Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.


Supporting Information

# Capturing The Dynamic Association Between A Tris-Dipicolinate Lanthanide Complex And A Decapeptide: A Combined Paramagnetic NMR And Molecular Dynamics Exploration

Sandrine Denis-Quanquin,[a] Alessio Bartocci,[a] Florence Szczepaniak,[a] Francois Riobé,[a] Olivier Maury,[a] Elise Dumont[a,c*] and Nicolas Giraud[b*]

a. Univ. Lyon, ENS de Lyon, CNRS UMR 5182, Université Claude Bernard Lyon 1, Laboratoire de Chimie, F69342, Lyon, France.
b. Université de Paris, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR CNRS 8601, Paris, France
c. Institut Universitaire de France, 5 rue Descartes, 75005 Paris

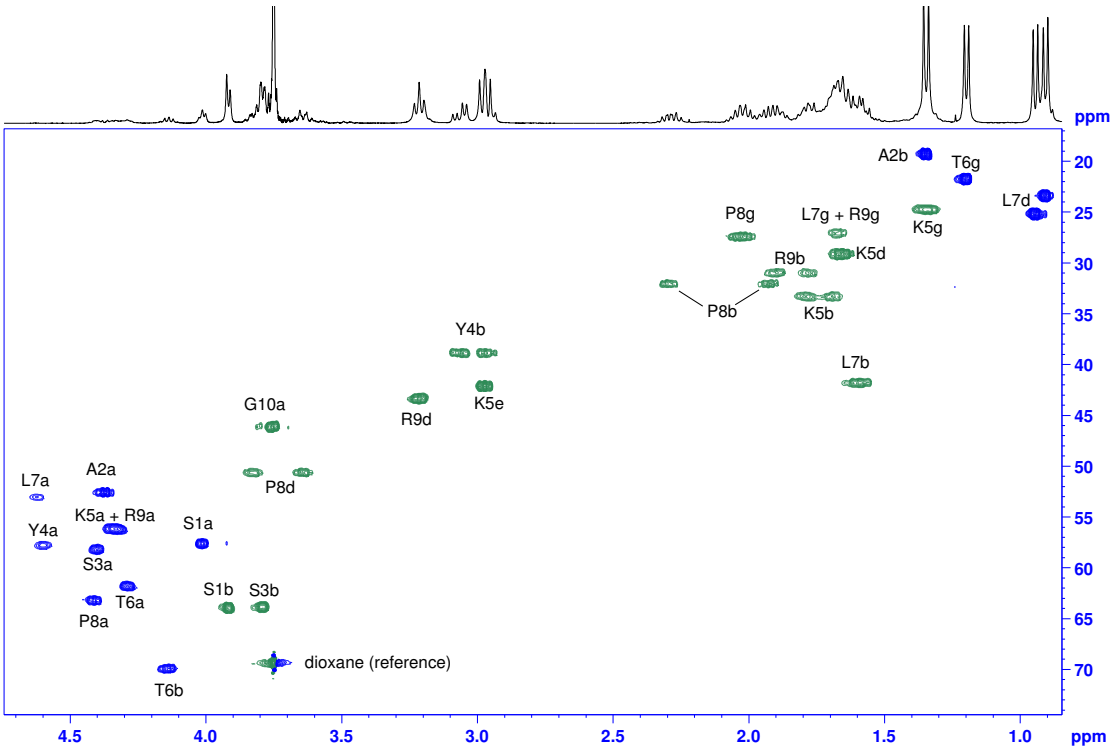


Fig S1: Edited $^{13}C$-$^{1}H$ HSQC spectrum of the peptide **P** 4 mM in 18 mM PBS, pH 7.0, with 5 mM dioxane as a reference (signals for the aromatic cycle of Y4 not shown).

| | HN | Ha | Hb | | Hg | Hd | | He | Haromatic1 | Haromatic2 |
|---|---|---|---|---|---|---|---|---|---|---|
| S1 | | 4.01 | 3.92 | - | - | - | - | - | - | - |
| A2 | | 4.37 | 1.35 | - | - | - | - | - | - | - |
| S3 | 8.34 | 4.4 | 3.79 | - | - | - | - | - | - | - |
| Y4 | 8.16 | 4.59 | 3.06 | 2.97 | - | - | - | - | 7.11 | 6.82 |
| K5 | 8.19 | 4.31 | 1.79 | 1.69 | 1.35 | 1.65 | - | 2.97 | - | - |
| T6 | 8.11 | 4.28 | 4.13 | - | 1.2 | - | - | - | - | - |
| L7 | 8.33 | 4.62 | 1.59 | - | 1.69 | 0.95 | 0.91 | - | - | - |
| P8 | - | 4.41 | 2.29 | 1.94 | 2.02 | 3.82 | 3.64 | - | - | - |
| R9 | 8.44 | 4.33 | 1.9 | 1.78 | 1.67 | 3.21 | - | - | - | - |
| G10 | 8.02 | 3.75 | - | - | - | - | - | - | - | - |

Table S1: Proton chemical shift assignment of the peptide **P** 4 mM in 18 mM PBS, pH 7.0, with 5 mM dioxane as a reference (at 3.75 ppm). No correlation was observed on the TOCSY spectrum for both S1 and A2 amide protons HN.

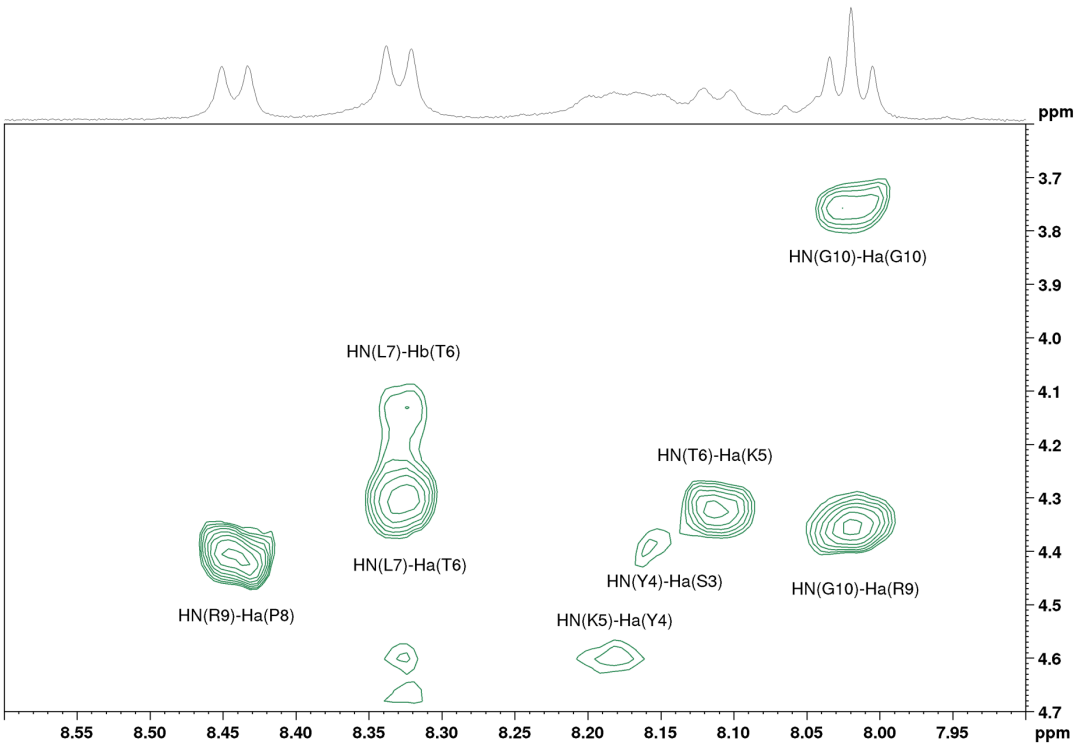


Fig S2: ROESY spectrum of the peptide **P** 4 mM in 18 mM PBS, pH 7.0, with 5 mM dioxane as a reference.

