Effects of Solvent Properties on the Anion-Binding of Neutral Water-Soluble Bis(cyclopeptides) in Water and Aqueous Solvent Mixtures

Fabian Sommer,† Yizhak Marcus,§ Stefan Kubik*,†

† Technische Universität Kaiserslautern, Fachbereich Chemie - Organische Chemie, Erwin-Schrödinger-Straße, 67663 Kaiserslautern, Germany. E-mail: kubik@chemie.uni-kl.de.
§ Institute of Chemistry, The Hebrew University, Edmund Safra Campus, Givat Ram, Jerusalem 91904, Israel

CONTENT

Synthesis of Bis(cyclopeptide) 2 ................................................................. S2

1H NMR, 13C NMR, and MS Spectra .......................................................... S9

Results of the Qualitative Binding Studies .................................................. S15

Selected ITC Titrations ............................................................................... S18

Solvent Dependence of Iodide Affinity of 1 and 2 .................................... S22

Solvent Dependence of Sulfate Affinity of 1 and 2 ................................. S25

Solvent Dependence of Solvent Properties ............................................. S27

Correlation of the Enthalpy of Iodide Binding to 1 With Preferential Solvation ................. S31

References ............................................................................................... S34
Synthesis of Bis(cyclopeptide) 2:

**General details.** Analyses were carried out as follows: melting points, Müller SPM-X 300; NMR, Bruker AVANCE III 400 and 600 (peak assignments were confirmed by using H,H-COSY and HMQC spectra, $^1$H and $^{13}$C NMR spectra were referenced to the residual solvent signals (CDCl$_3$: $\delta_H$ = 7.26 ppm, $\delta_C$ = 77.2 ppm; DMSO-$d_6$: $\delta_H$ = 2.50 ppm, $\delta_C$ = 39.5 ppm MeOH-$d_4$: $\delta_H$ = 3.31 ppm, $\delta_C$ = 49.0 ppm;), trifluoroacetic acid was used as an internal standard for the $^{19}$F NMR spectra with $\delta_F$(TFA) = –76.55 ppm; MALDI-TOF-MS, Bruker Ultraflex TOF/TOF; ESI-MS, Bruker amaZon SL; elemental analysis, Elementar vario Micro cube; optical rotation, JASCO P-2000 ($d$ = 10 cm); preparative HPLC, Dionex Ultimate 3000 (column, Supelco Ascentis®, 250 × 21.2 mm, 5 $\mu$m particle size; flow, 10 mL min$^{-1}$; eluent, aqueous: water, organic: acetonitrile; the following gradient was used for the isolation of 2: 0 min, 25% organic; 0-35 min, linear increase to 40% organic; 35-40 min, 40% organic; 40-41 min, linear increase to 95% organic; 41-46 min, 95% organic; 46-47 min, linear decrease to 25% organic; 47-55 min, 25% organic); ITC, Microcal VP-ITC; precision balance, Kern ABT 100-5M.

The following abbreviations are used: BCP, bis(cyclopeptide) Bta, 2,2',2''-(benzene-1,3,5-triyl)triacetic acid; DIEA, N-ethylidiisopropylamine; Pfp, pentafluorophenol; TBTU, O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate; Pro, L-proline; Apro, (4S)-4-amino-L-proline; Mapa, 4-[2-[2-(2-methoxyethoxy)ethoxy]ethoxy]-2-aminopyridine-6-carboxylic acid; Teg, triethylene glycol.

**Materials.** All solvents were dried according to standard procedures prior to use. DMF p.a. was purchased and used without further purification.
Tris(pentafluorophenyl) 2,2',2''-(benzene-1,3,5-triyl)triacetate (4).

Scheme S1: Synthesis of 4.

2,2',2''-(Benzene-1,3,5-triyl)triacetic acid (466 mg, 1.85 mmol) and pentafluorophenol (1.19 g, 6.47 mmol) were dissolved in dichloromethane (15 mL) and treated with a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.17 g, 6.12 mmol) and 4-dimethylaminopyridine (34 mg, 278 µmol) in dichloromethane (15 mL). A dark precipitate immediately formed, which slowly disappeared upon stirring at room temperature. The mixture was stirred for 18 h. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO2, ethylacetate/hexane, 1:3 (v/v)). The crude product was then precipitated from hexane to yield a colorless solid. Yield: 973 mg (70%); m.p. 120 °C; 1H NMR (400 MHz, 25 °C, CDCl3): δ = 7.35 (s, 3H, BtaH), 4.01 (s, 6H, BtaCH2) ppm; 13C NMR (101 MHz, 25 °C, CDCl3): δ = 167.2 (CO), 141.0 (dm, J(C,F) = 253 Hz, F5PhC(3)), 139.6 (dm, J(C,F) = 254 Hz, F5PhC(2)), 137.8 (dm, J(C,F) = 254 Hz, F5PhC(4)), 133.7 (BtaC(1,3,5)), 129.9 (BtaC(2,4,6)), 125.1 (m, F5PhC(1)), 40.0 (CH2) ppm; 19F NMR (376 MHz, 25 °C, CDCl3): δ = −151.6 (d, J(F,F) = 18.2 Hz, 6F, PfpF(2,6)), −156.4 (t, J(F,F) = 21.6 Hz, 3F, PfpF(4)), −161.1 (t, J(F,F) = 19.9 Hz, 6F, PfpF(3,5)) ppm; MS (MALDI-TOF) m/z (%) 772.9 (100) [M+Na]+, 788.9 (6) [M+K]+; elemental analysis calcd (%) for C30H9F15O6: C 48.02, H 1.21 found C 48.08, H 1.30.
Bis(pentafluorophenyl) 2,2'-(5-(12-oxo-2,5,8-trioxa-11-azatridecan-13-yl)-1,3-phenylene)diacetate (5).

Scheme S2: Synthesis of 5.

A solution of 4 (374 mg, 0.5 mmol) in acetonitrile (20 mL) was heated to reflux and a solution of 2-(2-(2-methoxyethoxy)ethoxy)ethanamine (82 mg, 0.5 mmol) in acetonitrile (30 mL) was added over a period of 3 h. After the addition was completed, the mixture was heated for further 20 h. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO\textsubscript{2}, dichloromethane, then dichloromethane/methanol, 10:1 (v/v)) to afford a colorless oil. The product could not be obtained in analytically pure form. Yield: 249 mg (68 %); \textsuperscript{1}H NMR (400 MHz, 25 °C, CDCl\textsubscript{3}): \(\delta = 7.27\) (s, 3H, BtaH), 6.37 (br s, 1H, NH), 3.98 (s, 4H, BtaCH\textsubscript{2}), 3.52-3.63 (m, 12H, 10 TegCH\textsubscript{2} + 2 BtaCH\textsubscript{2}), 3.43-3.48 (m, 2H, TegCH\textsubscript{2}), 3.37 (s, 3H, TegCH\textsubscript{3}) ppm.

