Electronic Supplemental Information for

Highly soluble bisurea derivatives for anion recognition

Tsubasa Mimuro,[†] Akihiro Yoshida[‡], Kazuyuki Kamo,[‡] Manabu Hirasawa,[‡] and Shin-ichi Kondo[†*]

[†]*Department of Chemistry, Faculty of Science, Yamagata University, Yamagata 990-8560, Japan*

[‡]*Institute for Advanced Integrated Technology, Resonac Co., 48 Wadai, Tsukuba, Ibaraki, 300-4247, Japan*

E-mail address: kondo@sci.kj.yamagata-u.ac.jp

Contents

General

All reagents used were of analytical grade. NMR spectra were measured on a JEOL ECA-500 (500 MHz) spectrometer. UV-vis spectra were recorded on a Shimadzu UV-2500PC spectrometer with a thermal regulator (± 0.5 ºC). HRMS were measure on JEOL JMS-T100LP and Agilent 1260Prime LC/6224 TOF systems. Column chromatography was performed by using Silica Gel 60N from Kanto Reagents. Melting points were determined with a Yanaco MP-J3 micro melting point apparatus and are uncorrected.

1,2-Bis(2-(3-butylureido)phenoxy)ethane (2a)

A mixture of 1,2-bis(2-aminophenoxy)ethane[1, 2] (148 mg, 0.606 mmol) and butyl isocyanate (132 mg, 2.2 eq) in EtOH (5 mL) was refluxed under argon atmosphere overnight. After cooled to r.t., the produced precipitates were collected by suction to give the product as colorless crystals (216 mg, 81%). M.p. 197–200 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, 2H, J_1 = 7.2 Hz, J_2 = 2.0 Hz), 7.0-6.98 (m, 4H), 6.94-9.62 (m, 2H), 6.91 (s, 2H), 5.51 (s, 2H), 4.31(s, 4H), 3.20 (q, 4H, J = 7.4 Hz), 1.47 (quint, 4H, J = 7.4 Hz), 1.32 (sext, 4H, J = 7.4 Hz), 0.89 (t, 6H, J = 7.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 148.5, 129.6, 123.5, 122.4, 121.9, 113.6, 68.2, 40.1, 32.1, 20.0, 13.8. HRMS (DART, positive mode) Calcd for $C_{24}H_{35}N_4O_4$ $[M+H]^+$, 443.2653. Found 443.2654.

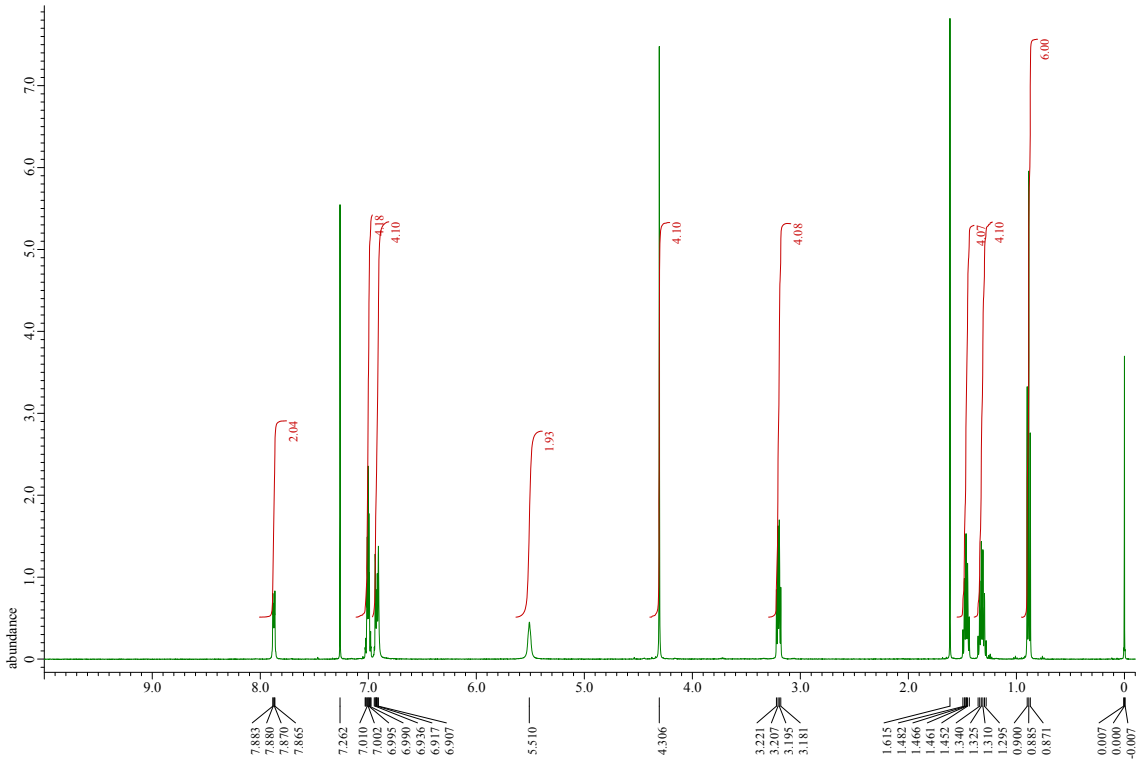

Fig. S1. ^{1}H NMR spectrum (500 MHz) of **2a** in $CDCl_3$.

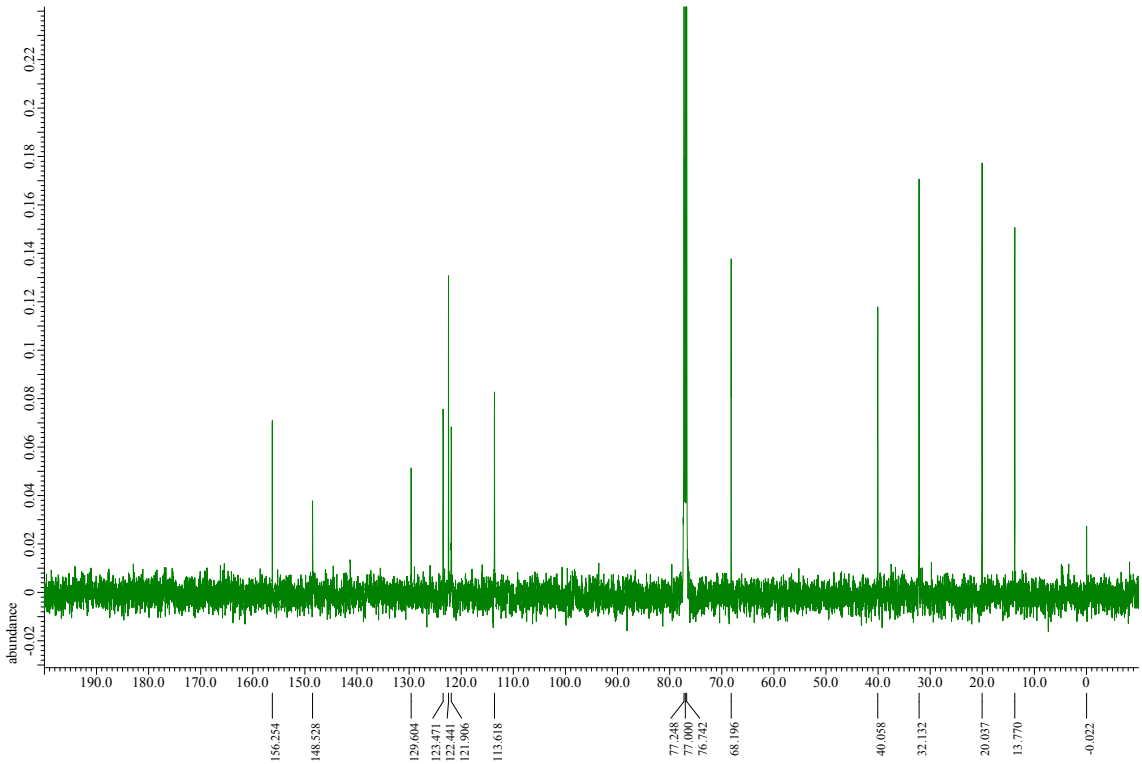

Fig. S2. ^{13}C NMR spectrum (126 MHz) of **2a** in $CDCl_3$.

