Electronic Supplementary Material (ESI) for ChemComm.

Ion mobility and gas phase H/D exchange: revealing the importance of a single hydrogen bond for the chiral recognition of crown ether ammonium complexes

Jan M. Wollschläger, Konstantin Simon, Marius Gaedke
and Christoph A. Schalley*
Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
*e-mail: c.schalley@fu-berlin.de

Supporting Information

Contents

1 General remarks **S2**
1.1 Reagents S2
1.2 Typical conditions for TWIMS measurements S2
2 Synthesis of hosts (*S*)- and (*R*)-1 **S3**
2.1 Synthesis of (*S*)-**1** S3
2.2 Synthesis of (*R*)-**1** S4
2.3 ^{1}H and ^{13}C NMR spectra S5
2.4 CD spectra of (*S*)/(*R*)-**1** S7
3 MS and MS/MS measurements **S8**
4 IMS measurements **S10**
4.1 CCS calibration S10
4.2 Measurements with host **1** S12
4.3 Control experiments S14
5 Gas-phase H/D-exchange (HDX) **S16**
6 References **S18**

1 General remarks

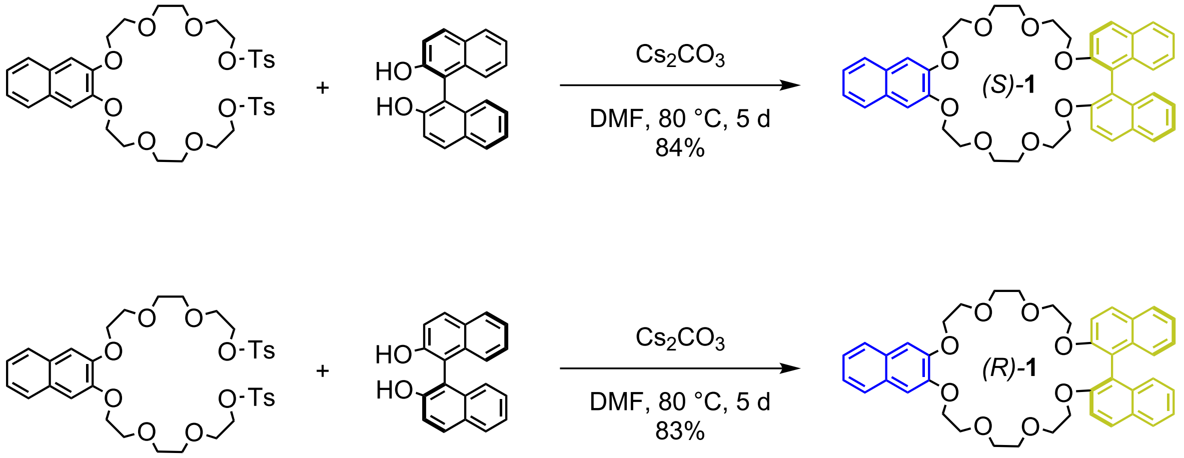
1.1 Reagents

Chemicals (-)-(18-Crown-6)-2,3,11,12-tetracarboxylic acid (CAS 73891-15-3), $\alpha/\beta/\gamma$-cyclodextrins, and all amino acids were purchased at Sigma-Aldrich and used as received.

1.2 Typical conditions for TWIMS measurements

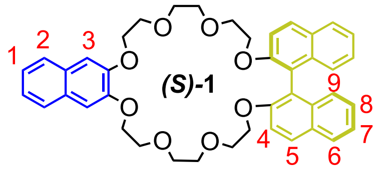
Travelling-wave ion-mobility spectrometry mass spectrometry (TWIMS) measurements were performed with a Waters Synapt G2-S HDMS quadrupole TWIMS time-of-flight mass spectrometer (Manchester, UK) utilizing an electrospray ionization (ESI) source. For the ion mobility experiments, the sample (2.5 μM host, 10-50 μM amino acid, MeOH:H_2O 1:1, 0.25% HCOOH) was directly infused using a syringe pump with a flow rate of 10 μL/min. If not noted otherwise, the concentration of the host is 2.5 μM, and the concentration of the guest is 50 μM. The capillary voltage was set to 2.6 kV, the source and desolvation temperature were 80 °C and 160 °C, respectively. Sample cone and source offset voltages were 30 V and 39 V. The desolvation gas flow was 600 L/h. The helium cell gas flow was set to 180 mL/min and the IMS gas flow (nitrogen) was set to 90 mL/min. The wave height and velocity were kept at 37.9 V and 300 m/s. IMS cell calibration was carried out using a polyalanine reference with a concentration of 0.2 mg/mL as described by Bush *et al.* (see main text).

2 Synthesis of hosts (*S*)- and (*R*)-1



Scheme 1: Synthesis of hosts (*S*)- and (*R*)-**1**. The ditosylate precursor was prepared according to a previously described procedure.[S1]

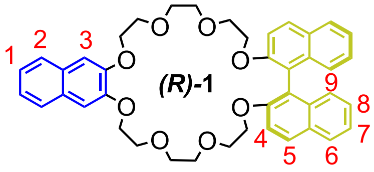
2.1 Synthesis of (*S*)-1



A solution of 197 mg (683 μmol, 1.0 equiv.) (*S*)-BINOL and 667 mg (2.05 mmol, 3.0 equiv.) Cs_2CO_3 in dry DMF (100 mL) was stirred for 15 min at 60 °C. A solution of 500 mg (683 μmol, 1.0 equiv.) ditosylate in dry DMF (25 mL) was added over 2 h at 60 °C. The combined solution was heated to 80 °C for 5 days while stirring under argon. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in DCM. The solution was washed with brine. After drying over $MgSO_4$, the crude product was purified by column chromatography (SiO_2, DCM/EtOAc, R_f = 0.4 in DCM/EtOAc = 1:1) to get the desired product (*S*)-**1** as a colorless solid in 84% yield (387 mg, 573 μmol).

M.p. 62-64 °C; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ [ppm] = 3.33–3.42 (m, 4H, O – CH_2), 3.46–3.63 (m, 8H, O – CH_2), 3.84–3.87 (m, 4H, O – CH_2), 4.04–4.09 (m, 2H, O – CH_2), 4.17–4.23 (m, 6H, O – CH_2), 7.05 (d, ^3J(H,H) = 8.9 Hz, 2H, H4), 7.15 (s, 2H, H3), 7.17–7.21 (m, 2H, H9), 7.29–7.33 (m, 2H, H8), 7.33–7.35 (m, 2H, H1), 7.46 (d, ^3J(H,H) = 9.3 Hz, 2H, H7), 7.67–7.72 (m, 2H, H2), 7.84 (d, ^3J(H,H) = 8.7 Hz, 2H, H6), 7.90 (d, ^3J(H,H) = 10.2 Hz, 2H, H5); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ [ppm] = 69.3, 70.0, 70.3, 71.2, 71.4, 108.4, 116.4, 120.8, 124.1, 124.7, 125.7, 126.7, 126.8, 128.5, 129.8, 129.9, 129.9, 134.6, 149.7, 155.1. **ESI-HRMS**: *m/z* calcd. for $[C_{42}H_{42}O_8]$: 697.2772 $[M + Na]^+$, found: 697.2819; 713.2511 $[M + K]^+$, found: 713.2554.