Bis(cyclopeptide) 2.

Scheme S3: Synthesis of 2.
The Z-protected form of cyclopeptide 3 was deprotected as described previously. The thus obtained deprotected cyclopeptide 3 (92 mg, 77 µmol) was dissolved in degassed DMF (3 mL). A solution of 5 (28 mg, 38 µmol) and DIEA (50 µL, 286 µmol) in degassed DMF (3 mL) was added and the mixture was stirred at 25 °C for 6 h. After evaporation of the solvent the residue was purified by preparative HPLC and dried by lyophilization to yield a colorless solid. Yield: 46 mg (45%); m.p. 87-92 °C; [α]_D^22 = -225 (c =1, methanol); ^1H NMR (600 MHz, 25 °C, MeOD-d_4/D_2O, 4:1 (v/v)): δ = 7.00-7.24 (m, 15H, MapaH(3)/MapaH(5)/BtaH), 5.81-5.85 (m, 2H, AproH(α)), 5.65-5.69 (m, 4H, Pro(α)), 4.45-4.51 (m, 2H, AproH(γ)), 4.04-4.12 (m, 14H, TegCH₂), 3.96-4.04 (m, 2H, AproH(δ)), 3.74-3.83 (m, 22H, 14×TegCH₂/8×ProH(δ)), 3.57-3.67 (m, 44H, 42×TegCH₂/2×AproH(δ)), 3.39-3.54 (m, 20H, 14×TegCH₂/6×BtaCH₂), 3.27-3.32 (m, 21H, OCH₃), 2.73-2.82 (m, 2H, AproH(β)), 2.56-2.69 (m, 4H, ProH(β)), 2.11-2.21 (m, 2H, AproH(β)), 1.89-2.15 (m, 12H, 8×ProH(γ)/4×ProH(β)) ppm; ^13C NMR (151 MHz, 25 °C, MeOD-d_4/D_2O, 4:1 (v/v)): δ = 174.5 + 174.2 + 173.0 + 172.9 + 172.4 (Pro-CO/Apro-CO/Bta-CO), 168.6 + 168.5 + 168.3 + 168.2 + 168.0 (MapaC(4)/Mapa-CO), 154.3 + 154.1 + 153.2 (MapaC(6)), 152.0 + 151.8 + 151.7 (MapaC(2)), 137.4 + 137.1 (BtaC(1)/BtaC(3)/BtaC(5)), 129.8 + 129.5 (BtaC(2)/BtaC(4)/BtaC(6)), 109.1 + 108.9 + 108.8 (MapaC(5)), 103.4 + 103.0 + 102.8 (MapaC(3)), 72.6 + 72.5 + 71.5 + 71.1 + 71.0 + 70.9 + 70.8 + 70.2 + 69.9 + 69.8 + 69.0 (TegCH₂), 63.6 + 63.5 (ProC(α)), 62.3 (AproC(α)), 59.1 (O-CH₃), 53.7 (AproC(δ)), 50.1 + 50.0 (ProC(δ)), 47.8 (AproC(γ)), 43.3 + 43.2 + 40.4 (BtaCH₂), 37.9 (AproC(β)), 33.8 (ProC(β)), 23.6 + 23.5 (ProC(γ)) ppm; MALDI-MS m/z (%) 2667.2 (100) [M+H]^+, 2689.3 (95) [M+Na]^+; elemental analysis calcd (%) for C_{127}H_{175}N_{21}O_{42}·5H₂O: C 55.31, H 6.76, N 10.67 found C 55.19, H 6.62, N 10.68.
ITC titrations. Solvents and solvent mixtures used in the ITC titrations were not degassed. The salts used as substrates were weighed using an analytical precision balance, dissolved in known volumes of the respective solvent or solvent mixture, and loaded into the system for immediate analysis. Solutions involved in the same titration experiment were made up from the same batch of solvent mixture. For the concentrations of 1 and 2 and the different salts used in the measurements, see Table S1 and Table S2.

A standard ITC experiment involved the titration of a solution of the salt into a solution of the receptor at 25 °C by using 30 injections of 8 µL, separated by an interval of 180 s or 240 s, with the exception of the first injection, which was 2 µL. For the measurements in water/DMSO the following conditions were used: DMSO: first injection 2 µL followed by 29 times 8 µL or first injection 2 µL followed by 9 times 4 µL and then 24 times 8 µL; 50 vol% water/DMSO: first injection 2 µL followed by 29 times 6 µL.

Binding constants and enthalpies of binding were obtained by curve fitting of the titration data using the one-site binding model except for iodide binding in DMSO and complexes with a log $K_a < 3$. In these cases, $n$ was fixed to 1. Data processing involved initial optimization of the raw thermogram with NITPIC$^2$ and subsequent non-linear regression of the binding isotherm with Sedphat.$^{3,4}$ The peak produced by the first injection was discarded prior to data processing.
Table S1: Concentrations of bis(cyclopeptides) 1 and 2 and the salts used in the ITC titrations in water, phosphate buffer, and organic solvents.

| solvent                      | BCP | guest salt | c(BCP) / mM | c(salt) / mM |
|------------------------------|-----|------------|-------------|--------------|
| water                        | 1   | NaI        | 0.5         | 10           |
|                              | 2   | NaI        | 0.5         | 10           |
|                              | 2   | NaBr       | 0.5         | 15           |
|                              | 2   | NaCl       | 0.5         | 15           |
|                              | 1   | Na₂SO₄     | 0.5         | 10           |
|                              | 2   | Na₂SO₄     | 0.5         | 10           |
| aqueous phosphate buffer (35 mM, pH 7.40) | 2   | Na₂SO₄     | 0.5         | 10           |
| methanol                     | 1   | NMe₄I      | 0.25        | 5            |
|                              | 1   | NMe₄I      | 0.25        | 5            |
| acetonitrile                 | 1   | NMe₄I      | 0.25        | 5            |
|                              | 1   | NBu₄I      | 0.25        | 5            |
| DMSO                         | 1   | NMe₄I      | 0.25 and 0.5| 5 and 10    |
Table S2: Concentrations of bis(cyclopeptides) 1 and 2 and the salts used in the ITC titrations in the aqueous solvent mixtures.

