Synthesis, characterization and X-ray crystal structures of cyclam derivatives. 7. Hydrogen-bond induced allosteric effects and protonation cooperativity in a macrotricyclic bisdioxocyclam receptor

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Electronic Supplementary Information

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Content

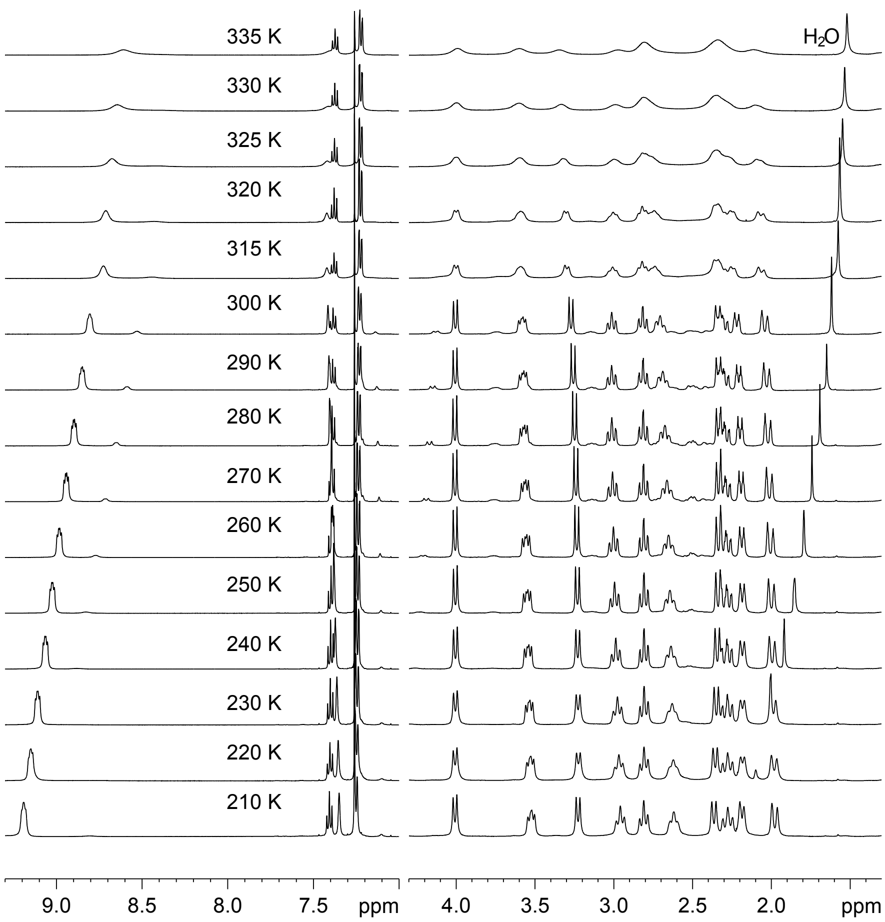


Fig. S1 Variable-temperature [1]H NMR spectra for compound **T1** recorded at 500 MHz in $CDCl_3$ solution.