2.2 Synthesis of (*R*)-1



A solution of 199 mg (683 μmol, 1.0 equiv.) (*R*)-BINOL and 680 mg (2.09 mmol, 3.0 equiv.) Cs_2CO_3 in dry DMF (100 mL) was stirred for 15 min at 60 °C. A solution of 507 mg (692 μmol, 1.0 equiv.) ditosylate in dry DMF (25 mL) was added over 2 h at 60 °C. The combined solution was heated to 80 °C for 5 days while stirring under argon. Afterwards the solvent was removed under reduced pressure and the residue was dissolved in DCM. The solution was washed with brine. After drying over $MgSO_4$, the crude product was purified by column chromatography (SiO_2, DCM/EtOAc, R_f = 0.4 in DCM/EtOAc = 1:1) to get the desired product (*R*)-**1** as a colorless solid in 83% yield (383 mg, 567 μmol).

M.p. 62-64 °C; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ [ppm] = 3.31–3.42 (m, 4H, $O - CH_2$), 3.45–3.64 (m, 8H, $O - CH_2$), 3.83–3.89 (m, 4H, $O - CH_2$), 4.03–4.12 (m, 2H, $O - CH_2$), 4.17–4.24 (m, 6H, $O - CH_2$), 7.05 (d, ^3J(H,H) = 8.6 Hz, 2H, H4), 7.15 (s, 2H, H3), 7.17–7.21 (m, 2H, H9), 7.28–7.33 (m, 2H, H8), 7.33–7.35 (m, 2H, H1), 7.46 (d, ^3J(H,H) = 9.0 Hz, 2H, H7), 7.68–7.73 (m, 2H, H2), 7.83 (d, ^3J(H,H) = 8.2 Hz, 2H, H6), 7.91 (d, ^3J(H,H) = 8.8 Hz, 2H, H5); **^{13}C NMR** (126 MHz, CD_2Cl_2) δ [ppm] = 69.2, 70.0, 70.3, 71.2, 71.4, 108.4, 116.4, 120.8, 124.1, 124.7, 125.7, 126.7, 126.8, 128.4, 129.8, 129.9, 129.9, 134.6, 149.7, 155.1. **ESI-HRMS**: *m/z* calcd. for $[C_{42}H_{42}O_8]$: 697.2772 $[M + Na]^+$, found: 697.2823; 713.2511 $[M + K]^+$, found: 713.2561.

2.3 ^{1}H and ^{13}C NMR spectra

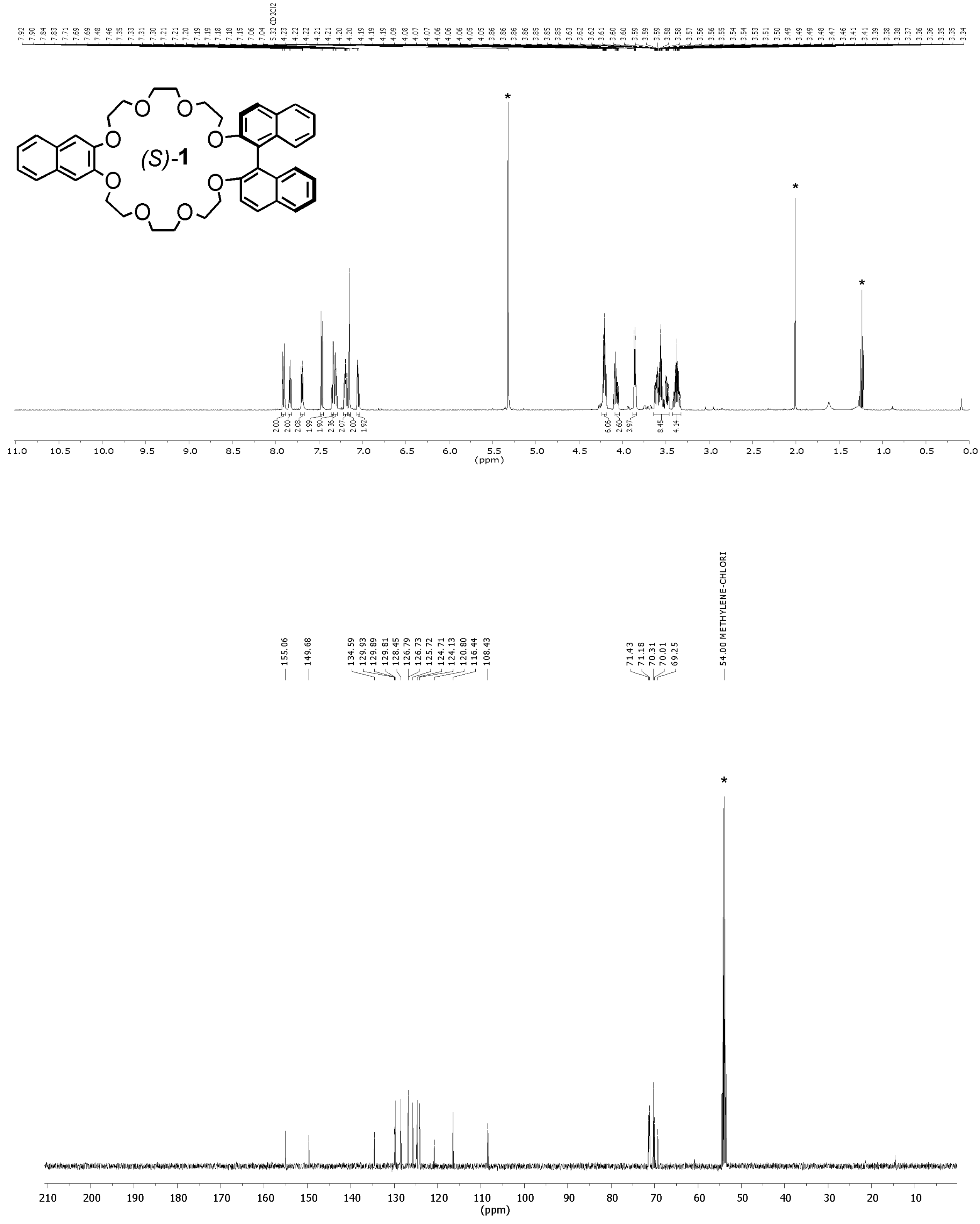


Figure S1: top) ^{1}H NMR (500 MHz, CD_2Cl_2, 298 K); bottom) ^{13}C NMR (126 MHz, CD_2Cl_2, 298 K) of (*S*)-**1**. Solvent signals are marked with an asterisk.