| co-solvent | vol% water | BCP | guest salt | c(BCP) / mM | c(salt) / mM |
|------------|------------|-----|------------|-------------|-------------|
| methanol   | 5          | 1   | NMe₄I      | 0.25        | 5           |
|            | 10         | 1   | NMe₄I      | 0.25        | 5           |
|            | 10         | 1   | NaI        | 0.25        | 5           |
|            | 20         | 1   | NaI        | 0.25        | 2.5         |
|            | 30         | 1   | NaI        | 0.25        | 5           |
|            | 30         | 1   | Na₂SO₄     | 0.25        | 2.5         |
|            | 50         | 1   | NaI        | 0.25        | 2.5         |
|            | 50         | 1   | Na₂SO₄     | 0.25        | 2.5         |
|            | 70         | 1   | NaI        | 0.25        | 5           |
|            | 70         | 1   | Na₂SO₄     | 0.25        | 2.5         |
|            | 70         | 2   | Na₂SO₄     | 0.25        | 2.5         |
|            | 90         | 1   | NaI        | 0.25        | 5           |
|            | 95         | 1   | NaI        | 0.25        | 5           |
|            | 95         | 2   | NaI        | 0.5         | 10          |
|            | 95         | 1   | Na₂SO₄     | 0.25        | 2.5         |
|            | 95         | 2   | Na₂SO₄     | 0.5         | 10          |
|            | 5          | 1   | NMe₄I      | 0.125 and 0.5 | 5   |
|            | 20         | 1   | NMe₄I      | 0.25        | 5           |
|            | 20         | 1   | NaI        | 0.25        | 5           |
|            | 30         | 1   | NaI        | 0.25        | 5           |
|            | 30         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 50         | 1   | NaI        | 0.25        | 5           |
|            | 50         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 50         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 70         | 1   | NaI        | 0.25        | 5           |
|            | 70         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 70         | 2   | Na₂SO₄     | 0.25        | 2.5         |
|            | 80         | 1   | NaI        | 0.25        | 5           |
|            | 80         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 95         | 1   | NaI        | 0.25        | 5           |
|            | 95         | 2   | NaI        | 0.5         | 10          |
|            | 95         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 95         | 2   | Na₂SO₄     | 0.5         | 10          |
| acetonitrile| 40         | 1   | Na₂SO₄     | 0.2 and 0.25 | 2 and 2.5 |
| DMSO       | 50         | 1   | Na₂SO₄     | 0.2 and 0.25 | 5           |
|            | 70         | 1   | NaI        | 0.25        | 5           |
|            | 70         | 1   | Na₂SO₄     | 0.25        | 5           |
|            | 90         | 1   | Na₂SO₄     | 0.25 and 0.5 | 5 and 10   |
Figure S1: $^1$H NMR spectrum of 4 (400 MHz, CDCl$_3$, 25 °C).

Figure S2: $^{13}$C NMR spectrum of 4 (101 MHz, CDCl$_3$, 25 °C).
Figure S3: $^{19}$F NMR spectrum of 4 (376 MHz, CDCl$_3$, 25 °C).

Figure S4: MALDI-TOF MS spectrum of 4 (positive mode).
|                  | m/z calcd. | m/z exp. |
|------------------|------------|----------|
| [M+Na]^+         | C_{30}H_{9}F_{15}O_{6} + Na^+ | 773.0    | 772.9    |
| [M+K]^+         | C_{30}H_{9}F_{15}O_{6} + K^+   | 789.0    | 788.9    |
Figure S5: $^1$H NMR spectrum of 2 (600 MHz, MeOD-$d_4$/$D_2$O, 4:1 (v/v), 25 °C).

Figure S6: $^{13}$C NMR spectrum of 2 (151 MHz, MeOD-$d_4$/$D_2$O, 4:1 (v/v), 25 °C).
Figure S7: MALDI-TOF MS spectrum of 2 (positive mode).

|                | m/z calcd. | m/z exp. |
|----------------|------------|----------|
| [M–CH₃+H]⁺     | C₁₂₆H₁₇₂N₂₁O₄₂ + H⁺ | 2652.2   | 2652.1   |
| [M+H]⁺         | C₁₂₇H₁₇₅N₂₁O₄₂ + H⁺ | 2667.2   | 2667.3   |
| [M+Na]⁺        | C₁₂₇H₁₇₅N₂₁O₄₂ + Na⁺ | 2689.1   | 2689.3   |
Figure S8: HPLC chromatogram of 2 (Dionex P680 HPLC Pump, ASI-100 Autosampler, TCC-100 Column Oven, UVD 170U UV/Vis Detector, Chromeleon V6.70 Software, Supelco Ascentis® C18 Column, 4.6 × 250 mm, 5 µm)

**257 FS-107d-T3+4**

| Sample Number: | FS-107d-T3+4 | Injection Volume [µl]: 20,0 |
| Vial Number: | RC1 | Channel: UV_VIS_2 |
| Sample Type: | unknown | Wavelength [nm]: 275 |
| Control Program: | FS_Supelco_BCP2Aufreinigung | Bandwidth: 1 |
| Quantif. Method: | default | Dilution Factor: 1,0000 |
| Recording Time: | 10.4.2017 13:02 | Sample Weight: 1,0000 |
| Run Time (min): | 42,00 | Sample Amount: 1,0000 |

| No. | Ret.Time min | Peak Name | Height mAU | Area mAU*min | Rel.Area % | Amount | Type |
|-----|--------------|-----------|------------|--------------|------------|--------|------|
| 1   | 26,88        | n.a.      | 101,943    | 57,952       | 3,19       | n.a.   | BMB* |
| 2   | 29,15        | n.a.      | 1902,881   | 1757,353     | 96,81      | n.a.   | BMB* |
| Total: |              |           | 2004,824   | 1815,305     | 100,00     | 0,000  |      |

WVL: 275 nm
Flow: 1,000 ml/min
Wasser: 75,0 %
Acetonitril: 0,1 % TFA: 0,0 %
Acetonitril: 25,0 %
Results of the Qualitative Binding Studies:

**^1H NMR spectroscopy:**

Figure S9: ^1H NMR spectrum (400MHz, 25°C) of 2 in D$_2$O (5 mM) (a) and spectra of 2 in D$_2$O (5 mM) in the presence of 2 equiv of NaI (b) and 2 equiv of Na$_2$SO$_4$ (c). The signals of the H($\alpha$) protons of the proline rings are marked with black dots.

