 2). This makes common binding isotherms built for variable total concentrations, as shown in Figure 1,

completely unusable for extracting reliable intrinsic host-guest affinities $\Delta G_{\mathrm{aff},i}^{\mathrm{H,G}} = -RT\ln\left(f_i^{\mathrm{G}}\right)$ and allosteric cooperativities $\Delta E_{1\text{-}2}^{\mathrm{G,G}}$

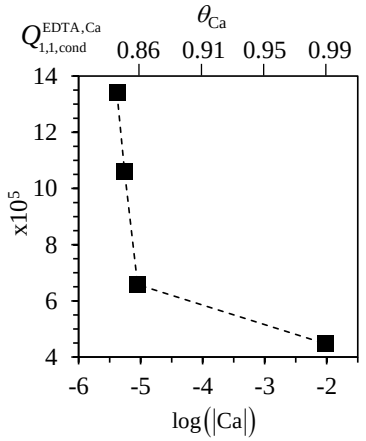


Figure 2 a) Variation of the quotient of reaction $Q_{1,1,\mathrm{cond}}^{\mathrm{EDTA,Ca}} = \dfrac{\left|\mathrm{Ca}\left(\mathrm{EDTA}\right)\right|_{\mathrm{eq}}}{\left|\mathrm{Ca}\right|_{\mathrm{eq}}\left|\mathrm{EDTA}\right|_{\mathrm{tot}}^{\mathrm{unbound}}}$ monitored for the complexation of EDTA with Ca^{2+} in aqueous buffer at pH = 6.2 and 298 K.[18] $\theta_{\mathrm{Ca}} = \left|\mathrm{Ca}\right|_{\mathrm{bound}} / \left|\mathrm{EDTA}\right|_{\mathrm{tot}}$ corresponds to the occupancy factor.

Chemists who favor the classical approach, may assign this drift to non-ideal behavior and apply a specific set of activity coefficients (γ^j in eq. 4) for each different mixture along the titration. The physical origin of this effect, often neglected in biology and in coordination chemistry,[18] can be traced back to the regular solution theory of binary mixtures, in which Margules equations[19] predict that the activity coefficients of the solute obeys $\ln(\gamma^{\mathrm{solute}}) = \xi(x^{\mathrm{solvent}})^2$, where x^{solvent} is the solvent mole fraction and ξ is a dimensionless parameter that is a measure of the energy of solute-solvent interactions relative to solute-solute and solvent-solvent interactions.[20] In this context, Castellano and Eggers explicitely considered in equilibrium 5 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.

$$\mathrm{H} + \mathrm{G} + p\,\mathrm{S}^{\mathrm{Solv}} \rightleftharpoons [\mathrm{HG}] + p\,\mathrm{S}^{\mathrm{bulk}} \qquad (5)$$

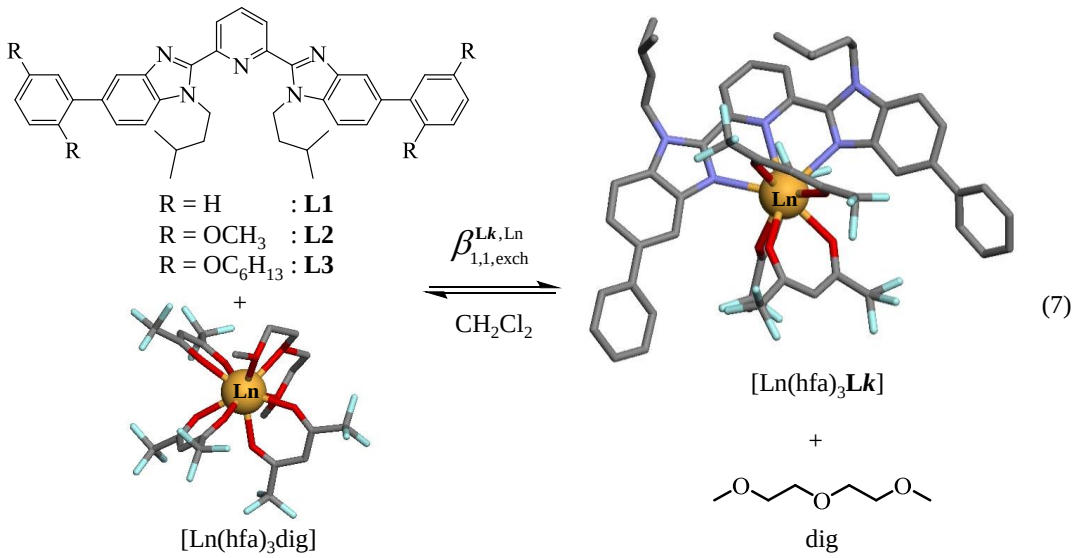
The thorough application of chemical potentials to equilibrium 5 led Castellano and Eggers (Appendix 1)[18] to propose eq. 6, which catches the variation of the activity coefficients with the progress of the reaction as measured by the formation of the final [HG] complex.[18] The

experimentally accessible quotient of the reaction at equilibrium $Q_{1,1}^{H,G} = \frac{|HG|_{eq}}{|H|_{eq}|G|_{eq}}$ now depends on (i) a true thermodynamic stability constant $\beta_{1,1}^{H,G}$ extrapolated at infinite dilution and (ii) a free energy change ΔG^{S} in the surface solvation (or second-sphere solvation for coordination chemists) accompanying the transformation of the reactants into products (c^{θ} is the standard concentration of the reference state taken as 1 mol/L).[18]

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

In simple words, eq. 6 predicts some obvious deviations from the Langmuir isotherm as soon as the product $\left(|HG|_{eq}/c^{\theta}\right)\Delta G^{S}$ is not negligible and thus varies within the 'useful dynamic range' of the target guest. The (novel) approach summarized in eq. 6 casts some embarassing doubts on a large part of the intrinsic affinities and cooperativity factors deduced from standard analyses of the Langmuir binding isotherms in biology and in chemistry (eqs 2 and 3), except when the experimental data are collected at very low concentrations. In this context, some alarming results were recently reported for the multiple binding of luminescent neutral lanthanide carriers [Ln(hfa)$_3$(dig)] (*i.e.* the guest where hfa = hexafluoroacetylacetonate and dig = 2-(2-methoxyethoxy)ethane)) to linear multi-tridentate ligands $\mathbf{L}^{N}$ (*i.e.* a host possessing *N* binding sites) because both the intrinsic affinities[21] and the cooperativity factors[22] extracted from the binding isotherms vary with polymer lengths and total concentrations, a limitation which prevented the rational design of luminescent {$\mathbf{L}^{N}$[Ln(hfa)$_3$]$_n$} metallopolymers in solution.[21b] These phenomena were tentatively assigned to global solvation effects with the help of Born-Haber cycles,[23] but the lack of true thermodynamic constants was a serious handicap for more accurate modeling and understanding. In order to circumvent these obstacles and to set a pertinent protocol for extracting reliable intermolecular host-guest affinities operating in non-polar solvents, we explore here the trivial host-guest association process depicted in equilibrium 7 (Scheme 1), for which it was established that no competitive or parasitic reaction occur in dichloromethane solution.[24] The increase in lipophilicity of the host in going from **L1** to **L3** is

expected to facilitate the interpretation of free energy change ΔG^{S} produced by differential surface solvation according to eq. 6.[23c]



Scheme 1 Host−guest association involving the exchange of diglyme (dig) with tridentate ligand **L1**-**L3** around [Ln(hfa)$_3$] (Ln = trivalent lanthanide). The molecular structures of the complexes are those found in the crystal structures of [Eu(hfa)$_3$dig][25] and [La(hfa)$_3$**L1**].[21a] Color code: C = grey, O = red, N = blue, F = light blue, Ln = orange. Hydrogen atoms are omitted for clarity.

EXPERIMENTAL SECTION

Chemicals were purchased from Sigma-Aldrich and Acros and used without further purification unless otherwise stated. The tridentate ligand 2,6-bis-(1-isopentyl-5-bromo-benzimidazol-2-yl)pyridine (**1**),[24] 3-nitro-4-isopentylamino-1-bromobenzene (**5**) [24] and [La(hfa)$_3$(diglyme)][26] were prepared according to literature procedures. The boronic acid **2c** and boronic ester **3** were obtained according to standard procedures (Appendix 2 in the Supporting Information).[27] Dichloromethane, diethyl ether and *N*,*N*-dimethylformamide were dried through an alumina cartridge. Silica-gel plates (Merck, 60 F_{254}) were used for thin-layer chromatography, SiliaFlash® silica gel P60 (0.04-0.063 mm,) and Acros silica gel 60 (0.035-0.07 mm) was used for preparative column chromatography. Abbreviations: $(dba)_2$ = dibenzylideneacetone , $P(Cy)_3$ = tricylohexylphosphine.