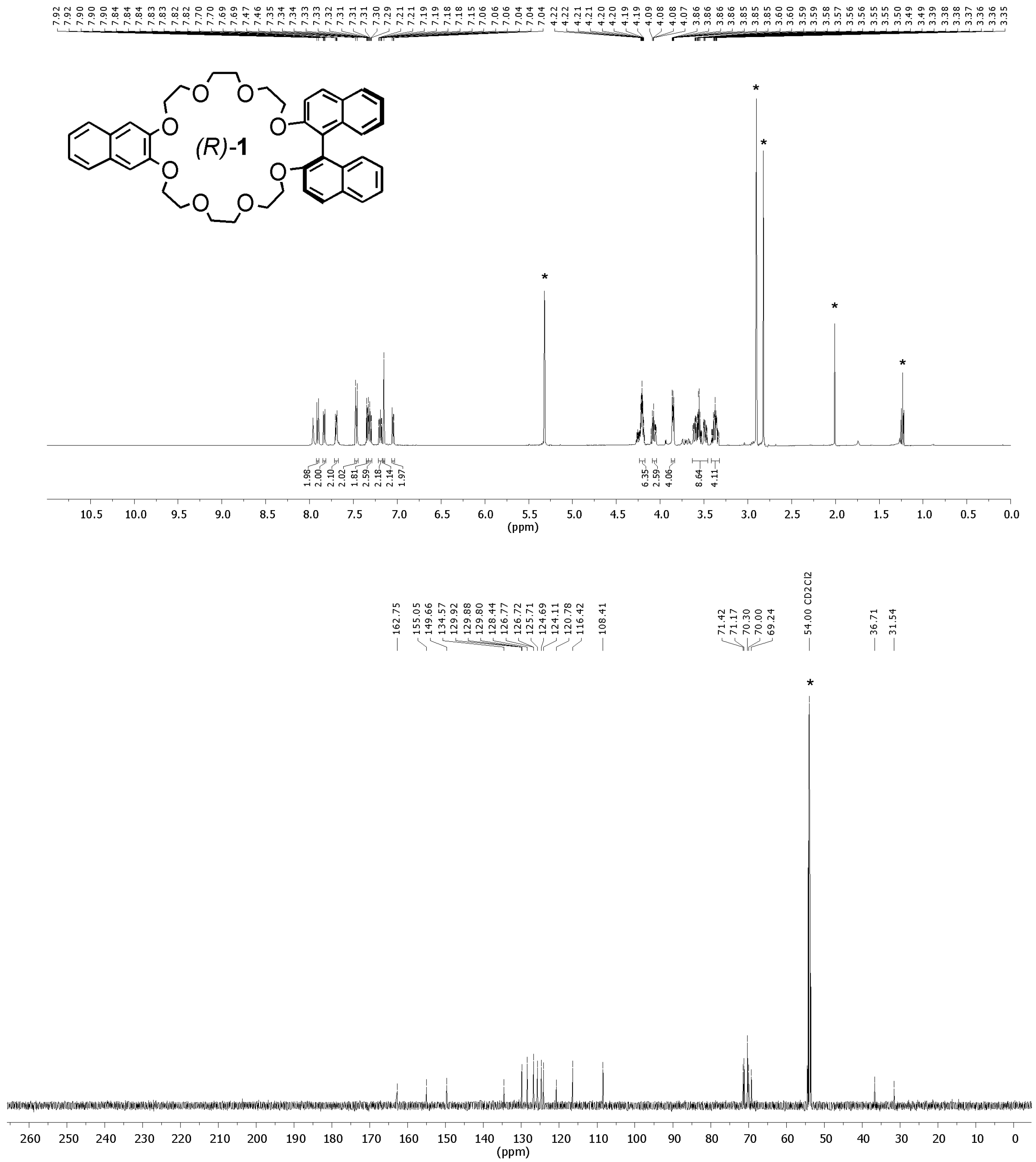


Figure S2: top) ^{1}H NMR (500 MHz, CD_2Cl_2, 298 K); bottom) ^{13}C NMR (126 MHz, CD_2Cl_2, 298 K) of (*R*)-**1**. Solvent signals are marked with an asterisk.

2.4 CD spectra of (*S*)/(*R*)-1

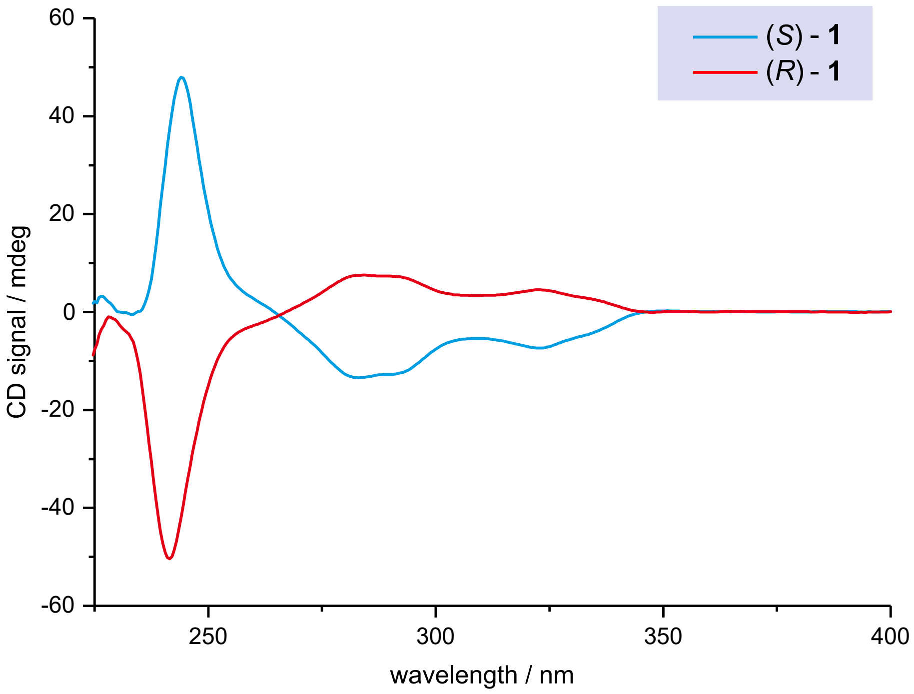


Figure S3: CD spectra (0.1 mM in DCM, 1 cm cuvette length) of (*S*)-**1** (blue) and (*R*)-**1** (red).