1,2-Bis(2-(3-(1,1-dimethylethyl)ureido)phenoxy)ethane (**2b**)

A mixture of 1,2-bis(2-aminophenoxy)ethane[1, 2] (321 mg, 1.31 mmol) and *tert*-butyl isocyanate (290 mg, 2.2 eq) in EtOH (7 mL) was refluxed under argon atmosphere overnight. The mixture was evaporated under reduced pressure. The residue was recrystallized from MeOH/$CHCl_3$ to give the product as colorless crystals. (443 mg, 76%). M.p. 189–192 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, 2H, J_1 = 7.2 Hz, J_2 = 2.6 Hz), 6.99-6.90 (m, 6H), 6.86 (s, 2H), 5.31 (s, 2H), 4.30 (s, 4H), 1.34 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 148.1, 130.1, 122.9, 122.5, 121.4, 113.9, 68.5, 50.6, 29.2. HRMS (ASAP, positive mode) Calcd for $C_{24}H_{35}N_4O_4$ $[M+H]^+$, 443.2653. Found 443.2650.

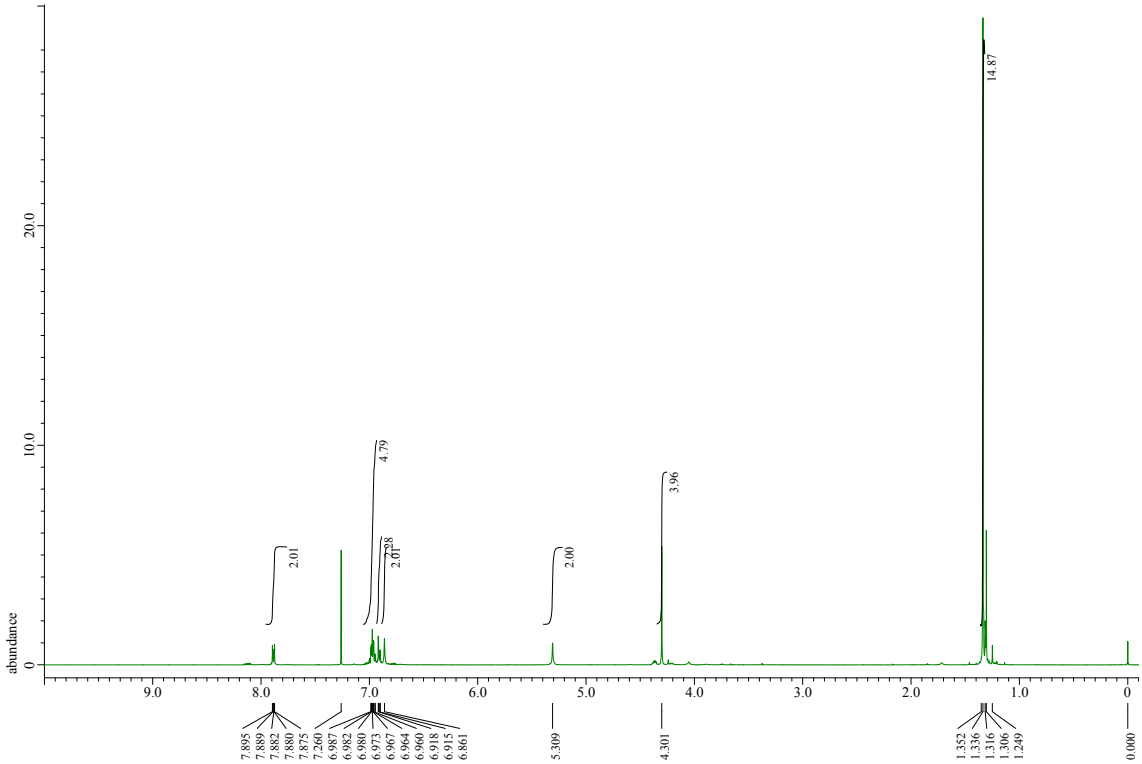

Fig. S3. ^{1}H NMR spectrum (500 MHz) of **2b** in $CDCl_3$.

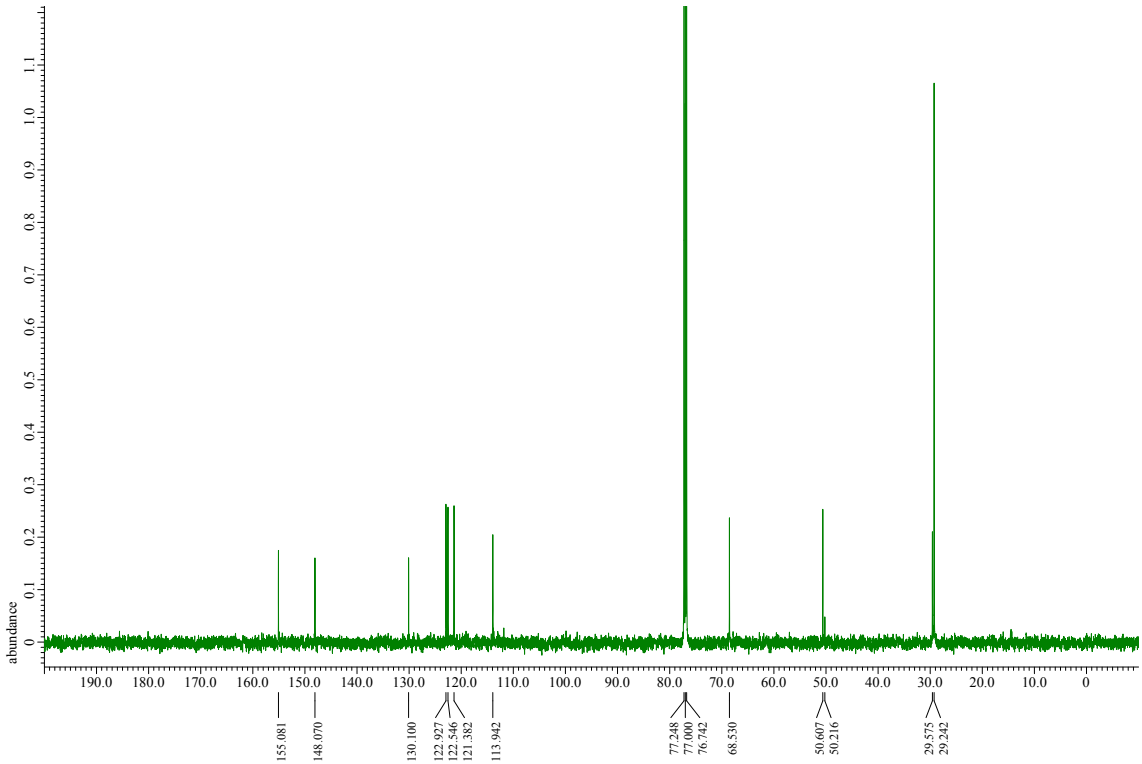

Fig. S4. ^{13}C NMR spectrum (126 MHz) of **2b** in $CDCl_3$.

1,2-Bis(2-(3-phenylureido)phenoxy)ethane (2c)

Into an ethanol solution of previously prepared 1,2-bis(2-aminophenoxy)ethane[1, 2] 304 mg (1.24 mmol), a solution of phenyl isocyanate 326 mg (2.74 mmol, 2.2 eq.) in ethanol (1 mL) was dropwised and the resulting mixture was refluxed for 1 h under argon atmosphere. After evaporation of the mixture under reduced pressure, the residue was recrystallized from toluene to give the product as colorless solids (496 mg, 83%). Mp. 230.0–231.0 °C.

^{1}H NMR (500 MHz, CD_3CN) δ 9.29 (s, 2H), 8.13 (dd, 2H, J_1 = 8.0, J_2 = 1.8 Hz), 8.11 (s, 2H), 7.43 (dd, 4H, J_1 = 8.6, J_2 = 1.2 Hz), 7.43 (dd, 4H, J_1 = 8.6, J_2 = 7.6 Hz), 7.13 (dd, 2H, J_1 = 7.8, J_2 = 1.2 Hz), 6.96 (dt, 2H, J_1 = 7.8, J_2 = 1.8 Hz), 6.94 (dt, 2H, J_1 = 7.6, J_2 = 1.2 Hz), 6.92 (dt, 2H, J_1 = 8.0, J_2 = 1.2 Hz), 4.50 (s, 4H). ^{13}C NMR (126 MHz, CD_3CN) δ 152.5, 146.9, 139.7, 129.0, 128.8, 122.0, 121.9, 121.1, 119.0, 118.2, 112.3, 67.5. HRMS (DART, positive mode) Calcd for $C_{28}H_{27}N_4O_4$ $[M+H]^+$, 483.2027. Found 483.2018.