Preparation of 2,6-bis(1-isopentyl-5-phenyl-1*H*-benzimidazol-2-yl)pyridine (L1). A mixture of 2,6-bis-(1-isopentyl-5-bromo-benzimidazol-2-yl)pyridine (**1**, 993 mg, 1.63 mmol), phenylboronic

acid (496 mg, 4.07 mmol), K_2CO_3 (1.13 g, 8.15 mmol) and tetrakis(triphenylphosphine)palladium (185 mg, 0.16 mmol) were loaded into a schlenk tube, previously flushed with nitrogen. A degassed solution of dioxane (17 mL) and ethanol (10 mL) was added. The reaction mixture was stirred at 100°C for 35h. A saturated solution of Na_2CO_3 (50 mL) was added and the resulting solution was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOAc 1:1) to give **L1** (690 mg, 70%) as a white powder. ^{1}H−NMR (CD_2Cl_2; 400 MHz), δ/ppm: 8.34 (d; ^3J = 7.9 Hz; 2H), 8.10 (t; ^3J = 7.9 Hz; 1H), 8.04 (d; ^3J = 1.2 Hz; 2H), 7.72 (dd; ^3J = 7.1 Hz; ^4J = 1.3 Hz; 4H), 7.64 (dd; ^3J = 6.8 Hz; ^4J = 1.7 Hz; 2H), 7.56 (d; ^3J = 8.4 Hz; 2H), 7.48 (t; ^3J = 7.5 Hz; 4H), 7.36 (t; ^3J = 7.5 Hz; 2H), 4.79 (t; ^3J = 7.7 Hz; 4H), 1.67 (q; ^3J = 6.9 Hz; 4H), 1.45 (sept; ^3J = 6.6 Hz; 2H), 0.73 (d; ^3J = 6.6 Hz; 12H). ^{13}C−NMR ($CDCl_3$; 100 MHz), δ/ppm: 150.73 (2 C_{quat}), 149.95 (2 C_{quat}), 143.42 (2 C_{quat}), 141.73 (2 C_{quat}), 138.25 (CH), 136.46 (2 C_{quat}), 135.73 (2 C_{quat}), 128.83 (4 CH), 127.44 (4 CH), 126.89 (2 CH), 125.53 (2 CH), 123.39 (2 CH), 118.69 (2 CH), 110.39 (2 CH), 43.62 (2 CH_2), 38.89 (2 CH_2), 25.81 (2 CH), 22.21 (2 CH_3). ESI−MS (CH_2Cl_2), *m/z*: 1208.0 $[2M+H]^+$, 604.5 $[M+H]^+$.

Preparation of 2,6-bis(5-(2,5-dimetoxyphenyl)-1-isopentyl-1*H*-benzimidazol-2-yl)pyridine (L2). To a solution of 2,6-bis-(1-isopentyl-5-bromo-benzimidazol-2-yl)pyridine (**1**, 427 mg, 0.70 mmol), 2,5-dimetoxypenylboronic acid (319 mg, 1.75 mmol), cesium fluoride (532 mg, 3.50 mmol) and tetrakis(triphenylphosphine)palladium (81 mg, 0.07 mmol) were added degassed dioxane (7 mL) and EtOH (5 mL). The reaction mixture was stirred at 100°C under inert atmosphere for 35h. A solution of saturated Na_2CO_3 (50 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/Acetone 10:1) to give **L2** (280 mg, 55%) as an orange oil. ^{1}H−NMR (CD_2Cl_2; 400 MHz), δ/ppm: 8.39 (d; ^3J = 7.8 Hz; 2H), 8.12 (t; ^3J = 7.8 Hz; 1H), 7.97 (s; 2H), 7.56 (d; ^3J = 8.5 Hz; 2H), 7.53 (d; ^3J = 8.5 Hz; 2H), 7.00 (d; ^4J = 3.0 Hz; 2H), 6.97 (s; 2H), 6.88 (dd; ^4J =

3.0 Hz; 2H), 4.80 (t; ^3J = 7.5 Hz; 4H), 3.81 (d; ^3J = 12.4 Hz; 12H), 1.68 (q; ^3J = 7.0 Hz; 4H), 1.47 (sept; ^3J = 6.6 Hz; 2H), 0.75 (d; ^3J = 6.6 Hz; 12H). ^{13}C−NMR (CD_2Cl_2; 100 MHz), δ/ppm: 154.40 (4 C_{quat}), 151.40 (2 C_{quat}), 150.61 (2 C_{quat}), 143.34 (2 C_{quat}), 138.64 (CH), 136.10 (2 C_{quat}), 133.69 (2 C_{quat}), 132.51 (2 C_{quat}), 125.98 (4 CH_2), 121.32 (2 CH_2), 117.49 (2 CH_2), 113.31 (4 CH_2), 110.25 (2 CH_2), 56.72 (2 CH_3), 56.26 (2 CH_3), 44.17 (2 CH_2), 39.39 (2 CH_2), 26.42 (2 CH), 22.54 (4 CH_3). ESI−MS (CH_2Cl_2), *m/z*: 1448.3 $[2M+H]^+$, 724.5 $[M+H]^+$.

Preparation of 2',5'-bis(hexyloxy)-*N*-isopentyl-3-nitro-[1,1'-biphenyl]-4-amine (6). A mixture of **3** (500 mg, 1.24 mmol), **5** (296 mg, 1.03 mmol), cesium fluoride (78 mg, 5.15 mmol), $Pd(dba)_2$ (30 mg, 0.05 mmol) and $P(Cy)_3$ (15 mg, 0.05 mmol) were introduced into a schlenk tube previously flushed with nitrogen. A solution of degassed dioxane (40 mL) and ethanol (25 mL) was added and the reaction mixture was stirred 24h under reflux. After extraction with CH_2Cl_2 (50 mL), the product was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH 100:1) to give pure **6** (70 mg, 15%) as an orange-red oil.^{1}H−NMR ($CDCl_3$; 400 MHz), δ/ppm: 8.43 (d; ^4J = 2.1 Hz; 1H), 8.07 (t; ^3J = 4.3 Hz; NH), 7.72 (dd; ^3J = 8.9 Hz; ^4J = 2.2 Hz; 1H), 6.90 (m; 1H), 6.88 (d; ^4J = 3.6 Hz; 1H), 6.86 (s; 1H), 6.80 (dd; ^3J = 8.9 Hz; ^4J = 3.0 Hz; 1H), 3.94 (t; ^3J = 6.5 Hz; 2H), 3.89 (t; ^3J = 6.5 Hz; 2H), 3.36 (td; ^3J = 7.3 Hz; ^4J = 4.8 Hz; 2H), 1.78 (m; 3H), 1.67 (dq; ^3J = 12.5 Hz; ^4J = 6.9 Hz; 4H), 1.47 (m; 4H), 1.34 (m; 4H), 1.27 (m; 4H), 1.00 (d; ^3J = 6.5 Hz; 6H), 0.91 (m; 3H), 0.85 (m; 3H). ^{13}C−NMR ($CDCl_3$; 100 MHz), δ/ppm: 153.40 (C_{quat}), 150.20 (C_{quat}), 144.60 (C_{quat}), 135.80 (CH), 131.46 (C_{quat}), 129.55(C_{quat}), 127.14 (CH), 125.65 (C_{quat}), 116.53 (CH), 114.11 (CH), 113.81 (CH), 113.08 (CH), 69.40 (CH_2), 68.71(CH_2), 41.33 (CH_2), 37.89 (CH_2), 31.62 (CH_2), 31.53 (CH_2), 39.39 (CH_2), 29.32 (CH_2), 25.99 (CH), 25.80 (CH_2), 25.76 (CH_2), 22.62 (CH_2), 22.57 (CH_2), 22.50 (2 CH_3), 14.05 (CH_3), 14.00 (CH_3). ESI−MS (MeOH-CH_2Cl_2), *m/z*: 485.6 $[M+H]^+$.