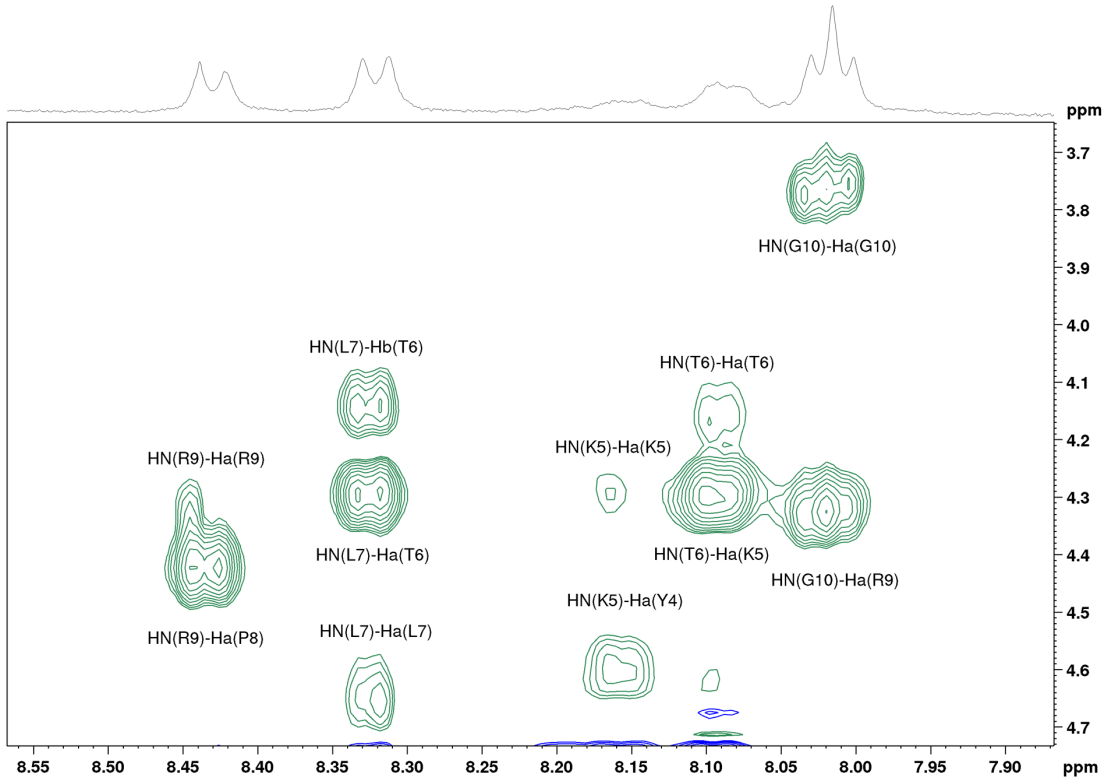


Fig S3: ROESY spectrum of the peptide **P** 4 mM, with 1 equivalent of $[Na]_3[Pr(DPA)_3]$ in 18 mM PBS, pH 7.0, with 5 mM dioxane as a reference.

| | | experimental chemical shifts (ppm) | | | | | |
|---|---|---|---|---|---|---|---|
| residue | proton | free peptide | 0.2eq Tb | 0.5eq Tb | 1eq Tb | 3eq Tb | 5eq Tb |
| S1 | S1(HN) | no | no | no | no | no | no |
| | S1(a) | 3.95 | 3.09 | 2 | 0.37 | -4.06 | -6.7 |
| | S1(b1) | 3.89 | 3.47 | 2.97 | 2.21 | 0.1 | -1.14 |
| | S1(b2) | 3.89 | 3.42 | 2.84 | 1.98 | -0.4 | -1.82 |
| A2 | A2(HN) | no | no | no | no | no | no |
| | A2(a) | 4.37 | 4.27 | 4.14 | 3.96 | 3.45 | 3.15 |
| | A2(b) | 1.35 | 1.35 | 1.35 | 1.36 | 1.38 | 1.38 |
| S3 | S3(HN) | 8.339 | 8.211 | 8.054 | 7.787 | | |
| | S3(a) | 4.4 | 4.33 | 4.24 | 4.14 | 3.81 | 3.63 |
| | S3(b1) | 3.79 | 3.71 | 3.61 | 3.52 | 3.19 | 3 |
| | S3(b2) | 3.79 | 3.71 | 3.61 | 3.41 | 2.91 | 2.62 |
| Y4 | Y4(HN) | 8.144 | 8.106 | 8.057 | 7.98 | 7.788 | 7.67 |
| | Y4(a) | 4.59 | 4.61 | 4.63 | 4.67 | - | 4.83 |
| | Y4(b1) | 3.06 | 3.1 | 3.16 | 3.25 | 3.51 | 3.69 |
| | Y4(b2) | 2.97 | 3.02 | 3.09 | 3.21 | 3.49 | 3.65 |
| | Y4(ar1) | 7.11 | 7.11 | 7.26 | 7.4 | 7.76 | 7.98 |
| | Y4(ar2) | 6.82 | 6.82 | 6.93 | 7.02 | 7.27 | 7.41 |
| K5 | K5(HN) | 8.178 | 8.16 | 8.138 | 8.098 | 7.995 | 7.93 |
| | K5(a) | 4.32 | 4.315 | 4.31 | 4.3 | 4.28 | 4.26 |
| | K5(b1) | 1.79 | 1.75 | 1.71 | 1.64 | 1.49 | 1.4 |
| | K5(b2) | 1.69 | 1.66 | 1.63 | 1.6 | 1.46 | 1.37 |
| | K5(g) | 1.35 | 1.27 | 1.21 | 1.11 | 0.79 | 0.59 |
| | K5(d) | 1.65 | 1.53 | 1.38 | 1.15 | 0.51 | 0.12 |
| | K5(e) | 2.97 | 2.75 | 2.47 | 2.04 | 0.86 | 0.12 |
| T6 | T6(HN) | 8.107 | 8.104 | 8.098 | 8.087 | 8.061 | 8.041 |
| | T6(a) | 4.29 | 4.31 | 4.33 | 4.37 | 4.46 | 4.51 |
| | T6(b) | 4.13 | 4.14 | 4.15 | 4.17 | 4.22 | 4.23 |
| | T6(g) | 1.2 | 1.23 | 1.27 | 1.33 | 1.5 | 1.59 |
| L7 | L7(HN) | 8.323 | 8.34 | 8.36 | 8.389 | 8.471 | 8.52 |
| | L7(a) | 4.62 | 4.65 | 4.69 | 4.73 | 4.9 | 4.99 |
| | L7(b) | 1.59 | 1.6 | 1.66 | 1.71 | 1.86 | 1.95 |
| | L7(g) | 1.69 | 1.71 | 1.76 | 1.82 | 2 | 2.11 |
| | L7(d1) | 0.95 | 0.99 | 1.03 | 1.12 | 1.33 | 1.47 |
| | L7(d2) | 0.91 | 0.94 | 0.98 | 1.06 | 1.24 | 1.36 |
| P8 | P8(a) | 4.41 | 4.44 | 4.47 | 4.53 | - | - |
| | P8(b1) | 2.29 | 2.33 | 2.39 | 2.46 | 2.68 | 2.8 |
| | P8(b2) | 1.93 | 1.95 | 1.99 | 2.06 | 2.21 | 2.32 |
| | P8(g) | 2.02 | 2.03 | 2.09 | 2.17 | 2.35 | 2.46 |
| | P8(d1) | 3.82 | 3.86 | 3.9 | 3.96 | 4.13 | 4.23 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | P8(d2) | 3.64 | 3.67 | 3.72 | 3.78 | 3.95 | 4.06 |
| R9 | R9(HN) | 8.444 | 8.434 | 8.423 | 8.402 | 8.34 | 8.294 |
| | R9(a) | 4.34 | 4.333 | 4.327 | 4.317 | 4.29 | 4.27 |
| | R9(b1) | 1.9 | 1.85 | 1.81 | 1.73 | 1.53 | 1.38 |
| | R9(b2) | 1.78 | 1.74 | 1.71 | 1.64 | 1.47 | 1.32 |
| | R9(g) | 1.67 | 1.6 | 1.51 | 1.37 | 0.96 | 0.69 |
| | R9(d) | 3.21 | 3.11 | 3 | 2.81 | 2.3 | 2 |
| G10 | G10(HN) | 8.021 | 8.019 | 8.017 | 8.016 | 8.013 | 8.005 |
| | G10(a) | 3.75 | 3.75 | 3.75 | 3.79 | 3.83 | 3.87 |

