Supplementary Material (ESI) for Chemical Communications

Supporting Information

Ca^{2+}-induced Folding of a Chiral Ditopic Receptor Based on a Pybox Ligand and Enhancement of Anion Recognition

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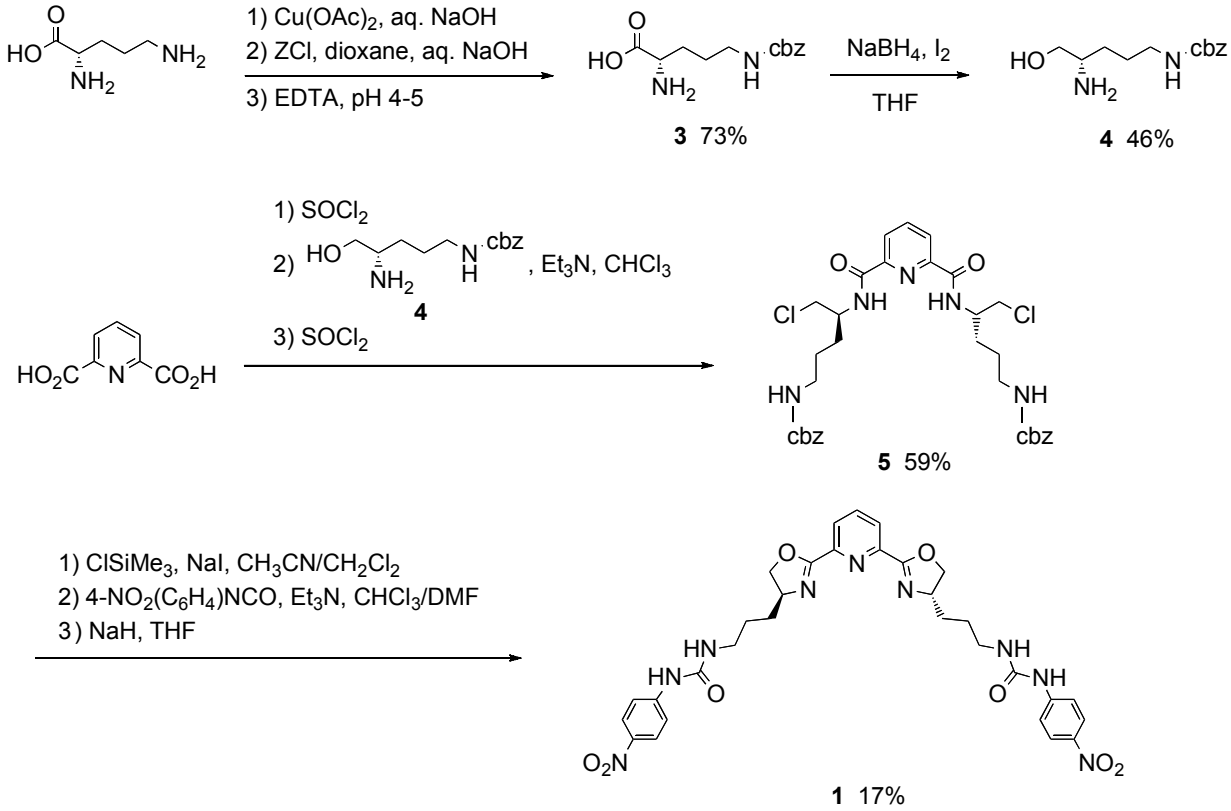
(1) General procedure

All reactions were performed under a dry nitrogen atmosphere. Organic solvents were purchased as pre-dried solvents and used without any further purification. H_2O was deionised and microfiltered using a Millipore machine, Milli-Q® Integral 3. ^1H and ^{13}C spectra were recorded by Bruker AVANCE400 using TMS as an internal reference. ESI Mass spectrum was recorded on an Applied Biosystems QStar Pulsar *i* spectrometer. UV-vis spectra were recorded by JASCO Ubest V-660. CD spectra were recorded by JASCO J-720W.

(2) Synthesis of Pybox Ligand 1

Pybox ligand **1** was synthesized by procedure shown in Scheme S1. Compound **3** was prepared by literature method.[1,2]



Scheme S1. Synthetic procedure

Synthesis of **4**

To a mixture of **2** (9.65 g, 36.4 mmol) and sodium borohydride (4.20 g, 111 mmol) in THF (180 mL) was added a THF solution (30 mL) of iodine (10.2 g, 40.0 mmol) at 0 ºC for 30 minutes, then the reaction mixture was refluxed for 18 hours. After quenching with methanol and evaporation, a crude mixture was dissolved into 20% potassium hydroxide solution, then stirred at room temperature for 4 hours. Extraction with chloroform and evaporation gave a crude oil. The crude mixture was separated by silica-gel column chromatography using 10:1 methanol/chloroform as an eluent to give a white powder of **4** (4.21 g, 46%).

4: white solid, ^1H NMR (300 MHz, $CDCl_3$) δ 1.27-1.31 (m, 1H), 1.44-1.63 (m, 3H), 2.84-2.86 (m, 1H), 3.17-3.24 (q, J = 6.9 Hz, 2H), 3.24-3.32 (m, 1H), 3.56-3.61 (dd, J = 4.2 Hz, 6.6 Hz, 1H), 5.03 (s, 1H), 5.09 (s, 2H), 7.30-7.36 (m, 5H).

Synthesis of **5**

To an $SOCl_2$ solution (5.0 mL) of pyridine-2,6-dicarboxylic acid (210.0 mg, 1.26 mmol) was added a three drops of dimethylformamid, then the reaction mixture was refluxed for 2 hours. After removal of an excess of $SOCl_2$ by distillation, dry chloroform (3.0 mL) was added. To this, a chloroform solution (25.0 mL) of **4** (700 mg, 2.77 mmol) and triethylamine (1.3 mL) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 30 minutes, then at room temperature for 16 hours. $SOCl_2$ (4.0 mL) was added to the reaction mixture and this was stirred at 50 °C for 2 hours. After the reaction mixture was slowly poured to ice, extraction with chloroform, washing with brine, and evaporation gave a crude brown solid. The crude mixture was separated by silica-gel column chromatography to give a white powder of **5** (502 mg, 59%).

5:white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (quint, J = 6.6 Hz, 4H), 1.77 (q, J = 6.6 Hz, 4H), 3.20-3.31 (m, 4H), 3.72 (dd, J = 10.5 Hz, J = 3.0 Hz, 2H), 3.77 (dd, J = 10.5 Hz, J = 4.0 Hz, 2H), 4.43-4.47 (m, 2H), 4.91 (brs, 2H), 5.08 (d, J = 12.5 Hz, 2H), 5.10 (d, J = 12.5 Hz, 2H), 7.26-7.35 (m, 10H), 8.05 (t, J = 7.5 Hz, 1H), 8.15 (brd, J = 7.0 Hz, 2H), 8.35 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.63 (*C*H_2), 28.86 (*C*H_2), 40.63 (*C*H_2), 48.26 (*C*H), 49.47 (*C*H_2), 66.76 (*C*H_2), 125.33 (*C*H), 128.09 (*C*H), 128.17 (*C*H), 128.55 (*C*H), 136.48 (*C*), 139.20 (*C*), 148.51 (*C*), 156.67 (*C*), 163.17 (*C*); ESI-TOF-MS observed *m/z* 694.5 [**5** + Na]$^+$.

Synthesis of **1**

To a dichloromethane (3.5 mL) and acetonitrile (5.0 mL) solution of **5** (250 mg, 0.372 mmol) and sodium iodide (335 mg, 2.23 mmol) was added trimethylsilyl chloride (0.190 mL, 1.49 mmol), and the reaction mixture was stirred at 0 °C for 2 hours. After quenching with methanol, evaporation and reprecipitation from acetonitrile/toluene gave a white powder. To a 6:1 dichloromethane/dimethylformamide (5.0 mL) and triethylamine (0.22 mL) solution of the white powder was added 4-nitrophenyl isocyanate (159 mg, 0.969 mmol) in 6:1 dichloromethane/dimethylformamide (1.0 mL), then reaction mixture was stirred at room temperature for 24 hours. After evaporation, silica-gel column chromatography followed by reprecipitation from chloroform/acetonitrile/hexane gave a yellow precipitate (364 mg). The precipitate was used for a following reaction without further purification. To a THF suspension (10 mL) of sodium hydrate (60% oil dispersion, 45.3 mg, 1.13 mmol) was added the mixture in THF (10 mL) at 0 °C, then the reaction mixture was stirred at 0 °C for one hour and at room temperature for 11 hours. After evaporation and quenching with water, extraction with dichloromethane, washing water and brine, and evaporation gave a crude brown solid. The crude mixture was separated by column chromatography (NH_2-substituted silica-gel, eluent: chloroform/methanol = 20/1) followed by repreciptation from chloroform/hexane to give a yellow powder of **1** (41.7 mg, 17%).

1: pale yellow solid, mp 132-134 ºC; ^{1}H NMR (400 MHz, $CD_3CN/CDCl_3$ = 1/4) δ 1.54-1.72 (m, 8H), 3.22 (ddd, J = 7.5 Hz, J = 7.2 Hz, J = 5.6 Hz, 4H), 4.08 (t, J = 7.5 Hz, 2H), 4.31 (quint, J = 8.0 Hz, 2H), 4.56 (dd, J = 8.0 Hz, J = 7.5 Hz, 2H), 5.79 (t, J = 5.6 Hz, 2H), 7.57 (d, J = 9.2 Hz, 4H), 7.96 (t, J = 7.0 Hz, 1H), 8.04 (brs, 2H), 8.05 (d, J = 7.0 Hz, 2H), 8.09 (d, J = 9.2 Hz, 4H); ^{13}C NMR (100 MHz, $CD_3CN/CDCl_3$ = 1/4) δ 26.71 (*C*H_2), 33.25 (*C*H_2), 39.99 (*C*H_2), 66.96 (*C*H), 73.85 (*C*H_2), 117.59 (*C*H), 125.37 (*C*H), 126.17 (*C*H), 138.64 (*C*H), 141.86 (*C*), 147.15 (*C*), 147.27 (*C*), 155.20 (*C*), 162.76 (*C*); ESI-TOF-MS observed *m/z* 660.3 [**1** + H]$^+$; Anal. Calcd for $C_{31}H_{33}N_9O_8 \cdot H_2O$: C, 54.94; H, 5.21; N, 18.60. Found: C, 54.54; H, 5.31; N, 18.18.