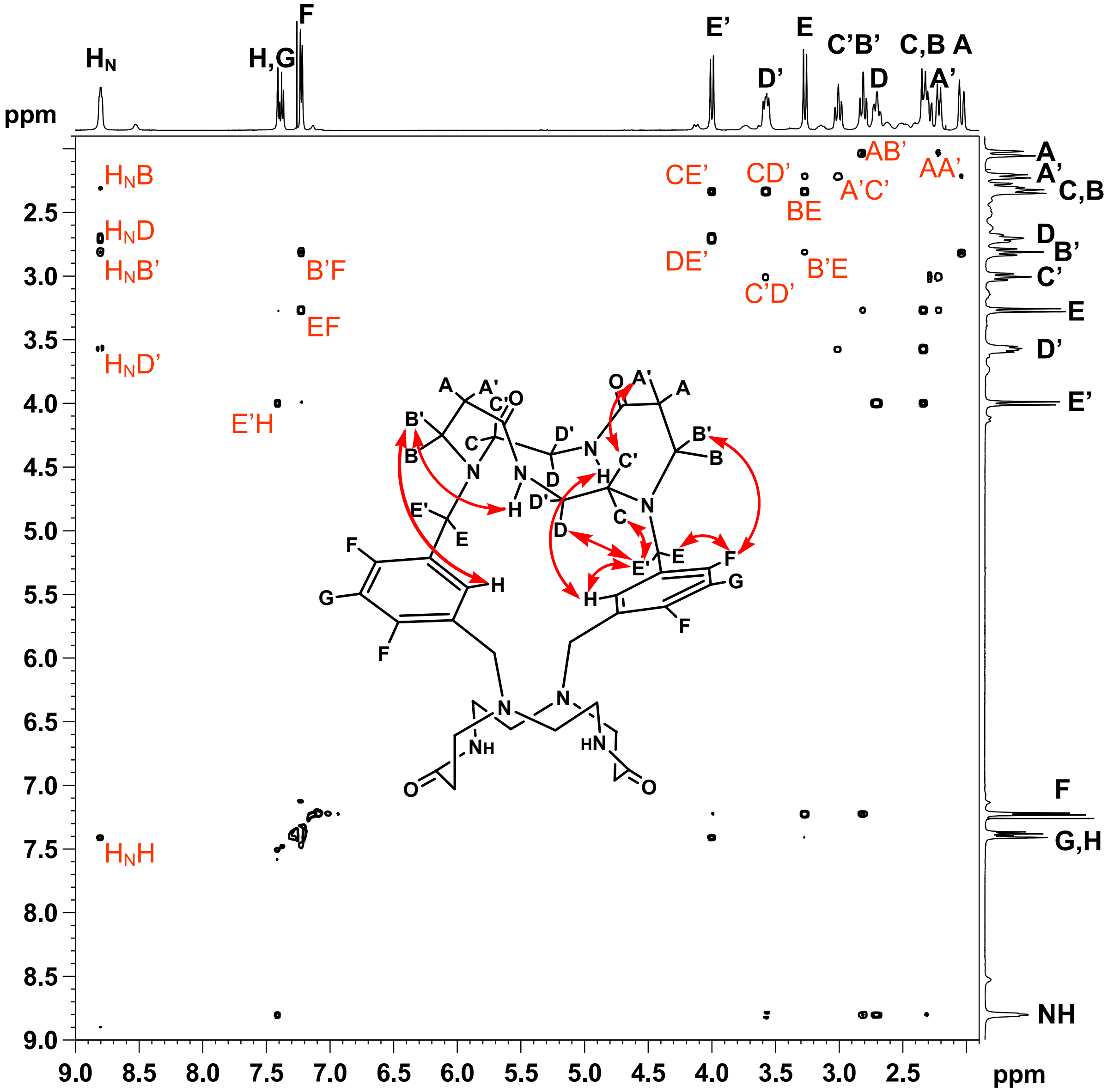


Fig. S2 ^{1}H–^{1}H NOESY chart (500 MHz) for compound **T1** showing the peak assignment and the relevant through space connectivities. Solvent: $CDCl_3$; T = 300 K; mixing time: 200 ms.