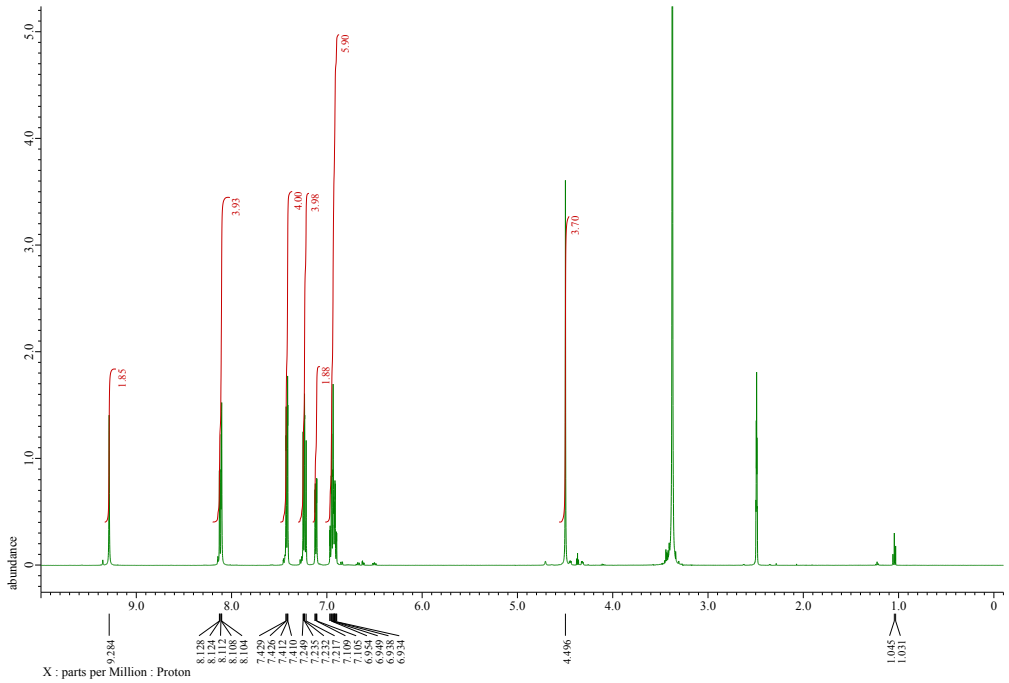

Fig. S5. ^{1}H NMR spectrum (500 MHz) of **2c** in $CDCl_3$.

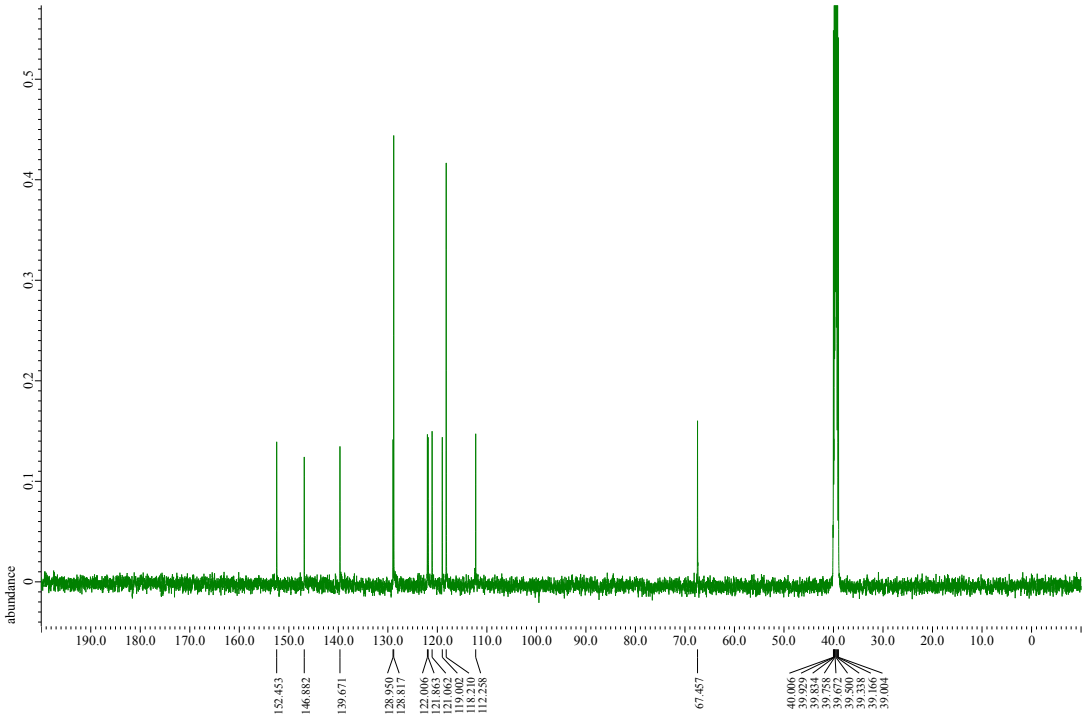

Fig. S6. ^{13}C NMR spectrum (126 MHz) of **2c** in $CDCl_3$.

a) Hammond, P. J.; Bell, A. P.; Hall, C. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 707-715.

1,2-Bis(2-(3-butylureido)ethoxy)ethane (3a)

A mixture of 1,2-bis(2-aminoethoxy)ethane (500 mg, 3.37 mmol) and butyl isocyanate (735 mg, 2.2 eq) in dry THF (5 mL) was refluxed under argon atmosphere overnight. The mixture was evaporated under reduced pressure. The residue was recrystallized from AcOEt to give colorless fiber-like solids as the product. (1.11 g, 95%). M.p. 127.5–128.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 2H), 5.17 (s, 2H), 3.62 (s. 4H), 3.58 (t, 4H, J = 5.2 Hz), 3.35 (q, 4H, J = 5.2 Hz), 3.17 (q, 4H, J = 6.9 Hz), 1.47 (quint, 4H, J = 7.4 Hz), 1.35 (sext, 4H, J = 7.4 Hz), 0.92 (t, 6H, J = 7.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 70.7, 70.3, 40.5, 40.1, 32.4, 20.1, 13.8. HRMS (ASAP, positive mode) Calcd for $C_{16}H_{35}N_4O_4$ $[M+H]^+$, 347.2653. Found 347.2649.

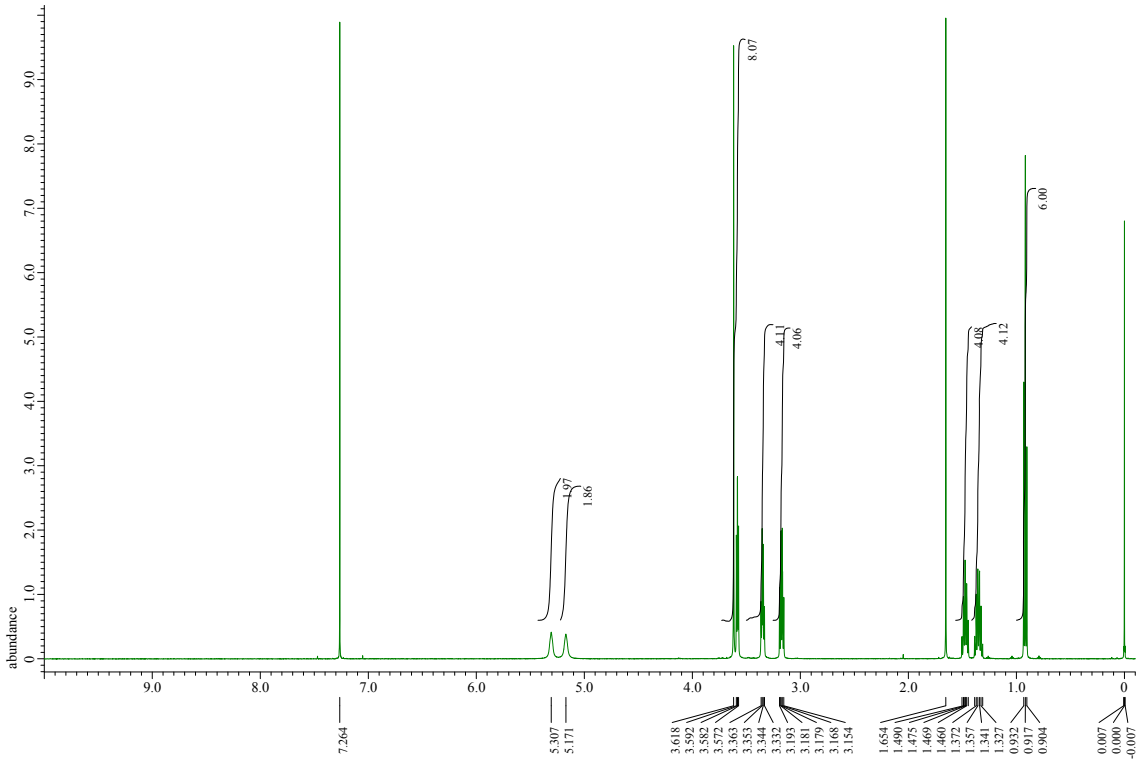

Fig. S7. ^{1}H NMR spectrum (500 MHz) of **3a** in $CDCl_3$.