Preparation of *N*2,*N*6-bis(2',5'-bis(hexyloxy)-3-nitro-[1,1'-biphenyl]-4-yl)-*N*2,*N*6-diisopentylpyridine-2,6-dicarboxamide (7). A solution of **6** (31 mg, 0.06 mmol) and pyridine-2,6-dicarbonyl dichloride (6 mg, 0.03 mmol) in dry CH_2Cl_2 (8 mL) was stirred under refluxed for 12 hours. Then the reaction was quenched with a saturated solution of NH_4Cl (30 mL). The crude mixture

was extracted with CH_2Cl_2 (3x50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The resulting oil was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH 100:1) to obtain pure **7** (33 mg, quantitative) as a yellow oil. ^{1}H−NMR ($CDCl_3$; 400 MHz), δ/ppm: the presence of conformers did not allow the assignment of the full spectrum. ESI-MS (MeOH/CH_2Cl_2), m/z: 1101.9 $[M+H]^+$.

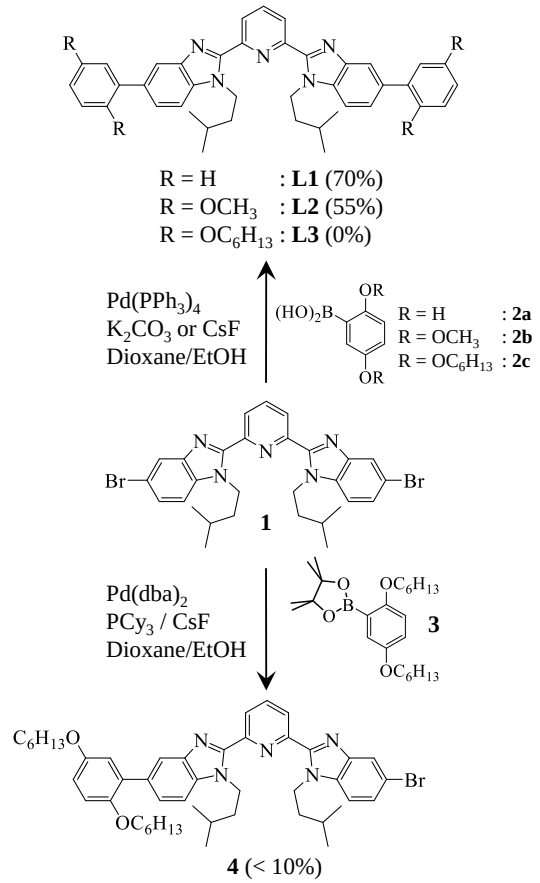
Preparation of 2,6-bis(5-(2,5-bis(hexyloxy)phenyl)-1-isopentyl-1*H*-benzimidazol-2-yl)pyridine (L3). A solution of **7** (35 mg, $3.2\cdot10^{-3}$ mmol) in ethanol (6 mL) and H_2O (3 mL) was introduced into a schlenk tube. Activated iron powder (44 mg, 0.80 mmol) and of HCl 37% (232 µL) were added and the reaction mixture was stirred at 80°C for 12h. Ethanol was disttiled and a saturated solution of EDTA (12.5 g in 50 mL of H_2O) was added. To reach a pH=8.5, an aqueous solution of NH_4OH (25%) was added. The resulting solution was extracted with CH_2Cl_2 (3x50 mL). 2 mL of H_2O_2 (30%) was added and the mixture was stirred 15 minutes. The aq. phase was further extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH 100:1) to give pure **L3** (23 mg, 72%) as a yellow oil. ^{1}H−NMR ($CDCl_3$; 400 MHz), δ/ppm: 8.33 (d; ^3J = 7.9 Hz; 2H), 8.07 (t; ^3J = 7.9 Hz; 1H), 8.03 (d; ^4J = 1.4 Hz; 2H), 7.62 (dd; ^3J = 8.4 Hz; ^4J = 1.5 Hz; 2H), 7.45 (d; ^3J = 8.5 Hz; 2H), 7.02 (d; ^4J = 3.0 Hz; 2H); 6.95 (d; ^3J =8.9 Hz; 2H), 6.85 (dd; ^3J = 8.8 Hz; ^4J = 3.1 Hz; 2H), 4.75 (m; 4H), 3.97 (t; ^3J = 6.5 Hz; 4H), 3.90 (t; ^3J = 6.5 Hz; 4H), 1.79 (dt; ^3J = 14.3 Hz; ^4J = 6.7 Hz; 4H), 1.67 (m; 8H), 1.46 (ddt; ^3J = 9.1 Hz; ^3J = 6.4 Hz; ^4J = 3.8 Hz; 6H), 1.35 (m; 8H), 1.24 (m; 8H), 0.91 (t; ^3J = 6.8 Hz; 6H); 0.83 (t; ^3J = 6.8 Hz, 6H), 0.74 (d; ^3J = 6.6 Hz; 12H). ^{13}C−NMR ($CDCl_3$; 100 MHz), δ/ppm: 153.57 (2 C_{quat}), 150.43 (4 C_{quat}), 150.17 (2 C_{quat}), 142.97 (2 C_{quat}), 138.28 (CH), 135.45 (2 C_{quat}), 133.66 (2 C_{quat}), 132.69 (2 C_{quat}), 125.98 (2 CH), 125.57 (2 CH), 121.14 (2 CH), 117.63 (2 CH), 114.94 (2 CH), 114.05 (2 CH), 109.41 (2 CH), 69.91 (2 CH_2), 68.83 (2 CH_2), 43.66 (2 CH_2), 39.03 (2 CH_2), 31.70 (4 CH_2), 29.85 (2 CH), 29.50 (4 CH_2), 25.91 (4 CH_2), 22.75 (4 CH_2), 22.36 (4 CH_3), 14.17 (4 CH_3). ESI−MS (MeOH/CH_2Cl_2), *m/z*: 1005.6 $[M+H]^+$.

Spectroscopic and analytic measurements

^{1}H− and ^{13}C−NMR spectra were recorded on a *Bruker Avance* 400 MHz spectrometer. Chemical shifts are given in ppm with respect to tetramethylsilane $Si(CH_3)_4$. Assignments of signals were deduced from COSY, HSQC, HMBC (and NOESY) NMR measurements. Pneumatically-assisted electrospray (ESI) mass spectra were recorded from 10^{-4} M solutions on an Applied Biosystems API 150EX LC/MS System equipped with a Turbo Ionspray source®. Mathematical fitting processes were performed using Microsoft excel® software.

RESULTS AND DISCUSSIONS

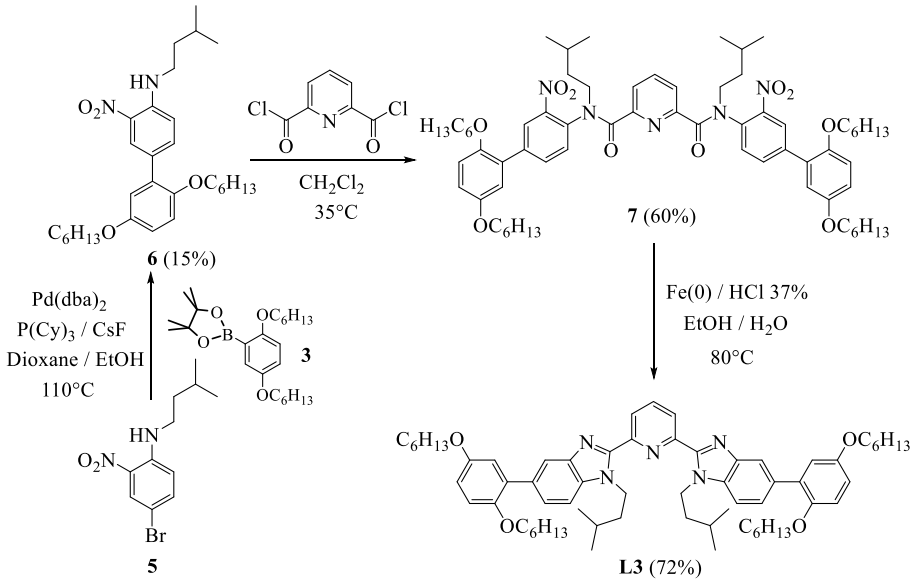
Synthesis of the ligands L1-L3.



Scheme 2 Synthesis of tridentate ligands **L1** and **L2** depicted in their average *trans*−*trans* C_{2v}-symmetrical arrangement observed by NMR in solution. PPh_3 = triphenylphosphine, PCy_3 = tricyclohexylphosphine, dba = dibenzylideneacetone.