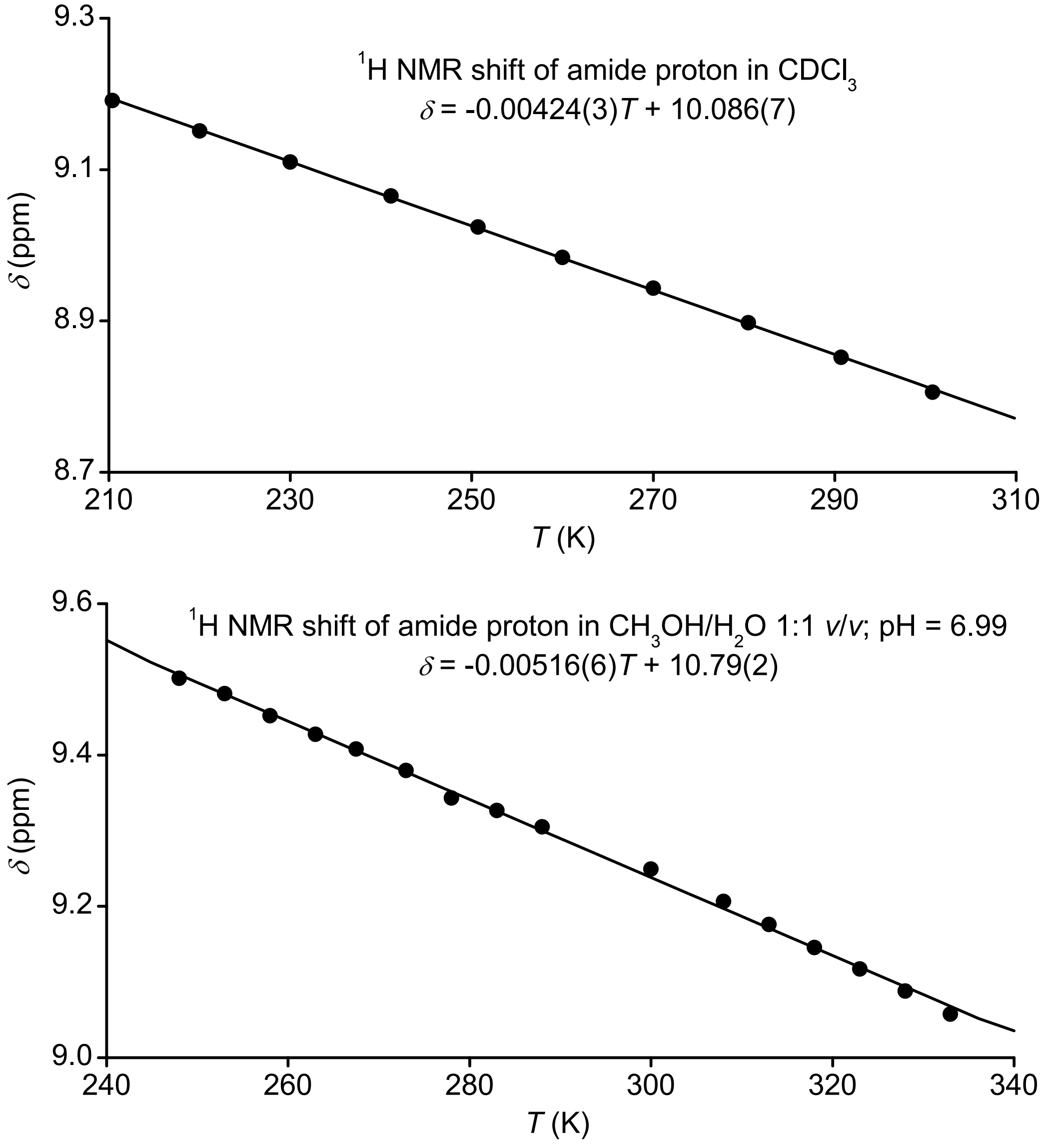


Fig. S3 Curie plots for compound **T1**.

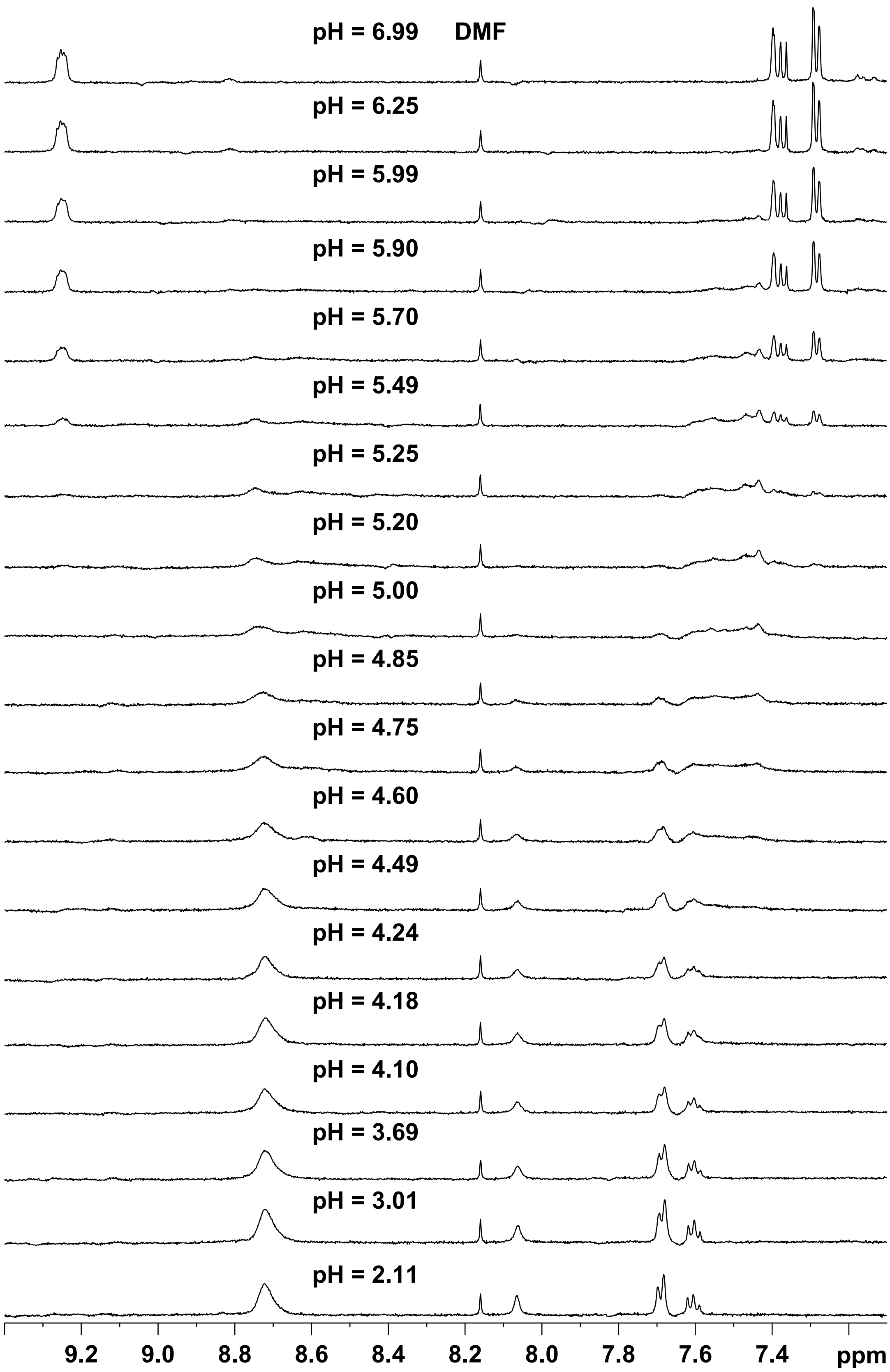


Fig. S4 Stack plot of representative ^{1}H NMR spectra of compound **T1** recorded at 500 MHz as a function of p[H]. Solvent: CH_3OH/H_2O 1:1 *v*/*v*; T = 300 K. Spectra are calibrated with respect to the residual peak of DMF-d_7 contained in a sealed capillary.