(3) NMR spectra

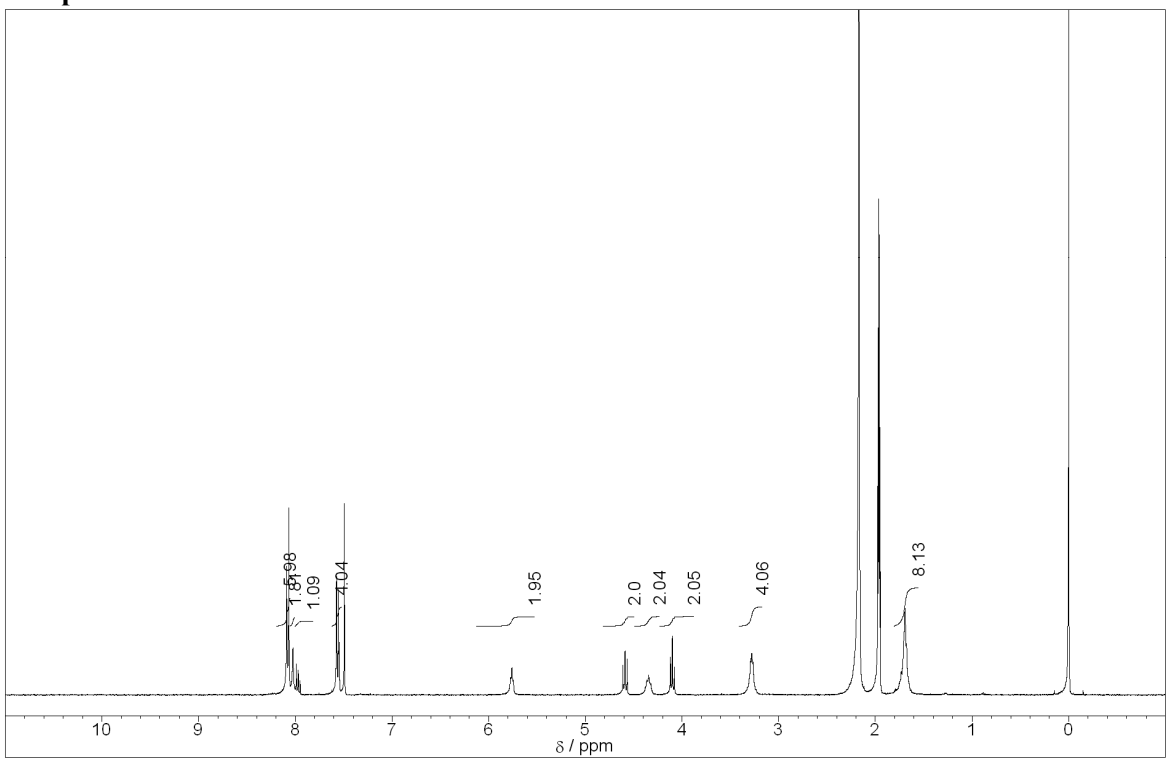


Figure S1. ^{1}H NMR spectrum of **1**, 400 MHz, $CDCl_3$: CD_3CN = 4 : 1, [**1**] = 1.0×10^{-3} M.

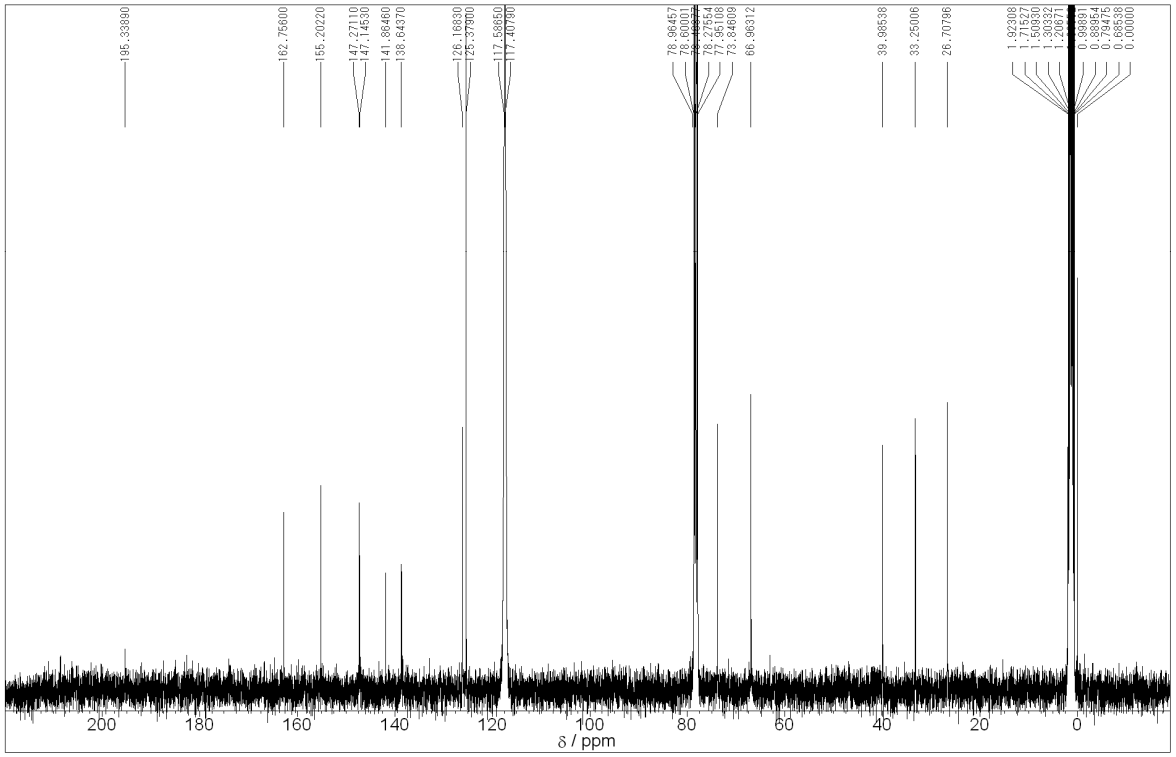


Figure S2. ^{13}C NMR spectrum of **1**, 100 MHz, $CDCl_3$: CD_3CN = 4 : 1, [**1**] = 2.0×10^{-3} M.

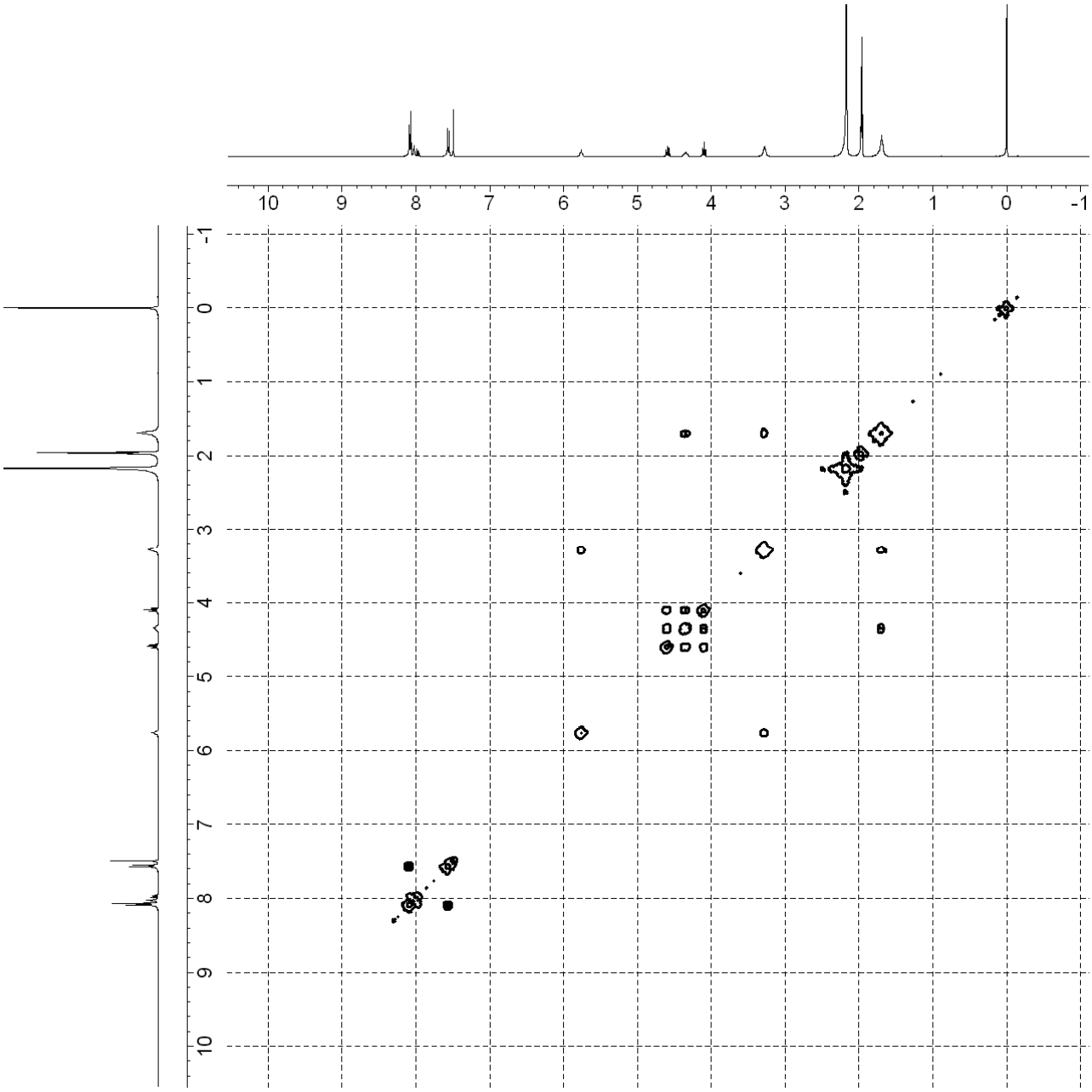


Figure S3. COSY spectrum of **1**, 400 MHz, $CDCl_3$: CD_3CN = 4 : 1, [**1**] = 2.0×10^{-3} M.