The central tridentate binding unit **1** was flanked with two identical phenyl groups to give **L1**[21a] using a standard Pd(0)-catalyzed Miyaura-Suzuki strategy based on phenylboronic acid **2a** (Scheme 2 top).[27] The same procedure using 2,5-dimethoxyphenyl boronic acid **2b** lead to ligand **L2** in fair

yield. We were however unable to get significant amount of the target lipophilic ligand **L3** with this strategy, and this despite systematic investigations testing various catalysts ($Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $PdCl_2$(dppf)), bases (CsF, K_2CO_3, KOAc) and boronic reagents (**2c** or **3**). Attempts to speed up the rate-limiting oxidative addition step[28] using the electron-rich tricyclohexylphosphine co-ligand (PCy_3) slightly improves the situation with the detection of intermediate mono-substituted tridentate ligand **4** (Scheme 2, bottom), but no trace of the target di-substituted ligand **L3**. As a last resort, we performed the limiting Suzuki coupling reaction at the beginning of the multistep strategy (Scheme 3).



Scheme 3 Synthesis of ligand **L3** depicted in its average *trans*−*trans* C_{2v}-symmetrical arrangement observed by NMR in solution. PCy_3 = tricyclohexylphosphine, dba = dibenzylideneacetone.

Despite major efforts for optimizing the initial coupling reaction with the help of acenaphthoimidazolylidene palladium complex (Pd−NHC), which are known to favor C−C coupling for hindered substrates,[29] we got the substituted biphenyl compound **6** in poor yield. Repeating this initial step several times eventually provided sufficient amount of material for the preparation of lipophilic **L3** (Scheme 3). The ^{1}H−NMR and ^{13}C−NMR spectra recorded for **L1**-**L3** are diagnostic for the ligands adopting the expected average *trans*−*trans* C_{2v}-symmetry on the NMR time scale. 1) The only five aromatic signals observed for the bis(benzimidazole-2-yl)pyridine implies a twofold axis (see signals a,b,g,h,j in Figure 3 and Figures S1-S3 in the Supporting Information). 2) The

enantiotopic methyl groups of the neopentyl residues involve a symmetry plane (see n = n' signals in Figures 3 and S1-S3). 3) the lack of detectable {^{1}H−^{1}H}−NOE effect between the central pyridine and the benzimidazole side arms is only possible when the two fused α,α'-diimine binding groups of the tridentate unit adopt a *transoid−transoid* arrangement.

Exchange of neutral [La(hfa)$_3$] guest between diglyme and L1-L3 tridentate host ligands.

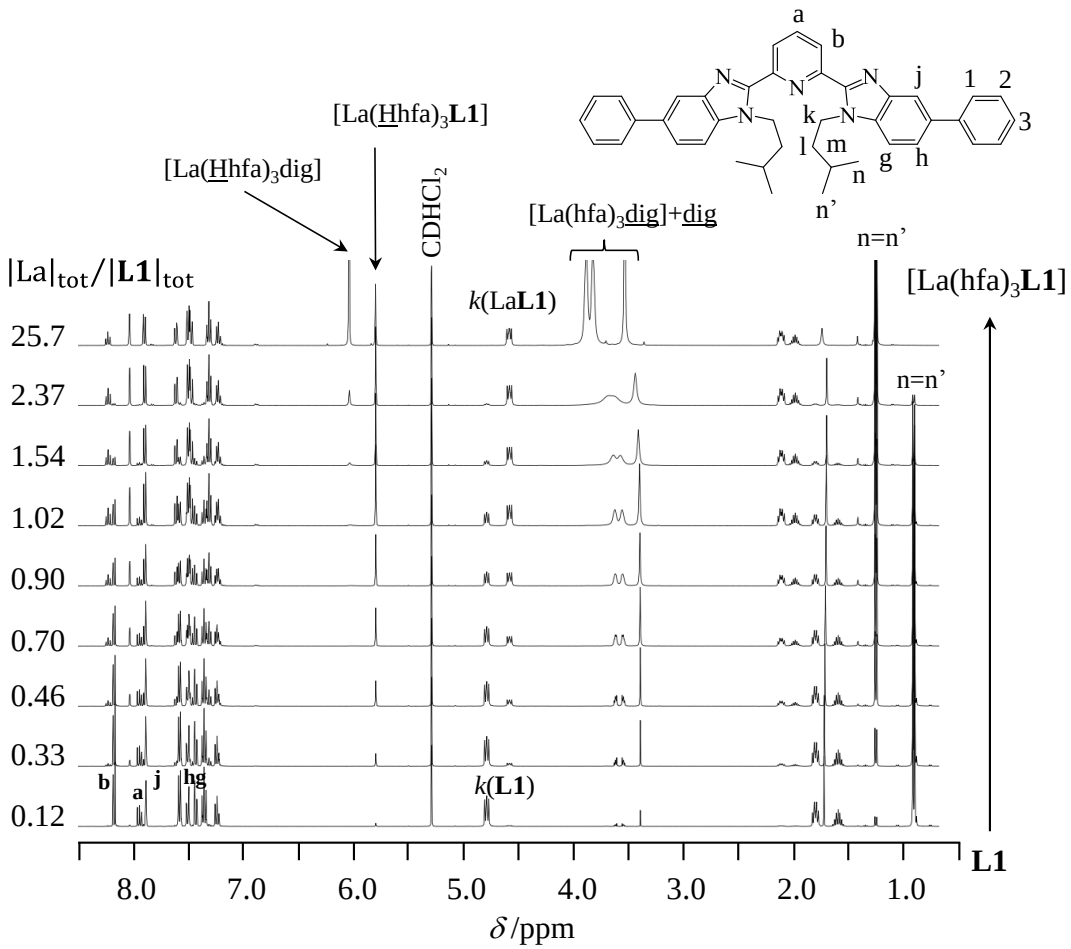


Figure 3 ^{1}H−NMR titration of **L1** with [La(hfa)$_3$(dig)] in CD_2Cl_2 at 298K with numbering scheme ($5.5\cdot10^{-3} \leq |\mathbf{L1}|_{tot} \leq 9.9\cdot10^{-3}$ M and $2.4\cdot10^{-4} \leq |La|_{tot} \leq 1.4\cdot10^{-1}$ M).

Since it was established that no significant dissociation of the complexes [La(hfa)$_3$dig] and [La(hfa)$_3$L***k***] occurs in dichloromethane within the 10^{-4} to 10^{-1} M concentration range,[21],[22],[24] these compounds exist as single species in solution along the NMR titrations (Figure 3) and equilibrium 7 gives rise to the only four species depicted in Scheme 1 in addition to the solvent molecules. For each [L***k***]$_{tot}$/[La]$_{tot}$ stoichiometric mixture produced along the titration procedure, the ^{1}H−NMR spectra,

recorded at thermodynamic equilibrium, showed no dynamic exchange process on the NMR time scale (Figure 3). Consequently, the intensity of the signals of the a given proton I^{H} in the free ligand **L*k*** (for instance *k*(**L1**) in Figure 3) and in the complex [La(hfa)$_3$**L*k***] (*k*(La**L1**) in Figure 3) can be exploited for estimating the experimental occupancy factor θ_{La}^{exp} (left part of eq. 8). The concentration of 'free metal' $|La(dig)| = |La|_{tot} - \theta_{La}|\mathbf{Lk}|_{tot}$ is easily deduced, while those of the other partners involved in equilibrium 7 are deduced from trivial mass balances $|dig| = |La(\mathbf{Lk})| = |La|_{tot} - |La(dig)| = \theta_{La}|\mathbf{Lk}|_{tot}$ and $|\mathbf{Lk}| = |\mathbf{Lk}|_{tot}(1-\theta_{La})$. The associated quotient of reaction at chemical equilibrium is then easily calculated using $Q_{1,1,exch}^{\mathbf{Lk},La} = |La(\mathbf{Lk})| \cdot |dig| / |La(dig)| \cdot |\mathbf{Lk}|$ (any reference to non-dissociated hfa co-ligands is removed for the sake of clarity, so the concentrations of the complexes are simply written as $|La(dig)|$ and $|La(\mathbf{Lk})|$).

$$\theta_{La}^{exp} = \frac{|La|_{bound}}{|\mathbf{Lk}|_{tot}} = \frac{|La|_{tot} - |La(dig)|}{|\mathbf{Lk}|_{tot}} = \frac{I_{La\mathbf{Lk}}^{H}}{I_{\mathbf{Lk}}^{H} + I_{La\mathbf{Lk}}^{H}} = \frac{Q_{1,1,exch}^{\mathbf{Lk},La}\left(|La(dig)|/|dig|\right)}{1 + Q_{1,1,exch}^{\mathbf{Lk},La}\left(|La(dig)|/|dig|\right)} \quad (8)$$