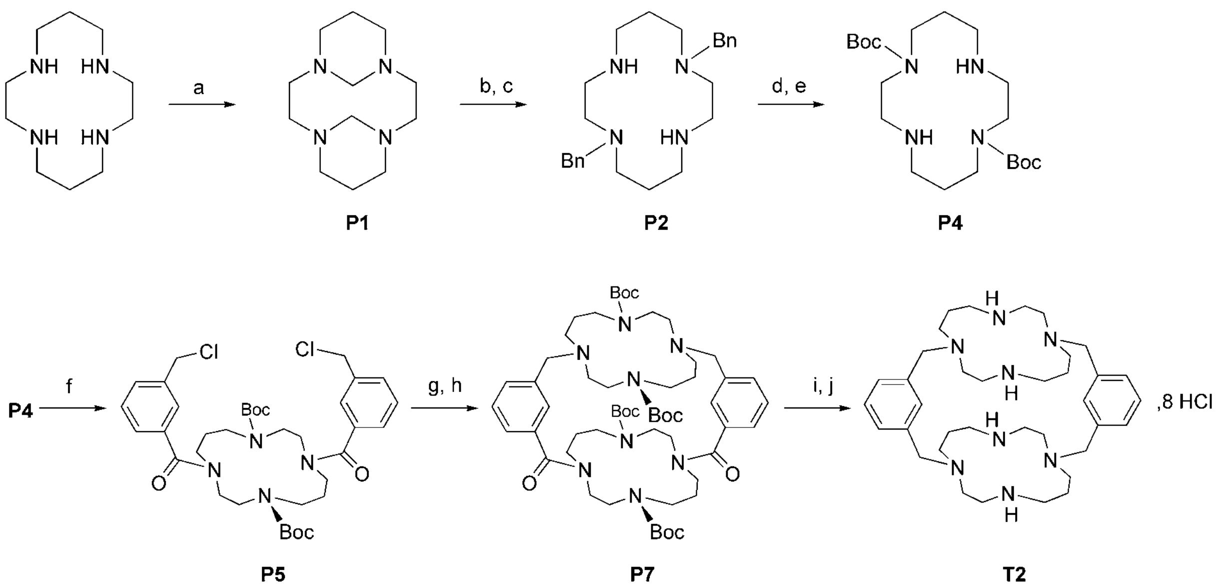
Experimental Section

Unless otherwise noted, all chemicals and starting materials were obtained commercially and used without further purification. 1,4,8,11-tetraazacyclotetradecane-5,12-dione (5,12-dioxocyclam),[1] 1,8-dimethyl-1,4,8,11-tetraazacyclotetradecane (**2**),[2] 1,4,8,11-tetraazatricyclo[9.3.1.1^{4,8}]hexa-decane (**P1**),[2] 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane (**P2**),[2] and receptor **T1**[3] were synthesized according to literature procedures. Analytical data were similar to those already published. Silica gel (Kieselgel 60 70–120 μm) or aluminum oxide 90 (Merck) was used for column chromatography. Organic solvents and mineral acids were of reagent grade and were used as supplied. ^{1}H and ^{13}C NMR spectra were recorded at the "Centre de Spectroscopie Moléculaire de l'Université de Bourgogne" on a Bruker Avance 300 or Avance DRX 500 superconducting Fourier transform spectrometer operating at 300.13 or 500.13 MHz, respectively. All chemical shifts were referenced to the solvent peak. Infrared spectra were measured on a Bruker IFS 66v Fourier transform spectrometer either as KBr pellets from 4000 to 400 cm^{-1} or in $CDCl_3$ solution from 4000 to 1000 cm^{-1} using a variable path-length cell from Perkin-Elmer equipped with IRTRAN-2 windows. MALDI/TOF mass spectra were obtained on a Bruker ProFLEX III spectrometer using either dithranol or α-cyano-4-hydroxycinnamic acid (CHCA) as matrix. Microanalyses and thermogravimetric analyses (TGA) were respectively performed on a Fisons EA 1108 CHNS instrument and a Netzsch STA 409 PC Luxx thermoanalyzer.