3 MS and MS/MS measurements

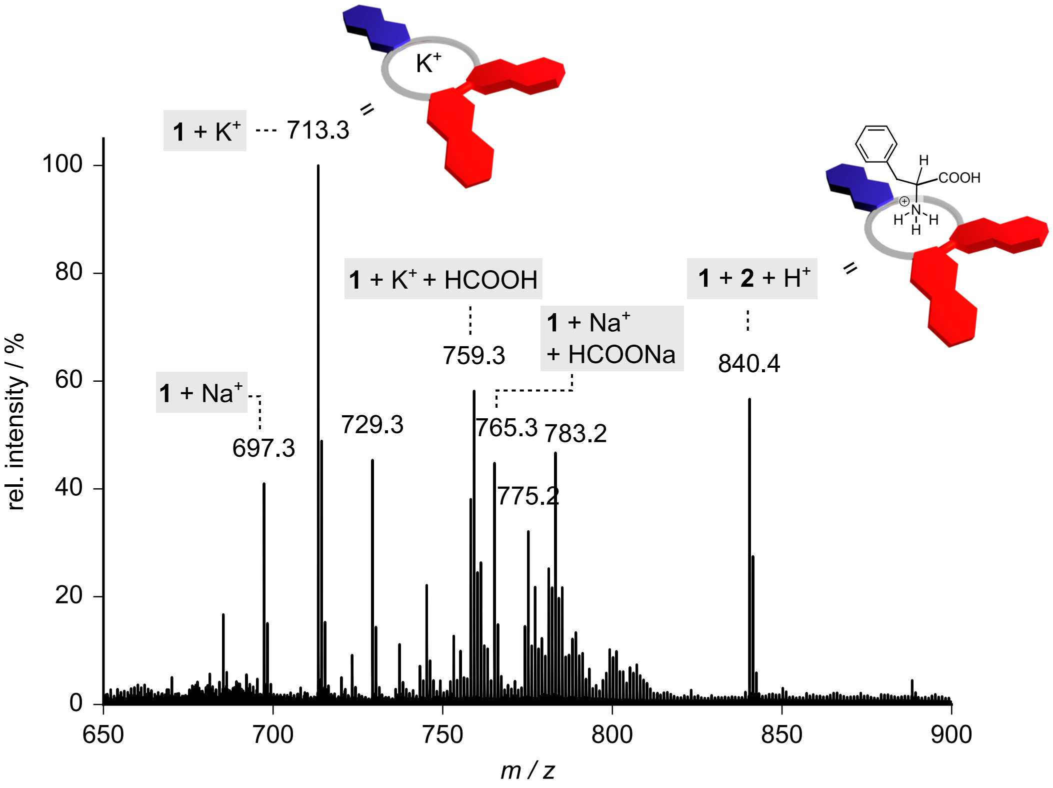


Figure S4: Mass spectrum of (*R*)-**1**+(*R*)-**2** (for conditions see general remarks).

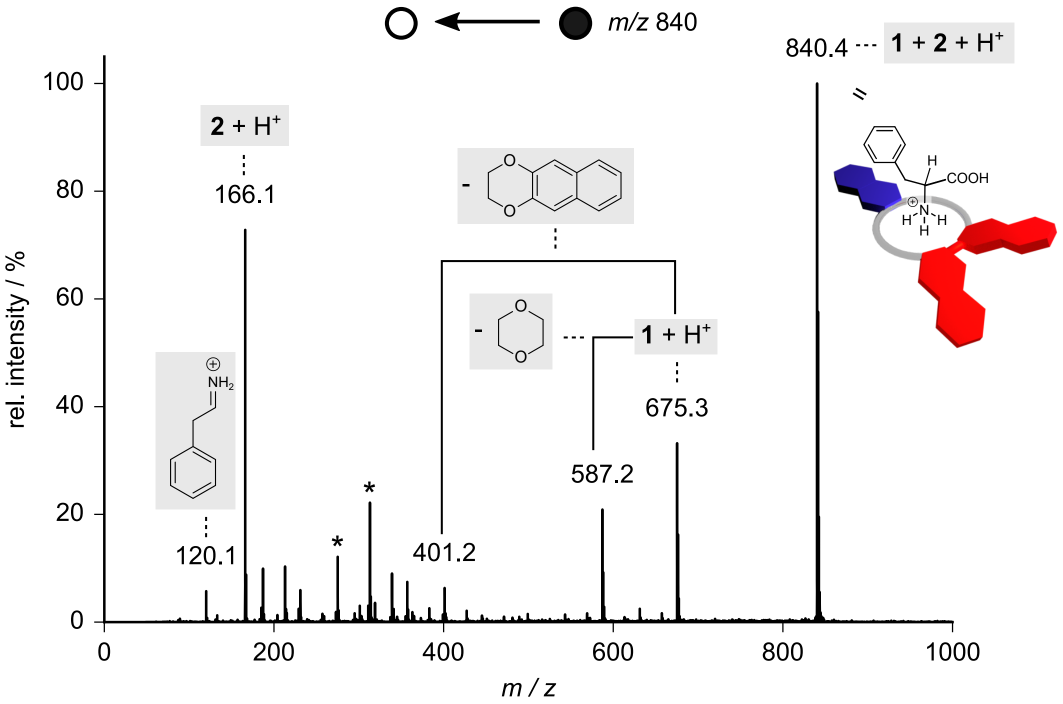


Figure S5: Collision-induced dissociation (CID) MS/MS experiment of mass-selected (*R*)-**1** + (*R*)-**2** + H$^+$ (for conditions see general remarks). Major fragments correspond to the free ammonium guest **2** + H$^+$ and the protonated host **1** + H$^+$, in accordance with the comparable gas-phase proton affinities of 967.0 kJ/mol and 922.9 kJ/mol for 18-crown-6 ether and phenylalanine, respectively.[S2] Peaks marked with an asterisk correspond to further fragmentation of the crown ether and have been omitted for brevity.