Expressing the occupancy factor θ_{La}^{exp} as a function of $Q_{1,1,exch}^{\mathbf{Lk},La}$ (right part of eq. 8) provides an expression reminiscent of the standard Langmuir binding isotherm characterizing host-guest association (right part of eq. 3) according that the concentration of free guest $|G|$ in eq. 3 is replaced with the ratio $|La(dig)|/|dig|$ in eq. 8. With this in mind, the titrations of **L*k*** with [La(hfa)$_3$(dig)] in CD_2Cl_2 at 298 K (Figure 3) give rise to pseudo-binding isotherms depicted in Figure 4a for **L*k*** = **L1** (black diamonds) and in Figures S4a-S5a for **L*k*** = **L2-L3** (supporting information). As predicted by Castellano and Eggers in eq. 6,[18] the free energy changes asssociated with the quotients of reaction 7 at equilibrium $-RT\ln\left(Q_{1,1,exch}^{\mathbf{Lk},La}\right)$ roughly linearly depend on the total concentrations of the formed product $|La(\mathbf{Lk})|_{eq}$ (Figures 4b and Figures S4b-S5b), and thus provide satisfying assessments for the free energy of guest exchange at infinite dilution $\Delta G_{1,1,exch}^{\mathbf{Lk},La} = -RT\ln\left(\beta_{1,1,exch}^{\mathbf{Lk},La}\right)$ together with the free energy change ΔG_{exch}^{S} in surface-contact solvation (Table 1, columns 2 and 3). Let's stress here that

$Q_{1,1,\mathrm{exch}}^{\mathbf{Lk},\mathrm{La}}$ should not be confused with the thermodynamic exchange constants $\beta_{1,1,\mathrm{exch}}^{\mathbf{Lk},\mathrm{La}}$ although this erroneous practice is common in supramolecular and in coordination chemistry

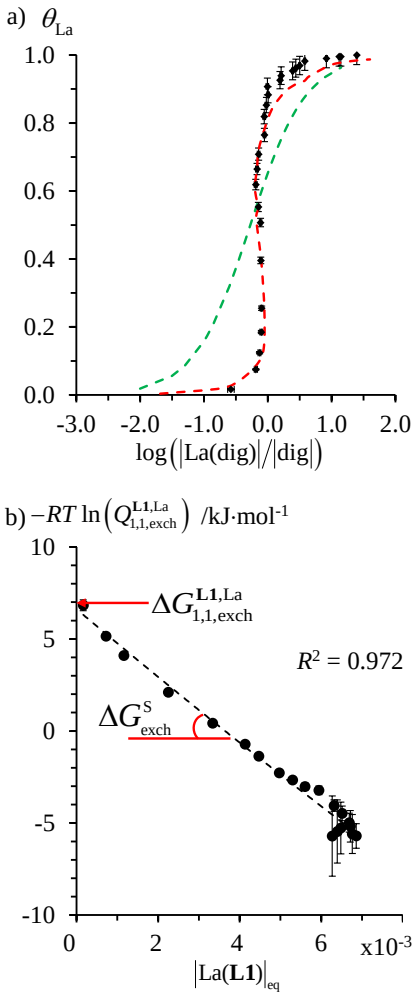


Figure 4 a) Experimental (black diamonds, eq. 7) and fitted (red trace using eq. 6 with $\Delta G_{1,1,\mathrm{exch}}^{\mathbf{L1},\mathrm{La}}$, $\Delta G_{\mathrm{exch}}^{\mathrm{S}}$ taken in Table 1) pseudo-binding isotherms for the titration of **L1** with [La(hfa)$_3$dig] in CD_2Cl_2 at 298 K. The green trace corresponds to the standard analysis using eq. 3 and an average constant free energy of association $\Delta\bar{G}_{1,1,\mathrm{exch}}^{\mathbf{L1},\mathrm{La}}$ (taken in table 1). b) Dependence of the quotient of reaction at equilibrium $Q_{1,1,\mathrm{exch}}^{\mathbf{L1},\mathrm{La}}$ with the progress of the exchange reaction highlighting $\Delta G_{1,1,\mathrm{exch}}^{\mathbf{L1},\mathrm{La}}$ and $\Delta G_{\mathrm{exch}}^{\mathrm{S}}$ according to eq. 6.

Introducing $Q_{1,1,\mathrm{exch}}^{\mathbf{Lk},\mathrm{La}} = \beta_{1,1,\mathrm{exch}}^{\mathbf{Lk},\mathrm{La}} e^{-\left(\frac{\Delta G_{\mathrm{exch}}^{\mathrm{S}}}{RT}\cdot\frac{|\mathrm{La}(\mathbf{Lk})|_{\mathrm{eq}}}{c^{\theta}}\right)}$ predicted by eq. 6 into eq. 8 (right) leads to occupancy factors reproducing well the experimental data (red traces in Figures 4a and S4-S5a). In contrast, attempts to use the classical analysis, which considers a unique exchange free energy

$\Delta\bar{G}^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}} = -RT\ln\left(\frac{1}{N}\sum_{i=1}^{N}\left(Q^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}\right)_i\right)$ taken as the average of N quotients of reaction measured during the titration procedure (Table 1, column 4) only failed (green traces in Figs 4a and S4a-S5a) and yielded exchange free energies with erroneous signs, magnitudes, and huge uncertainties (compare columns 2 and 4 in Table 1).

Table 1 Thermodynamic parameters $\Delta G^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}$, $\Delta G^{\mathrm{S}}_{\mathrm{exch}}$ (eq. 6) and average free energy $\Delta\bar{G}^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}} = -RT\ln\left(\frac{1}{N}\sum_{i=1}^{N}\left(Q^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}\right)_i\right)$ determined for the titration of **L*k*** with [La(hfa)$_3$dig] (eq. 7) in CD_2Cl_2 at 298 K.

Hosts	$\Delta G^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}$ [a] /kJ·mol^{-1}	$\Delta G^{\mathrm{S}}_{\mathrm{exch}}$ [a] /kJ·mol^{-1}	$\Delta\bar{G}^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}$ [b] /kJ·mol^{-1}	$-RT\ln\left(Q^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}\right)$ [c] /kJ·mol^{-1}	$-RT\ln\left(Q^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}\right)$ [d] /kJ·mol^{-1}
L1	5.9(3)	-1615(50)	-3.9(2.4)	4.3(3)	-156(5)
L2	5.6(3)	-1503(71)	-3.4(2.7)	4.1(3)	-145(7)
L3	4.0(3)	-2020(92)	-4.6(2.1)	2.0(3)	-198(9)

[a] Uncertainties are those obtained by linear least-square fit of eq. 6. [b] Uncertainties correspond to the standard deviation from the average values. [c] Computed with eq. 6 using $\left|\mathrm{La}(\mathbf{L}\boldsymbol{k})\right|_{\mathrm{eq}} = 10^{-3}$ M. [d] Computed with eq. 6 using $\left|\mathrm{La}(\mathbf{L}\boldsymbol{k})\right|_{\mathrm{eq}} = 10^{-1}$ M.

The free energies of exchange $\Delta G^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}$ at infinite dilution (Table 1, column 2) point to endergonic processes accompanying the replacement of the tridentate O−donor ligand (diglyme) with tridentate N−donor ligands (**L1-L3**) around [La(hfa)$_3$], a trend in agreement with gas-phase modelling and Hard-Soft Acid-Base (HSAB) theory.[30] The 30% less unfavorable exchange process found for the bulky **L3** ligand may originate from larger dihedral angles between the benzimidazole rings and the terminal phenyl rings, which limit electron delocalization and makes the binding nitrogen donors of **L3** more electron-rich. Any favorable driving force responsible for the replacement of diglyme with **L1-L3** around [La(hfa)$_3$] can be thus assigned to the solvation energies $\Delta G^{\mathrm{S}}_{\mathrm{exch}} << 0$ produced by the set of solvent molecules which are in surface-contact with the reactants and products. At millimolar