Table S2: Experimental chemical shifts for the peptide **P** upon the addition of $[Na]_3[Tb(DPA)_3]$.

| residu | proton | 0.2eq Tb | 0.5eq Tb | 1eq Tb | 3eq Tb | 5eq Tb | δcomp |
|---|---|---|---|---|---|---|---|
| S1 | S1(HN) | no | no | no | no | no | no |
| | S1(a) | -0.85 | -1.943 | -3.577 | -8.02 | -10.671 | -19.1484 |
| | S1(b1) | -0.41 | -0.91 | -1.67 | -3.78 | -5.02 | -9.044 |
| | S1(b2) | -0.46 | -1.04 | -1.9 | -4.28 | -5.7 | -10.2499 |
| A2 | A2(HN) | no | no | no | no | no | no |
| | A2(a) | -0.098 | -0.228 | -0.403 | -0.902 | -1.197 | -2.1214 |
| | A2(b) | 0.007 | 0.009 | 0.023 | 0.057 | 0.062 | 0.1235 |
| S3 | S3(HN) | -0.089 | -0.246 | -0.513 | | | -3.22313 |
| | S3(a) | -0.07 | -0.156 | -0.256 | -0.583 | -0.762 | -1.2885 |
| | S3(b1) | -0.08 | -0.18 | -0.268 | -0.592 | -0.78 | -1.2566 |
| | S3(b2) | -0.08 | -0.18 | -0.378 | -0.872 | -1.16 | -2.2941 |
| Y4 | Y4(HN) | 0 | -0.049 | -0.126 | -0.318 | -0.436 | -0.7967 |
| | Y4(a) | 0.015 | 0.035 | 0.078 | | 0.244 | 0.4738 |
| | Y4(b1) | 0.03 | 0.092 | 0.184 | 0.448 | 0.63 | 1.4339 |
| | Y4(b2) | 0.056 | 0.128 | 0.25 | 0.535 | 0.7 | 1.2136 |
| | Y4(ar1) | 0.002 | 0.152 | 0.295 | 0.664 | 0.888 | 1.7735 |
| | Y4(ar2) | -0.002 | 0.11 | 0.202 | 0.464 | 0.608 | 1.1546 |
| K5 | K5(HN) | 0.004 | -0.017 | -0.055 | -0.155 | 7.93 | 7.6574 |
| | K5(a) | -0.008 | -0.013 | -0.02 | -0.034 | -0.051 | -0.0912 |
| | K5(b1) | -0.04 | -0.076 | -0.146 | -0.288 | -0.374 | -0.5627 |
| | K5(b2) | -0.03 | -0.06 | -0.09 | -0.23 | -0.32 | -0.7161 |
| | K5(g) | -0.08 | -0.131 | -0.231 | -0.54 | -0.732 | -1.3914 |
| | K5(d) | -0.127 | -0.272 | -0.498 | -1.127 | -1.513 | -2.8408 |
| | K5(e) | -0.224 | -0.502 | -0.929 | -2.096 | -2.831 | -5.3654 |
| T6 | T6(HN) | 0.03 | 0.024 | 0.014 | -0.011 | -0.028 | 7.9841 |
| | T6(a) | 0.02 | 0.04 | 0.08 | 0.17 | 0.22 | 0.3799 |
| | T6(b) | -0.01 | 0 | 0.02 | 0.07 | 0.08 | 0.1889 |
| | T6(g) | 0.037 | 0.078 | 0.14 | 0.312 | 0.405 | 0.738 |
| L7 | L7(HN) | 0.061 | 0.083 | 0.115 | 0.203 | 0.259 | 8.6986 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | L7(a) | 0.03 | 0.07 | 0.11 | 0.28 | 0.37 | 0.7382 |
| | L7(b) | 0.02 | 0.08 | 0.13 | 0.28 | 0.37 | 0.6921 |
| | L7(g) | 0.04 | 0.09 | 0.15 | 0.33 | 0.44 | 0.9063 |
| | L7(d1) | 0.047 | 0.088 | 0.18 | 0.392 | 0.534 | 1.0811 |
| | L7(d2) | 0.034 | 0.074 | 0.156 | 0.338 | 0.46 | 0.9144 |
| P8 | P8(a) | 0.03 | 0.06 | 0.12 | | | 0.7061 |
| | P8(b1) | 0.039 | 0.1 | 0.172 | 0.395 | 0.518 | 0.9215 |
| | P8(b2) | 0.03 | 0.07 | 0.14 | 0.29 | 0.4 | 0.8371 |
| | P8(g) | 0.01 | 0.07 | 0.15 | 0.33 | 0.44 | 0.8638 |
| | P8(d1) | 0.04 | 0.08 | 0.14 | 0.31 | 0.41 | 0.7023 |
| | P8(d2) | 0.03 | 0.08 | 0.14 | 0.31 | 0.42 | 0.7784 |
| R9 | R9(HN) | 0.03 | 0.018 | -0.005 | -0.069 | -0.117 | 8.1657 |
| | R9(a) | -0.007 | -0.013 | -0.023 | -0.05 | -0.07 | -0.1339 |
| | R9(b1) | -0.05 | -0.089 | -0.166 | -0.36 | -0.508 | -1.1878 |
| | R9(b2) | -0.04 | -0.07 | -0.138 | -0.3 | -0.446 | -0.8746 |
| | R9(g) | -0.074 | -0.162 | -0.298 | -0.7 | -0.966 | -2.0599 |
| | R9(d) | -0.103 | -0.21 | -0.395 | -0.888 | -1.18 | -2.1803 |
| G10 | G10(HN) | 0.029 | 0.027 | 0.026 | 0.023 | 0.015 | 0.003 |
| | G10(a) | -0.01 | -0.01 | 0.03 | 0.07 | 0.11 | 0.207 |