**ESI mass spectrometry:**

ESI MS spectra were recorded on a Bruker amaZon SL machine by using a flow rate of 100-175 µL/h. Spectra acquisition was performed with the program Trapcontrol and for data processing the program Data Analysis was used. The samples were prepared as follows: an aqueous solution of 2 (1 mM) and the respective sodium salt (ca. 10 equiv) was prepared. This solution was diluted with methanol to afford a 1 µM concentration of the bis(cyclopeptide) prior to the measurement.
Figure S10: ESI mass spectrum (negative mode) of a solution of 2 in H2O (1 mM) containing 10 equiv of Na2SO4 after dilution with methanol to reach a final solution of the bis(cyclopeptide) of 1 µM.

| Fragment of the sulfate complex of 2 lacking the side chain in the linker | m/z calcd. | m/z exp. |
|--------------------------------------------------------------------------|------------|----------|
| C118H158N20O42 + SO4^{2-}                                               | 1279.5     | 1279.5   |
| [M+SO4]^{2-}                                                             | C127H175N21O42 + SO4^{2-} | 1381.0   | 1381.0   |
Figure S11: ESI mass spectrum (negative mode) of a solution of 2 in H₂O (1 mM) containing 10 equiv of NaI after dilution with methanol to reach a final solution of the bis(cyclopeptide) of 1 µM.

| Species                  | Formula                        | m/z calc. | m/z exp. |
|-------------------------|--------------------------------|-----------|----------|
| [M+I]⁻                   | C₁₁₈H₁₅₈N₂₀O₄₂ + I⁻             | 2793.1    | 2792.0   |
| [M+NaI+I]⁻               | C₁₁₈H₁₅₈N₂₀O₄₂ + NaI + I⁻       | 2943.0    | 2941.0   |
| [M+(NaI)₂+I]⁻            | C₁₁₈H₁₅₈N₂₀O₄₂ + (NaI)₂ + I⁻    | 3092.9    | 3090.0   |
Selected ITC Titrations:
The following graphs show the results of selected ITC titrations. The diagrams on the left hand side are optimized raw thermograms resulting from NITPIC\textsuperscript{2} while the ones on the right hand side are binding isotherms obtained with Sedphat.\textsuperscript{3,4}

Figure S12: Thermograms and binding isotherms of selected ITC titrations.

Titration of 1 with tetramethylammonium iodide in methanol:

Titration of 1 with tetramethylammonium iodide in acetonitrile:

Titration of 1 with tetramethylammonium iodide in 5 vol\% water/acetonitrile:
Titration of 1 with sodium iodide in 20 vol% water/acetonitrile:

Titration of 1 with sodium iodide in 50 vol% water/acetonitrile:

Titration of 1 with sodium iodide in 80 vol% water/acetonitrile:

Titration of 1 with sodium iodide in 95 vol% water/acetonitrile:
Titration of 1 with sodium iodide in water:

Titration of 2 with sodium iodide in water:

Titration of 2 with sodium bromide in water:

Titration of 2 with sodium chloride in water:
Titration of 1 with sodium sulfate in 50 vol% water/acetonitrile:

Titration of 1 with sodium sulfate in 80 vol% water/acetonitrile:

Titration of 1 with sodium sulfate in 95 vol% water/acetonitrile:

Titration of 1 with sodium sulfate in water:
Titration of 2 with sodium sulfate in water:

Titration of 1 with tetramethylammonium iodide in DMSO:

Titration of 1 with sodium iodide in 70 vol% water/DMSO:

Titration of 1 with sodium sulfate in 70 vol% water/DMSO:
Solvent Dependence of Iodide Affinity of 1:

Table S3:  Gibbs free energies $\Delta G$, enthalpies $\Delta H$, and entropies $T\Delta S$ of the binding of iodide to bis(cyclopeptide) 1 and 2 in different water/methanol mixtures including the corresponding association constants $\log K_a$ and stoichiometry factors $n$.\(^a\)

| vol% water\(^b\) | mol% water\(^c\) | BCP\(^d\) | $\Delta G$  | $\Delta H$  | $T\Delta S$ | $\log K_a$ | $n$    |
|------------------|------------------|----------|------------|------------|------------|------------|-------|
| 0\(^f\)          | 0                | 1        | −35.1 ± 0.1| −35.5 ± 0.2| −0.5 ± 0.3 | 6.14 ± 0.01| 0.84 ± 0.01|
| 0\(^f\)          | 10.6             | 1        | −33.4 ± 0.3| −17.3 ± 0.2| 16.1 ± 0.1 | 5.85 ± 0.05| 0.89 ± 0.04|
| 10\(^f\)         | 20.0             | 1        | −31.6 ± 0.1| −13.0 ± 0.2| 18.6 ± 0.2 | 5.53 ± 0.01| 0.89 ± 0.04|
| 10\(^f\)         | 20.0             | 1        | −30.8 ± 0.5| −11.1 ± 0.3| 19.7 ± 0.4 | 5.40 ± 0.08| 1.05 ± 0.03|
| 20\(^e\)         | 36.0             | 1        | −28.3 ± 0.1| −9.8 ± 0.3  | 18.5 ± 0.3 | 4.96 ± 0.02| 1.01 ± 0.04|
| 30\(^e\)         | 49.1             | 1        | −26.9 ± 0.1| −11.9 ± 0.2 | 15.0 ± 0.2 | 4.72 ± 0.01| 0.99 ± 0.09|
| 50\(^e\)         | 69.2             | 1        | −26.2 ± 0.1| −16.2 ± 0.8 | 10.0 ± 0.7 | 4.59 ± 0.01| 1.03 ± 0.04|
| 70\(^e\)         | 84.0             | 1        | −25.3 ± 0.1| −14.8 ± 0.2 | 10.5 ± 0.3 | 4.43 ± 0.02| 1.03 ± 0.06|
| 90\(^e\)         | 95.3             | 1        | −23.4 ± 0.1| −8.0 ± 0.4  | 15.4 ± 0.5 | 4.10 ± 0.02| 1.08 ± 0.06|
| 95\(^e\)         | 97.7             | 1        | −22.6 ± 0.2| −6.6 ± 0.3  | 16.0 ± 0.5 | 3.96 ± 0.03| 1.18 ± 0.05|
| 95\(^e\)         | 97.7             | 2        | −21.3 ± 0.2| −4.6 ± 0.1  | 16.7 ± 0.3 | 3.73 ± 0.03| 1.27 ± 0.02|
| 100\(^e\)        | 100              | 1        | −21.7 ± 0.2| −4.8 ± 0.1  | 16.9 ± 0.3 | 3.80 ± 0.03| 1.11 ± 0.11|
| 100\(^e\)        | 100              | 2        | −20.6 ± 0.4| −3.2 ± 0.4  | 17.4 ± 0.8 | 3.62 ± 0.06| 1.23 ± 0.15|

\(^a\) Recorded at 298 K; $\Delta G$, $\Delta H$, and $T\Delta S$ in kJ mol\(^{-1}\); the values are means of at least three independent measurements with the standard deviations specified, \(^b\) vol% of water in the water/methanol mixture, \(^c\) mol% of water in the water/methanol mixture, \(^*\) counterion: sodium, \(^f\) counterion: tetramethylammonium, \(^g\) counterion: tetrabutylammonium.