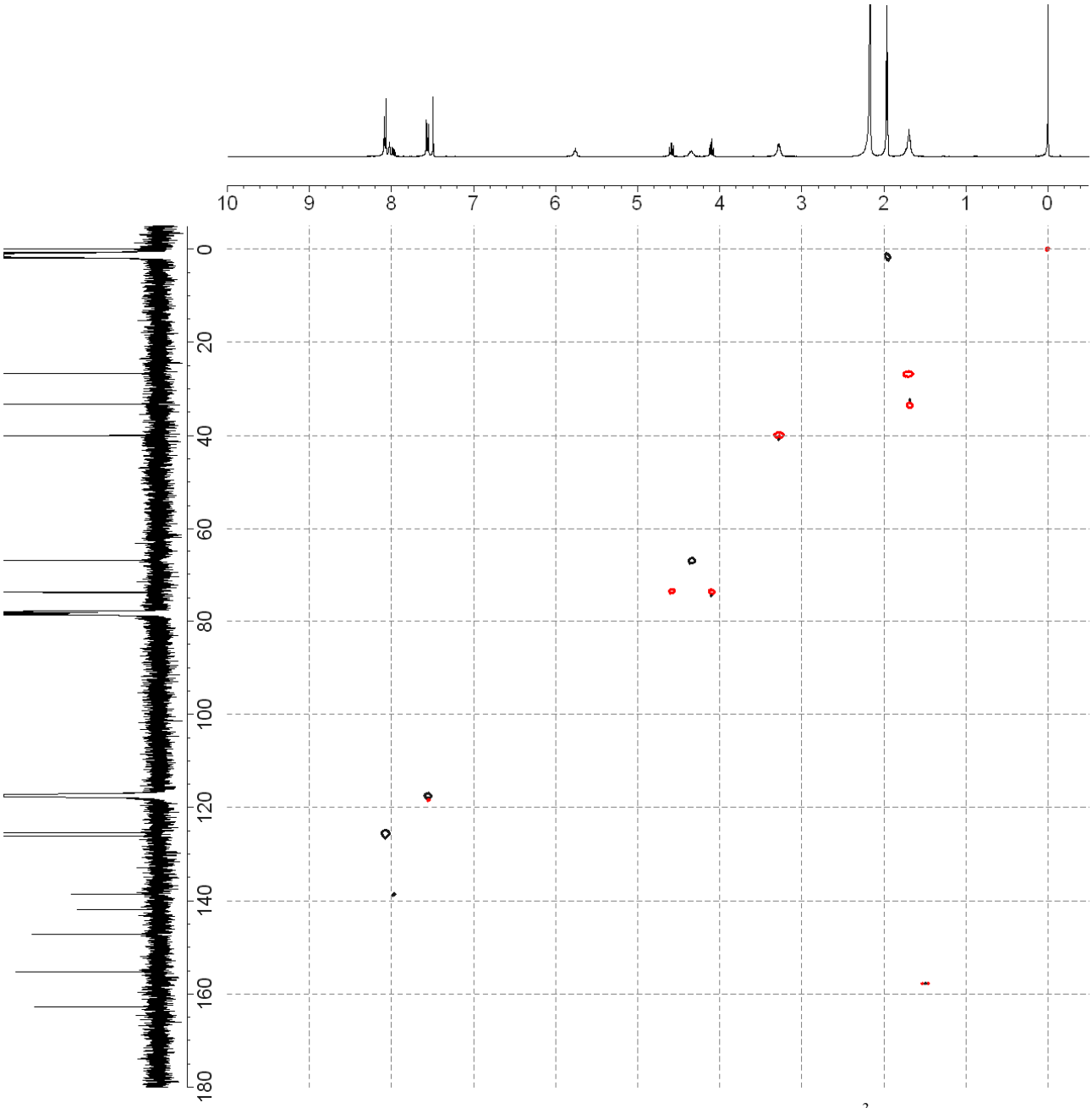


Figure S4. HSQC spectrum of **1**, 400 MHz, $CDCl_3$: CD_3CN = 4 : 1, [**1**] = 2.0×10^{-3} M. Black cross peaks represent positive signals that mean carbons for CH or CH_3, and red ones represent negative signals that mean carbons for CH_2.

(4) X-ray crystallographic analysis

The single crystal of the complex $\mathbf{2}_2Ca(ClO_4)_2$ was obtained by recrystallization of **2** in the presence of 20 equiv of $Ca(ClO_4)_2$ from chloroform/methanol. The complex $\mathbf{2}_2Ca(ClO_4)_2$ was characterized by ^{1}H NMR and an elemental analysis: mp 175 ºC (dec); ^{1}H NMR (400 MHz, CD_3CN) δ0.57 (d, J = 7.5 Hz, 6H), 0.77 (d, J = 7.5 Hz, 6H), 1.32-1.46 (m, 2H), 4.22 (ddd, J = 10.0 Hz, J = 7.2 Hz, J = 3.0 Hz, 2H), 4.53-4.62 (m, 4H), 8.14 (d, J = 8.0 Hz, 2H), 8.32 (t, J = 8.0 Hz, 1H); Found: C, 48.26; H, 5.47; N, 9.83 and calcd for $C_{34}H_{46}N_6O_{12}Cl_2Ca$: C, 48.51; H, 5.51; N, 9.98. CCD area-detector diffractometer data were measured with monochromatic MoKα radiation (λ = 0.71073 Å), and yielded reflections was merged after multi-scan absorption correction (Sheldrick, G. M. (1996). SADABS. University of Göttingen, Germany.) The structure was solved by dual methods using SHELX-97 and expanded using Fourier techniques.[3] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically with reflection weights using SHELX-97.[3] Crystal data for $\mathbf{2}_2Ca(ClO_4)_2$: $C_{34}H_{46}N_6O_{12}Cl_2Ca$, monoclinic, $P2_1$, a = 17.061(6), b = 11.823(4), c = 21.703(7) Å, β = 109.419(4), V = 4129(2) Å^3, MW = 841.75, Z = 4, D_{calc} = 1.354 g/cm^3, 22542 measured, 15952 independent, GOF = 1.026, $R1[I > 2\sigma(I)]$ = 0.0622%, $wR2$(all data) = 0.1550. CCDC 805519 contains the supplementary crystallographic data for this paper, which can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

(5) Optimized geometries and energies of *cisoid*- and *transoid*-isomers of pybox by PBE1PBE/6-31G(d,p)[4,5]

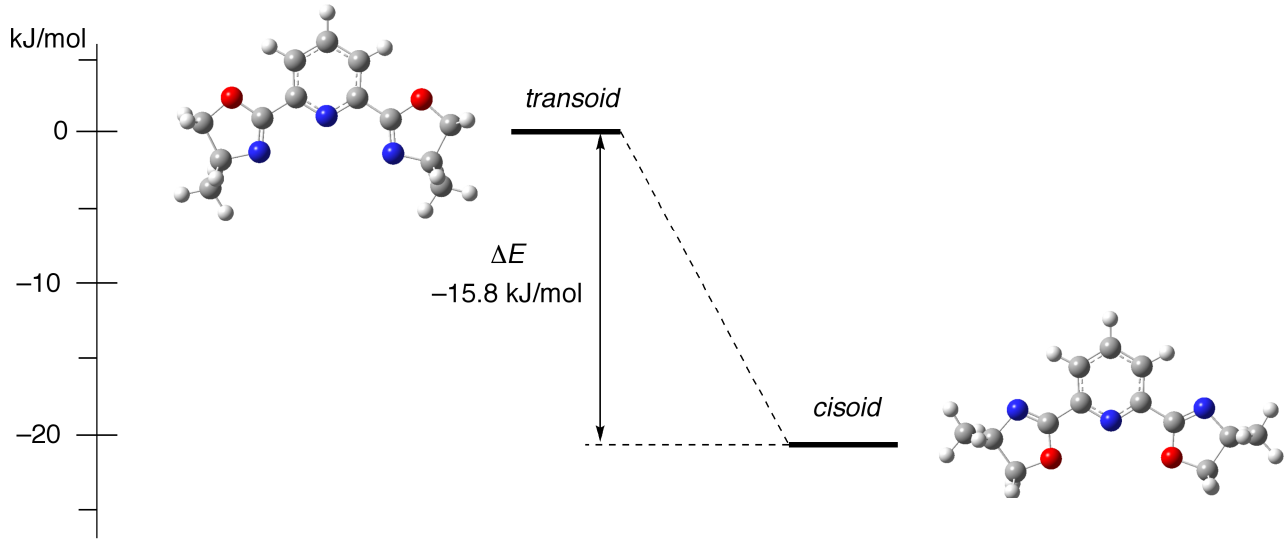


Figure S5. Ball and stick representation of the optimized geometry and energy diagram of *cisoid*- and *transoid*-(*S*,*S*)-dimethylPybox, grey: C, small white: H, red: O, blue: N. ΔE represents the energy difference of two conformers, whose total energy is calculated by the sum of electron energy and zero-point vibration energy.