1,8-Dimethyl-1,4,8,11-tetraazacyclotetradecane-5,12-dione (1). Iodomethane (7,00 g, 49.3 mmol) diluted in 100 mL DMF was added dropwise over a period of 5 h to a solution of 1,4,8,11-tetraazacyclotetradecane-5,12-dione dihydrate (4.04 g, 15.3 mmol) dissolved in 400 mL DMF. The stirred reaction mixture was heated at 50 °C for 12 h before evaporating the solvent under vacuum. The orange residue was dissolved in 300 mL water and NaOH pellets were added (pH > 12) until the mixture became clear and colorless. The crude compound was then extracted with 4 × 100 mL $CHCl_3$. The combined organic phases were dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting solid was further purified by column chromatography on silica gel using a CH_2Cl_2/CH_3OH (98:2 *v/v*) mixture as eluent to yield 1.74 g (38%) of a white powder. IR (KBr, cm^{-1}): 3188 (br, ν_{NH} bonded), 3057 ($\nu_{NH} + \delta_{CNH}$ combination band), 2983 (ν_{CH_3} asym), 2940 (ν_{CH_2} asym), 2849 (ν_{CH_3} sym), 2808 (ν_{CH_2} sym), 1653 ($\nu_{C=O}$), 1551 (δ_{CNH}), 1468, 1459, 1455, 1445 (δ_{CH_2}), 1430, 1417 (δ_{CH_3}). ^{1}H NMR (300 MHz, $CDCl_3$, T = 300 K): δ 2.19 (s, 6H, NCH_3), 2.42 (t, ^3J = 5.65 Hz, 4H,

$COCH_2$), 2.50 (bs, 4H, $NHCH_2CH_2$), 2.60 (bs, 4H, $COCH_2CH_2$), 3.39 (bs, 4H, $NHCH_2$), 8.85 ppm (bs, 2H, CON*H*). ^{13}C NMR (75 MHz, $CDCl_3$, T = 300 K): δ 32.1 ($COCH_2$), 35.8 ($NHCH_2$), 39.0 (NCH_3), 54.2 ($COCH_2CH_2$), 56.2 ($NHCH_2CH_2$), 172.4 ppm (*C*O). MALDI/TOF MS (dithranol matrix): *m/z* (calcd.) = 256.4 (256.2) [$M^{+\bullet}$], 278.5 (278.2) [M + Na^+ – H], 294.5 (294.2) [M + K^+ – H]. Anal. Calcd for $C_{12}H_{24}N_4O_2$ (256.35): C, 56.23; H, 9.44; N, 21.86. Found: C, 56.82; H, 9.77; N, 21.73.

Macrotricycle T2. The general synthetic route depicted in Scheme S1 proceeds in six steps starting from 1,4,8,11-tetraazacyclotetradecane (cyclam). 1,8-dibenzyl-1,4,8,11-tetraazacyclotetradecane (**P2**) was conveniently obtained in almost quantitative yield following a published procedure from our laboratory.[2]



Scheme S1. (a) CH_2O aq; (b) BnBr, CH_3CN; (c) NaOH aq; (d) Boc_2O, CH_2Cl_2 → **P3**; (e) H_2, Pd/C, AcOH/CH_3OH; (f) 3-chloromethylbenzoyl chloride, THF, $(C_2H_5)_3N$; (g) NaI, acetone → **P6**; (h) 1 equiv. **P4**, CH_3CN, K_2CO_3, 10^{-2} M, reflux; (i) BH_3, THF, reflux; (j) HCl conc., C_2H_5OH.

1,8-di(*tert*-butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (P4). To a solution of **P2** (10.35 g, 27.23 mmol) in CH_2Cl_2 (150 mL) di(*tert*-butyl)dicarbonate (14.84 g, 68.09 mmol) dissolved in CH_2Cl_2 (50 mL) was added dropwise at room temperature. The solution was stirred for 1 h and the solvent removed under vacuum. The crude residue was purified by column chromatography on silica gel. The intermediate tetrasubstituted cyclam derivative **P3** was eluted with CH_2Cl_2/CH_3OH (96:4 *v/v*) to afford a colorless oil in 87% yield (13.80 g, 23.79 mmol) after removal of the solvents. The entire amount was dissolved under argon in AcOH (200 mL) and CH_3OH (50 mL), and 1 g of 10% Pd/C was added. The reaction mixture was stirred under H_2 until the gas adsorption has ceased. After filtration on a Celite pad and evaporation of solvents, the oily residue was dissolved in CH_2Cl_2 (200 mL) and neutralized with an aqueous 1 M NaOH solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to yield **P4** as a pale-yellow oil (9.50 g, yield = 97%). ^1H NMR (500 MHz, $CDCl_3$, T = 300 K): δ 1.43 (s, 18H, CH_3), 1.75 (q, 4H, ^3J = 6.5 Hz, $CH_2CH_2CH_2$), 2.66 (t, 4H, ^3J = 6.5 Hz, $NHCH_2CH_2CH_2$), 2.78 (t, 4H, ^3J = 5.5 Hz, $NHCH_2CH_2NBoc$), 3.33 ppm (m, 8H, CH_2NBoc). ^{13}C NMR (125 MHz, $CDCl_3$, T = 300 K): δ 28.9 (CH_3), 30.1 ($CH_2CH_2CH_2$), 46.7 (CH_2N), 47.3 (CH_2N), 48.8 (CH_2N), 49.8 (CH_2N), 79.6 ($C(CH_3)_3$), 156.4 ppm (CO). MALDI/TOF MS (dithranol matrix): m/z (calcd.) = 401.2 (401.3) [M + H^+], 301.1 (301.2) [M + H^+ – Boc]. Anal. Calcd for $C_{20}H_{40}N_4O_4{\bullet}0.6H_2O$ (411.37): C, 58.40; H, 10.09; N, 13.62. Found: C, 58.27; H, 10.40; N, 13.10.