Sample preparation involved mixing of precise volumes of the individual solvents so that excess volumes were not considered in the calculation of the water content.
Table S4: Gibbs free energies $\Delta G$, enthalpies $\Delta H$, and entropies $T\Delta S$ of the binding of iodide to bis(cyclopeptides) 1 and 2 in different water/acetonitrile mixtures including the corresponding association constants $\log K_a$ and stoichiometry factors $n$.$^a$

| vol% water$^b$ | mol% water$^c$ | BCP$^d$ | $\Delta G$  | $\Delta H$  | $T\Delta S$ | $\log K_a$ | $n$     |
|----------------|----------------|---------|-------------|-------------|------------|------------|---------|
| 0$^f$          | 0              | 1       | $-35.7 \pm 0.8$ | $-49.3 \pm 0.5$ | $-13.6 \pm 0.5$ | $6.25 \pm 0.14$ | 0.81 $\pm 0.01$ |
| 0$^f$          | 0              | 1       | $-35.6 \pm 0.1$ | $-48.0 \pm 0.2$ | $-12.4 \pm 0.1$ | $6.24 \pm 0.02$ | 0.87 $\pm 0.01$ |
| 5$^f$          | 13.2           | 1       | $-31.7 \pm 0.9$ | $-7.1 \pm 0.8$ | $24.6 \pm 0.5$ | $5.55 \pm 0.15$ | 0.89 $\pm 0.06$ |
| 20$^e$         | 42.0           | 1       | $-27.1 \pm 0.2$ | $-3.4 \pm 0.3$ | $23.7 \pm 0.5$ | $4.74 \pm 0.03$ | 0.94 $\pm 0.04$ |
| 20$^e$         | 42.0           | 1       | $-26.9 \pm 0.2$ | $-2.6 \pm 0.1$ | $24.3 \pm 0.3$ | $3.72 \pm 0.03$ | 1.07 $\pm 0.05$ |
| 30$^e$         | 55.4           | 1       | $-24.8 \pm 0.1$ | $-6.7 \pm 0.1$ | $18.1 \pm 0.3$ | $4.35 \pm 0.02$ | 0.97 $\pm 0.05$ |
| 50$^e$         | 74.3           | 1       | $-24.0 \pm 0.1$ | $-10.3 \pm 0.3$ | $13.7 \pm 0.3$ | $4.20 \pm 0.01$ | 1.05 $\pm 0.01$ |
| 70$^e$         | 87.1           | 1       | $-24.1 \pm 0.1$ | $-12.8 \pm 0.1$ | $11.3 \pm 0.1$ | $4.23 \pm 0.01$ | 1.01 $\pm 0.03$ |
| 80$^e$         | 92.1           | 1       | $-24.1 \pm 0.1$ | $-13.4 \pm 0.1$ | $10.7 \pm 0.2$ | $4.22 \pm 0.01$ | 1.02 $\pm 0.02$ |
| 95$^e$         | 98.2           | 1       | $-22.5 \pm 0.1$ | $-7.8 \pm 0.2$ | $14.7 \pm 0.3$ | $3.94 \pm 0.01$ | 1.15 $\pm 0.10$ |
| 95$^e$         | 98.2           | 2       | $-21.5 \pm 0.3$ | $-6.1 \pm 0.2$ | $15.4 \pm 0.4$ | $3.77 \pm 0.04$ | 1.17 $\pm 0.03$ |

$^a$ Recorded at 298 K; $\Delta G$, $\Delta H$, and $T\Delta S$ in kJ mol$^{-1}$; the values are means of at least three independent measurements with the standard deviations specified, $^b$ vol% of water in the water/acetonitrile mixture, $^c$ mol% of water in the water/acetonitrile mixture, $^d$ bis(cyclopeptide), $^e$ counterion: sodium, $^f$ counterion: tetramethylammonium, $^g$ counterion: tetrabutylammonium.

Table S5: Gibbs free energies $\Delta G$, enthalpies $\Delta H$, and entropies $T\Delta S$ of the binding of iodide to bis(cyclopeptide) 1 in different water/DMSO mixtures including the corresponding association constants $\log K_a$ and stoichiometry factors $n$.$^a$

| vol% water$^b$ | mol% water$^c$ | BCP$^d$ | $\Delta G$  | $\Delta H$  | $T\Delta S$ | $\log K_a$ | $n$     |
|----------------|----------------|---------|-------------|-------------|------------|------------|---------|
| 0$^f$          | 0              | 1       | $-18.3 \pm 0.3$ | $7.1 \pm 0.7$ | $25.4 \pm 0.5$ | $3.21 \pm 0.05$ | fixed to |
| 70$^e$         | 90.2           | 1       | $-18.3 \pm 0.6$ | $2.2 \pm 0.5$ | $20.5 \pm 0.1$ | $3.20 \pm 0.10$ | 1.00    |

$^a$ Recorded at 298 K; $\Delta G$, $\Delta H$, and $T\Delta S$ in kJ mol$^{-1}$; the values are means of at least three independent measurements with the standard deviations specified, $^b$ vol% of water in the water/DMSO mixture, $^c$ mol% of water in the water/DMSO mixture, $^d$ bis(cyclopeptide), $^e$ counterion: sodium, $^f$ counterion: tetramethylammonium.
Solvent Dependence of Sulfate Affinity of 1:

Table S6:  Gibbs free energies $\Delta G$, enthalpies $\Delta H$, and entropies $T\Delta S$ of the binding of sulfate to bis(cyclopeptides) 1 and 2 in different water/methanol mixtures including the corresponding association constants $\log K_a$ and stoichiometry factors $n$.a