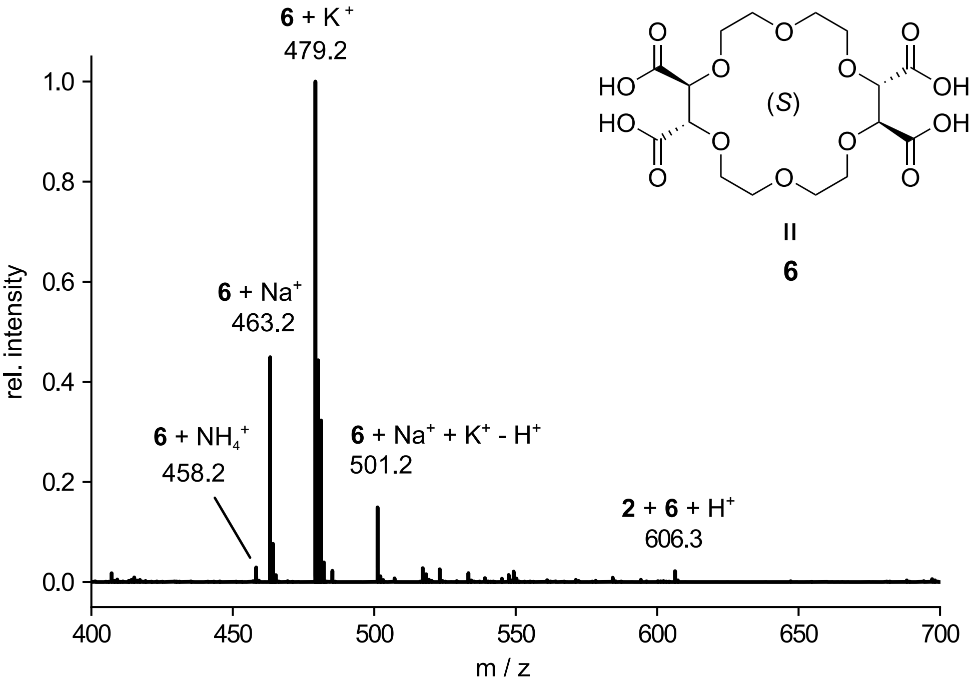


Figure S6: Mass spectrum of (*S*)-(-)-18-crown-6-2,3,11,12-tetracarboxylic acid **6** (5 μM), and **2** (50 μM) in MeOH:H_2O 1:1 (0.25% HCOOH).

4 IMS measurements

4.1 CCS calibration

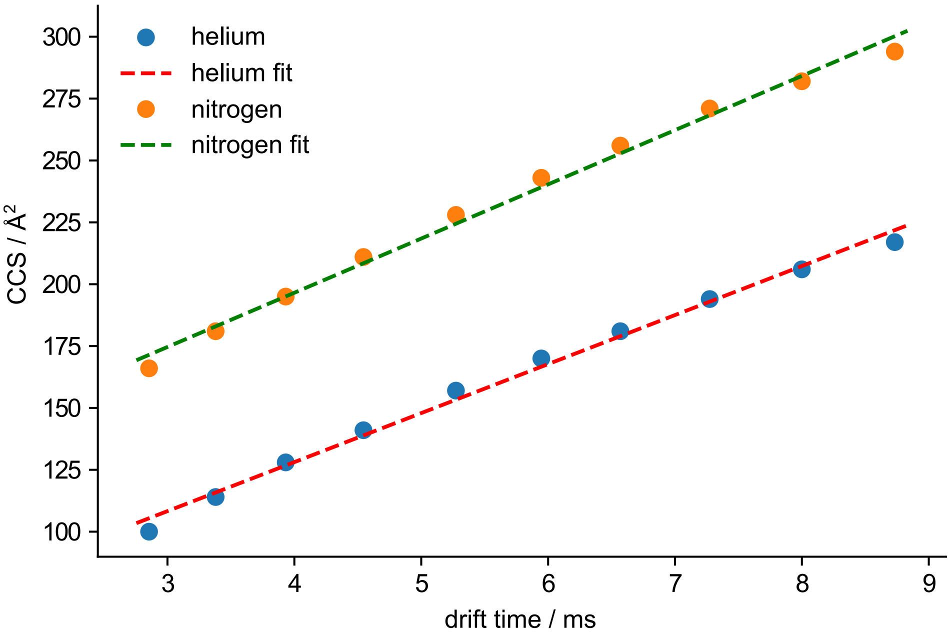


Figure S7: Typical polyalanine CCS calibration result.

Table S1: Calibration in the range of *m*/*z* 50 to 1000.

m/*z*	drift time / ms	CCS in Helium / Å^2	CCS in Nitrogen / Å^2
303	2.85	100	166
374	3.38	114	181
445	3.93	128	195
516	4.54	141	211
587	5.27	157	228
658	5.95	170	243
729	6.57	181	256
800	7.27	194	271
871	8.00	206	282
942	8.73	217	294

Table S2: Statistics for calibrations performed with different *m*/*z* ranges. While all three calibrations are highly linear, the best R^2-value is obtained for the narrow mass range 650-900. Hence, this calibration was used for measurements with host **1**. In the case of **3**, the calibration for the mass range *m*/*z* 50-1000 was employed, as complex **2** + **3** + H^+ lies outside the mass range 650-900.

m/*z*	slope / $Å^2 \cdot ms^{-1}$	intercept $Å^2$	R^2
50–1000	19.807	48.881	0.9934
50–2000	19.199	50.637	0.9930
650–900	17.622	65.625	0.9995