(6) UV-vis spectroscopic titration of 1 with $Ca(ClO_4)_2$

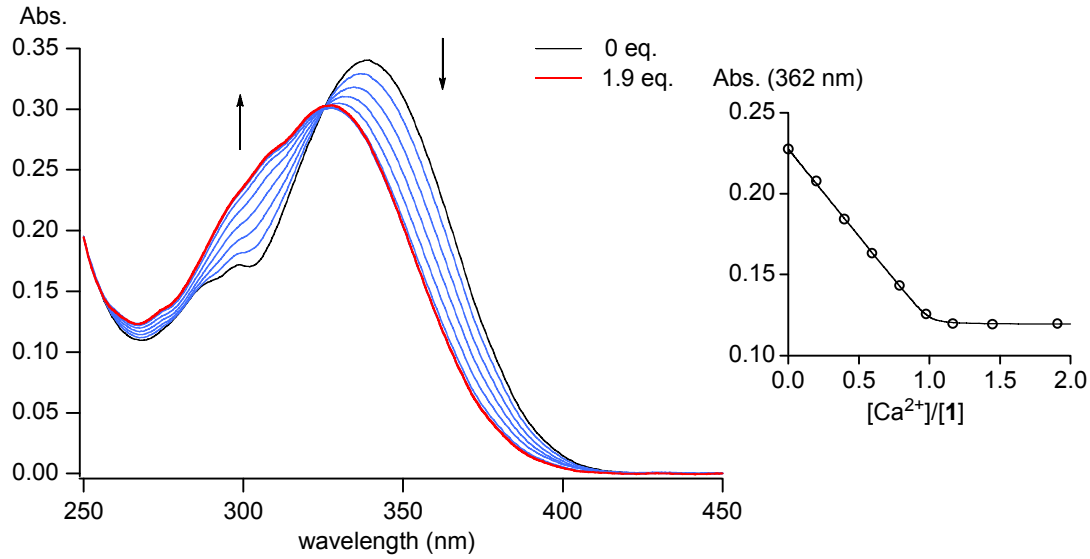


Figure S6. UV-vis spectral changes in **1** on the addition of $Ca(ClO_4)_2$. Inset shows the change of the absorption at 362 nm with a calculated curve. ($CHCl_3$: CH_3CN = 4 : 1, [**1**] = 1.0×10^{-5} M)

(7) CD spectroscopic titration of 1 with $Ca(ClO_4)_2$

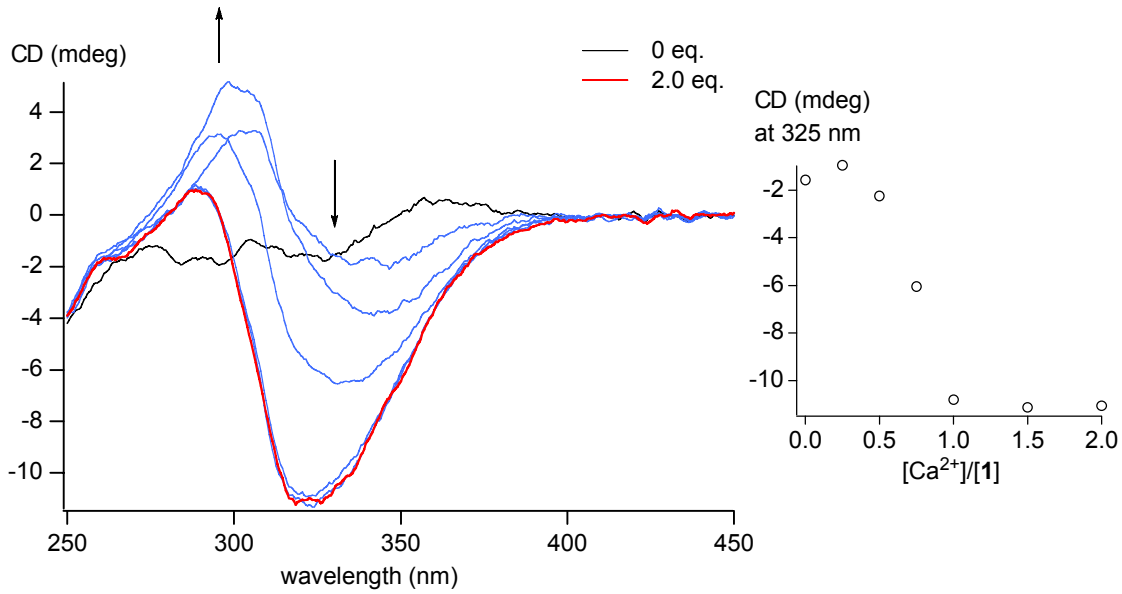


Figure S7. CD spectral changes in **1** on the addition of $Ca(ClO_4)_2$. ($CHCl_3$: CH_3CN = 4 : 1, [**1**] = 3.0×10^{-5} M)

(8) ESI-MS of 1·Ca(ClO$_4$)$_2$

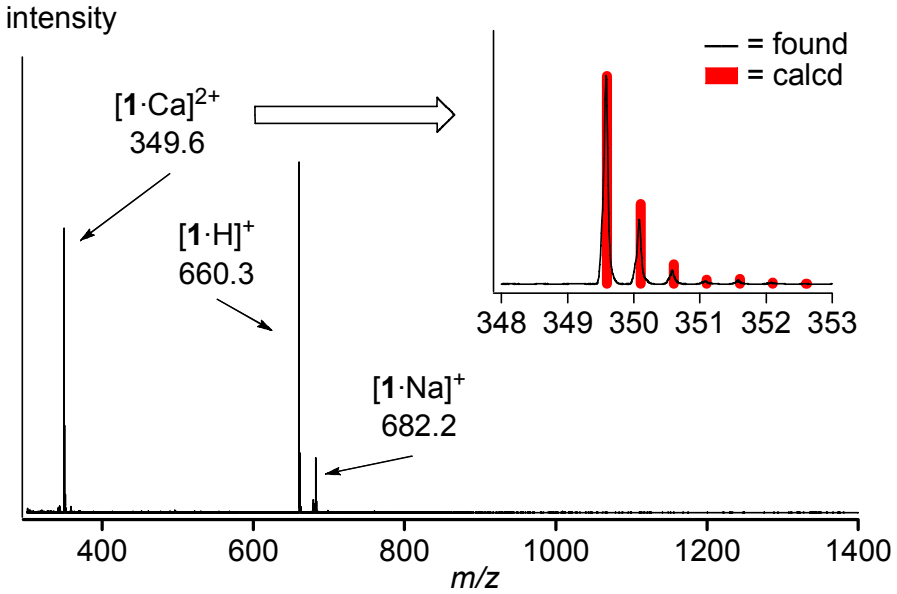


Figure S8. ESI mass spectrum of a mixture of **1** and Ca(ClO$_4$)$_2$. A black line and red bars represents an experimental data and a isotope simulation for [**1**·Ca]$^{2+}$, respectively.

(9) NOESY spectra of 1·Ca(ClO$_4$)$_2$

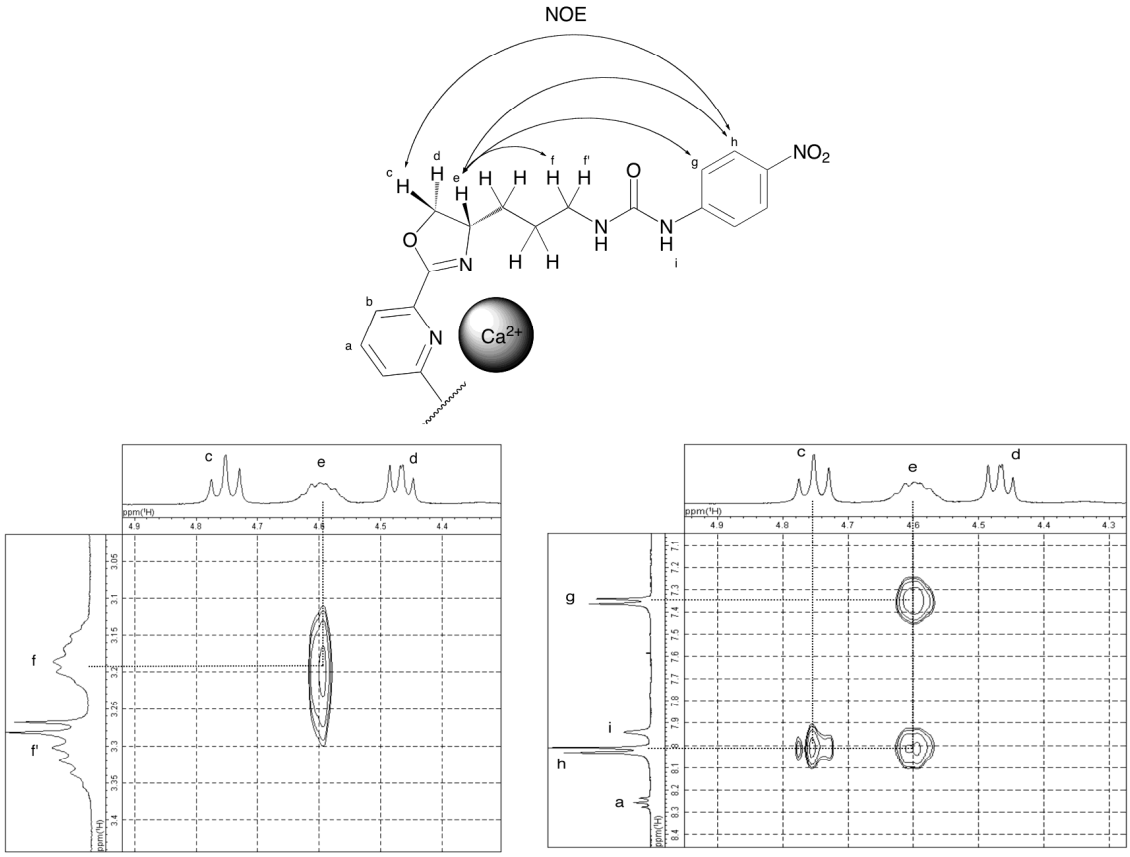
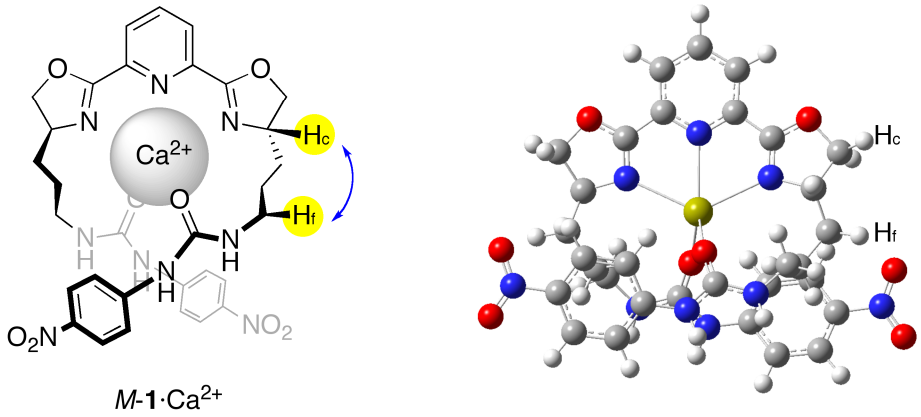