| vol% waterb | mol% waterc | BCPd | $\Delta G$   | $\Delta H$   | $T\Delta S$ | $\log K_a$  | n     |
|-------------|-------------|------|--------------|--------------|-------------|------------|-------|
| 30e         | 49.1        | 1    | $-38.6 \pm 0.3$ | $-11.7 \pm 0.6$ | $26.9 \pm 0.7$ | $6.76 \pm 0.05$ | 0.93 ± 0.13 |
| 50e         | 69.2        | 1    | $-33.5 \pm 0.2$ | $-14.7 \pm 0.8$ | $18.8 \pm 0.8$ | $5.87 \pm 0.02$ | 0.93 ± 0.03 |
| 70e         | 84.0        | 1    | $-28.8 \pm 0.1$ | $-8.5 \pm 0.3$  | $20.3 \pm 0.4$ | $5.04 \pm 0.02$ | 0.93 ± 0.04 |
| 70e,f       | 84.0        | 2    | $-27.6 \pm 0.1$ | $-8.8 \pm 0.1$  | $18.8 \pm 0.1$ | $4.82 \pm 0.01$ | 0.82 ± 0.02 |
| 95e         | 97.7        | 1    | $-21.1 \pm 0.3$ | $4.1 \pm 0.8$   | $25.2 \pm 0.5$ | $3.69 \pm 0.05$ | 0.80 ± 0.05 |
| 95e         | 97.7        | 2    | $-20.7 \pm 0.2$ | $5.1 \pm 0.1$   | $25.7 \pm 0.2$ | $3.62 \pm 0.05$ | 0.75 ± 0.03 |
| 100e        | 100         | 1    | $-19.9 \pm 0.1$ | $4.9 \pm 0.2$   | $24.8 \pm 0.2$ | $3.49 \pm 0.01$ | 0.81 ± 0.07 |
| 100e        | 100         | 2    | $-18.9 \pm 0.2$ | $5.9 \pm 0.3$   | $24.8 \pm 0.2$ | $3.31 \pm 0.03$ | 0.73 ± 0.01 |

a Recorded at 298 K; $\Delta G$, $\Delta H$, and $T\Delta S$ in kJ mol$^{-1}$; the values are means of at least three independent measurements with the standard deviations specified, b vol% of water in the water/methanol mixture, c mol% of water in the water/methanol mixture, * d bis(cyclopeptide), e counterion: sodium, f only measured twice.
Table S7: Gibbs free energies $\Delta G$, enthalpies $\Delta H$, and entropies $T\Delta S$ of the binding of sulfate to bis(cyclopeptides) 1 and 2 in different water/acetonitrile mixtures including the corresponding association constants $\log K_a$ and stoichiometry factors $n$.\(^a\)

| vol% water\(^b\) | mol% water\(^c\) | BCP\(^d\) | $\Delta G$ | $\Delta H$ | $T\Delta S$ | $\log K_a$ | $n$     |
|-------------------|------------------|-----------|-----------|-----------|-----------|-----------|--------|
| 30\(^e\)         | 55.4             | 1         | $-35.7 \pm 0.3$ | $4.5 \pm 0.5$ | $40.2 \pm 0.8$ | $6.25 \pm 0.05$ | $0.90 \pm 0.14$ |
| 50\(^e\)         | 74.3             | 1         | $-29.9 \pm 0.1$ | $-6.4 \pm 0.2$ | $23.5 \pm 0.3$ | $5.24 \pm 0.02$ | $0.92 \pm 0.03$ |
| 70\(^e\)         | 87.1             | 1         | $-27.3 \pm 0.1$ | $-11.4 \pm 0.2$ | $15.9 \pm 0.2$ | $4.78 \pm 0.02$ | $0.90 \pm 0.03$ |
| 70\(^e,f\)       | 87.1             | 2         | $-26.6 \pm 0.1$ | $-13.0 \pm 0.1$ | $13.6 \pm 0.1$ | $4.66 \pm 0.01$ | $0.86 \pm 0.01$ |
| 80\(^e\)         | 92.1             | 1         | $-25.6 \pm 0.1$ | $-10.4 \pm 0.4$ | $15.2 \pm 0.5$ | $4.48 \pm 0.02$ | $0.91 \pm 0.03$ |
| 95\(^e\)         | 98.2             | 1         | $-22.6 \pm 0.2$ | $1.5 \pm 0.1$   | $24.1 \pm 0.1$ | $3.97 \pm 0.02$ | $0.69 \pm 0.03$ |
| 95\(^e\)         | 98.2             | 2         | $-22.7 \pm 0.3$ | $1.7 \pm 0.2$   | $24.5 \pm 0.1$ | $3.98 \pm 0.04$ | $0.66 \pm 0.01$ |

\(^a\) Recorded at 298 K; $\Delta G$, $\Delta H$, and $T\Delta S$ in kJ mol\(^{-1}\); the values are means of at least three independent measurements with the standard deviations specified, \(^b\) vol% of water in the water/acetonitrile mixture, \(^c\) mol% of water in the water/acetonitrile mixture, \(^*\) bis(cyclopeptide), \(^e\) counterion: sodium, \(^f\) only measured twice.

Table S8: Gibbs free energies $\Delta G$, enthalpies $\Delta H$, and entropies $T\Delta S$ of the binding of sulfate to bis(cyclopeptide) 1 in different water/DMSO mixtures including the corresponding association constants $\log K_a$ and stoichiometry factors $n$.\(^a\)

| vol% water\(^b\) | mol% water\(^c\) | BCP\(^d\) | $\Delta G$ | $\Delta H$ | $T\Delta S$ | $\log K_a$ | $n$     |
|-------------------|------------------|-----------|-----------|-----------|-----------|-----------|--------|
| 40\(^e\)         | 72.4             | 1         | $-38.3 \pm 0.6$ | $-6.3 \pm 0.4$ | $32.0 \pm 0.6$ | $6.72 \pm 0.10$ | $0.88 \pm 0.04$ |
| 50\(^e\)         | 79.8             | 1         | $-33.6 \pm 0.6$ | $-2.8 \pm 0.1$ | $30.8 \pm 0.5$ | $5.89 \pm 0.10$ | $0.87 \pm 0.04$ |
| 70\(^e\)         | 90.2             | 1         | $-27.7 \pm 0.2$ | $3.2 \pm 0.2$   | $30.9 \pm 0.1$ | $4.85 \pm 0.03$ | $0.77 \pm 0.06$ |
| 90\(^e\)         | 97.3             | 1         | $-22.0 \pm 0.1$ | $6.1 \pm 0.2$   | $28.1 \pm 0.3$ | $3.86 \pm 0.01$ | $0.80 \pm 0.01$ |

\(^a\) Recorded at 298 K; $\Delta G$, $\Delta H$, and $T\Delta S$ in kJ mol\(^{-1}\); the values are means of at least three independent measurements with the standard deviations specified, \(^b\) vol% of water in the water/DMSO mixture, \(^c\) mol% of water in the water/DMSO mixture, \(^*\) bis(cyclopeptide), \(^e\) counterion: sodium.
Solvent Dependence of Solvent Properties:

Figure S13: Dependence of the Gibbs free energies $\Delta G_{tr}$ of transferring sulfate (a) iodide (b) ions from water to water/methanol (black), water/acetonitrile (red), and water/DMSO (blue) on the solvent composition.$^{5,6}$

Figure S14: Dependence of the hydrogen bond donation ability $\alpha$ on the solvent composition (water/methanol, black; water/acetonitrile, red; and water/DMSO, blue).$^7$
Figure S15: Dependence of the stabilities in $\Delta G$ of the sulfate (a) and iodide (b) complexes of bis(cyclopeptides) 1 on the solvent composition $SC$ (water/methanol, black; water/acetonitrile, red; water/DMSO, blue). The circles denote the experimental results and the lines the regression curves describing the experimental results fitted to appropriate polynomials. The corresponding equations are summarized below.

