Supporting Information

Selective Recognition of Neutral Guests in an Aqueous Medium by a Biomimetic Calix[6]cryptamide Receptor

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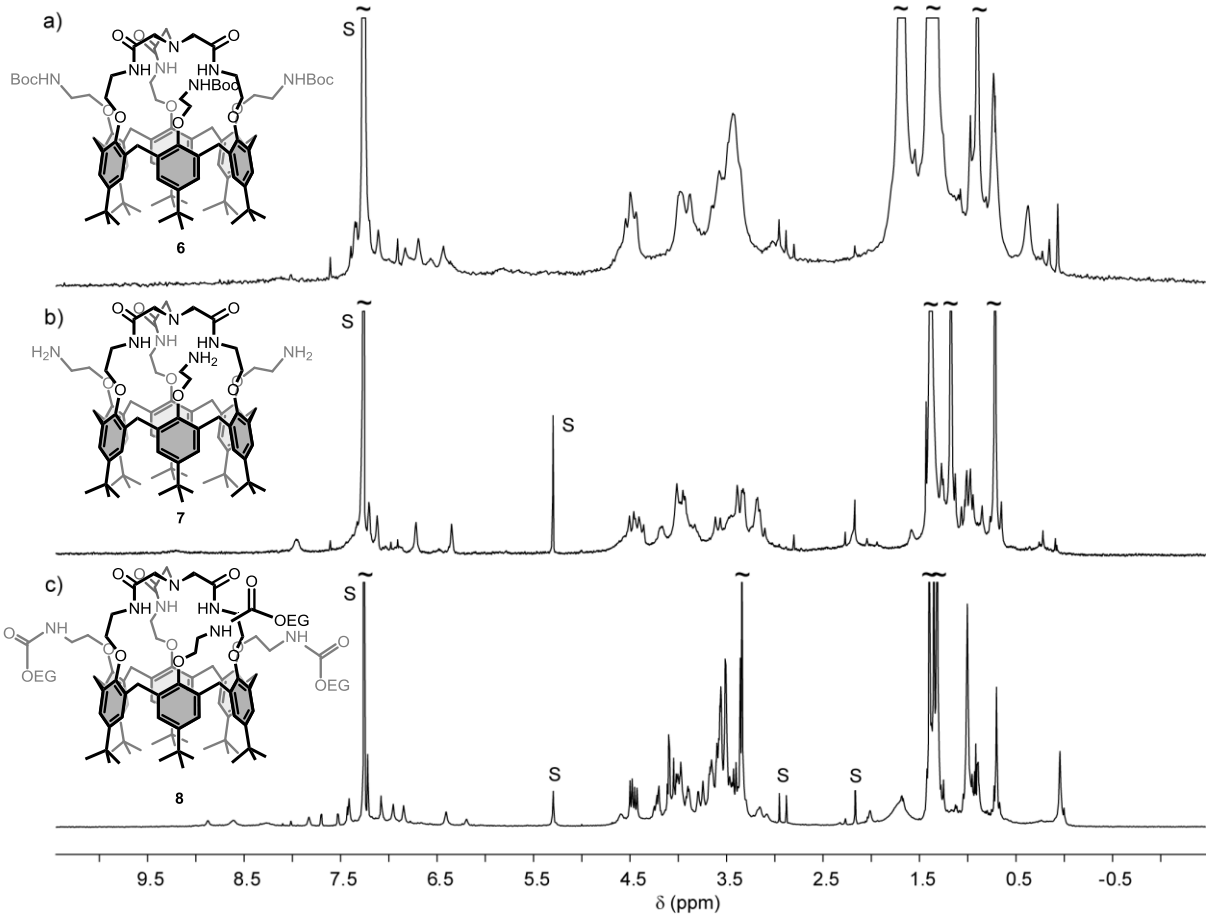
General experimental methods