concentrations, the solvation contribution $\left(\left|\mathrm{La}(\mathbf{L}\boldsymbol{k})\right|_{\mathrm{eq}}/c^{\theta}\right)\Delta G^{\mathrm{S}}_{\mathrm{exch}}$ is dominated by the intermolecular guest exchange process $\Delta G^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}$ and the apparent free energy changes $-RT\ln\left(Q^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}\right)$ remain positive and unfavorable (Table 1, column 5). Howewer, decimolar concentrations are sufficient to reverse the trend with the operation of large exergonic contributions $-RT\ln\left(Q^{\mathbf{L}\boldsymbol{k},\mathrm{La}}_{1,1,\mathrm{exch}}\right) < 0$ and the emergence of some apparent preference of [La(hfa)$_3$] for coordinating N-donor ligands (Table 1, column 6). The molecular interpretation of the latter $\Delta G^{\mathrm{S}}_{\mathrm{exch}}$ contribution is difficult and challenging, which probably explains the so far limited impact produced by the report of eq. 6 in 2013.[18] It is worth reminding here that, according to the classical approach illustrated for [Ca(EDTA)] in eq. 4, $\Delta G^{\mathrm{S}}_{\mathrm{exch}}$ reflects the change in activity coefficients γ occurring along the titration process.[20] Within the frame of the regular solution theory of mixing,[20] deviation from ideality for a binary mixture (solute/solvent) can be ascribed to some unbalanced enthalpic contribution ξ measuring the energy of the solvent−solute interactions relative to that of solute−solute and solvent−solvent interactions. As a first rough approximation, the neutral partners contributing to equilibrium 7 can be considered as a global solute dispersed in a large amount of dichloromethane solvent. Then, the Margules equations[19] suggest $\ln(\gamma^{\mathrm{solute}}) = \xi(x^{\mathrm{solvent}})^2$ (Fig. S6a in the Supporting Information), which leads to the solute activity $a^{\mathrm{solute}} = \gamma^{\mathrm{solute}} x^{\mathrm{solute}} = \gamma^{\mathrm{solute}}\left(1-x^{\mathrm{solvent}}\right) = e^{\xi\left(x^{\mathrm{solvent}}\right)^2}\left(1-x^{\mathrm{solvent}}\right)$ where x^{solvent} and x^{solute} are the mole fractions of each component in the binary mixture (Fig. S6b). In dilute solution considered along the titration procedures of **L*k*** with [La(hfa)$_3$(dig)], the mole fraction of the solvent is close to unity ($x^{\mathrm{solvent}}\rightarrow 1$) and the activity coefficient of the solute $\gamma^{\mathrm{solute}} = e^{\xi\left(x^{\mathrm{solvent}}\right)^2}$ is extremely sensitive to faint changes in composition as soon as $\xi \neq 0$ (Figure S6a), a situation found when the solute-solvent interactions are more ($\xi < 0$) or less ($\xi > 0$) favorable than solvent−solvent and solute−solute interactions.[20] Combining the concept of Eggers and Castellano (eq. 5) with the predictions of regular solution theory suggests that the considerable negative values of $\Delta G^{\mathrm{S}}_{\mathrm{exch}}$ found

for equilibrium 7 with **L1**-**L3** can be assigned to solvent−solute interactions, which are significantly different in the reactants **L*k*** and [La(hfa)$_3$dig] compared to those found in the products [La(hfa)$_3$**L*k***] and dig. Some surface contact solvent molecules are thus released in, or extracted from the bulk when the exchange reaction proceeds (eq. 5 highlights the case of a release of contact-surface solvent molecules). Since the magnitude of ΔG^{S}_{exch} mirrors ξ, the larger negative value found for lipophilic **L3**, compared with **L1** and **L2**, indicates that the connection of flexible and poorly polarizable alkyl chains to the aromatic backbone drastically affects solute-solvent and solute-solute interactions, a phenomenon at the origin of demixing in block co-polymers[31] and of microphase separations in liquid crystals.[32]

Association of neutral [La(hfa)$_3$] guest with L1-L3 ligands hosts: the conditional approach. Building on the interpretation of ΔG^{S} as being a measure of change in activity coefficients of the solute produced by minor changes in the mole fraction of the solvent as the reaction proceeds (see previous section), one predicts that fixing the concentration of one of the partner of the exchange reaction 7 at a sufficient level for being large and invariant during the titration should limit the contact-surface solvent contribution ΔG^{S}. In analytical chemistry, this procedure is referred to as a conditional approach. Fixing the total concentration of diglyme at $|\text{dig}|_{tot}$ = 0.14 M transforms eq. 7 into the conditional host−guest association reaction 9 characterized by its (conditional) quotient of reaction $Q^{\mathbf{L}k,\text{La}}_{1,1,\text{cond}} = Q^{\mathbf{L}k,\text{La}}_{1,1,\text{exch}} \big/ |\text{dig}|_{tot}$.[21],[22]

$$\mathbf{L}k \quad + \quad [\text{La(hfa)}_3] \quad \rightleftharpoons \quad [\text{La(hfa)}_3\mathbf{L}k] \qquad Q^{\mathbf{L}k,\text{La}}_{1,1,\text{cond}} = \frac{Q^{\mathbf{L}k,\text{La}}_{1,1,\text{exch}}}{|\text{dig}|_{tot}} = \frac{|\text{La}(\mathbf{L}k)|}{|\text{La(dig)}||\mathbf{L}k|} \qquad (9)$$

Repeating the titrations of **L*k*** with [La(hfa)$_3$(dig)] in CD_2Cl_2+014 M diglyme at 298 K (Figure 5) gives rise to the binding isotherms depicted in Figure 6a for **L*k*** = **L1** and Figures S7a-S8a for **L*k*** = **L2**-**L3**, together with dependences of $Q^{\mathbf{L}k,\text{La}}_{1,1,\text{cond}}$ with the progress of the reaction (Figure 6b, S7b-S8b). Linear fits with the help of eq. 6 provide conditional free energy of guest association at infinite dilution $\Delta G^{\mathbf{L}k,\text{La}}_{1,1,\text{cond}} = -RT \ln\left(\beta^{\mathbf{L}k,\text{La}}_{1,1,\text{cond}}\right)$ together with free energy change ΔG^{S}_{cond} in surface-contact

solvation (Table 2, columns 3 and 4), which satisfyingly reproduce the experimental data (red traces in Figures 6a, S7a-S8a).

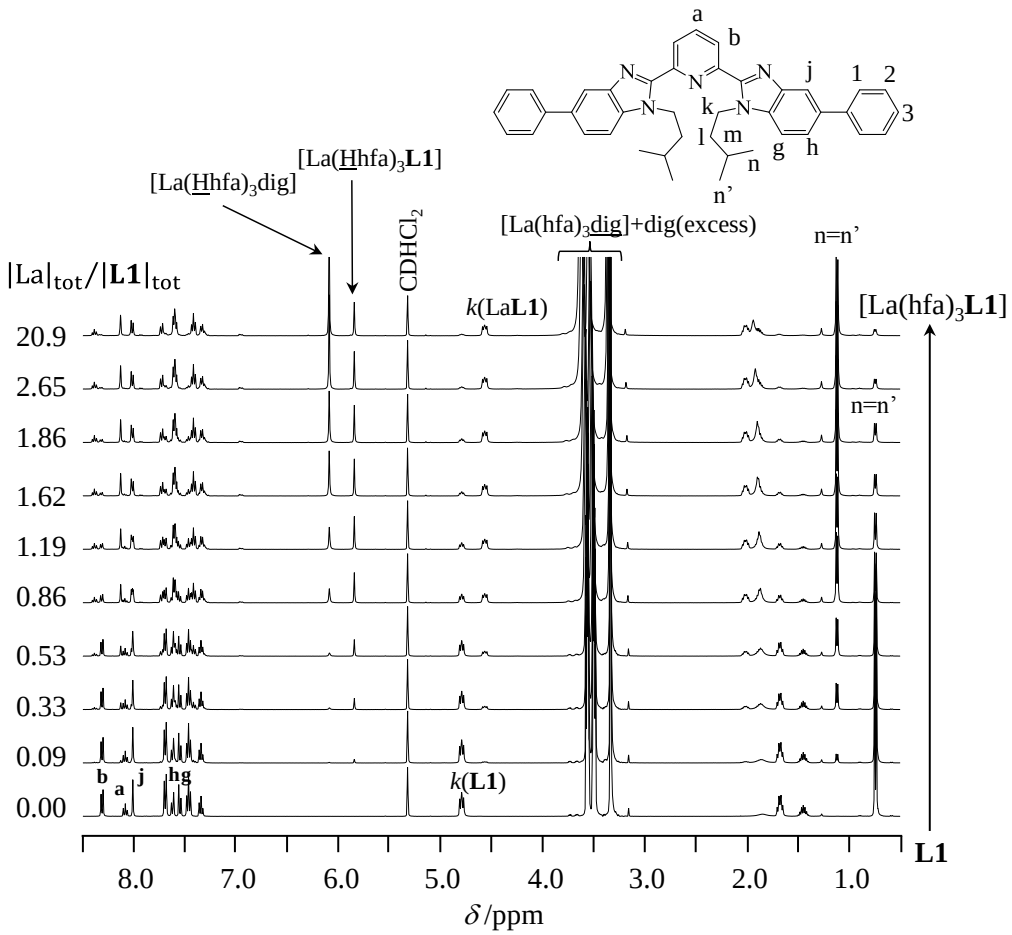


Figure 5 ^{1}H−NMR titration of **L1** with [La(hfa)$_3$(dig)] in CD_2Cl_2+0.14 M diglyme at 298K with numbering scheme ($2.9\cdot10^{-3} \le |\mathbf{L1}|_{tot} \le 2.5\cdot10^{-2}$ M and $4.3\cdot10^{-5} \le |La|_{tot} \le 5.5\cdot10^{-2}$ M).