1,8-di(*tert*-butyloxycarbonyl)-4,11-bis(3'-chloromethylbenzoyl)-1,4,8,11-tetra-azacyclotetradecane (P5). To a degassed THF solution (130 mL) of **P4** (6 g, 15 mmol) was added under argon triethylamine (6.07 g, 60 mmol) followed by 3-chloromethylbenzoyl chloride (5.68 g, 30 mmol). After stirring for 1 h at room temperature, the solvent was removed under vacuum. The oily residue was dissolved in CH_2Cl_2 (200 mL) and washed with a diluted aqueous NaOH solution. The organic layer was concentrated and the crude compound was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH 98:2 *v/v*) to give **P5** as a white solid foam (9.00 g, yield = 85%). ^1H NMR (500 MHz, $(CD_3)_2SO$, T = 330 K): δ 1.35 (bs, 18H, CH_3), 1.86 (bs, 4H, $CH_2CH_2CH_2$), 3.10–3.80 (m, 18H, CH_2N), 4.79 (s, 4H, CH_2Cl), 7.20–7.70 ppm (m, 8H, CH_{Ar}). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, T = 373 K): δ 27.2 ($CH_2CH_2CH_2$), 27.6 (CH_3), 45.1 (CH_2Cl), 46.1 (CH_2N), 46.6 (CH_2N), 78.6 ($C(CH_3)_3$), 125.5 (CH_{Ar}), 126.0 (CH_{Ar}), 128.2 (CH_{Ar}), 128.7 (CH_{Ar}), 137.1 (C_{Ar}), 137.4 (C_{Ar}), 154.6 (CO_{Boc}), 169.7 ppm (ArCO). MALDI/TOF MS (CHCA matrix): m/z (calcd.) = 727.1 (727.3) [M + Na^+], 743.1 (743.3) [M + K^+]. Anal. Calcd for $C_{36}H_{50}N_4Cl_2O_6$ (705.72): C, 61.27; H, 7.14; N, 7.94. Found: C, 61.52; H, 7.24; N, 8.02.

1,8-di(*tert*-butyloxycarbonyl)-4,11-bis(3'-iodomethylbenzoyl)-1,4,8,11-tetraaza-cyclotetradecane (P6). Solid NaI (2.65 g, 17.70 mmol) was added to a solution of **P5** (5 g, 7.08 mmol) in acetone (450 mL) and the reaction mixture was refluxed for 2 h. The sodium salts were filtered off and the solvent removed under vacuum. The residue was dissolved in CH_2Cl_2 (250 mL) and washed with a diluted aqueous sodium thiosulfate solution, followed by water (100 mL). The organic phase was dried over anhydrous $MgSO_4$ and evaporated to dryness to yield **P6** as a pale-yellow solid (6.17 g, yield = 98%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$, T = 330 K): δ 1.35 (bs, 18H, CH_3), 1.87 (bs, 4H, $CH_2CH_2CH_2$), 3.00–3.80 (m, 18H, CH_2N), 4.64 (s, 4H, CH_2I), 7.10–7.80 ppm (m, 8H, CH_{Ar}). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, T = 373 K): δ 6.9 (CH_2I), 28.5 ($CH_2CH_2CH_2$), 29.0 (CH_3), 47.5 (CH_2N), 48.0 (CH_2N), 80.0 ($C(CH_3)_3$), 126.3 (CH_{Ar}), 127.6 (CH_{Ar}), 129.6 (CH_{Ar}), 130.3 (CH_{Ar}), 138.4 (C_{Ar}), 140.8 (C_{Ar}), 156.0 (CO_{Boc}), 171.1 ppm (ArCO). MALDI/TOF MS (CHCA matrix): m/z (calcd.) = 910.1 (910.2) [M + Na^+ – H], 926.0 (926.1) [M + K^+ – H]. Anal. Calcd for $C_{36}H_{50}N_4I_2O_6$ (888.62): C, 48.66; H, 5.67; N, 6.30. Found: C, C 48.72; H, 5.73; N, 6.45.

Macrotricycle P7. Cyclization was achieved in refluxing CH_3CN (570 mL) containing K_2CO_3 (2.92 g). The diamide **P6** (4.42 g, 4.97 mmol) and the diprotected cyclam **P4** (1.99 g, 4.97 mmol), each dissolved in CH_3CN (10 mL), were added simultaneously and dropwise over a period of 24 h. The stirred mixture was kept at reflux for further 12 h. After filtration, the solvent was evaporated and the residue purified by chromatography on silica gel using CH_2Cl_2/CH_3OH (97:3 v/v) as eluent to give the macrotricycle **P7** as a white solid (2.10 g, yield = 41%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$, T = 378 K): δ 1.35 (bs, 36H, CH_3), 1.60–2.00 (m, 8H, $CH_2CH_2CH_2$), 2.30–2.75 (m, 8H, CH_2N), 2.90–3.50 (m, 24H, CH_2N), 3.56 (bs, 4H, ArCH_2), 7.10–7.60 ppm (m, 8H, CH_{Ar}). MALDI/TOF MS (dithranol matrix): m/z (calcd.) = 1033.9 (1033.6) [M + H^+], 934.0 (933.6) [M + H^+ – Boc]. Anal. Calcd for $C_{56}H_{88}N_8O_{10}\cdot H_2O$ (1051.37): C, 63.97; H, 8.63; N, 10.66. Found: C, 63.88; H, 8.54; N, 10.40.