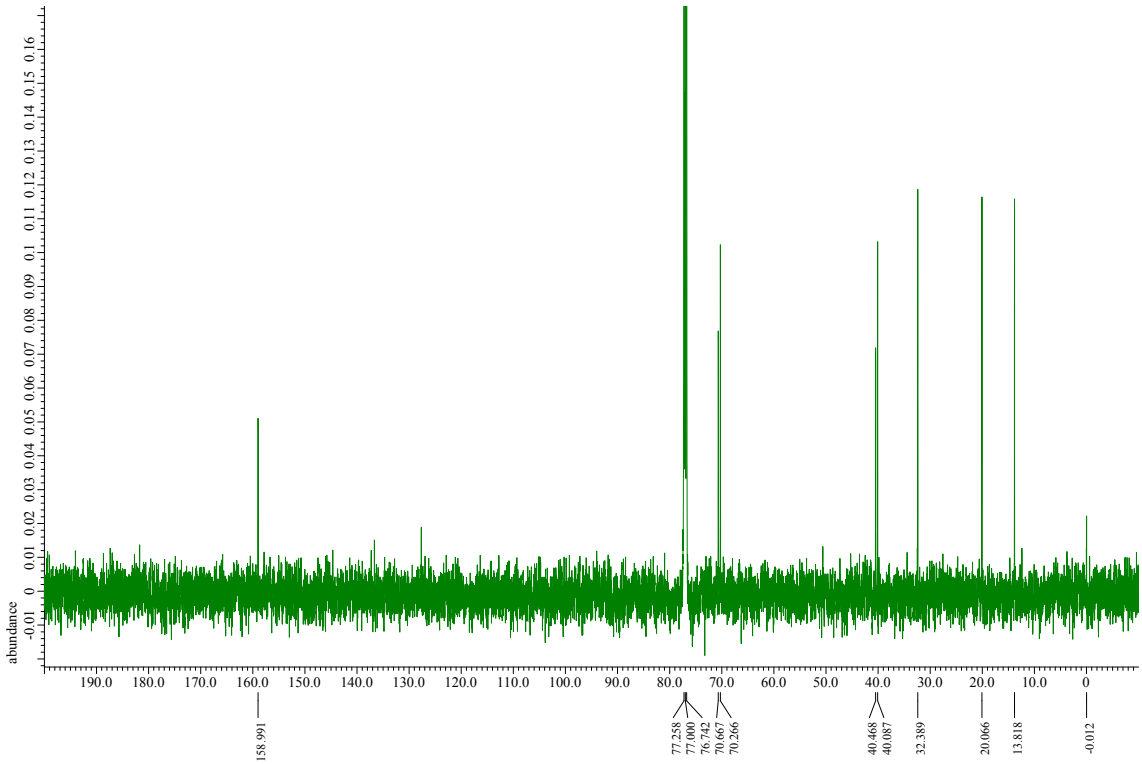

Fig. S8. ^{13}C NMR spectrum (126 MHz) of **3a** in $CDCl_3$.

1,2-Bis(2-(3-(1,1-dimethylethyl)ureido)ethoxy)ethane (3b)

A mixture of 1,2-bis(2-aminoethoxy)ethane (500 mg, 3.37 mmol) and *tert*-butyl isocyanate (735 mg, 2.2 eq) in dry THF (6 mL) was refluxed under argon atmosphere overnight. The mixture was cooled to 0 °C to give colorless solids as the product. (804 mg, 69%). M.p. 151–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (s, 2H), 5.15 (s, 2H), 3.75 (s, 4H), 3.56 (t, 4H, J = 4.6 Hz), 3.31 (q, 4H, J = 4.6 Hz), 1.33 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2, 70.8, 70.2, 50.1, 40.0, 29.5. HRMS (ASAP, positive mode) Calcd for $C_{16}H_{35}N_4O_4$ $[M+H]^+$, 347.2653. Found 347.2649.

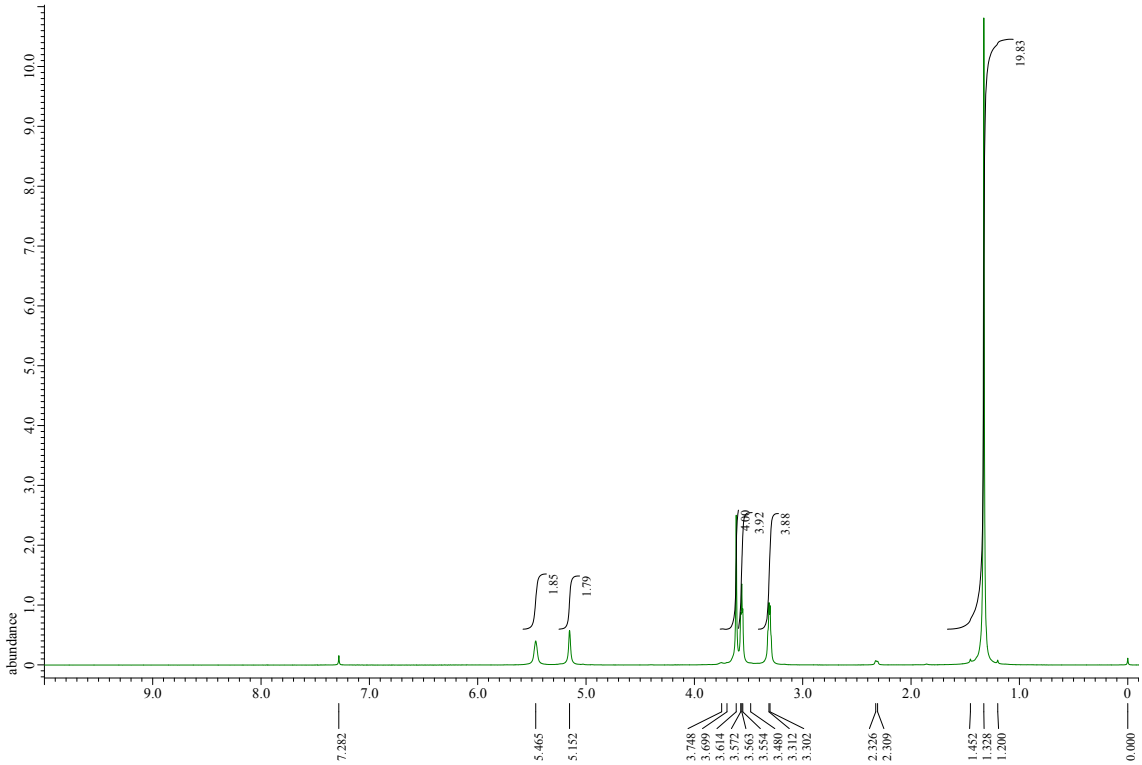

Fig. S9. ^{1}H NMR spectrum (500 MHz) of **3b** in $CDCl_3$.

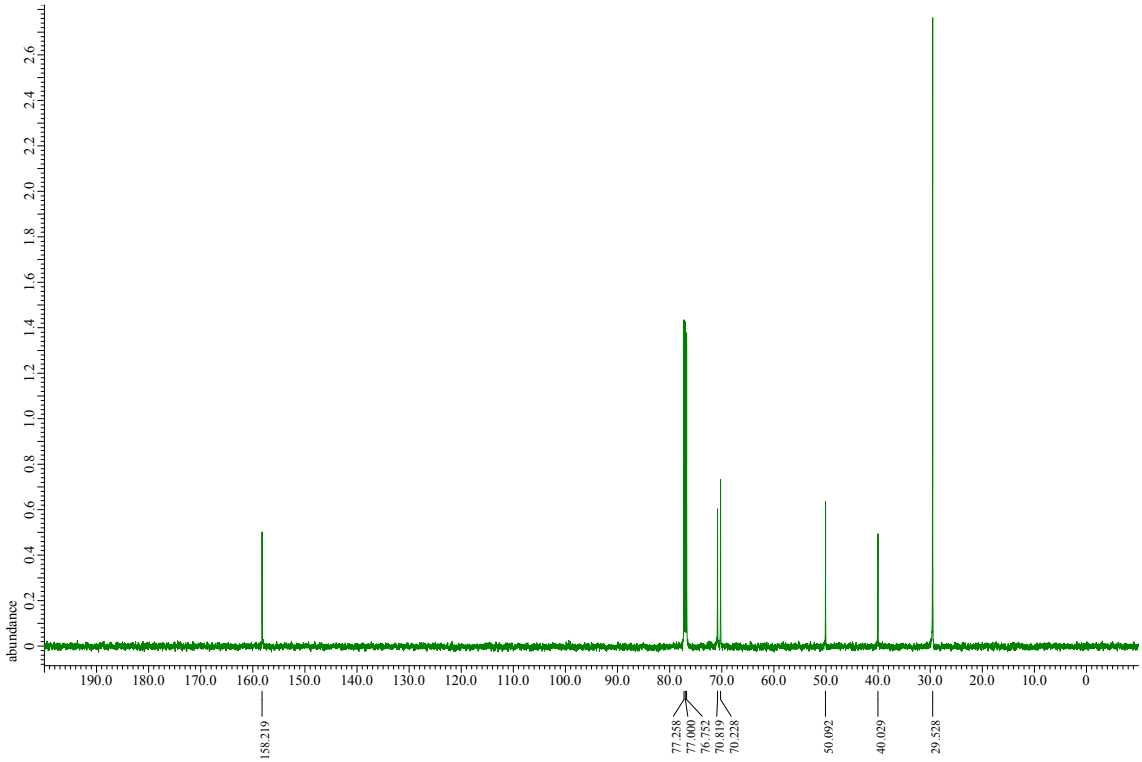

Fig. S10. ^{13}C NMR spectrum (126 MHz) of **3b** in $CDCl_3$.