As expected, the magnitude of ΔG^{S}_{cond} (Table 2, column 4 at 298 K) is reduced by factors 5-10 compared with ΔG^{S}_{exch} (Table 1, column 3) as a result of the limited variation of the mole fraction of the solvent during the titrations performed in excess of diglyme. In these conditions, the deviation from the classical treatment which considers fixed activity coefficients and a single average association energy $\Delta\bar{G}^{\mathbf{Lk},La}_{1,1,cond} = -RT\ln\left(\frac{1}{N}\sum_{i=1}^{N}\left(Q^{\mathbf{Lk},La}_{1,1,cond}\right)_i\right)$ is much less significant (green traces in Figures 6a, S7a-S8a). Comparison of columns 5 and 3 in Table 2 indeed displays drifts of only 10 %, while the same calculation performed using the data collected for the exchange reaction 7 (columns

4 and 2 in Table 1) amounts to 160-200% discrepancies. Upon fixing the concentration of diglyme in CD_2Cl_2 + 0.14 M diglyme, we note that the connections of [La(hfa)$_3$] to **L*k*** at infinite dilution become exergonic (-12.2 $\leq \Delta G^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}} \leq$ -8.8 kJ/mol, Table 2) with a slight preference for the non-substituted ligand **L1** (Table 2, column 3).

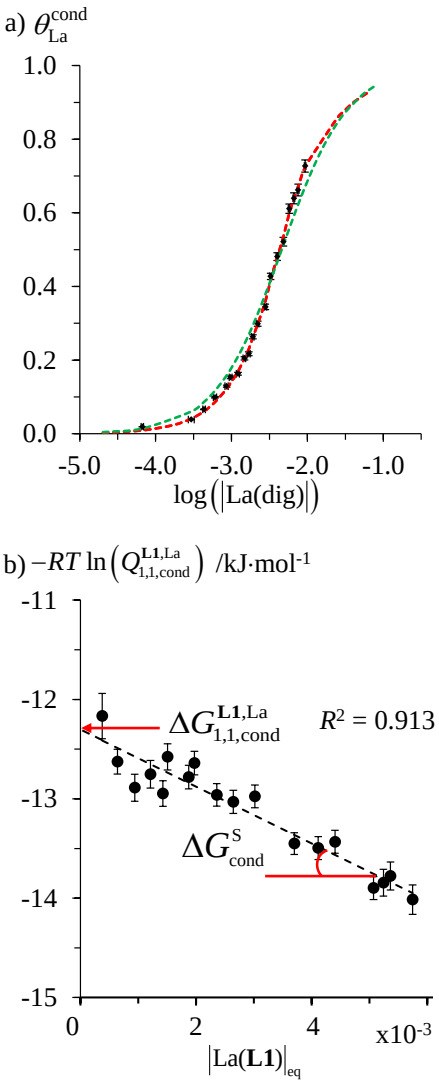


Figure 6 a) Experimental (black diamonds, eq. 9) and fitted (red trace using eq. 6 with $\Delta G^{\mathbf{L1},\mathrm{La}}_{1,1,\mathrm{cond}}$, $\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ taken in Table 2) binding isotherms for the titration of **L1** with [La(hfa)$_3$dig] in CD_2Cl_2 + 0.14 M diglyme at 298 K. The green trace corresponds to the standard analysis using eq. 3 and an average constant free energy of association $\Delta \bar{G}^{\mathbf{L1},\mathrm{La}}_{1,1,\mathrm{cond}}$ (taken in Table 2). b) Dependence of the quotient of reaction $Q^{\mathbf{L1},\mathrm{La}}_{1,1,\mathrm{cond}}$ with the progress of the association reaction highlighting $\Delta G^{\mathbf{L1},\mathrm{La}}_{1,1,\mathrm{cond}}$ and $\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ according to eq. 6.

Table 2 Thermodynamic parameters $\Delta G^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$ and $\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ (eq. 6), average association energy $\Delta \bar{G}^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}} = -RT \ln\left(\frac{1}{N}\sum_{i=1}^{N}\left(Q^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}\right)_i\right)$, $\Delta H^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$, $\Delta H^{\mathrm{S}}_{\mathrm{cond}}$, $\Delta S^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$ and $\Delta S^{\mathrm{S}}_{\mathrm{cond}}$ determined for the titration of **L*k*** with [La(hfa)$_3$dig] (eq. 9) in CD_2Cl_2 + 0.14 M diglyme .

Hosts	T /K	$\Delta G^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$ [a] /kJ·mol^{-1}	$\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ [a] /kJ·mol^{-1}	$\Delta \bar{G}^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$ [b] /kJ·mol^{-1}	$\Delta H^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$ /kJ·mol^{-1}	$\Delta S^{\mathbf{L}k,\mathrm{La}}_{1,1,\mathrm{cond}}$ /J·mol^{-1}·K^{-1}	$\Delta H^{\mathrm{S}}_{\mathrm{cond}}$ [c] /kJ·mol^{-1}	$\Delta S^{\mathrm{S}}_{\mathrm{cond}}$ [c] /J·mol^{-1}·K^{-1}
L1	298	-12.2(1)	-305(22)	-13.2(6)	1.4(2.8)	46(10)	40(94)	1128(357)
L1	273	-11.5(1)	-247(22)	-13.5(5)				
L1	253	-9.6(1)	-254(34)	-12.2(4)				
L1	233	-9.5(1)	-224(32)	-13.1(9)				
L2	298	-8.8(1)	-254(24)	-9.8(6)	-2.6(5)	21(2)	-5826(2875)	19761(10834)
L2	273	-8.3(1)	-131(24)	-9.7(7)				
L2	253	-7.7(1)	-398(27)	-9.2(7)				
L2	233	-7.4(1)	-1634(111)	-9.7(9)				
L3	298	-9.0(1)	-285(36)	-9.5(8)	9.5(2.5)	63(10)	-3979(1093)	-12813(4119)
L3	273	-8.0(1)	-355(31)	-9.6(8)				
L3	253	-6.8(1)	-583(28)	-10.6(9)				
L3	233	-4.8(2)	-1148(75)	-9.7(9)				

[a] Uncertainties are those obtained by linear least-square fit of eq. 6. [b] Uncertainties correspond to the standard deviation from the average values. [c] Because of experimental limitations, the dependence of $\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ in function of the temperature gives scattered data. The proposed uncertainties affecting $\Delta H^{\mathrm{S}}_{\mathrm{cond}}$ and $\Delta S^{\mathrm{S}}_{\mathrm{cond}}$ are those calculated using linear least-square techniques.

The collection of accurate variable-temperature data were limited by our ^{1}H−NMR setup, which required the systematic removal of the NMR tube from the thermostated cavity for each addition of [La(hfa)$_3$dig], followed by thermal re-equilibration. The resulting van't Hoff plots (Figures 7 and S9-S10) therefore delivered only rough enthalpic ($\Delta H^{\mathbf{Lk},\mathrm{La}}_{1,1,\mathrm{cond}}$ and $\Delta H^{\mathrm{S}}_{\mathrm{cond}}$) and entropic ($\Delta S^{\mathbf{Lk},\mathrm{La}}_{1,1,\mathrm{cond}}$ and $\Delta S^{\mathrm{S}}_{\mathrm{cond}}$) contributions gathered in Table 2 (columns 6-9).