Table S3: Pseudo Contact Shifts (PCS) for the peptide **P** upon the addition of $[Na]_3[Tb(DPA)_3]$.. PCS are determined as the difference between chemical shifts in the presence of paramagnetic Tb and chemical shifts in the presence of diamagnetic Y.

| | | calculated chemical shifts and affinity | | |
|---|---|---|---|---|
| residu | proton | δcomp | Kd (M) | δcomp - δfree |
| S1 | S1HN | | | |
| | S1alpha | -15.1531 | 0.00708 | -19.10 |
| | S1beta1 | -5.164 | 0.00713 | -9.05 |
| | S1beta2 | -6.3699 | 0.00712 | -10.26 |
| A2 | A2HN | | | |
| | A2alpha | 2.2046 | 0.00691 | -2.17 |
| | A2beta | 1.4138 | | 0.06 |
| S3 | S3HN | 5.07687 | | -3.26 |
| | S3alpha | 3.0937 | 0.00615 | -1.31 |
| | S3beta1 | 2.5147 | 0.00551 | -1.28 |
| | S3beta2 | 1.4772 | 0.00868 | -2.31 |
| Y4 | Y4HN | 7.3093 | 0.00683 | -0.83 |
| | Y4alpha | 5.051 | 0.00877 | 0.46 |
| | Y4beta1 | 4.4837 | 0.01150 | 1.42 |
| | Y4beta2 | 4.1503 | 0.00651 | 1.18 |
| | Y4ar1 | 8.8489 | 0.00891 | 1.74 |
| | Y4ar2 | 7.9343 | 0.00785 | 1.11 |
| K5 | K5HN | 7.6574 | 0.00990 | -0.52 |
| | K5alpha | 4.2088 | | -0.11 |
| | K5beta1 | 1.197 | 0.00468 | -0.59 |
| | K5beta2 | 0.9739 | 0.01128 | -0.72 |
| | K5gamma | -0.096 | 0.00814 | -1.45 |
| | K5delta | -1.2317 | 0.00792 | -2.88 |
| | K5epsilon | -2.4392 | 0.00807 | -5.41 |
| T6 | T6HN | 7.9841 | | -0.12 |
| | T6alpha | 4.6699 | 0.00636 | 0.38 |
| | T6beta | 4.3389 | | 0.21 |
| | T6gamma | 1.9139 | 0.00731 | 0.71 |
| L7 | L7HN | 8.6986 | 0.00808 | 0.38 |
| | L7alpha | 5.3582 | 0.00882 | 0.74 |
| | L7beta | 2.2721 | 0.00796 | 0.68 |
| | L7gamma | 2.5763 | 0.01005 | 0.89 |
| | L7delta1 | 2.0089 | 0.00934 | 1.06 |
| | L7delta2 | 1.8062 | 0.00894 | 0.90 |
| P8 | P8alpha | 5.1161 | | 0.71 |
| | P8beta1 | 3.1943 | 0.00683 | 0.90 |
| | P8beta2 | 2.7571 | 0.01021 | 0.83 |
| | P8gamma | 2.8838 | 0.00860 | 0.86 |
| | P8delta1 | 4.5223 | 0.00637 | 0.70 |
| | P8delta2 | 4.4184 | 0.00767 | 0.78 |
| R9 | R9HN | 8.1657 | | -0.28 |
| | R9alpha | 4.2061 | | -0.13 |
| | R9beta1 | 0.6812 | 0.01277 | -1.22 |
| | R9beta2 | 0.8923 | 0.01032 | -0.89 |
| | R9gamma | -0.4216 | 0.01030 | -2.09 |
| | R9delta | 0.9671 | 0.00761 | -2.24 |
| G10 | G10HN | 7.993 | | -0.03 |
| | G10alpha | 3.967 | | 0.22 |

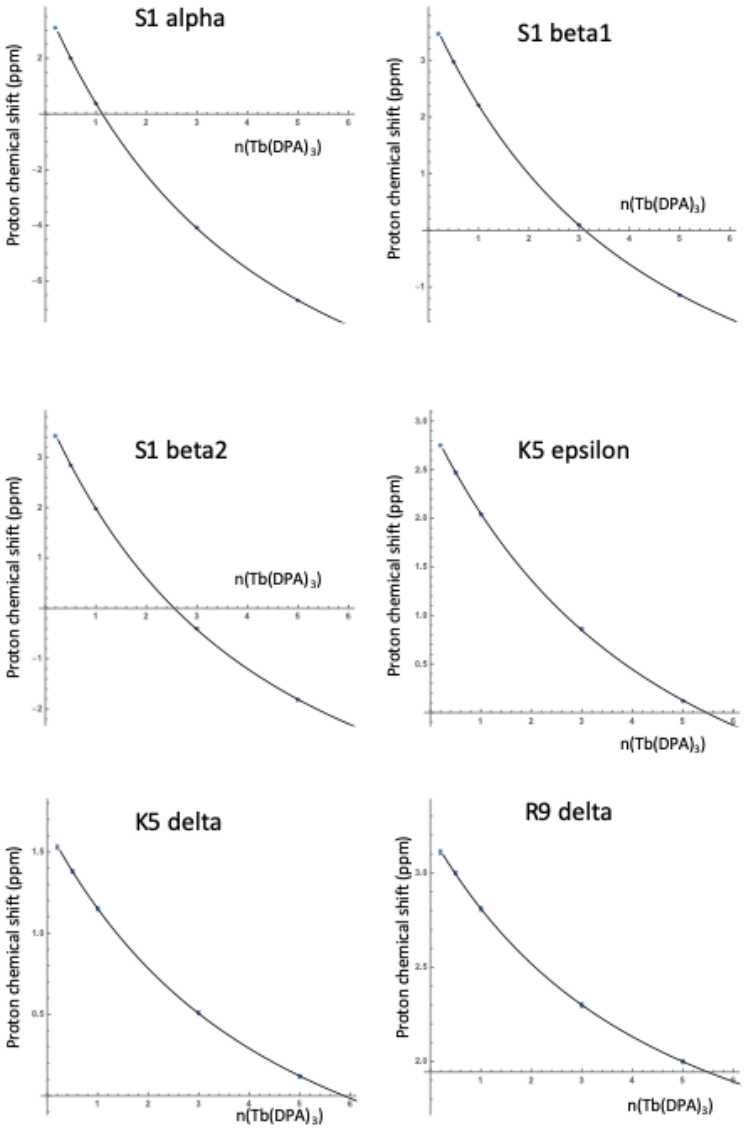


Fig S4: Calculated dissociation constant Kd and chemical shift for the fully complexed peptide δcomp. Chemical shift titration curves from the titration data show a good fit modelling the interaction between **P** and the ion $Tb(DPA)_3^{3-}$ in a 1:1 equilibrium.