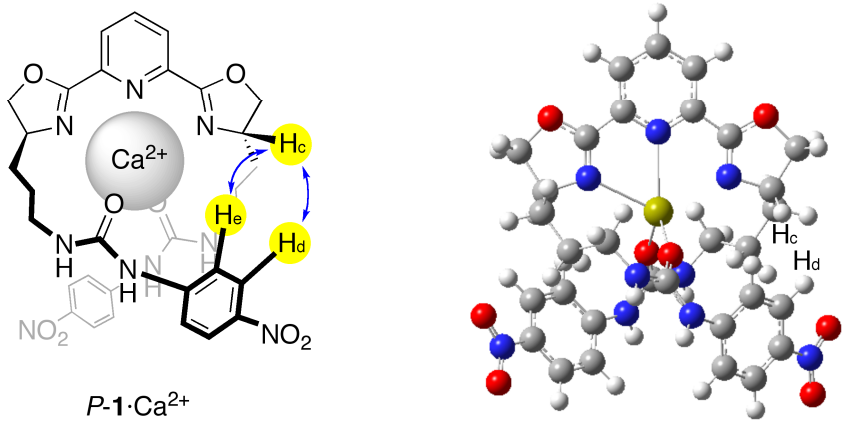
Figure S9. NOESY spectra of **1**·Ca^{2+} (CDCl$_3$: CD$_3$CN = 4 : 1, [**1**·Ca(ClO$_4$)$_2$] = 8.0 × 10^{-3} M)

(10) Optimized geometries and energies of *P*- and *M*-isomers of 1·Ca^{2+} by PBE1PBE/6-31G(d,p)[4,5]



M-**1**·Ca^{2+}

Figure S10. Schematic structure and ball and stick representation of the optimized geometry of *M*-**1**·Ca^{2+}, grey: C, small white: H, red: O, blue: N, yellow: Ca.



P-**1**·Ca^{2+}

Figure S11. Schematic structure and ball and stick representation of the optimized geometry of *P*-**1**·Ca^{2+}, grey: C, small white: H, red: O, blue: N, yellow: Ca.

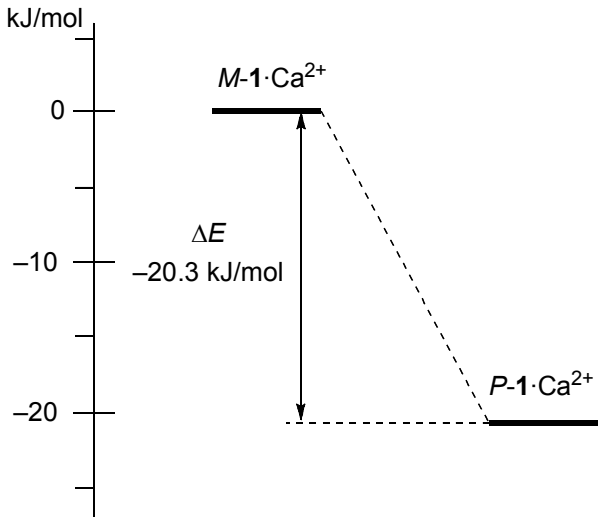


Figure S12. Energy diagram of *M*-**1**·Ca^{2+} and *P*-**1**·Ca^{2+}. ΔE represents the energy difference of two conformers, whose total energy is calculated by the sum of electron energy and zero-point vibration energy.

(11) UV-vis spectroscopic titration of 1 with $^{n}Bu_4N^{+}X^{-}$ (X = Cl, Br) in 4:1 $CHCl_3/CH_3CN$

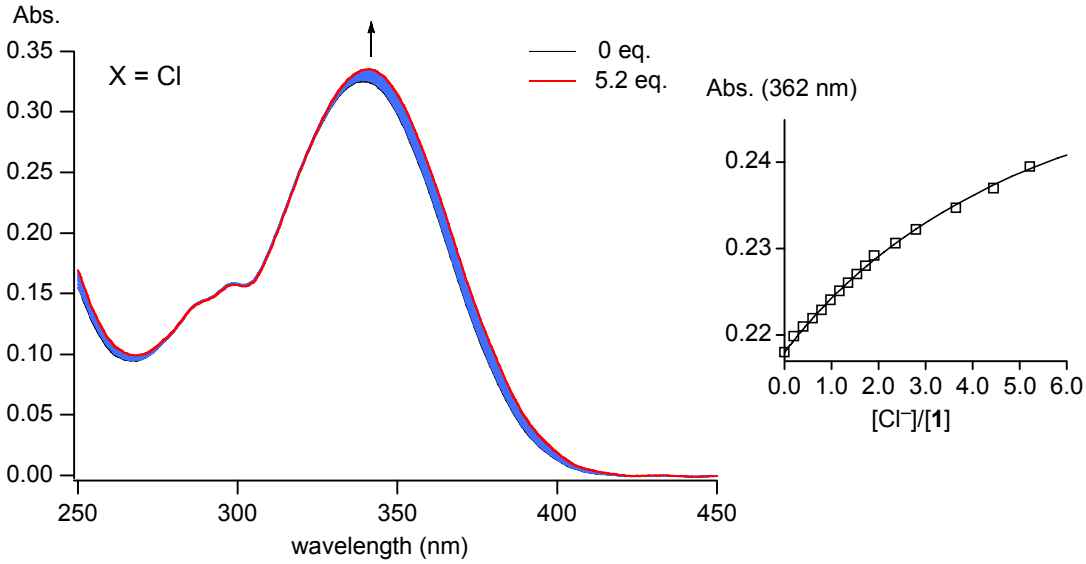


Figure S13. UV-vis spectral changes in **1** on the addition of $^{n}Bu_4N^{+}Cl^{-}$. Inset shows the change of the absorption at 362 nm with a calculated curve. ($CHCl_3$: CH_3CN = 4 : 1, [**1**] = 1.0×10^{-5} M)

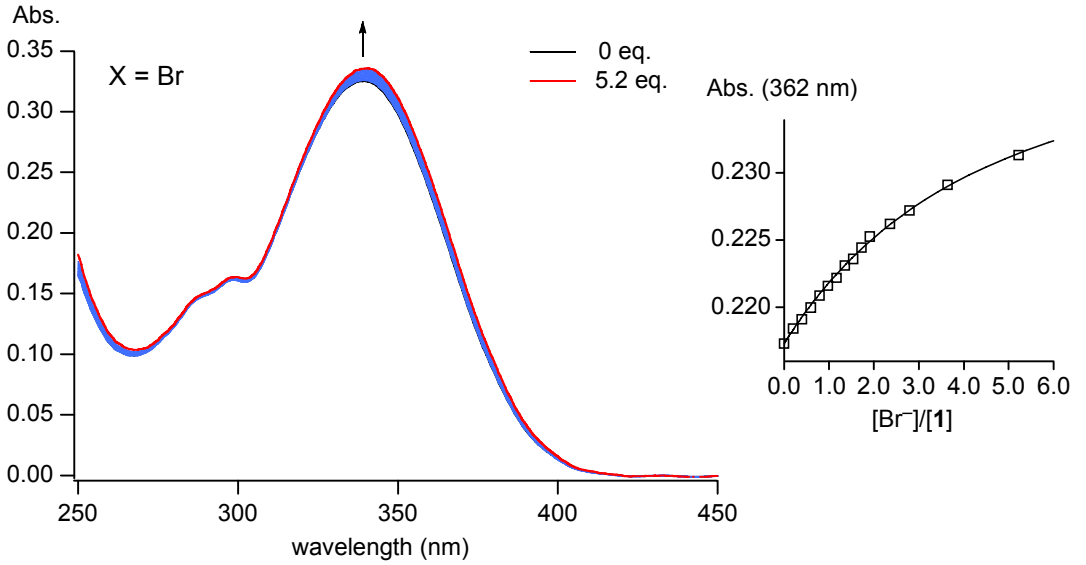


Figure S14. UV-vis spectral changes in **1** on the addition of $^{n}Bu_4N^{+}Br^{-}$. Inset shows the change of the absorption at 362 nm with a calculated curve. ($CHCl_3$: CH_3CN = 4 : 1, [**1**] = 1.0×10^{-5} M)

(12) CD spectroscopic titration of 1 with $^{n}Bu_4N^+Cl^-$ in 4:1 $CHCl_3/CH_3CN$

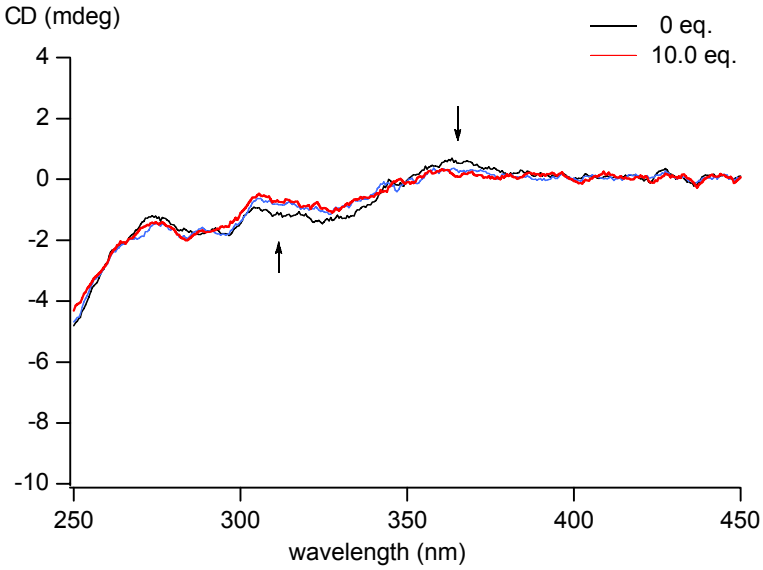


Figure S15. CD spectral changes in **1** on the addition of $^{n}Bu_4N^+Cl^-$. ($CHCl_3$: CH_3CN = 4 : 1, [**1**] = 3.0×10^{-5} M)