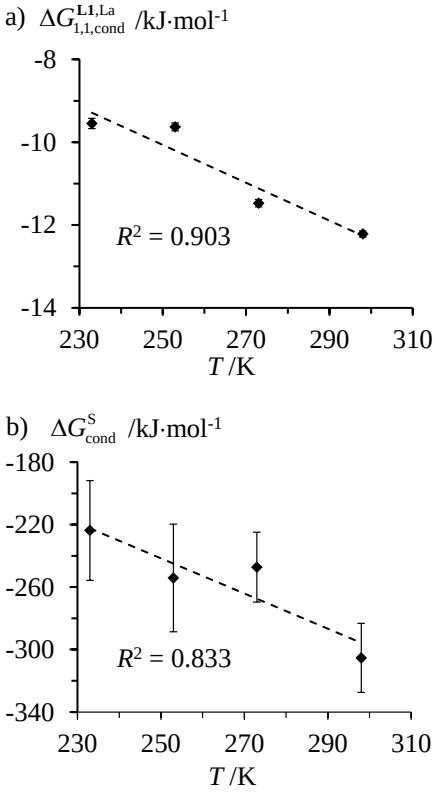


Figure 7 Van't Hoff plots for a) $\Delta G^{\mathbf{L1},\mathrm{La}}_{1,1,\mathrm{cond}}$ and b) $\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ measured in equilibrium 9 for **L1** in CD_2Cl_2 + 0.14 M diglyme.

Got rid of surface contact solvent effects, the dependence of $\Delta G^{\mathbf{Lk},\mathrm{La}}_{1,1,\mathrm{cond}}$ on the temperature shows that the connection of [La(hfa)$_3$] to **L*k*** according to equilibrium 9 is driven by entropy ($\Delta S^{\mathbf{Lk},\mathrm{La}}_{1,1,\mathrm{cond}}$ >>0), whereas the enthalpic contributions $\Delta H^{\mathbf{Lk},\mathrm{La}}_{1,1,\mathrm{cond}}$ are either unfavorable (**L3**) or negligible (**L1** or **L2**), a trend in complete agreement with thermodynamic two-steps *Choppin*'s model of lanthanide complexation relying on ligand exchanges occurring in the first coordination sphere.[33] The van't Hoff plots observed for the surface-contact solvation contribution $\Delta G^{\mathrm{S}}_{\mathrm{cond}}$ are too scattered (Figures

7b and S9b-S10b) for being safely analyzed for our set of experimental data. We however note the reversal of the global trend in going from the rigid polyaromatic **L1** ligand ($\Delta H^{S}_{cond} > 0$ and $\Delta S^{S}_{cond} > 0$) to the lipophilic and flexible **L3** ligand ($\Delta H^{S}_{cond} < 0$ and $\Delta S^{S}_{cond} < 0$), while **L2** is intermediate ($\Delta H^{S}_{cond} < 0$ and $\Delta S^{S}_{cond} > 0$). This suggests completely different mechanisms for the contact surface desolvation process accompanying the equilibrium 9 when flexible alkyl chains are connected to the host receptor.

CONCLUSIONS

The trivial guest exchange reaction 7 (Scheme 1) undeniably demonstrates that the quotient of reaction at equilibrium $Q^{\mathbf{Lk},La}_{1,1,exch}$ varies during a titration process involving neutral species in organic solvent within the submillimolar to decimolar concentration range. Consequently, it cannot be simply taken as a pertinent thermodynamic constant and no reliable host-guest affinity can be deduced from this procedure, this regardless its common and well-accepted use in biology, in coordination chemistry and in supramolecular chemistry. This drawback was early recognized for charged species in polar solutions (electrolytes) and led to the development of the ionic atmosphere theory (Debye-Hückel), which requires a constant ionic strength for fixing the activity coefficients. To the best of our knowledge, no such procedure is available for mastering reactions involving neutral species in non-polar solvents. A recent proposal by Castellano and Eggers (eqs 5-6) assigns the variation of the activity coefficients to some change in solvation energies (second sphere effects) accompanying the host-guest association,[18] which is not considered in the chemical potential of the pure species (which include first-sphere solvation). Application of this concept to the titration of receptor **L1**-**L3** with [La(hfa)$_3$dig] translates the 'anomalous' variation of the quotients of reaction at equilibrium into two true thermodynamic contributions: the free energy of guest exchange at infinite dilution $\Delta G^{\mathbf{Lk},La}_{1,1,exch} = -RT \ln\left(\beta^{\mathbf{Lk},La}_{1,1,exch}\right)$ and the free energy change in the surface-contact solvation ΔG^{S}_{exch}. Comfortingly, some well-accepted gas-phase predictions, which claims that O−donor ligands form more stable complexes with hard trivalent lanthanides than N−donor ligand,[30] are obeyed by the

experimental thermodynamic $\Delta G_{1,1,\mathrm{exch}}^{\mathbf{Lk},\mathrm{La}}$ obtained for **L1**-**L3** (Table 1, column 2). The erroneous, but common assignment of quotient of reactions as direct estimations of stability constants predicts the reverse situation (Table 1, column 4). Going further into the physical origin of this effect, the change in 'surface contact' solvation seems to reflect the variation of the activity coefficients of the solute (i.e. the partner of the host−guest reaction) produced by minor variations of the mole fraction of the solvent, in other words by minor variations of the chemical potential of the solvent in the mixture during the titration procedure (Margules equations). With this in mind, we reasoned that fixing one of the concentration of the partner of the reaction at a constant and sufficiently high concentration should fix the chemical potential of the solvent during the titration procedure, a phenomenon reminiscent to that of fixing the ionic strengh in electrolytes. Setting the total concentration of diglyme at 0.14 M for the [La(hfa)$_3$] guest exchange between diglyme and **L1**-**L3** indeed significantly reduces the variation of the quotient of reaction $Q_{1,1,\mathrm{exch}}^{\mathbf{Lk},\mathrm{La}}$ during the titration procedure, which welcomely restores the classical procedure $\beta_{1,1,\mathrm{cond}}^{\mathbf{Lk},\mathrm{La}} \simeq Q_{1,1,\mathrm{cond}}^{\mathbf{Lk},\mathrm{La}}$ as a satisfying approximation for estimating host−guest affinities. The erroneous assignment of the quotient of reaction to thermodynamic constant in association reactions has deep consequences in biology, in medicine and in pharmacy since the optimum dose of an effector (i.e. a drug) acting on a receptor is a priori fixed around $1/\beta_{1,1}^{\mathrm{H,G}}$ because the slope of the binding isotherm is very steep around $\theta_{\mathrm{G}} \rightarrow 0.5$. Moreover, in supramolecular and polymer chemistry, the estimation of cooperativity factors, which are crucial for rationalizing guest loading, entirely relies on the determination of reliable and pertinent host−guest affinities. We are currently exploring the effect of the change in solvent potentials on the determination of reliable cooperativity factors assigned to multi-site binding reactions. According that the regular solution theory is quite general, there is no obvious reason for considering this proof-of-concept as arising from any combination of circumstances. The large majority of titrations involving non-charged host-guest assemblies performed in the millimolar to decimolar range are expected to deviate from the 'uncorrected' law of mass action because of the operation of non-

negligible contributions of differential surface solvation ΔG^{S}. Since the latter factor mirrors the dimensionless parameter ξ, which measures the energy of the solute−solvent interactions relative to that of the solute−solute and solvent−solvent interactions, specific structural parameters of the guests and/or the hosts are expected to specifically tune the disruption of the chemical potential of the solvent, but a rational correlation between these parameters remains to be explored.

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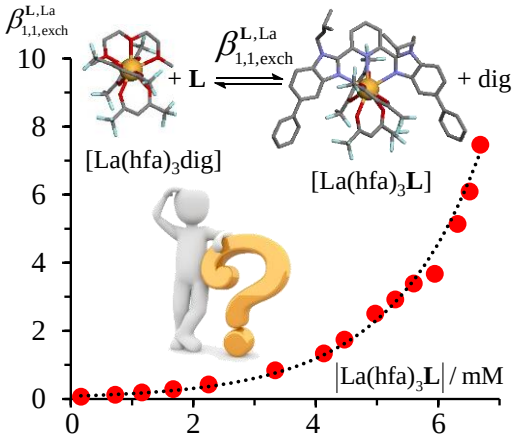
TOC



During the straightforward titration of tridentate host-receptors **L** with the [La(hfa)$_3$dig] guest in dichloromethane, the apparent exchange constants $\beta^{L,La}_{1,1,exch}$ exponentially increase with the amount of formed complex [La(hfa)$_3$**L**]. How is it possible?