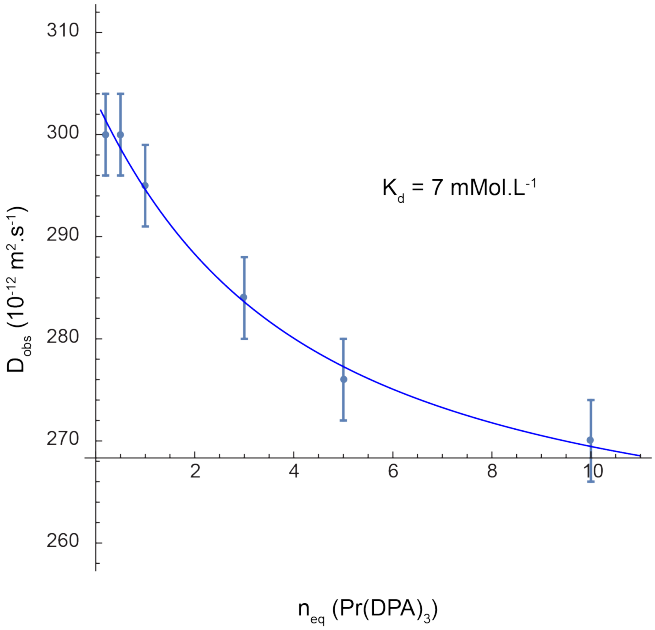


Figure S5. The evolution of the observed diffusion coefficient ratio of the peptide **P** at initial concentration 2 mM in 18 mM PBS, pH 7.0, with 1 mM dioxane, upon addition of $n_{eq}$ equivalents of $[Na]_3[Pr(DPA)_3]$. The blue curve (solid line) corresponds to the best fit obtained by adjusting $K_d$, as well as the diffusion coefficients of the adduct and the peptide alone.

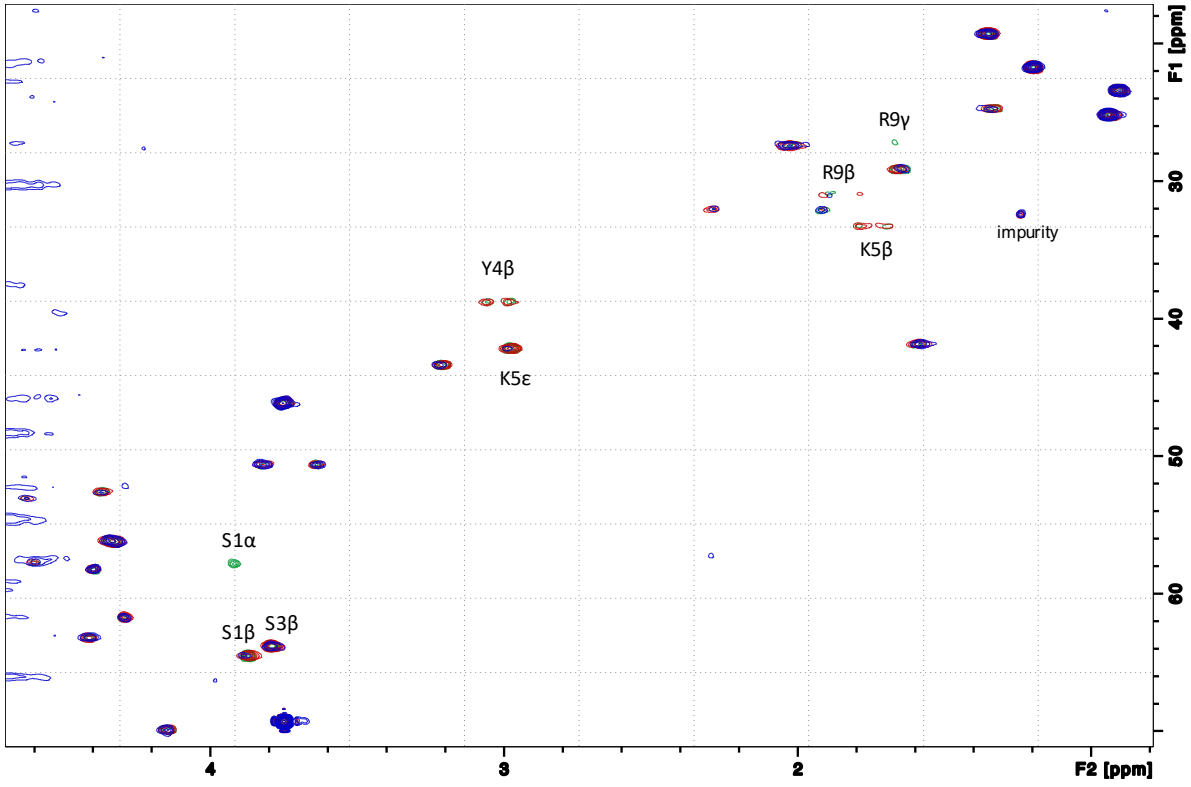


Fig S6: $^{13}C$-$^{1}H$ HSQC spectrum of the peptide free (green), and with 0.2 (red) and 0.4 (blue) equivalents of $[Na]_3[Gd(DPA)_3]$. Assigned signals show some of the most significant signal attenuation due to Paramagnetic Relaxation enhancement (PRE).

**Free energy calculations following the APR protocol.**

By following the APR protocol (see references 1-4 for the method details) after the initial attachment phase (14 windows with increasing value of the restraints, 1.4 μs), the ligand was pulled away from **P** towards the reaction coordinate with an increment of 0.4 Å from 0 to 28 Å, to ensure a sufficient overlap, and with a pull force constant of 5 kcal/(mol.Å$^2$) (71 windows in total). The three anchor dummy particles (zero charge, zero LJ radius and well-depth, mass of 220 Da), used for orienting the two macromolecules (see references 1-4 for details), were subject to positional restraints of 50 kcal/(mol.Å$^2$). The reaction coordinate adopted is represented by the distance between a dummy particle and the central Y atom ($R_{D\text{-}Y}$). The force constants of the distance and of the angles constraints applied between the anchor particles, **P** and the complex were, respectively, 5 kcal/(mol.Å$^2$) and 100 kcal/(mol.rad$^2$).
The direct binding $\Delta G_{bind}$ energy calculation has been done through the use of the APR (attach-pull-release) method. $\Delta G_{bind}$ is evaluated as a sum of works of different processes: $W_{attach}$, where constraints are attached to the ligand; $W_{pull}$, where the ligand is pulled away of **P**, and $W_{release\text{-}std}$, namely the work of releasing the ligand at the standard concentration. All the paths are reported in Figure S7 for both the enantiomers systems, and the obtain energies in Table S5. The are no such big differences on the paths, and this leads to a very similar interaction of the two enantiomers with **P**. Moreover, the quantity obtained experimentally (-2.9 kcal.mol$^{-1}$), is in a good agreement with the results presented in Table 2.