(13) UV-vis spectroscopic titration of 1 with $^{n}Bu_4N^+X^-$ (X = Cl, Br, I) in 1:99 H_2O/CH_3CN

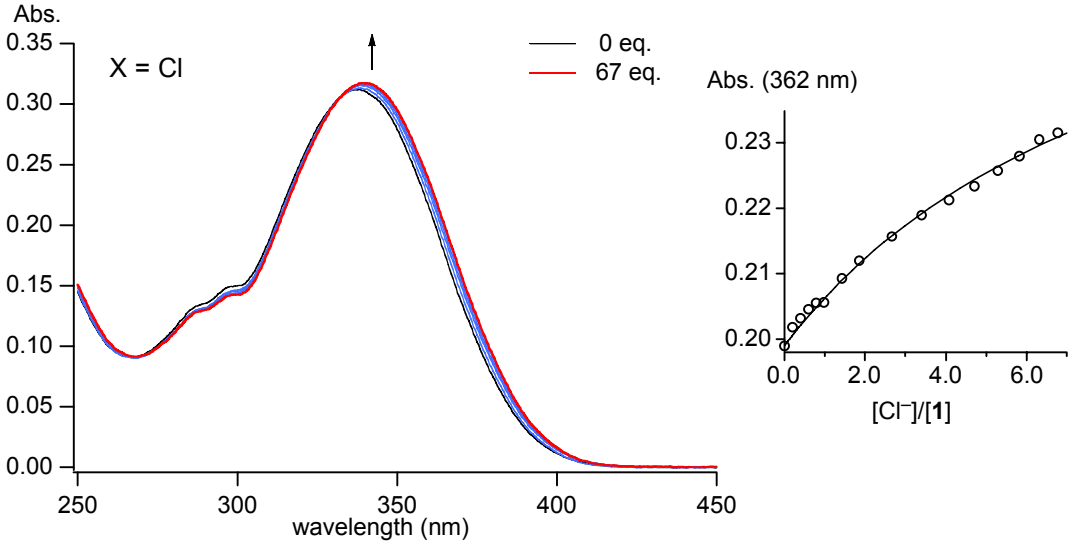


Figure S16. UV-vis spectral changes in **1** on the addition of $^{n}Bu_4N^+Cl^-$. Inset shows the change of the absorption at 362 nm with a calculated curve. (CH_3CN containing 1%water, [**1**] = 1.0×10^{-5} M)

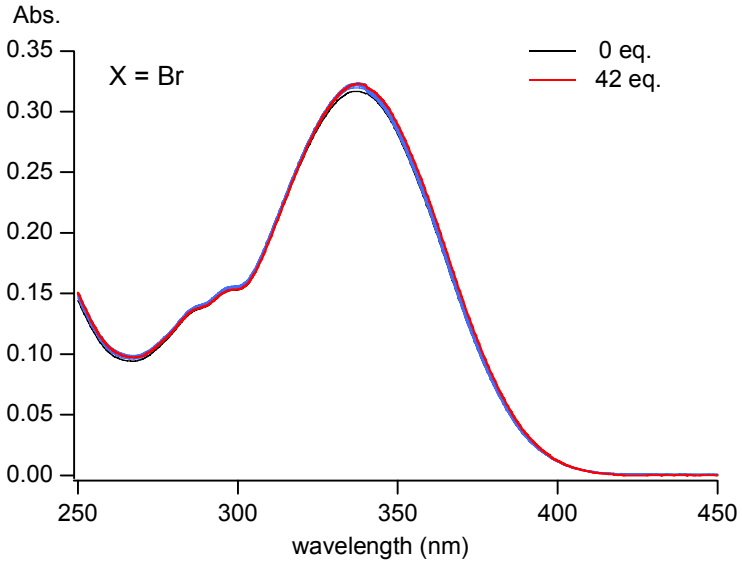


Figure S17. UV-vis spectral changes in **1** on the addition of $^{n}Bu_4N^{+}Br^{-}$. (CH_3CN containing 1%water, [**1**] = 1.0×10^{-5} M)

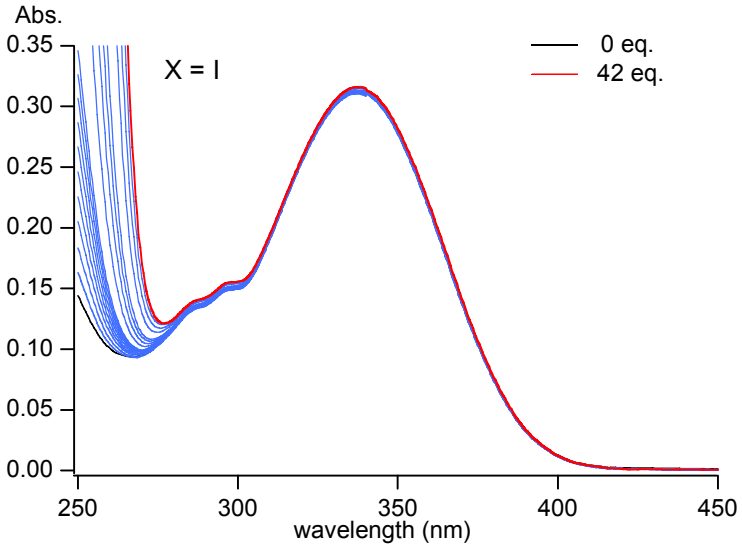


Figure S18. UV-vis spectral changes in **1** on the addition of $^{n}Bu_4N^{+}I^{-}$. (CH_3CN containing 1%water, [**1**] = 1.0×10^{-5} M)

(14) Job's plot for 1·Ca^{2+} with $^{n}Bu_4N^+Cl^-$

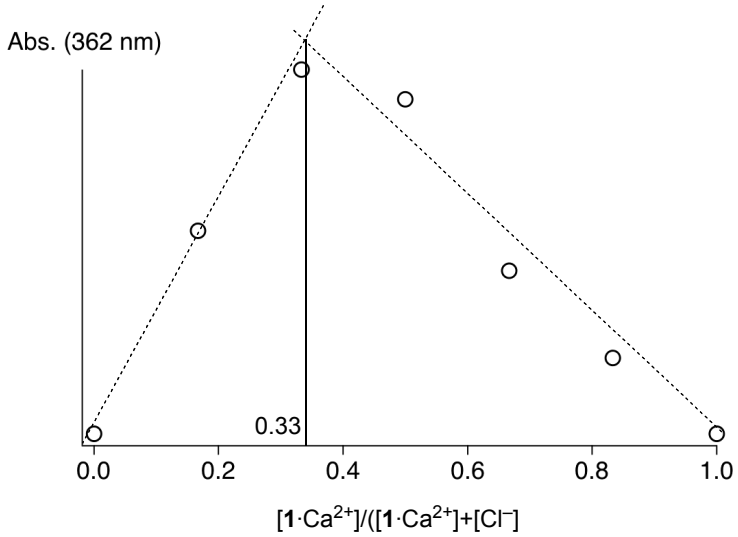


Figure S19. Job plot for the mixture of **1**·Ca^{2+} and Cl^- ($CHCl_3$:CH_3CN = 4:1, [**1**·Ca^{2+}] + [Cl^-] = 1.0×10^{-5} M)

(15) UV-vis spectroscopic titration of 1·Ca^{2+} with $^{n}Bu_4N^+X^-$ (X = Cl, Br) in 4:1 $CHCl_3/CH_3CN$

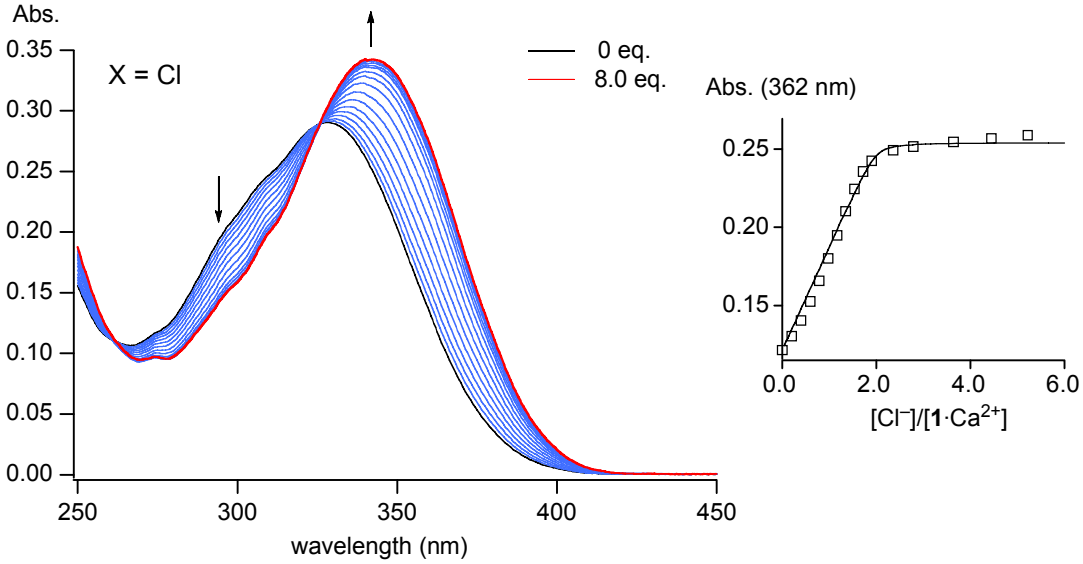


Figure S20. UV-vis spectral changes in **1**·Ca^{2+} on the addition of $^{n}Bu_4N^+Cl^-$. Inset shows the change of the absorption at 362 nm with a calculated curve. ($CHCl_3$: CH_3CN = 4 : 1, [**1**·$Ca(ClO_4)_2$] = 1.0×10^{-5} M)