Macrotricycle T2. The diamide **P7** (2.10 g, 2.03 mmol) was dissolved in degassed THF (5 mL) under argon and a 1 M borane solution in THF (18 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 15 min and then refluxed for 13 h. After cooling, the borane in excess was hydrolyzed with a 1:1 v/v H_2O/CH_3OH mixture (5 mL) and the solvents were evaporated. The residue was then refluxed in a 4 M HCl solution (25 mL) for 3 h, after which the cooled mixture was neutralized by the addition of NaOH pellets (pH > 11). Extraction with CH_2Cl_2 (2 × 100 mL) followed by drying and removing of the solvent under vacuum afforded the deprotonated macrotricycle **T2** (1.05 g, yield = 85%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$, T = 391 K): δ 1.75 (q, 8H, ^3J = 5.5 Hz, $CH_2CH_2CH_2$), 2.50 (m + solvent residual peak, 8H, CH_2N), 2.57 (m, 8H, CH_2N), 2.69 (m, 16H, CH_2N), 3.64 (s, 8H, ArCH_2), 7.09 (d, 4H, ^3J = 7.3 Hz, CH_{Ar}), 7.23 (t, 2H, ^3J = 7.3 Hz, CH_{Ar}), 7.50 ppm (s, 2H, CH_{Ar}). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, T = 390 K): δ 25.0 ($CH_2CH_2CH_2$), 46.8 (CH_2N), 48.6 (CH_2N), 50.7 (CH_2N), 52.1 (CH_2N), 56.9 (ArCH_2), 126.8 (CH_{Ar}), 127.6 (CH_{Ar}), 130.0 (CH_{Ar}), 137.2 ppm (C_{Ar}). MALDI/TOF MS (dithranol matrix): m/z (calcd.) = 605.2 (605.5) [M + H^+].

The compound was isolated as the octaprotonated salt in analytical pure form by adding a large excess of a concentrated HCl solution to an ethanolic solution of the deprotonated ligand. The white precipitate formed was filtrated and dried under vacuum. Anal. Calcd for $C_{56}H_{88}N_8O_{10}$•8HCl•6.5H_2O (1013.71): C, 42.65; H, 8.05; N, N 11.05. Found: C, 42.60; H, 7.79; N, 10.94. Water content by TGA MS: Δm (calcd.) = 11.64% (11.55%), T_{onset} = 58 °C, T_{end} = 165 °C.

X-Ray Diffraction Study of T1•4H$_2$O. Colourless prisms (0.32 × 0.25 × 0.20 mm) were crystallized from a saturated ethanol/water (50:50 *v/v*) solution. Crystal data for **T1**•4H_2O are as following: $C_{36}H_{60}N_8O_8$, M_r = 732.92, orthorhombic, space group *P bcn*, a = 12.9970(2), b = 18.4860(2), c = 16.1270(3) Å, V = 3874.7(1) Å^3, Z = 4, ρ_{calcd} = 1.256 g cm^{-3}, μ = 0.090 mm^{-1}, λ(Mo-Kα) = 0.71073 Å (graphite monochromator), T = 110(2) K, 1.92 ≤ θ ≤ 30.02°, 10778 reflections collected, 5657 independent reflections [R(int) = 0.0630], 255 refined parameters, 4 restrains, R_1 = 0.0532, wR_2 = 0.0992 [$I > 2\sigma(I)$], R_1 = 0.1415, wR_2 = 0.1288 (all data), GoF (F^2) = 1.004, $\Delta\rho_{\text{min/max}}$ = –0.245 and 0.210 e Å^{-3}. Data were collected with a KappaCCD (Nonius) diffractometer as φ and ω scans with κ offsets. The programs used were DENZO for data reduction,[4] SIR92 for the structure solution,[5] SHELXL97 for the structure refinements on F^2,[6] and ORTEP-3 for Windows for the structural drawings.[7] Hydrogen atoms were refined with isotropic thermal factors constrained to 1.2 times the equivalent isotropic thermal factor of their respective bonded atom. Those attached to carbon atoms were placed at calculated positions using a riding model, while those belonging to amid groups and water molecules were located in the Fourier map and their positional parameters refined (Ow–H distances restrained to 0.96 Å). Two water oxygen atoms (Ow2, Ow3) were found on special positions and their site occupation factors were fixed at 0.5.