1,2-Bis(2-(3-phenylureido)ethoxy)ethane (**3c**)

A mixture of 1,2-bis(2-aminoethoxy)ethane 1.01 g (6.82 mmol) and phenyl isocyanate 1.77 g (14.9 mmol, 2.2 eq) in dry THF (10 mL) was refluxed under argon atmosphere for 1 h. The mixture was evaporated under reduced pressure and the residue was recrystallized from ethyl acetate giving colorless solids as the product. (2.51 g, 95%). Mp. 130.0–130.5 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.33 (d, 4H, J = 7.5 Hz), 7.23 (t, 4H, J = 7.5 Hz), 6.99 (t, 2H, J = 7.5 Hz), 5.64 (bs, 2H), 3.63 (s, 4H), 3.58 (t, 4H, J = 5.2 Hz), 3.39 (t, 4H, J = 5.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 139.0, 129.0, 122.9, 119.9, 70.6, 70.2, 40.3. HRMS (DART, positive mode) Calcd for $C_{20}H_{27}N_4O_4$ $[M+H]^+$, 387.2027. Found 387.2022.

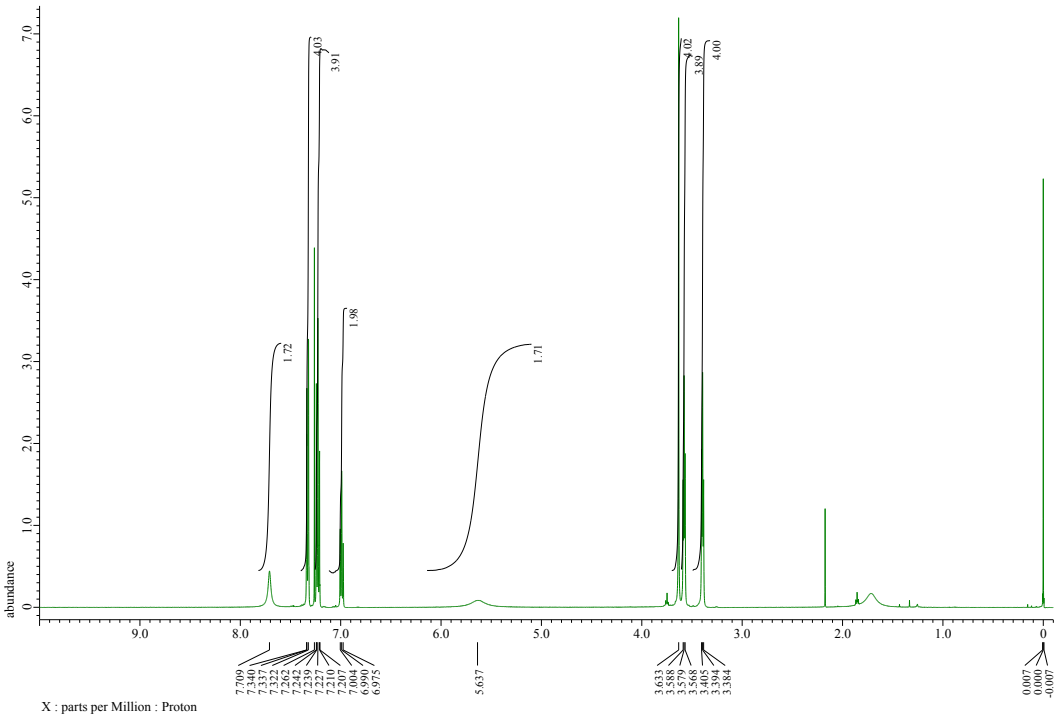

Fig. S11. ^{1}H NMR spectrum (500 MHz) of **3c** in $CDCl_3$.

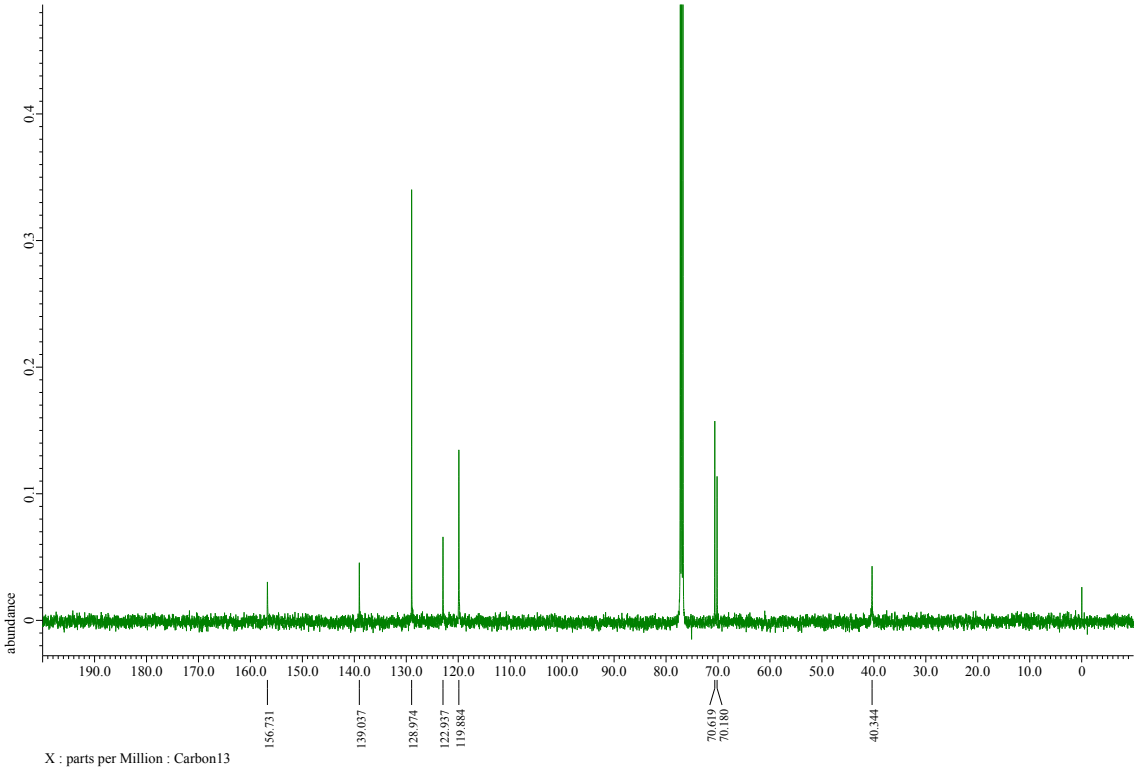

Fig. S12. ^{13}C NMR spectrum (126 MHz) of **3c** in $CDCl_3$.

Preparation of saturation solutions of receptors

A distilled solvent (MeCN, $CHCl_3$, 2-butanone, toluene) was added to an excess receptor and the suspension was stirred overnight at 25 °C. After centrifugation for 30 min, the supernatant was filtered to give the saturated solution.

Determination of the saturated concentrations of the receptors by UV-vis spectroscopy

To acetonitrile (3 mL) in a cuvette, 1.0×10^{-3} mol dm^{-3} of a receptor in MeCN was added via syringe and the UV-vis spectrum was measured. The procedure was repeated four times, then the molar absorption coefficient was determined from the absorbances and the concentrations. To acetonitrile (3 mL) in another cuvette, an appropriate volume of saturated solutions of the receptors was added via syringe and the UV-vis spectrum was measured. The saturation concentration was calculated from the absorbance of the diluted solution and the molar absorption coefficient.