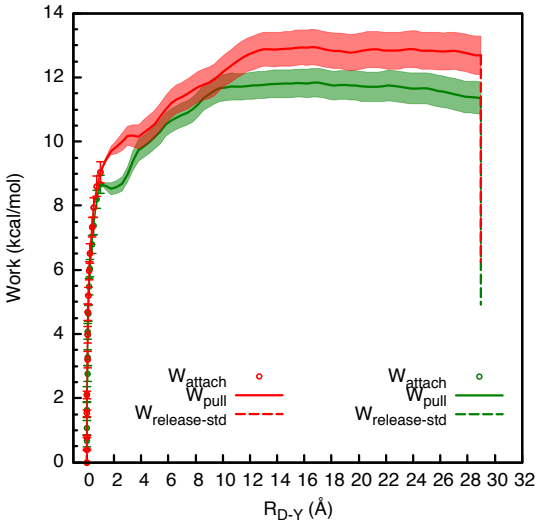


Figure **S7**. $\Delta G_{bind}$ obtained from the within the APR method as thermodynamic integration approach ($\Delta G_{bind}$ = -($W_{attach}$+$W_{pull}$+$W_{release\text{-}std}$)) (see references for the method details) for **P**-Δ orange circles) and **P**-Λ (green circles). The $W_{pul}$ is represented by the potential of mean force (PMF) along the coordinate reaction (see text for details), while $W_{release\text{-}std}$ corresponds to the work of releasing the ligand at the standard concentration and it is evaluated semi-analytically. The x-axis is defined as the pulling reaction, but the pull starts at 1 Å. The points from 0 to 1 Å must be considered as the values (increasing of the value of the constraints) during the attaching phase ($W_{attach}$).

| System | Simulation time | Dh-t (in Å) | SASA (in Å$^2$) | RMSD (in Å) |
|---|---|---|---|---|
| **Enantiomer D** | | | | |
| Trajectory 1 | 1μs | 15.6 ±4.0 Å | 1000.0 ±81.4 Å$^2$ | |
| Trajectory 2 | 1μs | 13.8 ±5.2 Å | 999.3 ±86.4 Å$^2$ | |
| Trajectory 3 | 1μs | 13.7 ±5.2 Å | 1005.0 ±83.3 Å$^2$ | |
| Trajectory 4 | 1μs | 14.2 ±4.5 Å | 975.2 ±76.9 Å$^2$ | |
| Overall | 4μs | 14.3 ±5.0 Å | 994.9 ±82.9 Å$^2$ | 5.8 ±1.0 Å |
| **Enantiomer L** | | | | |
| Trajectory 1 | 1μs | 15.7 ±4.5 Å | 1026.0 ±82.3 Å$^2$ | |
| Trajectory 2 | 1μs | 13.6 ±4.5 Å | 1010.0 ±74.9 Å$^2$ | |
| Trajectory 3 | 1μs | 15.4 ±5.6 Å | 1028.0 ±98.4 Å$^2$ | |
| Trajectory 4 | 1μs | 14.6 ±4.8 Å | 1007.0 ±89.4 Å$^2$ | |
| Overall | 4μs | 14.8 ±5.0 Å | 1018.0 ±87.2 Å$^2$ | 5.5 ±0.7 Å |
| **Peptide** | | | | |
| Trajectory 1 | 0.5μs | 17.2 ±5.7 Å | 1196.0 ±99.1 Å$^2$ | 5.1 ±1.0 Å |

Table S4. $D_{h\text{-}t}$, calculated for the complex enantiomers interacting with the peptide and for the peptide alone, is reported in Å and represents the head-tail distance between the Cα of S1 and G10. SASA represents the solvent accessible surface area of the peptide when interacting with the complex enantiomers and when being alone, and is reported in Å$^2$. The errors are reported as standard deviation. The RMSD value for the whole trajectories is reported in Å.

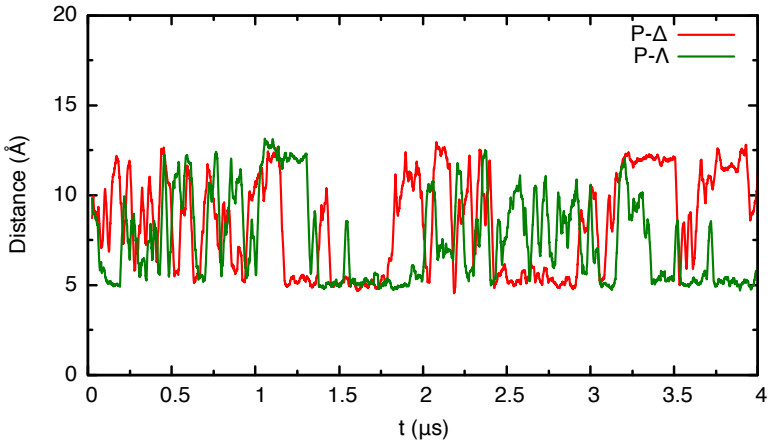


Figure S8. Overall simulation time Y4-K5 distance in Å. The systems are represented as follows: red line for **P**-Δ, green line for **P**-Λ.

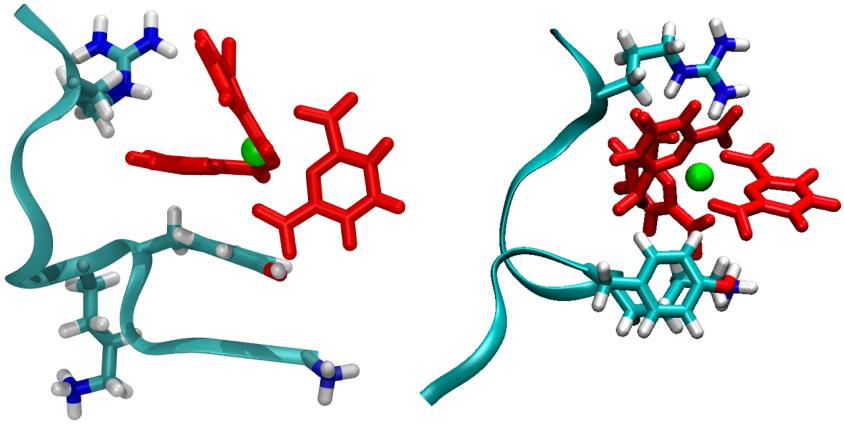

Figure S9. Cartoon representations for **P** corresponding to a short center of mass distance (below 7 Å) between the tyrosine Y4 and the lanthanide complex. π-stacking interaction are seldom, shown left side for the Λ-enantiomer, but can also correspond to hydrogen bonding opportunistic interaction (Δ-enantiomer, rightside).

| System | Simulation time | $\Delta G_{bind}$ (in kcal.mol$^{-1}$) |
|---|---|---|
| **Enantiomer Δ** | 8.5 μs | -6.26 ±0.67 |
| **Enantiomer Λ** | 8.5 μs | -5.00 ±0.57 |

Table S5. $\Delta G_{\mathbf{bind}}$ calculated for the complex enantiomers interacting with **P** within the APR method.

| Level of theory | d(Ln-O) in Å | d(Ln-N) in Å | Force constant Ln-O (kcal.Å$^{-2}$) | Force constant Ln-N (kcal.Å$^{-2}$) |
|---|---|---|---|---|
| ωB97XD 6-31+G(d)/LANL2DZ | 2.417 | 2.523 | 64.6 | 49.3 |
| CAM-B3LYP-D3BJ 6-31+G(d)/LANL2DZ | 2.410 | 2.516 | 62.8 | 52.4 |
| ωB97XD 6-31+G(d)/SDD | 2.415 | 2.520 | 64.5 | 53.3 |
| CAM-B3LYP-D3BJ 6-31+G(d)/SDD | 2.408 | 2.518 | 62.8 | 53.8 |
| X-ray structure | 2.426 (average over 6 distances: 2.445, 2.405, 2.398, 2.466, 2.407, 2.438 (Δ and Λ)) | 2.511 (average over 3 distances: 2.502, 2.508, 2.523 (Δ and Λ) | n/a | n/a |
| MCPB force field based on the reference (5) | 2.418 | 2.525 | 59.9 | 53.1 |

Table S6. Assessment of the Ln-O and Ln-N coordination distances upon DFT geometry optimization, for two different density functionals (ωB97XD and CAM-B3LYP with the D3BJ dispersion correction) and two pseudo-potentials vs. the X-ray structure. The value inferred by the MCPB approach is in very good agreement.