4.2 Measurements with host 1

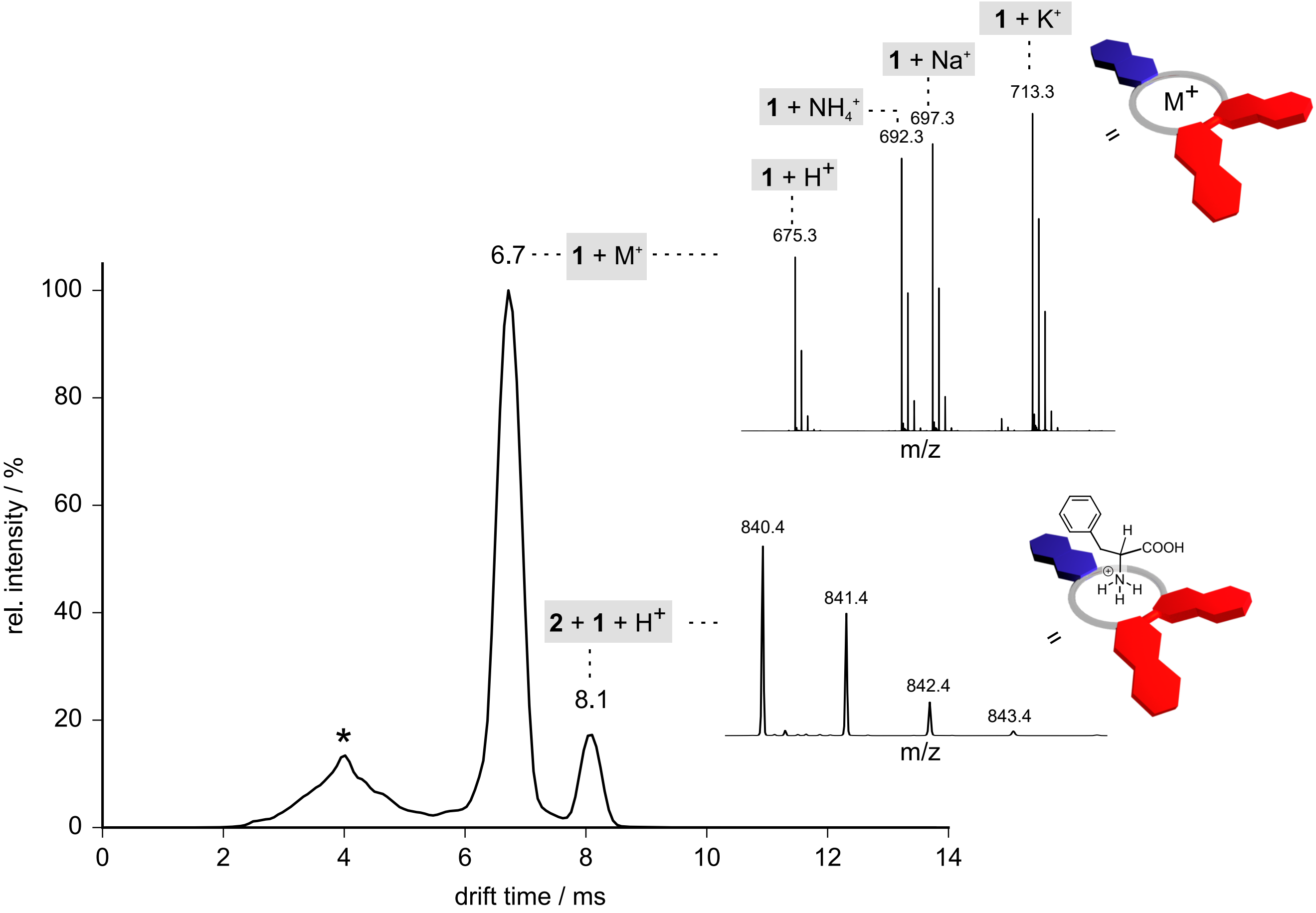


Figure S8: Arrival time distribution (ATD) of (*R*)-**1** and (*R*)-**2** in the overall mass range *m*/*z* 650-900. The component marked by an asterisk corresponds to Triton X, a common trace impurity.

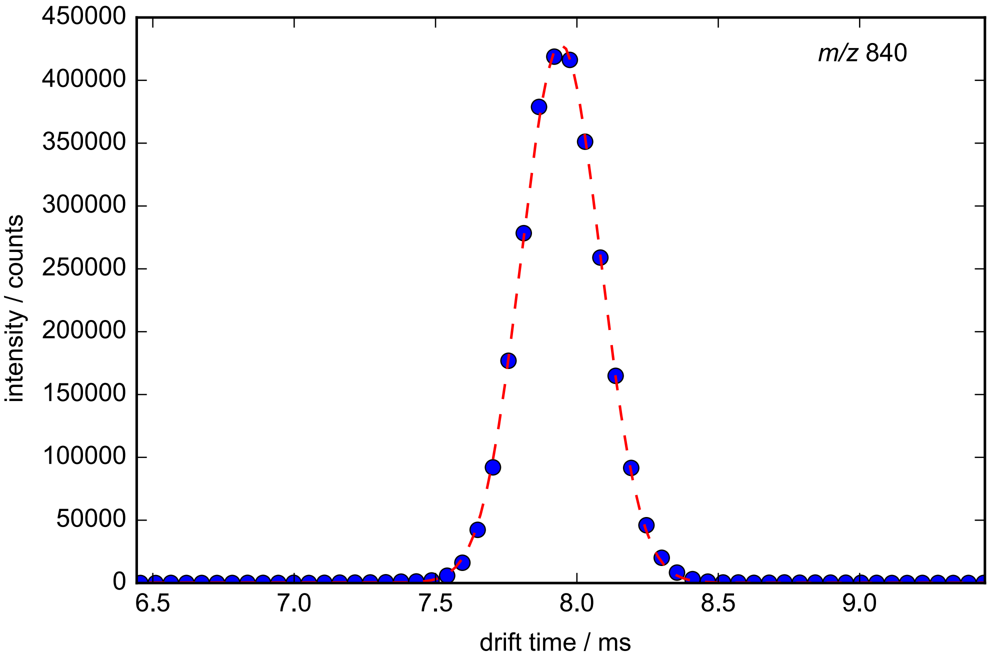


Figure S9: ATD of (*R*)-**1**+(*R*)-**2**+H^+ at *m*/*z* 840. The ATD features a single species corresponding to a single gaussian-shaped peak.

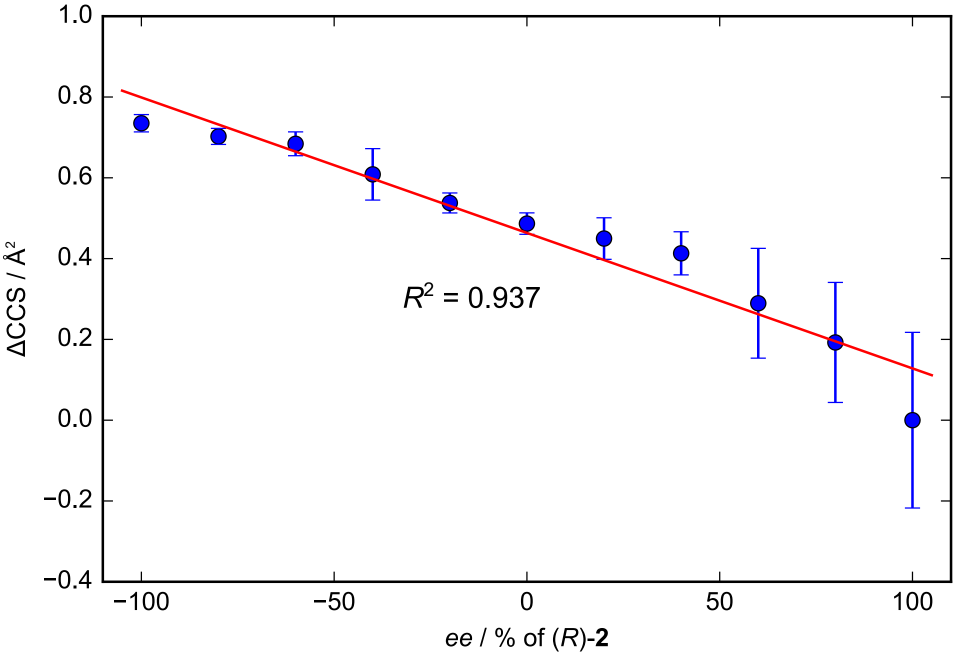


Figure S10: Linear correlation of ΔCCS of (*R*)-**1** + (*R*)/(*S*)-**2** + H^+ with varying ee of **2**. A linear trend is observed here, but the linear correlation is significantly better for host **6** (see main text).