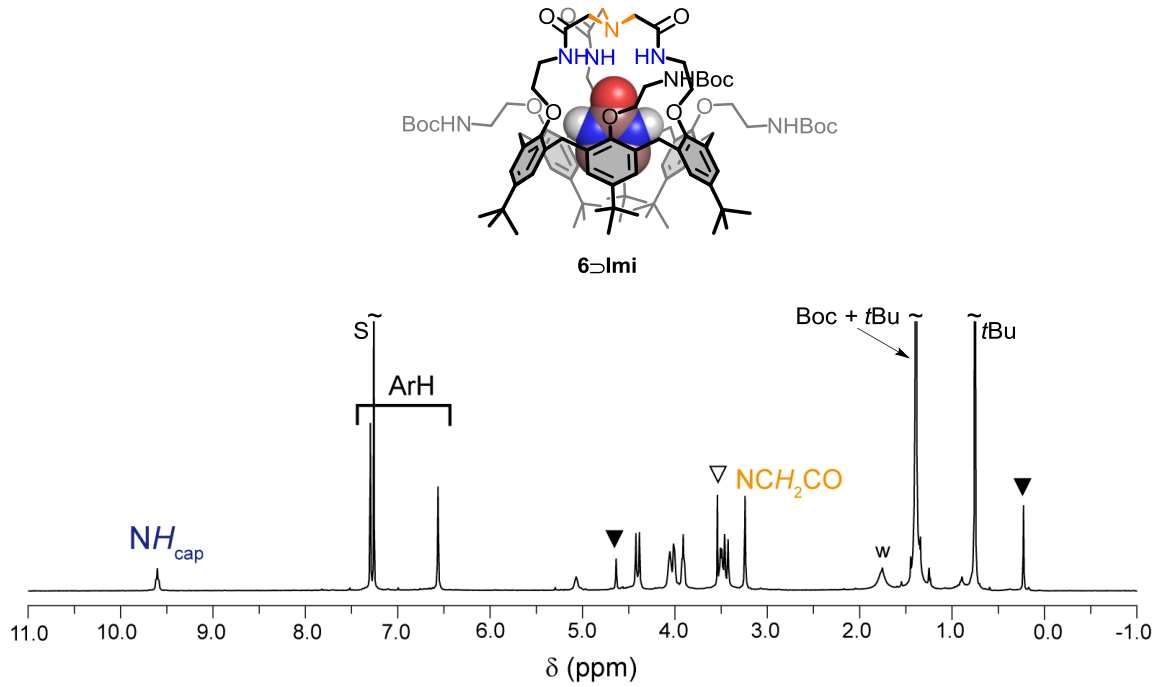
^{1}H NMR spectra were recorded at either 600, 400 or 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz using Varian VNMRS-600, VNMRS-400 or Bruker Avance-300 spectrometers equipped with a 5 mm probe. The solvent was used as internal standard for both ^{1}H and ^{13}C chemical shift referencing (δ ^{1}H = 7.26 ppm for residual $CHCl_3$ and 3.31 ppm for residual CHD_2OD; δ ^{13}C = 77.16 ppm for $CDCl_3$ and 49.00 ppm for CD_3OD). $CDCl_3$ was filtered over a short column of basic alumina in order to remove traces of DCl. Most of the ^{1}H NMR spectra signals were assigned through 2D NMR analyses (COSY, HSQC, HMBC). For the edited-HSQC spectra, the blue signals are negatively phased and the red signals are positively phased. s: singlet, s_b: broaden singlet, d: doublet, d_b: broaden doublet, t_b : broaden triplet, m: massif.

^{1}H NMR (298K) spectra of **6**, **7** and **8** in $CDCl_3$



a) **6** (300MHz); b) **7** (300MHz); c) **8** (600MHz). S: solvent.

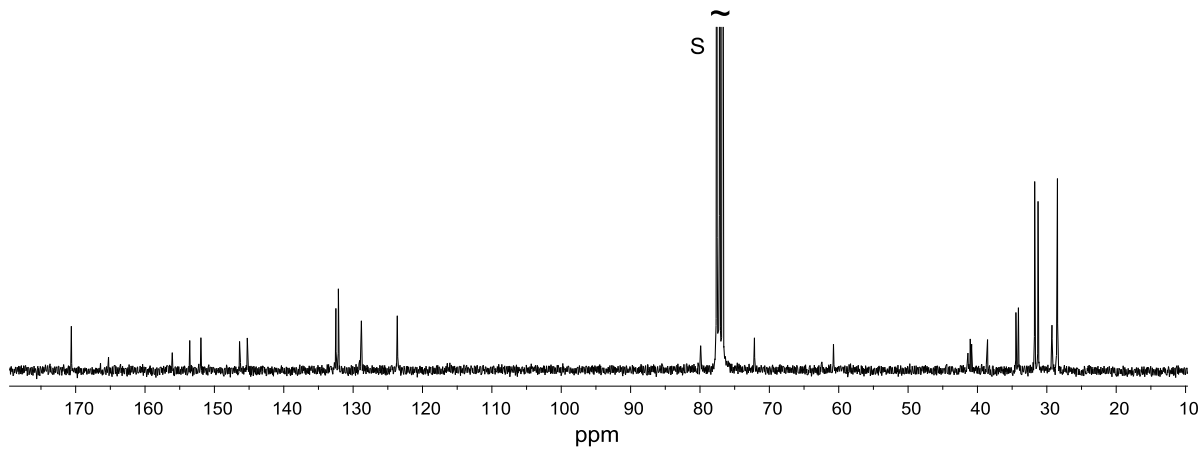
^{1}H NMR (400MHz, 298K) spectrum of **6⊃Imi** in $CDCl_3$