Potentiometric Titrations. Protonation constants were determined at constant temperature (T = 298.2(1) K) and ionic strength (I = 0.1 KCl) in a methanol/water (1:1 *v/v*) mixture for solubility reasons. Water was deionized and further purified by passage through an Elgastat UHQII (Elga) ion-exchange cartridge system (resistivity 18 MΩ cm). All 0.1 M titrant solutions were prepared in a 1 L volumetric flask containing 500 mL methanol (Merck) from concentrates (Titrisol®, Merck) diluted with double-deionized, argon-purged boiled water. They were stored under an atmosphere of purified argon using Ascarite II (Acros, 20-30 mesh) scrubbers in order to prevent absorption of carbon dioxide. The carbonate-free KOH solution was standardized against oven-dried (120 °C for 2 h) potassium hydrogen phthalate (Aldrich, 99.99%), while 0.1 M HCl solutions were titrated against oven-dried (120 °C for 2

h) TRIS buffer (Aldrich, 99.9%) using a combined Ag/AgCl glass semimicroelectrode (Mettler-Toledo) filled with a KCl and AgCl-saturated solution. Equivalent points were calculated by the second-derivative method. The concentration of the standardized solutions corresponded to the average of at least five replicates and was known with a relative precision of less than 0.15%.

All titrations were performed using a T110 (Schott) piston burette equipped with a calibrated TA10 interchangeable unit of 10 mL. The volumes of the delivered aliquots were corrected according to a linear calibration function obtained by weighing known quantities of water and by taking into account the buoyancy effect. The burette and the TR250 (Schott) data acquisition unit were controlled by the TR600 software (release 5.2) running on a IBM-compatible PC computer. Solutions were maintained under an argon atmosphere at constant temperature (298.2(1) K) by using a jacketed titration vessel fitted to a Lauda RE 106 water bath and equipped with a magnetic stirrer. The pH-metric measurements were carried out with a combined Ag/AgCl glass semimicroelectrode (Mettler-Toledo). The filling solution of the reference compartment was replaced with an AgCl-saturated methanol/water (50:50 *v/v*) solution containing 0.1 M KCl. The electrode was stored in water and soaked in the binary mixture for one hour at least prior to use in order to equilibrate. Before each titration, the electrochemical cell was calibrated to read hydronium ion concentrations ($p[H] = -\log [H^+]$) by titrating 4.000 mL of standardized HCl diluted in 50 mL of 0.100 M KCl with 9.010 mL of standardized KOH in 0.12 mL increments. The sum of the unweighted square residuals on the observed potential readings (E_{mes}) were minimized according to the modified Nernst equation ($E_{mes} = E^0 + S \log [H^+] + J_a [H^+] + J_b K_w [H^+]^{-1}$) by using the Solver routine implemented in Microsoft Excel. The minimization procedure allowed the simultaneous refinement of the standard cell potential (E^0), the Nernst slope (S), the correction terms accounting for the changes in liquid-junction potential in strongly acid (J_a) or alkaline (J_b) media, and the base-concentration factor (γ). Calibration data were rejected when the standard deviation of the residuals exceeded 0.1 mV, indicating a carbonate contamination of the base usually higher than 0.5%. The ionic product of water was determined from independent experiments following the method of Fischer and Byé.[8] The experimental value ($pK_w = 13.89$ at 298.2(1) K) is in good agreement with that reported by Costa *et al*.[9]

Protonation constants were measured by titrating ca. 0.1 mmol of compound dissolved in 50 mL of supporting electrolyte solution (0.1 M KCl). The electrochemical cell was allowed to equilibrate for at least 30 s after each addition of a titrant increment (0.03

mL). The collected potential readings were converted into p[H] values with the help of an Microsoft Excel spreadsheet by solving iteratively the rearranged Nernst equation: p[H] = $(E^0 - E_{mes} + J_a [H^+] + J_b K_w [H^+]^{-1})/S$. The titration data were analyzed by the weighted nonlinear least-squares program HYPERQUAD 2000.[10] The selected weighting-scheme derived from the error-propagation law,[11] seeks to reduce the weight of the less accurate measurements (i.e. points located in the steep region of a titration curve). Based on the instrument's calibration, the uncertainties associated with the experimental p[H] values (σ_{pH}) and the volumes delivered by the piston burette (σ_v) were estimated as 0.003 pH unit (or ~0.1 mV) and 0.005 mL, respectively. In the final refinement step, the total amounts of titrated ligand and initially added acid were also allowed to vary. The goodness of fit between calculated and experimental p[H] values was evaluated through the squared sum of residuals ($1 < \sigma < 1.75$) and an approximately normal distribution of the residues.[11] The thermodynamic reversibility was checked by cycling from low to high p[H] and vice versa. Data from forward and backward titrations afforded statistically identical values of the adjusted thermodynamic parameters, pointing out chemical stability of the ligand over the explored pH range. For each data set, the standard deviations of the log K_{01h} values were derived from the full variance/covariance matrix of the refined global constants (log β_{01h}).[12] The final values are reported as the arithmetic mean of four independent measurements together with their standard deviations, which were systematically higher compared to those derived from the full variance/covariance matrix for an individual determination.

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