4.3 Control experiments

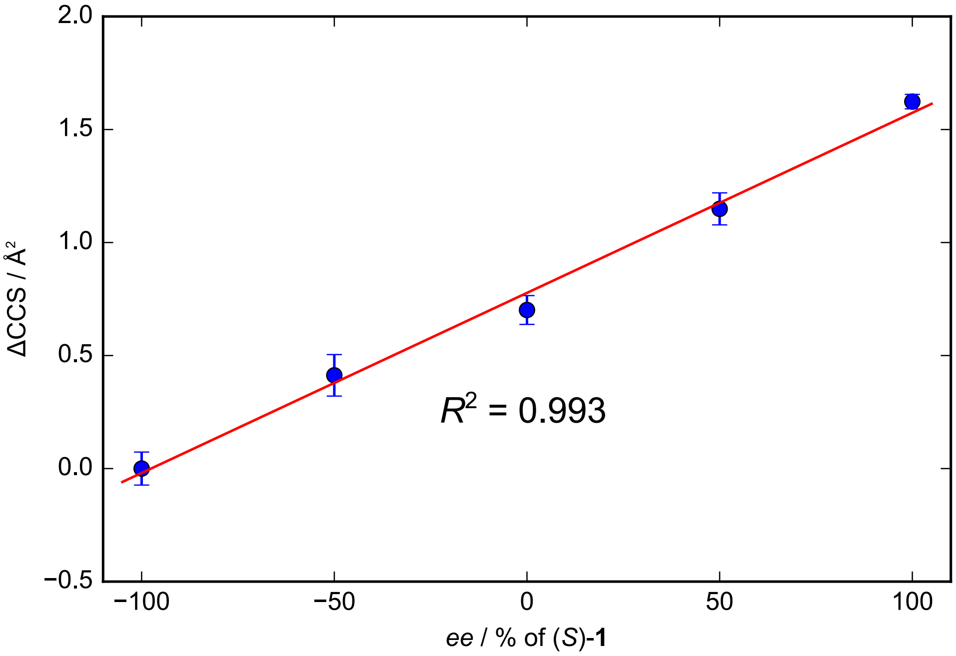


Figure S11: Control experiment, showing the dependence of the CCS difference (ΔCCS) of (*R*)-**4**+**1**+H^+ for a varying *ee* of **1**. The experiment confirms that the same linear dependency of ΔCCS on the *ee* is observed. Furthermore, the linear correlation is better compared to the experiment with phenylalanine, reflecting the fact that the overall CCS difference is larger.

Table S3: Overview over drift time differences for complexes of (*R*)/(*S*)-**2** with different hosts, including control experiments with complexes of α-,β-,γ-CD.

complex	t_d / ms with (*S*)-**2**	t_d / ms with (*R*)-**2**	Δt_d / ms
(*R*)-**1** + **2** + H^+	8.080	8.039	0.041 ± 0.004
(*S*)-**6** + **2** + H^+	4.925	4.975	0.050 ± 0.003
α-CD + **2** + H^+	9.606	9.581	0.025 ± 0.006
$2 \times \left(\alpha\text{-CD} + \mathbf{2} + H^+\right)$	5.624	5.590	0.034 ± 0.005
β-CD + **2** + H^+	10.783	10.762	0.021 ± 0.005
$2 \times \left(\beta\text{-CD} + \mathbf{2} + H^+\right)$	6.115	6.115	-0.000 ± 0.007
γ-CD + **2** + H^+	13.040	13.064	-0.024 ± 0.008
$2 \times \left(\gamma\text{-CD} + \mathbf{2} + H^+\right)$	6.777	6.833	-0.056 ± 0.006

Table S4: Comparison of CCS differences obtained with **1** + K^+ as internal reference and without the use of an internal standard.

guest	$CCS_{homochiral}$ / Å^2	$CCS_{heterochiral}$ / Å^2	ΔCCS / Å^2	$\Delta CCS^{int.ref.}$ / Å^2
2	205.0	205.8	0.8 ± 0.1	0.9 ± 0.2
3	194.4	194.7	0.3 ± 0.2	0.3 ± 0.3
4	215.2	216.7	1.5 ± 0.1	1.5 ± 0.2
5	211.4	211.7	0.3 ± 0.2	0.3 ± 0.2

5 Gas-phase H/D-exchange (HDX)

HDX experiments were conducted with an Ionspec QFT-7 FT-ICR mass spectrometer (Varian, USA) with a 7 T superconducting magnet and a Micromass Z-Spray ESI source (Waters, France). Samples were prepared as noted before and then introduced into the ion source with a flow rate of 2 μL·min^{-1}. The source temperature was kept constant at 40 °C. The capillary voltage was 3.7 kV, while sample and extractor cone were set to 40 V and 10 V, respectively.