Determination of the saturated concentrations of the receptors by ^{1}H NMR

The saturated solution of the receptor (80 μL) was added via syringe to an NMR tube. The solution was evaporated under reduced pressure. A solution of naphthalene (1.6×10^{-3} mol dm^{-3}) in $CDCl_3$ or DMSO-d_6 (600 μL) was added to the NMR tube and the NMR spectrum was measured. From the integrations of the receptors and the naphthalene, the saturation concentrations of the receptors were calculated.

Determination of the association constants by UV-vis titrations

All titration experiments were carried out with receptors solution (3 mL) in a quartz cell at 25 ± 0.5 ºC, and UV-vis spectra were recorded upon the addition of aliquots of a stock solution of appropriate guest anions with a microsyringe. Titration data in the appropriate wavelength range were analyzed with BindFit[3]. The titration experiments were at least duplicated independently and the mean value and the standard deviation were reported.

Determination of the association constants by ^{1}H NMR titrations

A stock solution of receptors in MeCN-d_3 ([receptor] = 1.0×10^{-2} mol dm^{-3}) was prepared. Into a NMR tube, 500 mL of the stock solution was placed and a NMR spectrum of the solution was measured. An aliquot of a stock solution of guest as tetrabutylammonium salts in MeCN-d_3 containing same receptor (1.0×10^{-2} mol dm^{-3}) was added to the NMR tube and a NMR was recorded, repeatedly. Titration data in the appropriate wavelength range were analyzed with BindFit[3]. The titration experiments were at least duplicated independently and the mean value and the standard deviation were reported.

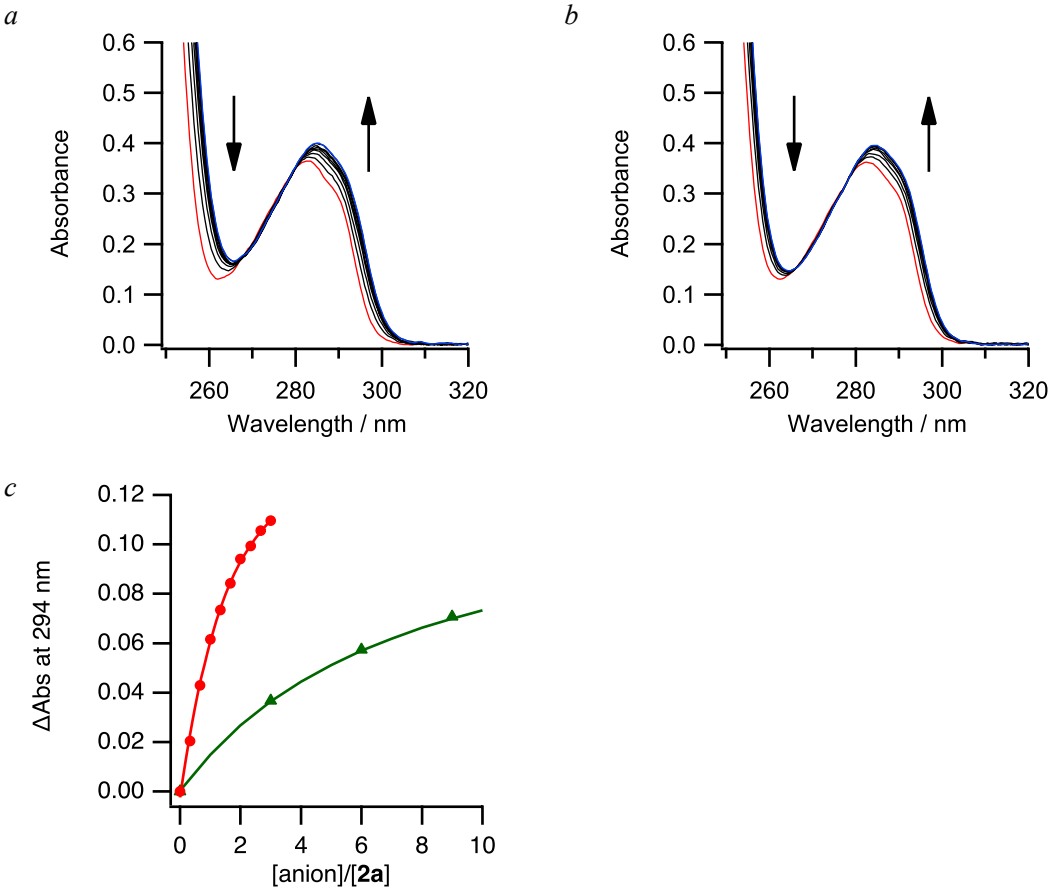

Fig. S13. UV-vis spectral titrations of **2a** with (*a*) AcO^- and (*b*) Cl^- in MeCN at 298 K. UV-vis spectral changes of **2a** at 294 nm upon the addition of AcO^- (●) and Cl^- (▲) (*c*). [**2a**] = 5.0×10^{-5} mol dm^{-3}.

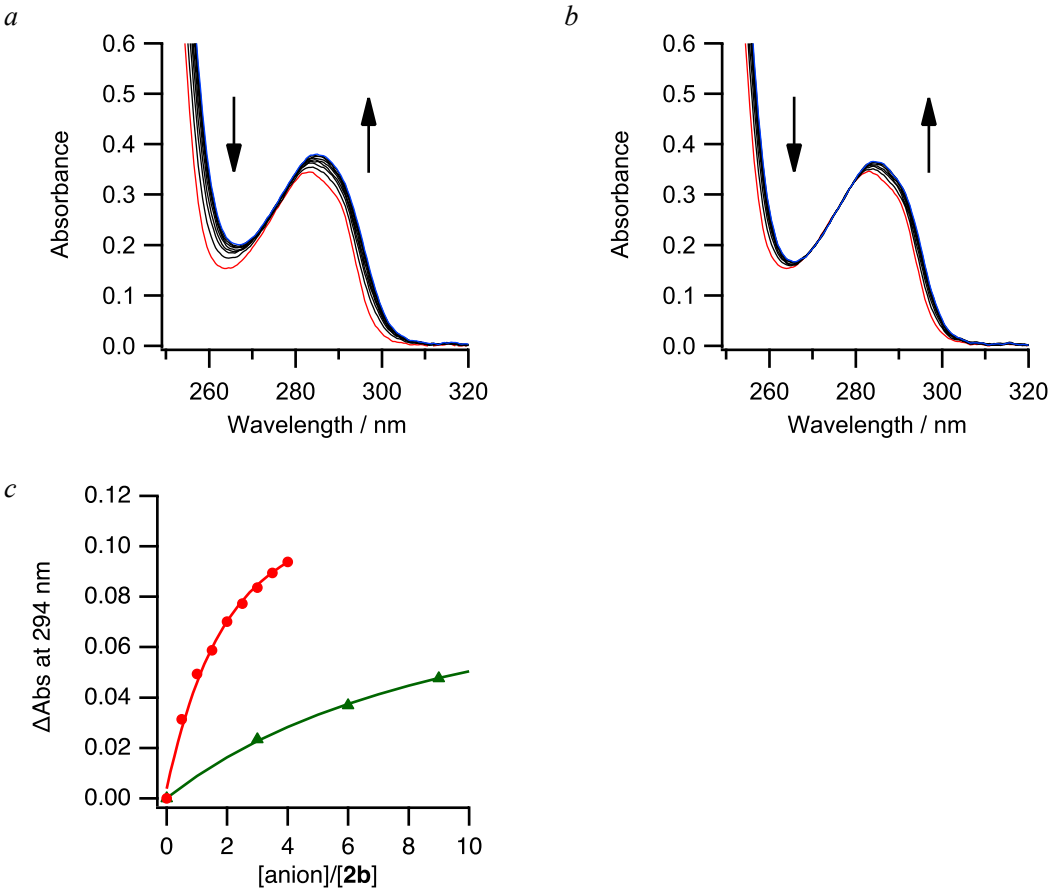

Fig. S14. UV-vis spectral titrations of **2b** with (*a*) AcO^- and (*b*) Cl^- in MeCN at 298 K. UV-vis spectral changes of **2b** at 294 nm upon the addition of AcO^- (●) and Cl^- (▲) (*c*). [**2b**] = 5.0×10^{-5} mol dm^{-3}.