**YDPA_mcpbpy.frcmod file:**

```
REMARK GOES HERE, THIS FILE IS GENERATED BY MCPB.PY
MASS
M1 88.91                Y ion
Y1 14.01        0.530     Sp2 N in pure aromatic systems
Y2 16.00        0.434     Oxygen with one connected atom
Y3 16.00        0.434     Oxygen with one connected atom
Y4 14.01        0.530     Sp2 N in pure aromatic systems
Y5 16.00        0.434     Oxygen with one connected atom
Y6 16.00        0.434     Oxygen with one connected atom
Y7 14.01        0.530     Sp2 N in pure aromatic systems
Y8 16.00        0.434     Oxygen with one connected atom
Y9 16.00        0.434     Oxygen with one connected atom

BOND
M1-Y1   53.1    2.5248     Created by Seminario method using MCPB.py
M1-Y2   59.9    2.3381     Created by Seminario method using MCPB.py
M1-Y3   59.9    2.3382     Created by Seminario method using MCPB.py
M1-Y4   53.1    2.5249     Created by Seminario method using MCPB.py
M1-Y5   60.0    2.3381     Created by Seminario method using MCPB.py
M1-Y6   59.9    2.3382     Created by Seminario method using MCPB.py
M1-Y7   53.1    2.5250     Created by Seminario method using MCPB.py
M1-Y8   59.8    2.3382     Created by Seminario method using MCPB.py
M1-Y9   59.8    2.3382     Created by Seminario method using MCPB.py
Y1-ca  488.0    1.3390     SOURCE3_SOURCE5    6806    0.0055
Y2-c   637.7    1.2183     SOURCE1_SOURCE5   27083    0.0110
Y3-c   637.7    1.2183     SOURCE1_SOURCE5   27083    0.0110
Y4-ca  488.0    1.3390     SOURCE3_SOURCE5    6806    0.0055
Y5-c   637.7    1.2183     SOURCE1_SOURCE5   27083    0.0110
Y6-c   637.7    1.2183     SOURCE1_SOURCE5   27083    0.0110
Y7-ca  488.0    1.3390     SOURCE3_SOURCE5    6806    0.0055
Y8-c   637.7    1.2183     SOURCE1_SOURCE5   27083    0.0110
Y9-c   637.7    1.2183     SOURCE1_SOURCE5   27083    0.0110

ANGL
M1-Y1-ca    92.78     120.01    Created by Seminario method using MCPB.py
M1-Y2-c     45.97     128.68    Created by Seminario method using MCPB.py
M1-Y3-c     46.10     128.68    Created by Seminario method using MCPB.py
M1-Y4-ca    92.80     120.01    Created by Seminario method using MCPB.py
M1-Y5-c     46.01     128.67    Created by Seminario method using MCPB.py
M1-Y6-c     47.87     128.69    Created by Seminario method using MCPB.py
M1-Y7-ca    92.94     120.02    Created by Seminario method using MCPB.py
M1-Y8-c     47.67     128.69    Created by Seminario method using MCPB.py
M1-Y9-c     46.06     128.68    Created by Seminario method using MCPB.py
Y2-M1-Y1    65.33      66.11    Created by Seminario method using MCPB.py
Y3-M1-Y1    64.97      66.12    Created by Seminario method using MCPB.py
Y3-M1-Y2    63.85     132.23    Created by Seminario method using MCPB.py
Y4-M1-Y1    66.77     120.08    Created by Seminario method using MCPB.py
Y4-M1-Y2    53.28     137.31    Created by Seminario method using MCPB.py
```

Y4-M1-Y3 29.36 70.75 Created by Seminario method using MCPB.py
Y5-M1-Y1 29.34 70.74 Created by Seminario method using MCPB.py
Y5-M1-Y2 34.82 79.29 Created by Seminario method using MCPB.py
Y5-M1-Y3 44.13 85.28 Created by Seminario method using MCPB.py
Y5-M1-Y4 64.84 66.12 Created by Seminario method using MCPB.py
Y6-M1-Y1 54.39 137.28 Created by Seminario method using MCPB.py
Y6-M1-Y2 30.32 141.43 Created by Seminario method using MCPB.py
Y6-M1-Y3 34.00 79.25 Created by Seminario method using MCPB.py
Y6-M1-Y4 65.20 66.11 Created by Seminario method using MCPB.py
Y6-M1-Y5 63.57 132.23 Created by Seminario method using MCPB.py
Y7-M1-Y1 66.81 119.99 Created by Seminario method using MCPB.py
Y7-M1-Y2 29.35 70.73 Created by Seminario method using MCPB.py
Y7-M1-Y3 53.05 137.35 Created by Seminario method using MCPB.py
Y7-M1-Y4 66.76 119.92 Created by Seminario method using MCPB.py
Y7-M1-Y5 52.75 137.37 Created by Seminario method using MCPB.py
Y7-M1-Y6 28.74 70.70 Created by Seminario method using MCPB.py
Y8-M1-Y1 54.02 137.32 Created by Seminario method using MCPB.py
Y8-M1-Y2 34.75 79.23 Created by Seminario method using MCPB.py
Y8-M1-Y3 30.25 141.42 Created by Seminario method using MCPB.py
Y8-M1-Y4 28.77 70.68 Created by Seminario method using MCPB.py
Y8-M1-Y5 38.61 79.27 Created by Seminario method using MCPB.py
Y8-M1-Y6 45.96 85.40 Created by Seminario method using MCPB.py
Y8-M1-Y7 65.05 66.11 Created by Seminario method using MCPB.py
Y9-M1-Y1 29.46 70.68 Created by Seminario method using MCPB.py
Y9-M1-Y2 44.37 85.34 Created by Seminario method using MCPB.py
Y9-M1-Y3 37.26 79.30 Created by Seminario method using MCPB.py
Y9-M1-Y4 52.90 137.35 Created by Seminario method using MCPB.py
Y9-M1-Y5 30.97 141.42 Created by Seminario method using MCPB.py
Y9-M1-Y6 37.06 79.24 Created by Seminario method using MCPB.py
Y9-M1-Y7 65.15 66.11 Created by Seminario method using MCPB.py
Y9-M1-Y8 63.72 132.22 Created by Seminario method using MCPB.py
Y1-ca-c 67.7 117.78 SOURCE4_SOURCE5 262 1.1507
Y1-ca-ca 68.8 122.94 SOURCE3_SOURCE5 5507 1.1495
Y2-c -ca 68.7 122.60 SOURCE3_SOURCE5 3960 1.5802
Y2-c -o 77.9 130.25 SOURCE4_SOURCE5 1037 1.2396
Y4-ca-c 67.7 117.78 SOURCE4_SOURCE5 262 1.1507
Y4-ca-ca 68.8 122.94 SOURCE3_SOURCE5 5507 1.1495
Y5-c -ca 68.7 122.60 SOURCE3_SOURCE5 3960 1.5802
Y5-c -o 77.9 130.25 SOURCE4_SOURCE5 1037 1.2396
Y6-c -ca 68.7 122.60 SOURCE3_SOURCE5 3960 1.5802
Y7-ca-c 67.7 117.78 SOURCE4_SOURCE5 262 1.1507
Y7-ca-ca 68.8 122.94 SOURCE3_SOURCE5 5507 1.1495
Y8-c -ca 68.7 122.60 SOURCE3_SOURCE5 3960 1.5802
Y8-c -o 77.9 130.25 SOURCE4_SOURCE5 1037 1.2396
Y9-c -ca 68.7 122.60 SOURCE3_SOURCE5 3960 1.5802
ca-Y1-ca 68.3 117.22 SOURCE3_SOURCE5 3343 1.0306
ca-Y4-ca 68.3 117.22 SOURCE3_SOURCE5 3343 1.0306
ca-Y7-ca 68.3 117.22 SOURCE3_SOURCE5 3343 1.0306
ca-c -Y3 68.7 122.60 SOURCE3_SOURCE5 3960 1.5802
o -c -Y3 77.9 130.25 SOURCE4_SOURCE5 1037 1.2396

```
o -c -Y6    77.9     130.25     SOURCE4_SOURCE5       1037    1.2396
o -c -Y9    77.9     130.25     SOURCE4_SOURCE5       1037    1.2396

DIHE
X -Y1-ca-X     2       9.6     180.0   2.0      same as X-CA-NC-X
X -Y4-ca-X     2       9.6     180.0   2.0      same as X-CA-NC-X
X -Y7-ca-X     2       9.6     180.0   2.0      same as X-CA-NC-X
M1-Y1-ca-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y1-ca-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y2-c -ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y2-c -o     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y3-c -ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y3-c -o     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y4-ca-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y4-ca-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y5-c -ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y5-c -o     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y6-c -ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y6-c -o     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y7-ca-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y7-ca-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y8-c -ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y8-c -o     3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y9-c -ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
M1-Y9-c -o     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y2-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y3-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y3-M1-Y2-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y4-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y4-M1-Y2-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y4-M1-Y3-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y5-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y5-M1-Y2-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y5-M1-Y3-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y5-M1-Y4-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y6-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y6-M1-Y2-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y6-M1-Y3-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y6-M1-Y4-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y6-M1-Y5-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y7-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y7-M1-Y2-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y7-M1-Y3-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y7-M1-Y4-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y7-M1-Y5-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y7-M1-Y6-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y8-M1-Y1-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y8-M1-Y2-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y8-M1-Y3-c     3      0.00      0.00   3.0    Treat as zero by MCPB.py
Y8-M1-Y4-ca    3      0.00      0.00   3.0    Treat as zero by MCPB.py
```