∇: free Imi; ▼: Imi included; S: solvent; w: water.

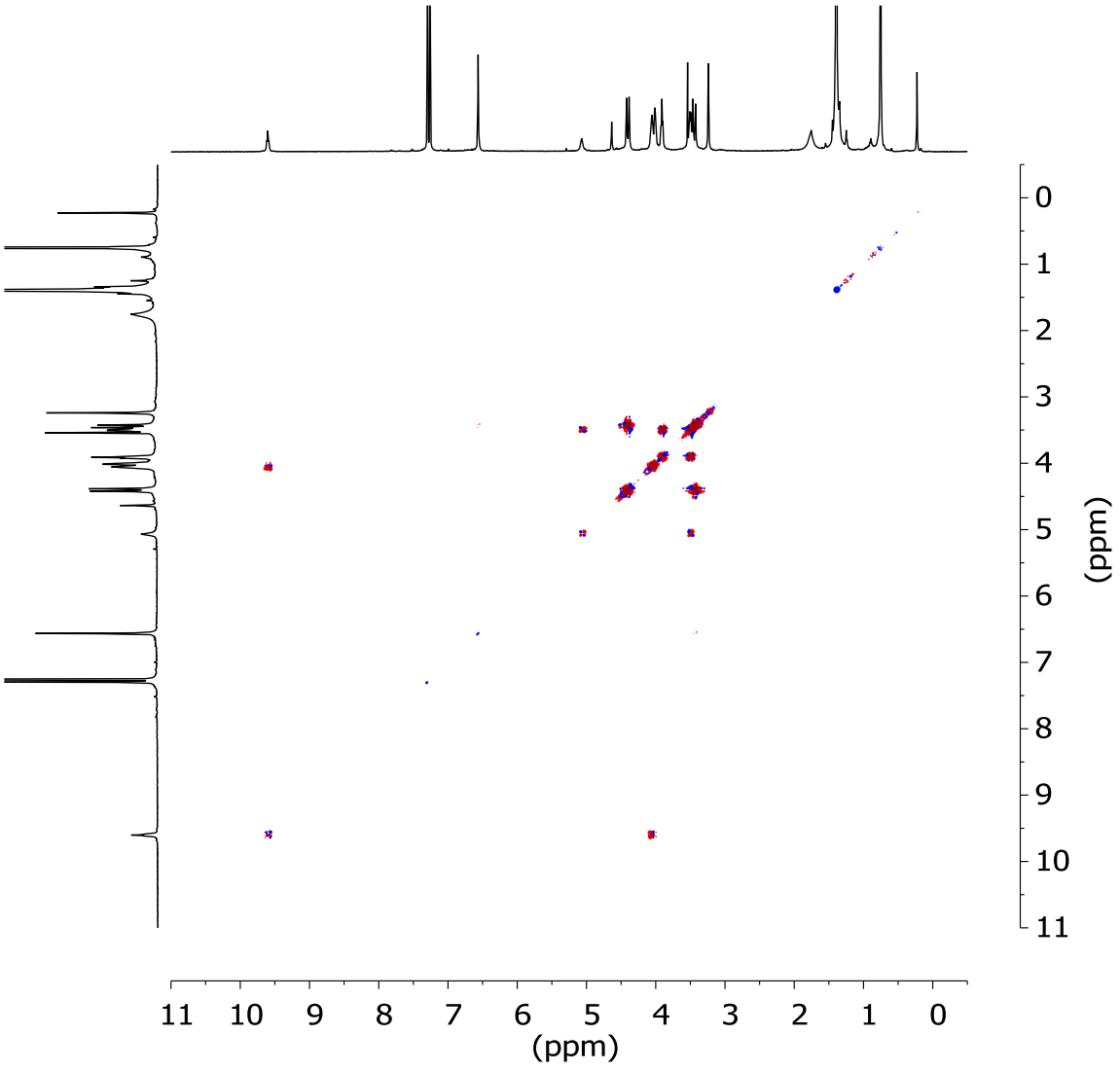
	δ (ppm) of **6⊃Imi**
CONH $_{cap}$	9.60 (s_b)
ArH $_{out}$	7.30 (s)
ArH $_{in}$	6.56 (s)
NH $_{Boc}$	5.07 (s_b)
ArCH$_2$ $_{ax}$	4.40 (d, *J* = 15.1 Hz)
ArCH$_2$ $_{eq}$	3.44 (d, *J* = 15.1 Hz)
OCH$_2$CH$_2$NHBoc	3.91 (s_b)
OCH$_2$ $_{cap}$	4.02 (s_b)
CH$_2$NHCO	4.05 (s_b)
NCH$_2$CONH	3.24 (s)
CH$_2$NHBoc	3.50 (s_b)
*t*Bu $_{out}$	1.39 (s)
*t*Bu Boc	1.39 (s)
*t*Bu $_{in}$	0.75 (s)
NH $_{Imi\ in}$	4.64 (s)
CH$_2$ $_{Imi\ in}$	0.23 (s)