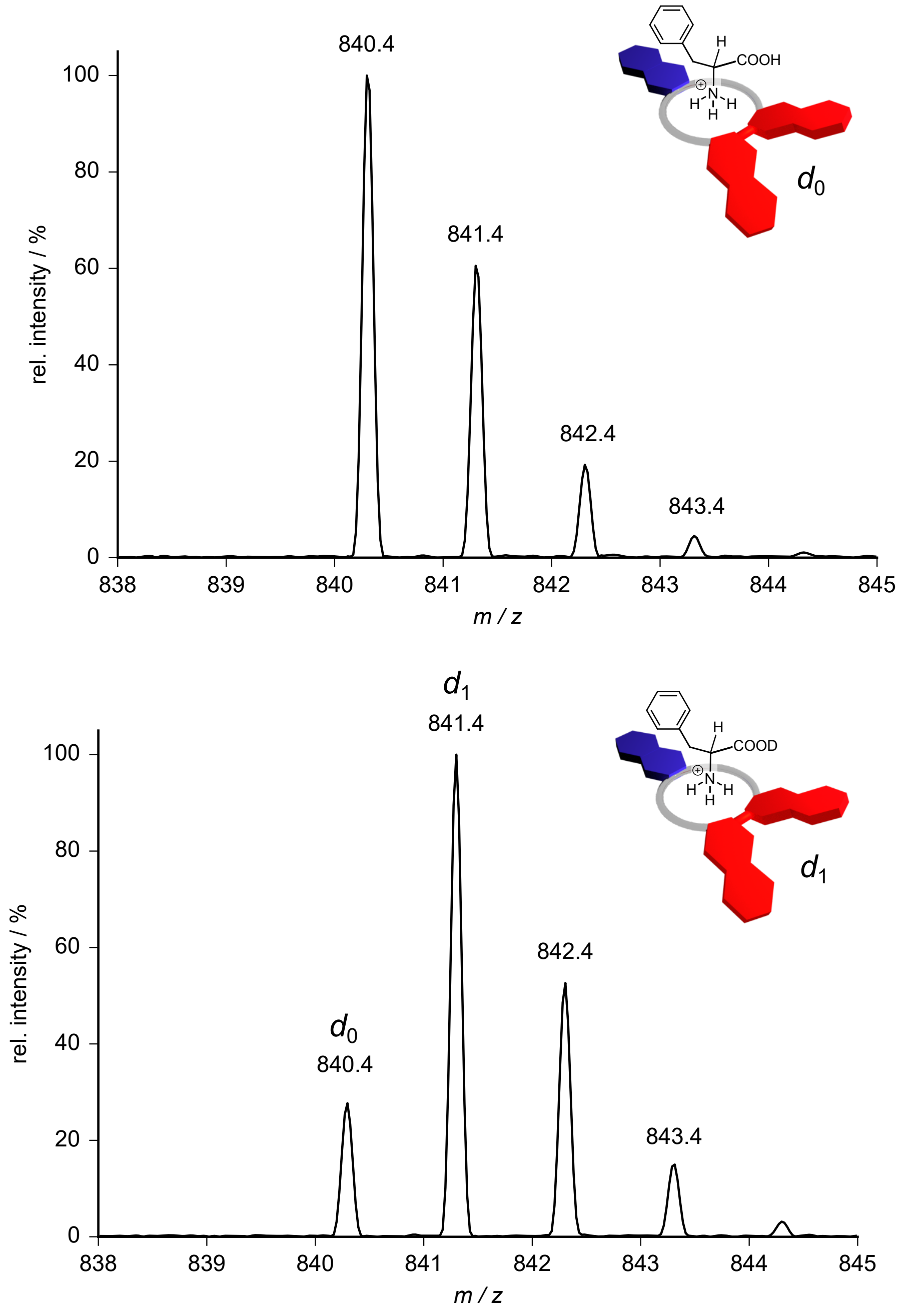


Figure S12: Mass spectra of (*R*)-**1**+(*R*)-**2** before (top) and after gas-phase HDX with a 100 ms pulse of MeOD (bottom). Exchange of a single proton is observed, that corresponds to the carboxyl group.

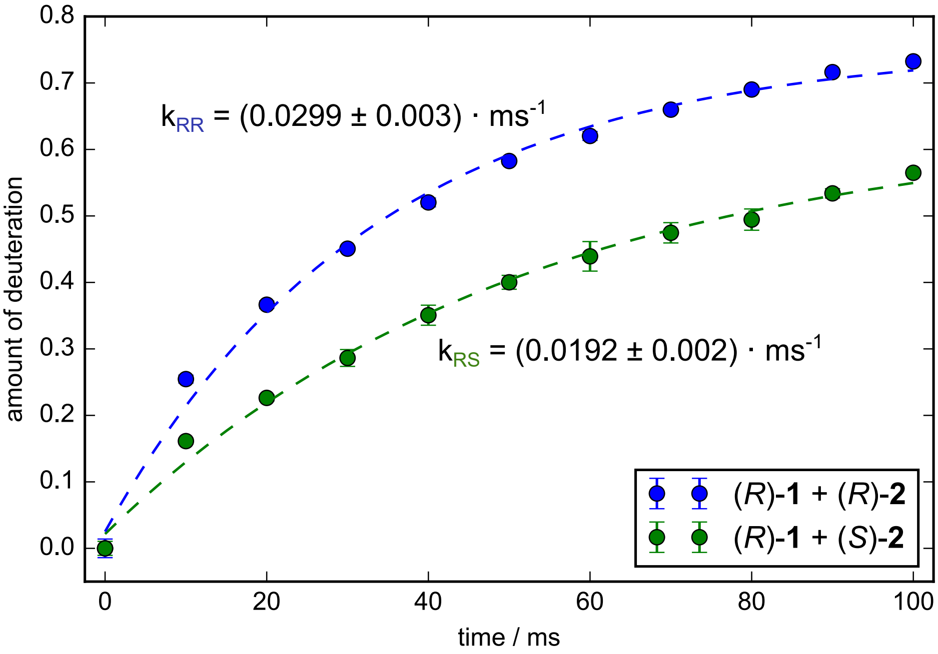


Figure S13: Gas-phase HDX of (*R*)-**1**+(*R*)-**2** (blue) and (*R*)-**1**+(*S*)-**2** (green) plotted against MeOD pulse time. Every point corresponds to an average of three measurements, error bars represent two standard deviations. Rate constants are relative as the absolute MeOD pressure remains unknown. All four measurements were performed under the same instrument conditions to give relative HDX rates.

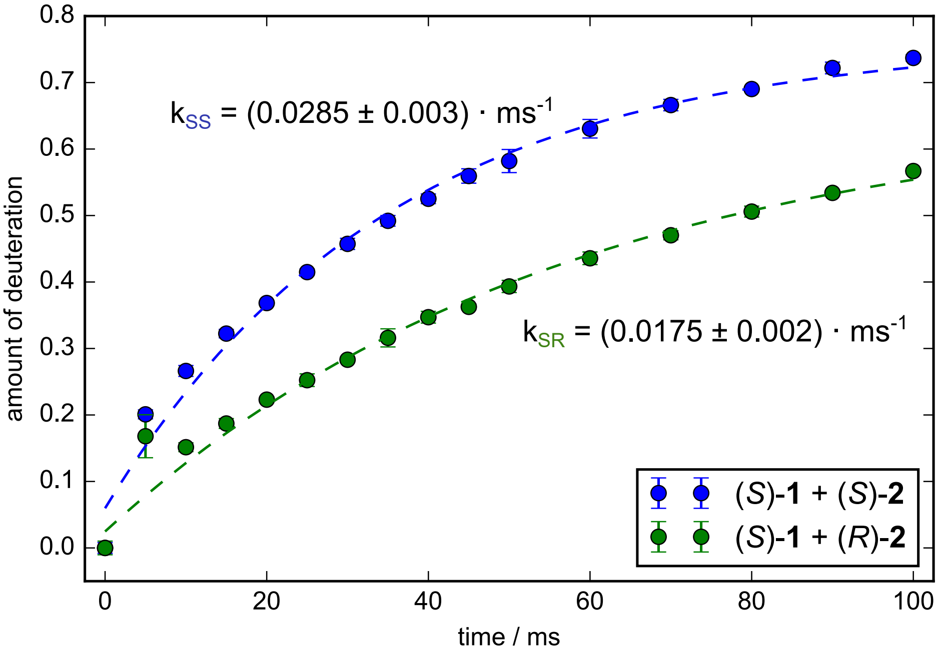


Figure S14: Gas-phase HDX of (*S*)-**1**+(*S*)-**2** (blue) and (*S*)-**1**+(*R*)-**2** (green) plotted against MeOD pulse time. Every point corresponds to an average of three measurements, error bars represent two standard deviations. In the case of (*S*)-**1**+(*R*)-**2**, a single measurement was excluded from fitting, as it was clearly identified as an outlier.

6 References

[S1] J. D. Badjic, C. M. Ronconi, J. F. Stoddart, V. Balzani, S. Silvi and A. Credi, *J. Am. Chem. Soc.*, 2006, **128**, 1489.

[S2] E. Hunter and S. Lias, *J. Phys. Chem. Ref. Data*, 1998, **27**, 413; http://webbook.nist.gov/cgi/cbook.cgi?ID=C17455139&Mask=20; http://webbook.nist.gov/cgi/cbook.cgi?ID=C63912&Mask=20.