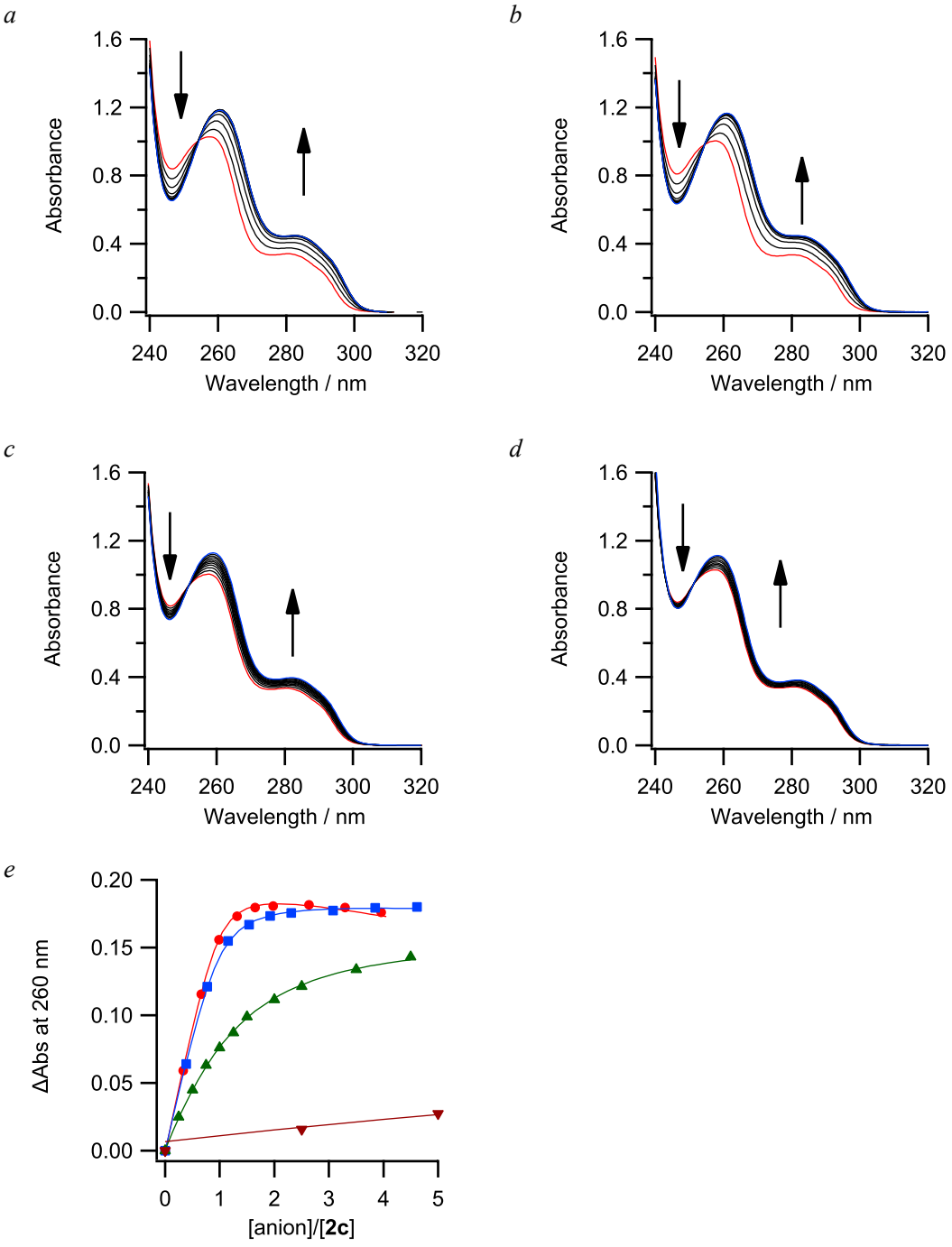

Fig. S15. UV-vis spectral titrations of **2c** with (*a*) AcO^-, (*b*) $H_2PO_4^-$, (*b*) Cl^-, and (*d*) Br^- in MeCN at 298 K. UV-vis spectral changes of **2c** at 260 nm upon the addition of AcO^- (●) $H_2PO_4^-$ (■), Cl^- (▲), and Br^- (▼) (*c*). [**2c**] = 2.0×10^{-5} mol dm^{-3}.

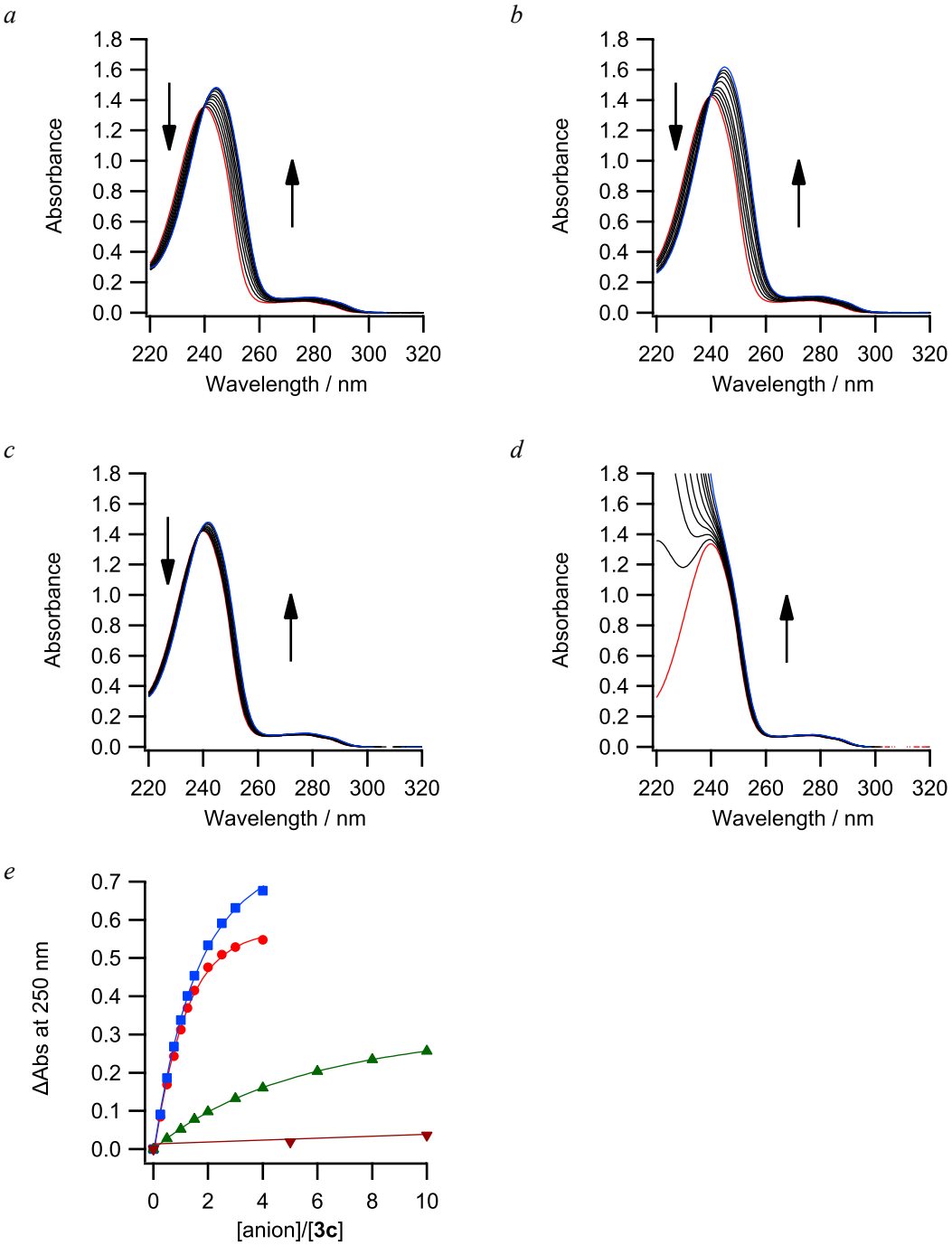

Fig. S16. UV-vis spectral titrations of **3c** with (*a*) AcO^-, (*b*) $H_2PO_4^-$, (*b*) Cl^-, and (*d*) Br^- in MeCN at 298 K. UV-vis spectral changes of **3c** at 250 nm upon the addition of AcO^- (●) $H_2PO_4^-$ (■), Cl^- (▲), and Br^- (▼) (*c*). [**3c**] = 4.0×10^{-5} mol dm^{-3}.