^{13}C NMR (75MHz, 298K) spectrum of **6⊃Imi** in $CDCl_3$

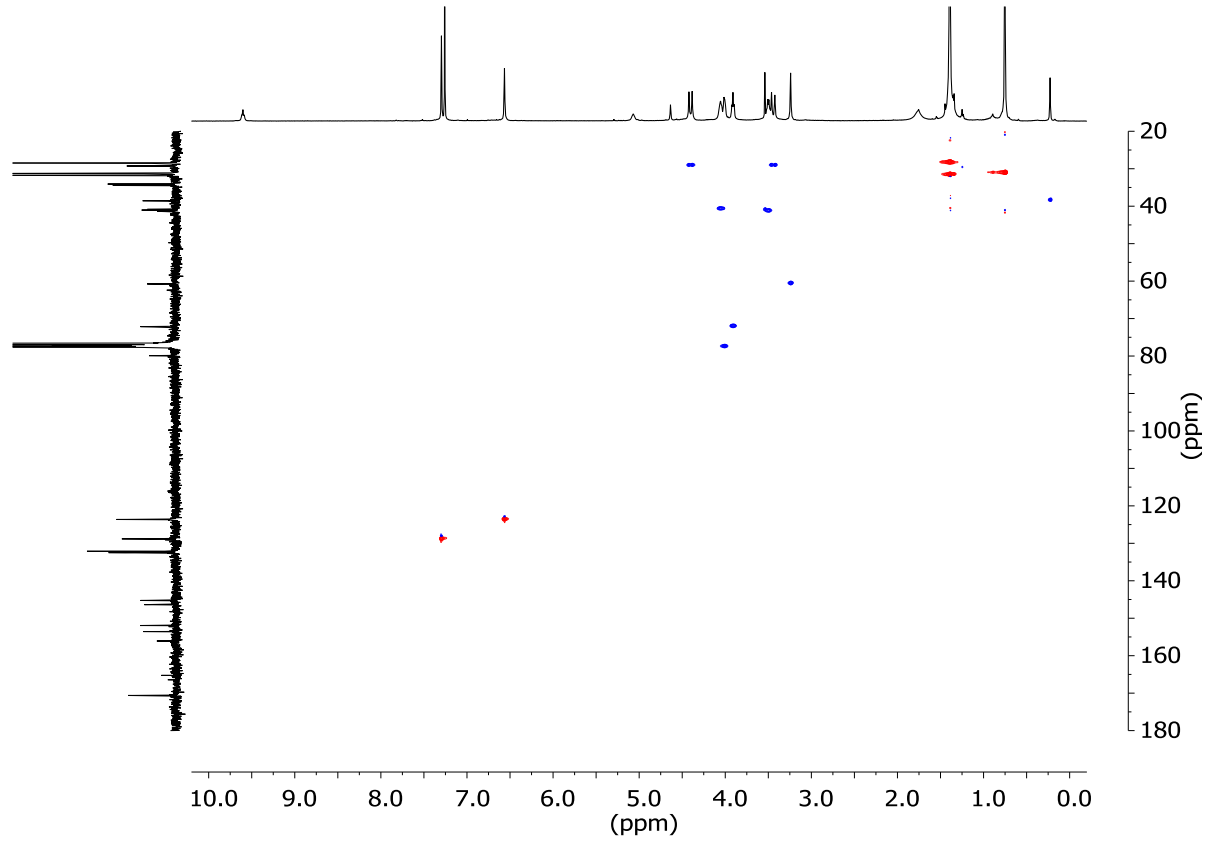


S: solvent.