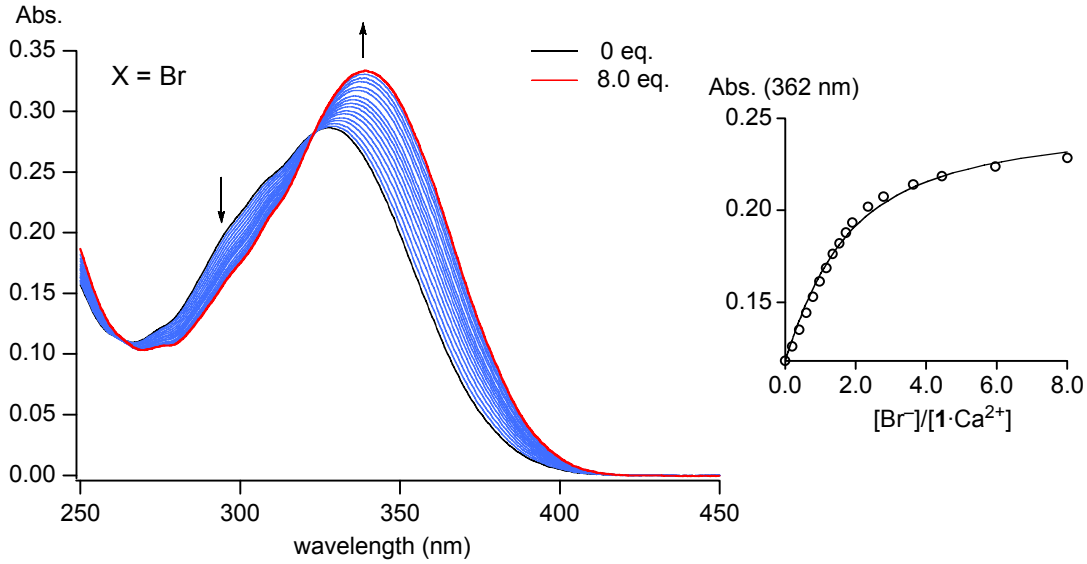


Figure S21. UV-vis spectral changes in $\mathbf{1}\cdot Ca^{2+}$ on the addition of ${}^{n}Bu_4N^{+}Br^{-}$. Inset shows the change of the absorption at 362 nm with a calculated curve. ($CHCl_3$: CH_3CN = 4 : 1, [$\mathbf{1}\cdot Ca(ClO_4)_2$] = 1.0×10^{-5} M)

(17) CD spectroscopic titration of $\mathbf{1}\cdot Ca^{2+}$ with ${}^{n}Bu_4N^{+}Cl^{-}$ in 4:1 $CHCl_3/CH_3CN$

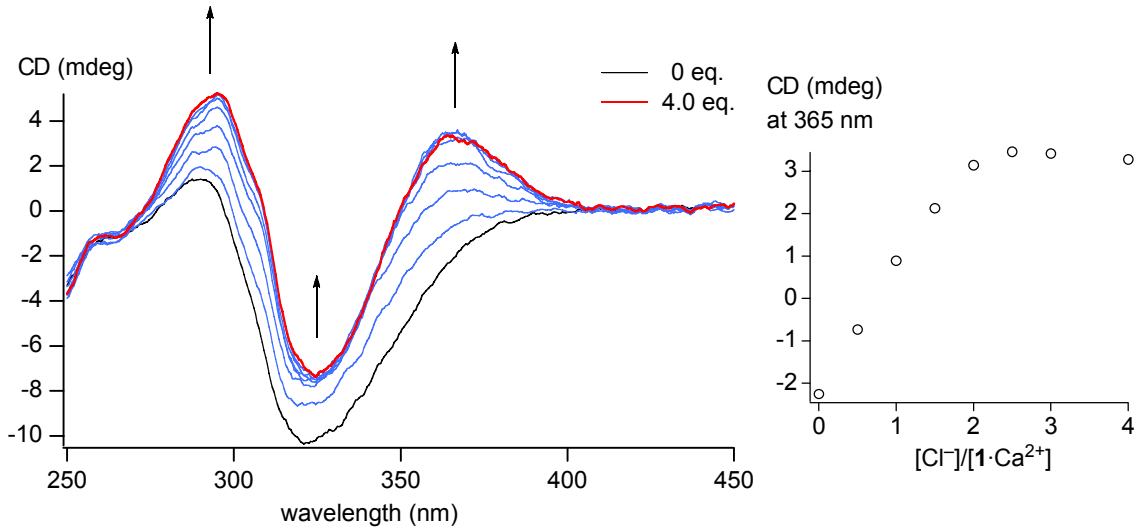


Figure S22. CD spectral changes in $\mathbf{1}\cdot Ca^{2+}$ on the addition of ${}^{n}Bu_4N^{+}Cl^{-}$. ($CHCl_3$: CH_3CN = 4 : 1, [$\mathbf{1}\cdot Ca(ClO_4)_2$] = 3.0×10^{-5} M)

(18) UV-vis spectroscopic titration of 1·Ca^{2+} with $^{n}Bu_4N^+X^-$ (X = Cl, Br, I) in 1:99 H_2O/CH_3CN

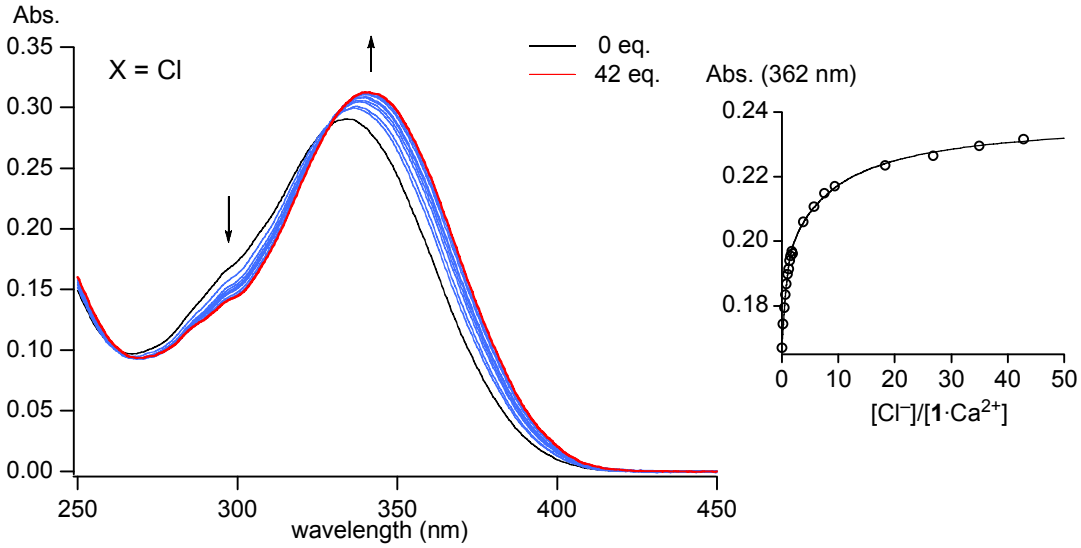


Figure S23. UV-vis spectral changes in **1**·Ca^{2+} on the addition of $^{n}Bu_4N^+Cl^-$. Inset shows the change of the absorption at 362 nm with a calculated curve. (CH_3CN containing 1%water, [**1**·$Ca(ClO_4)_2$] = 1.0×10^{-5} M)

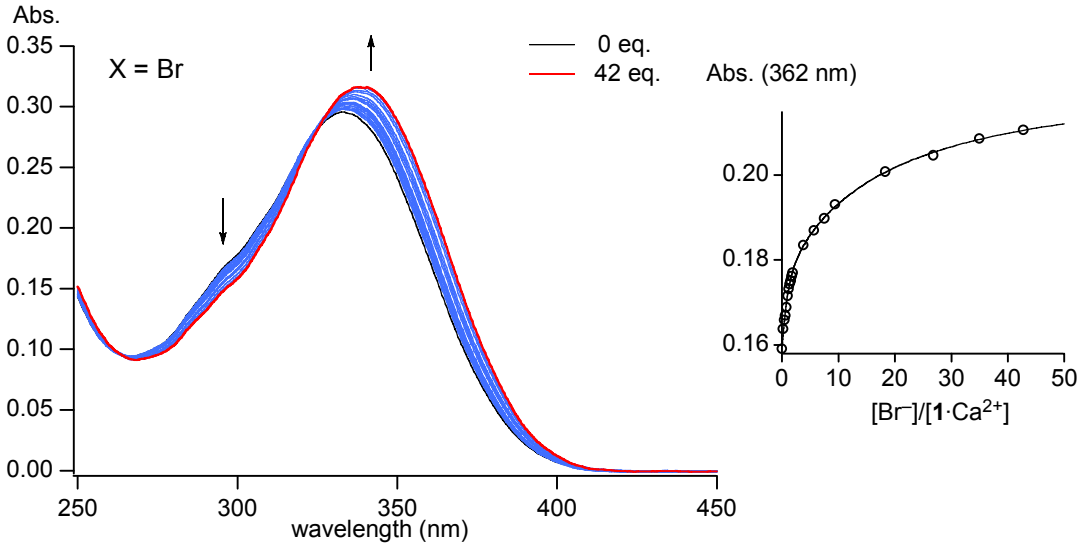


Figure S24. UV-vis spectral changes in **1**·Ca^{2+} on the addition of $^{n}Bu_4N^+Br^-$. Inset shows the change of the absorption at 362 nm with a calculated curve. (CH_3CN containing 1%water, [**1**·$Ca(ClO_4)_2$] = 1.0×10^{-5} M)