Table S9: Coefficients of the regression equations resulting after fitting the dependence of the stabilities in $\Delta G$ of the sulfate and iodide complexes of bis(cyclopeptides) 1 on the solvent composition to polynomials ($SC = $ solvent composition in mol%).

| solvent          | anion | $\Delta G_{\text{calcd}} = c_4 SC^4 + c_3 SC^3 + c_2 SC^2 + c_1 SC + \text{const}$ |
|------------------|-------|----------------------------------------------------------------------------------|
| water/methanol   | sulfate | $c_4$ | $c_3$ | $c_2$ | $c_1$ | const |
| water/DMSO      | sulfate | 0     | 0     | $-3.430E+1$ | $-3.063E-1$ | 4.500E–3 |
| water/methanol   | iodide  | $4.548E-7$ | $-5.462E-5$ | $-6.560E-4$ | $3.028E-1$ | $-3.640E+1$ |
| water/acetonitrile| iodide  | $-3.546E+1$ | 2.495E–1 | 1.613E–3 | $-7.646E-5$ | 4.875E–7 |

Based on the above regression equations (Table S9), the $\Delta G_{\text{calcd}}$ values in the different solvent mixtures were calculated at the mol% solvent compositions for which the Gibbs free energies of transferring iodide or sulfate anions into the respective solvent mixture $\Delta G_t$ and the hydrogen donator ability $\alpha$ of the mixture are available. These values were then used for the fitting analysis, which was performed by using StatPlus:mac 6.0.3 (AnalystSoft Inc.). Table S10 and Table S11 summarize the starting values. The results are collected in Table 4 of the main text.
Table S10: Extrapolated Gibbs free energies of iodide binding $\Delta G$ by bis(cyclopeptide) 1 in water/methanol and water/acetonitrile along with the respective $\Delta G_{ir}$ and $\alpha$ values at the respective solvent compositions.

| mol% water | $\Delta G_{\text{calc}}^a$ | $\Delta G_{ir}^a$ | $\alpha$ | $\Delta G_{\text{calc}}^a$ | $\Delta G_{ir}^a$ | $\alpha$ |
|----------|-----------------|-----------------|--------|-----------------|-----------------|--------|
| 0.0      | -36.40          | 7.30            | 1.00   | -35.46          | 20.30           | 0.25   |
| 10.0     | -33.49          | 6.10            | 1.01   | -32.87          | 16.90           | 0.55   |
| 20.0     | -30.97          | 4.90            | 1.01   | -30.36          | 14.00           | 0.70   |
| 30.0     | -29.01          | 3.70            | 1.00   | -28.19          | 11.10           | 0.78   |
| 40.0     | -27.67          | 2.60            | 0.99   | -26.54          | 9.20            | 0.83   |
| 50.0     | -26.89          | 1.70            | 0.98   | -25.46          | 7.70            | 0.86   |
| 60.0     | -26.50          | 0.90            | 0.98   | -24.88          | 6.40            | 0.89   |
| 70.0     | -26.23          | 0.30            | 1.01   | -24.61          | 5.50            | 0.92   |
| 80.0     | -25.71          | -0.10           | 1.04   | -24.36          | 4.20            | 0.96   |
| 90.0     | -24.44          | -0.30           | 1.11   | -23.70          | 2.30            | 1.05   |
| 100.0    | -21.82          | 0.00            | 1.17   | -22.09          | 0.00            | 1.17   |

$^a$ in kJ mol$^{-1}$.

Table S11: Extrapolated Gibbs free energies of sulfate binding $\Delta G$ by bis(cyclopeptide) 1 in water/methanol and water/DMSO along with the respective $\Delta G_{ir}$ and $\alpha$ values at the respective solvent compositions.

| mol% water | $\Delta G_{\text{calc}}^a$ | $\Delta G_{ir}^a$ | $\alpha$ | $\Delta G_{\text{calc}}^a$ | $\Delta G_{ir}^a$ | $\alpha$ |
|----------|-----------------|-----------------|--------|-----------------|-----------------|--------|
| 70.0     | -33.69          | 16.00           | 1.01   | -39.34          | 52.70           | 0.46   |
| 80.0     | -30.00          | 11.70           | 1.04   | -33.90          | 32.70           | 0.59   |
| 90.0     | -25.41          | 6.30            | 1.11   | -27.45          | 11.40           | 0.81   |
| 100.0    | -19.93          | 0.00            | 1.17   | -19.97          | 0.00            | 1.17   |

$^a$ in kJ mol$^{-1}$.
Figure S16: Solvent dependence of the Gibbs free energy of binding of iodide to bis(cyclopeptide) 1 in water/DMSO predicted by using $\Delta G_{\text{calc}} = -1.26 \Delta G_{tr} - 19.92 \alpha$ for solvent compositions for which $\Delta G_{tr}$ and $\alpha$ are available (black line). The blue circles represent the experimental results.
Correlation of the Enthalpy of Iodide Binding to 1 With Preferential Solvation:

To assess whether the enthalpy of iodide binding in water/methanol or water/acetonitrile could be correlated with preferential solvation parameters, the binding enthalpies in Table S3 and Table S4 were first fitted to a 4th and 5th degree polynomial, respectively.

Table S12: Coefficients of the regression equations resulting after fitting the dependence of the enthalpies of iodide binding of bis(cyclopeptides) 1 on the solvent composition to a 4th and 5th degree polynomial (SC = solvent composition in mol%).

| co-solvent   | $\Delta H_{\text{calcd}} = c_5 \text{SC}^5 + c_4 \text{SC}^4 + c_3 \text{SC}^3 + c_2 \text{SC}^2 + c_1 \text{SC} + \text{const}$ |
|--------------|--------------------------------------------------------------------------------------------------|
| methanol     | $c_5$  $c_4$  $c_3$  $c_2$  $c_1$  const                                             |
|              | 0  $-1.283\times10^{-6}$  $4.872\times10^{-4}$  $-5.333\times10^{-2}$  $2.036\times10^{0}$  $-3.400\times10^{1}$ |
| acetonitrile | $1.448\times10^{-7}$  $-4.036\times10^{-5}$  $4.344\times10^{-3}$  $-2.255\times10^{-1}$  $5.419\times10^{0}$  $-4.804\times10^{1}$ |

As preferential solvation parameters, $\delta x_{X,S}$, describing the preferential solvation of iodide anions by water over solvation by methanol or acetonitrile in the respective solvent mixtures was used$^8$ and Reichardt's $E_T(30)^9$ value as a measure for preferential receptor solvation. In addition, also a related parameter $E_T$(dye) recently introduced for 4-[4-(dimethylamino)styryl]-1-methylpyridinium iodide as dye was tested.$^{10}$ It should be noted that the authors of the latter paper showed that solvatochromism of the dye is not influenced by the presence of iodide anions as counterions.