| | | | | | |
|---|---|---|---|---|---|
| Y8-M1-Y5-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y8-M1-Y6-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y8-M1-Y7-ca | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y1-ca | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y2-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y3-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y4-ca | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y5-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y6-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y7-ca | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| Y9-M1-Y8-c | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y2-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y3-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y3-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y5-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y5-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y5-M1-Y3 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y5-M1-Y4 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y6-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y6-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y6-M1-Y3 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y6-M1-Y4 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y6-M1-Y5 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y3 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y4 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y5 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y6 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y8-M1-Y7 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y3 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y4 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y5 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y6 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y7 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| c -Y9-M1-Y8 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y4-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y4-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y4-M1-Y3 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y7-M1-Y1 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y7-M1-Y2 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y7-M1-Y3 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y7-M1-Y4 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y7-M1-Y5 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |
| ca-Y7-M1-Y6 | 3 | 0.00 | 0.00 | 3.0 | Treat as zero by MCPB.py |

IMPR

| | | | | |
|---|---|---|---|---|
| X -X -c -Y8 | 10.5 | 180. | 2. | JCC,7,(1986),230 |

X -X -c -Y9 10.5 180. 2. JCC,7,(1986),230
X -X -c -Y5 10.5 180. 2. JCC,7,(1986),230
X -X -c -Y3 10.5 180. 2. JCC,7,(1986),230
X -X -c -Y6 10.5 180. 2. JCC,7,(1986),230
X -X -c -Y2 10.5 180. 2. JCC,7,(1986),230
X -Y3-c -o 1.1 180. 2. JCC,7,(1986),230
X -Y2-c -o 1.1 180. 2. JCC,7,(1986),230
X -Y8-c -o 1.1 180. 2. JCC,7,(1986),230
X -Y9-c -o 1.1 180. 2. JCC,7,(1986),230
X -Y5-c -o 1.1 180. 2. JCC,7,(1986),230
X -Y6-c -o 1.1 180. 2. JCC,7,(1986),230
Y8-ca-c -o 1.1 180.0 2.0 General improper torsional angle (1 general atom type)
Y7-c -ca-ca 1.1 180.0 2.0 Using default value
Y1-c -ca-ca 1.1 180.0 2.0 Using default value
Y9-ca-c -o 1.1 180.0 2.0 General improper torsional angle (1 general atom type)
Y5-ca-c -o 1.1 180.0 2.0 General improper torsional angle (1 general atom type)
Y3-ca-c -o 1.1 180.0 2.0 General improper torsional angle (1 general atom type)
Y6-ca-c -o 1.1 180.0 2.0 General improper torsional angle (1 general atom type)
Y2-ca-c -o 1.1 180.0 2.0 General improper torsional angle (1 general atom type)
Y4-c -ca-ca 1.1 180.0 2.0 Using default value

NONB
M1 1.6020 0.0803423100 IOD set for Y3+ ion in TIP3P water from Li et al. JPCB, 2015, 119, 883
Y1 1.8240 0.1700 OPLS
Y2 1.6612 0.2100 OPLS
Y3 1.6612 0.2100 OPLS
Y4 1.8240 0.1700 OPLS
Y5 1.6612 0.2100 OPLS
Y6 1.6612 0.2100 OPLS
Y7 1.8240 0.1700 OPLS
Y8 1.6612 0.2100 OPLS
Y9 1.6612 0.2100 OPLS

## References

(1) Velez-Vega, C. ; Gilson, M.K. ; Overcoming Dissipation in the Calculation of Standard Free Energies by Ligand Extraction. *J. Comput. Chem.* **2013**, *34*, 2360-2371
(2) Henriksen, N.M.; Fenley, A.T ; Gilson, M.K.; Computational Calorimetry : High-Precision Calculation of Host-Guest Binding Thermodynamics. *J. Chem. Theory Comput.* **2015**, *11*, 4377-4394
(3) Yin, J.; Henriksen, N.M.; Slochower, D.R. ; Gilson, M.K.; Computational Calorimetry : The SAMPL5 Host-guest challenge : computing binding free energies from explicit solvent simulations by the attach-pull-release (APR) method. *J. Computer-Aided Molecular Design.* **2017**, *31*, 133-145
(4) Heinzelmann, G.; Henriksen, N.M.; Gilson, M.K.; Attach-Pull-Release Calculations of Ligand Binding and Conformational Changes on the First BRD4 Bromodomain. *J. Chem. Theory Comput.* **2017**, *13*, 3260-3275
(5) Seminario, J. M.; Calculation of intramolecular force fields from second-derivative tensors. *Int. J. Quantum Chem*., **1996**, *60*, 1271−1277