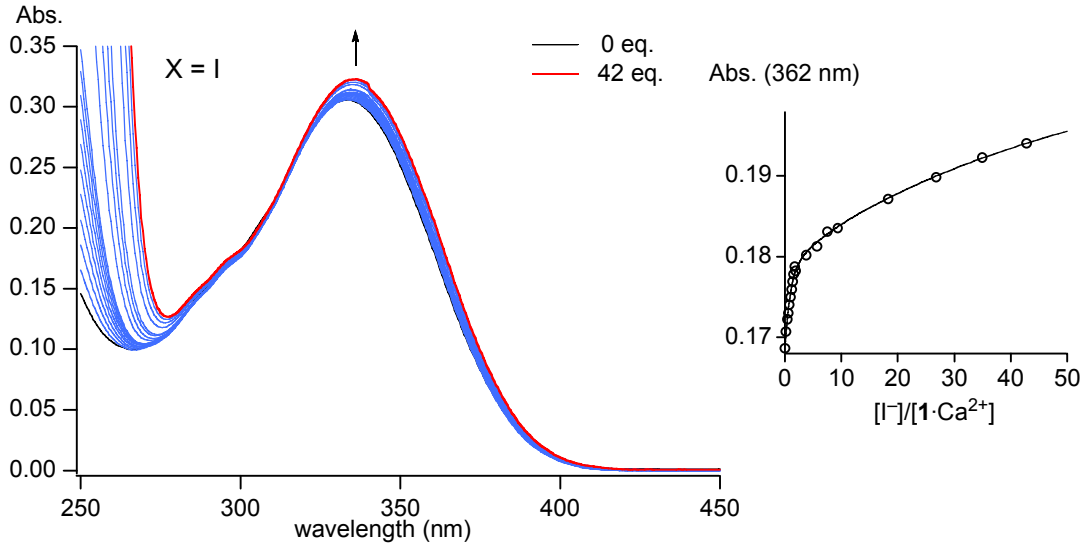


Figure S25. UV-vis spectral changes in **1**·Ca^{2+} on the addition of $^{n}Bu_4N^{+}I^{-}$. Inset shows the change of the absorption at 362 nm with a calculated curve. (CH_3CN containing 1%water, [**1**·$Ca(ClO_4)_2$] = 1.0×10^{-5} M)

(19) ^{1}H NMR spectroscopic titration of 1 with $^{n}Bu_4N^{+}ClO_4^{-}$

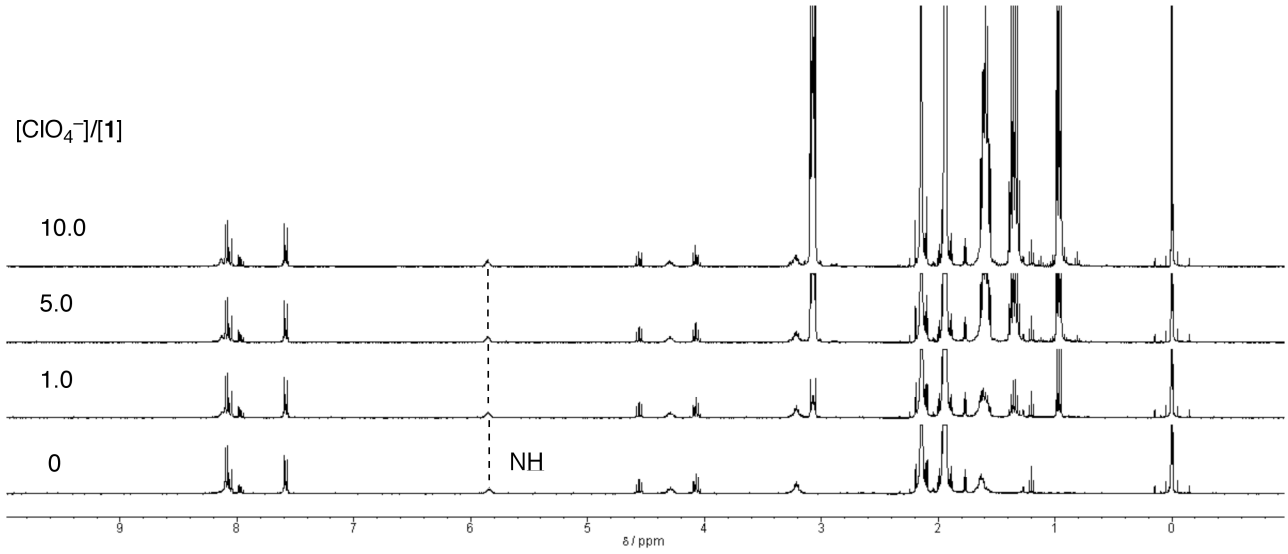


Figure S26. ^{1}H NMR spectral changes in **1** on the addition of $^{n}Bu_4N^{+}ClO_4^{-}$. (CD_3CN, [**1**] = 5.0×10^{-4} M, 400 MHz)

(20) ^{1}H NMR spectroscopic titration of 1·Ca^{2+} with ^{n}Bu$_4$N$^+$ClO$_4^-$

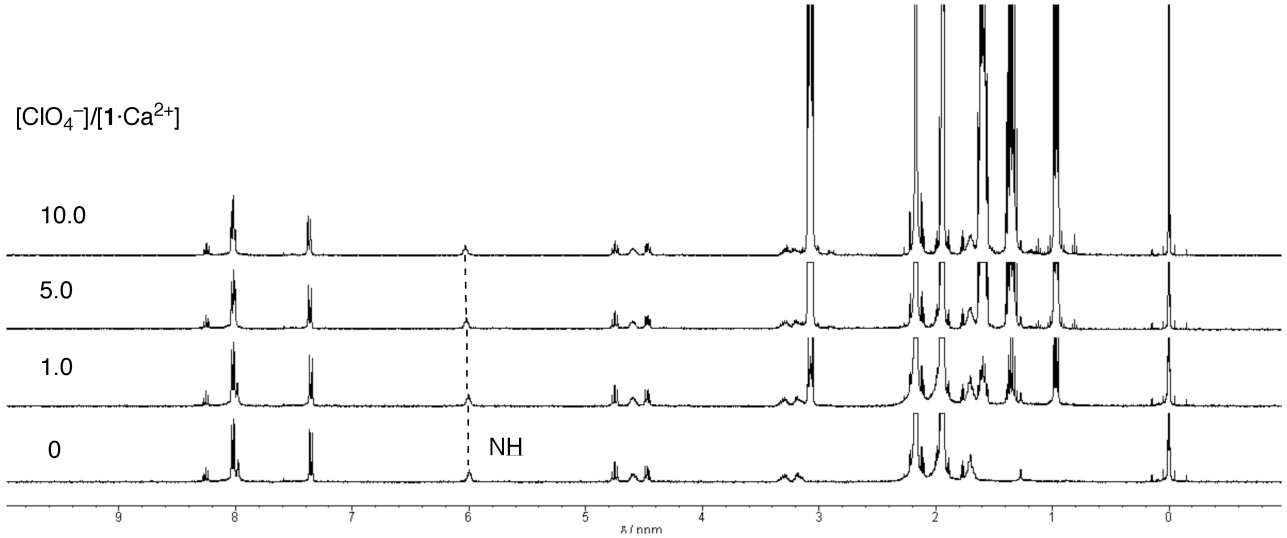


Figure S27. ^{1}H NMR spectral changes in **1**·Ca^{2+} on the addition of ^{n}Bu$_4$N$^+$ClO$_4^-$. (CD_3CN, [**1**·Ca$(ClO_4)_2$] = 5.0 × 10^{-4} M, 400 MHz)

(21) ^{1}H NMR spectroscopic titration of 1·Ca^{2+} with ^{n}Bu$_4$N$^+$Cl$^-$

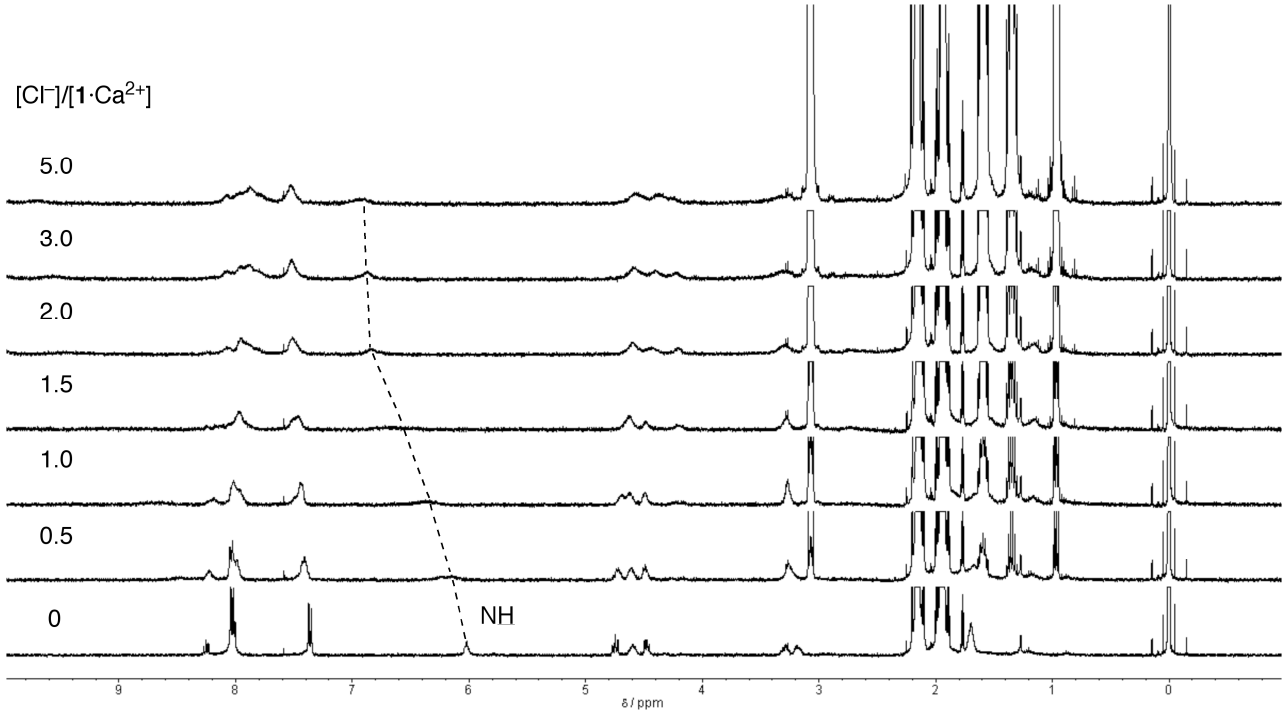


Figure S28. ^{1}H NMR spectral changes in **1**·Ca^{2+} on the addition of ^{n}Bu$_4$N$^+$Cl$^-$. (CD_3CN, [**1**·Ca$(ClO_4)_2$] = 5.0 × 10^{-4} M, 400 MHz)

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