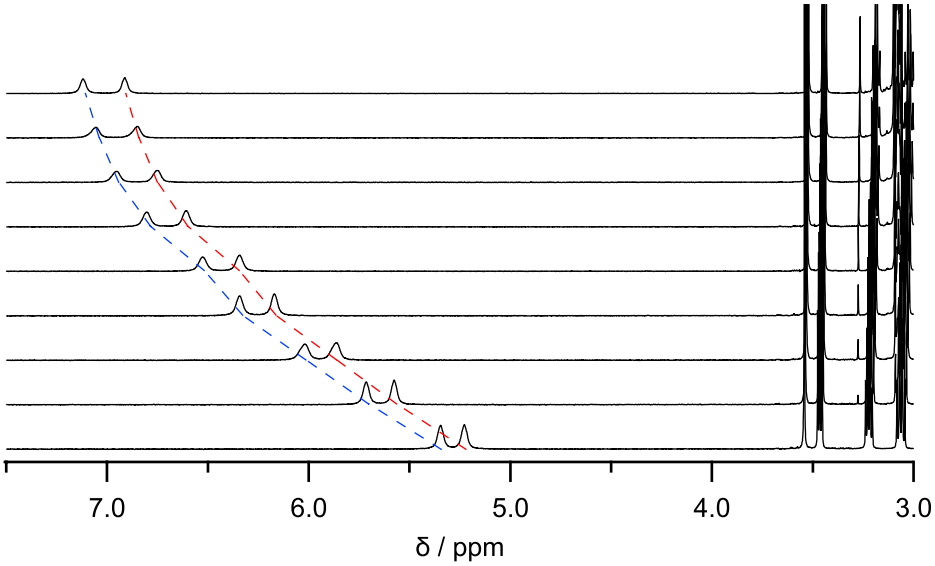

Fig. S17. ^{1}H NMR spectral change and chemical sift changes of receptor **3a** upon the addition of AcO^{-} (0-3.0 eq. for receptor) in MeCN-d_3 at 298 K. [**3a**] = 1.0×10^{-2} mol dm^{-3}.

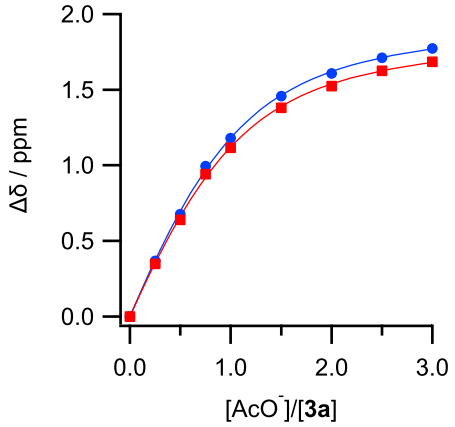

Fig. S18. The chemical shift changes of NH protons of **3a** upon the addition of AcO^{-} (0-3.0 eq. for receptor) in MeCN-d_3 at 298 K. [**3a**] = 1.0×10^{-2} mol dm^{-3}.

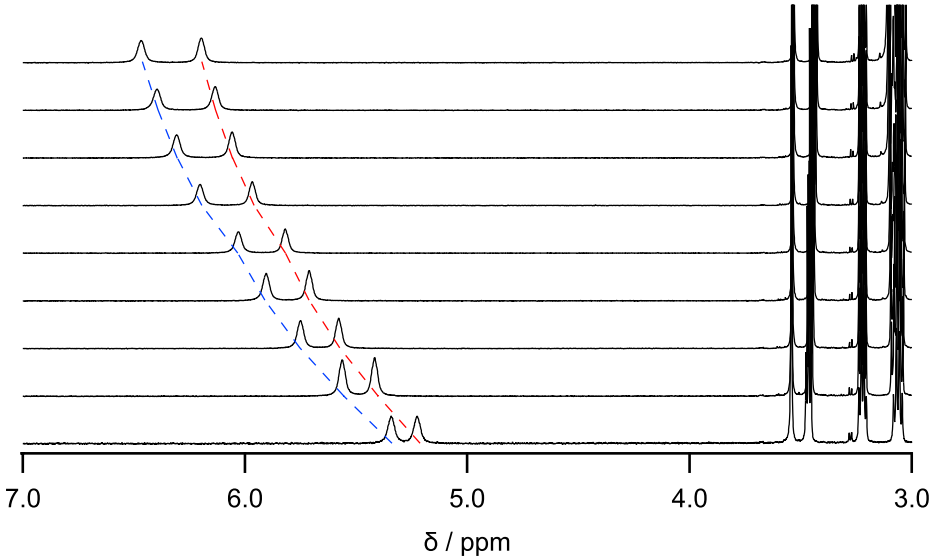

Fig. S19. ^{1}H NMR spectral change and chemical sift changes of receptor **3a** upon the addition of Cl^{-} (0-3.0 eq. for receptor) in MeCN-d_3 at 298 K. [**3a**] = 1.0×10^{-2} mol dm^{-3}.

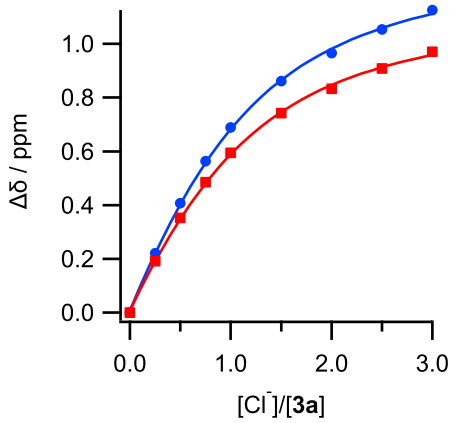

Fig. S20. The chemical shift changes of NH protons of **3a** upon the addition of Cl^{-} (0-3.0 eq. for receptor) in MeCN-d_3 at 298 K. [**3a**] = 1.0×10^{-2} mol dm^{-3}.

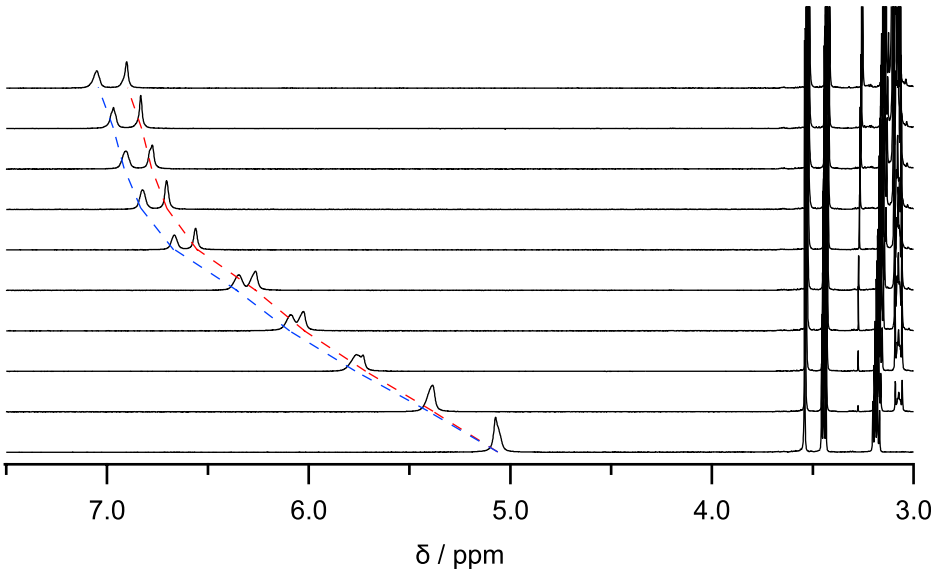

Fig. S21. ^{1}H NMR spectral change and chemical sift changes of receptor **3b** upon the addition of AcO^{-} (0-3.33 eq. for receptor) in MeCN-d_3 at 298 K. [**3b**] = 1.0×10^{-2} mol dm^{-3}.

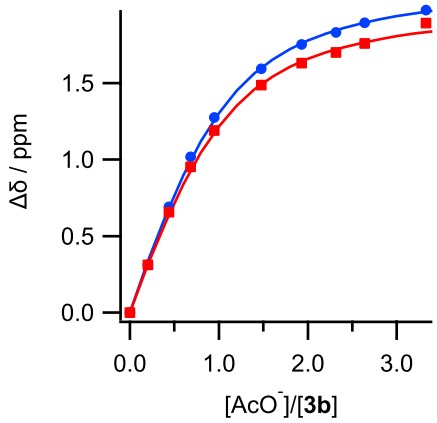

Fig. S22. The chemical shift changes of NH protons of **3b** upon the addition of AcO^{-} (0-3.33 eq. for receptor) in MeCN-d_3 at 298 K. [**3b**] = 1.0×10^{-2} mol dm^{-3}.

References

1. M. Zühlke, S. Sass, D. Riebe, T. Beitz and H. G. Löhmannsröben, *ChemPlusChem*, 2017, **82**, 1266-1273.
2. A. A. Contractor and E. W. Miller, *Biochemistry*, 2018, **57**, 237-240.
3. D. B. Hibbert and P. Thordarson, *Chem. Commun.*, 2016, **52**, 12792-12805.