Based on the above regression equations (Table S12), the $\Delta H$ values in the different solvent mixtures were calculated at the mol% solvent compositions for which $\delta x_{X,S}$, $E_T(30)$, and $E_T$(dye) are available. These values were then used for the fitting analysis, which was performed by using StatPlus:mac 6.0.3 (AnalystSoft Inc.). Table S13 summarizes the starting values and Table S14 the coefficients $d$ and $e$ obtained after fitting this data to $\Delta H = d \delta x_{X,S} + e E_T(30)$ or $\Delta H = d \delta x_{X,S} + e E_T$(dye). The values in the pure solvent mixtures were not considered in the analysis. The goodness of the correlations is depicted graphically in Figure S17.
Table S13: Extrapolated enthalpies of iodide binding $\Delta H$ by bis(cyclopeptide) 1 in water/methanol and water/acetonitrile along with the respective $\delta_{X,S}$, $E_{T(30)}$, and $E_{T(dye)}$ at the respective solvent compositions.

| mol% | water/methanol $\Delta H^a$ | $\delta_{X,S}$ | $E_{T(30)}$ | $E_{T(dye)}$ | water/acetonitrile $\Delta H^a$ | $\delta_{X,S}$ | $E_{T(30)}$ | $E_{T(dye)}$ |
|------|----------------------------|----------------|-------------|-------------|-------------------------------|----------------|-------------|-------------|
| 0.0  | -34.00                     | 0.000          | 55.70       | 60.1        | -48.04                        | 0.00           | 46.00       | 60.8        |
| 10.0 | -18.49                     | -0.019         | 55.80       | 60.1        | -12.44                        | -0.09          | 50.80       | 61.0        |
| 20.0 | -10.91                     | -0.032         | 56.10       | 60.2        | -1.10                         | -0.21          | 53.60       | 61.1        |
| 30.0 | -8.79                      | -0.041         | 56.50       | 60.3        | -0.30                         | -0.27          | 54.90       | 61.1        |
| 40.0 | -9.97                      | -0.043         | 56.80       | 60.3        | -2.54                         | -0.25          | 55.40       | 61.1        |
| 50.0 | -12.62                     | -0.036         | 57.30       | 60.5        | -4.81                         | -0.20          | 55.60       | 61.2        |
| 60.0 | -15.18                     | -0.023         | 57.80       | 60.7        | -6.81                         | -0.15          | 55.80       | 61.3        |
| 70.0 | -16.44                     | -0.008         | 58.50       | 61.0        | -9.26                         | -0.12          | 56.50       | 61.3        |
| 80.0 | -15.47                     | 0.002          | 59.50       | 61.5        | -12.12                        | -0.09          | 57.60       | 61.5        |
| 90.0 | -11.66                     | 0.005          | 61.00       | 62.5        | -12.90                        | -0.05          | 59.80       | 61.9        |
| 100.0| -4.70                      | 0.000          | 63.10       | 63.8        | -4.86                         | 0.00           | 63.10       | 63.9        |

$^a$ in kJ mol$^{-1}$.

Table S14: Coefficients $d$ and $e$ of the equation $\Delta H = d \delta_{X,S} + e E_{T(30)}$ or $\Delta H = d \delta_{X,S} + e E_{T(dye)}$, which describes the dependence of the enthalpy of iodide binding to 1 in water/methanol and water/acetonitrile with preferential solvation parameters $\delta_{X,S}$, $E_{T(30)}$, and $E_{T(dye)}$.

| solvents       | $E_T$     | $d$   | $e$   | $R^2$   |
|----------------|-----------|-------|-------|---------|
| water/methanol | $E_{T(30)}$ | -75.24 | -0.26 | 0.9587  |
| water/methanol | $E_{T(dye)}$ | -87.50 | -0.25 | 0.9614  |
| water/acetonitrile | $E_{T(30)}$ | -59.96 | -0.29 | 0.9727  |
| water/acetonitrile | $E_{T(dye)}$ | -63.30 | -0.28 | 0.9810  |
Figure S17: Correlation of the experimental $\Delta H$ values with the ones calculated on the basis of the regression analyses by using $E_T(30)$ (a) or $E_T(\text{dye})$ (b) for the preferential solvation of the receptor; iodide binding in water/methanol (black), iodide binding in water/acetonitrile (red).

Table S14 shows that the correlation is not yet satisfactory but that the dependence of the experimental enthalpy of iodide to 1 in water/methanol and in water/acetonitrile can be reasonably well described by using the preferential solvation parameters for the anion in the respective solvents, $\delta x_{X,S}$, and the ones assumed for the receptor, $E_T(30)$, and $E_T(\text{dye})$. The individual coefficients $d$ and $e$ for the two solvent systems are in acceptable agreement, considering the assumptions made. They show that the anion has the more pronounced effect on the solvent-dependence of binding enthalpy, which is expected. Figure S17 illustrates that the correlation is better in water/acetonitrile. The largest deviations are observed in mixtures in which one component of the solvent strongly dominates, indicating that other solvent properties contribute to binding in these mixtures more strongly than in the medium region of solvent composition.
References

1. Sommer, F.; Kubik, S. Org. Biomol. Chem. 2014, 12, 8851-8860.
2. Keller, S.; Vargas, C.; Zhao, H.; Piszczek, G.; Brautigam, C. A.; Schuck, P. Anal. Chem. 2012, 84, 5066-5073.
3. Houtman, J. C. D.; Brown, P. H.; Bowden, B.; Yamaguchi, H.; Appella, E.; Samelson, L. E.; Schuck, P. Protein Sci. 2007, 16, 30-42.
4. http://www.analyticalultracentrifugation.com/sedphat/download.htm.
5. Marcus, Y. Z. Naturforsch., A 1995, 50, 51-58.
6. Marcus, Y. Chem. Rev. 2007, 107, 3880-3897.
7. Marcus, Y. J. Chem. Soc., Perkin Trans. 2 1994, 1751-1758.
8. Marcus, Y. J. Chem. Thermodynamics 2007, 39, 1338-1345.
9. Reichardt, C. Chem. Rev. 1994, 94, 2319-2358.
10. Bevilaqua, T.; Gonçalves, T. S.; Venturini, C. D. G.; Machado, V. G. Spectrochim. Acta, Part A 2006, 65, 535-542.