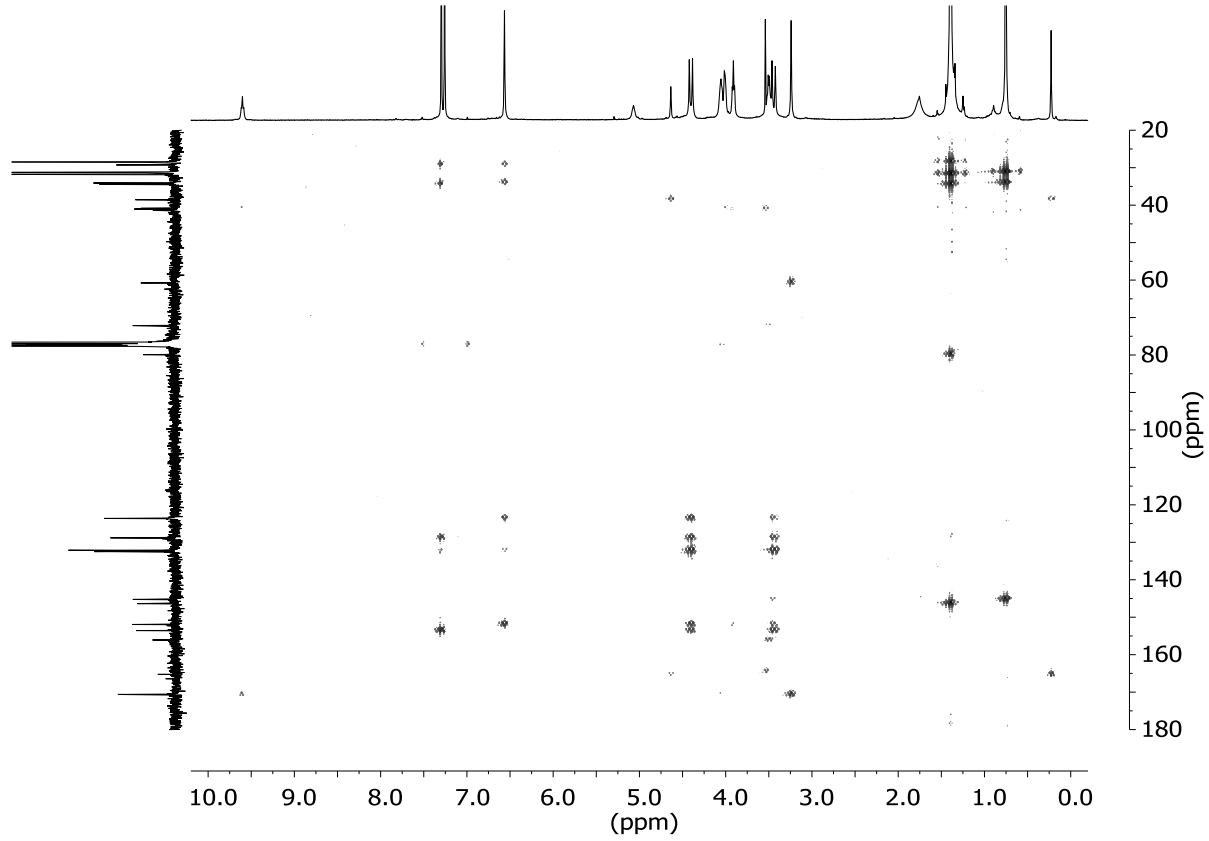
Symmetrized dqfCOSY NMR (400MHz, 298K) spectrum of **6⊃Imi** in $CDCl_3$



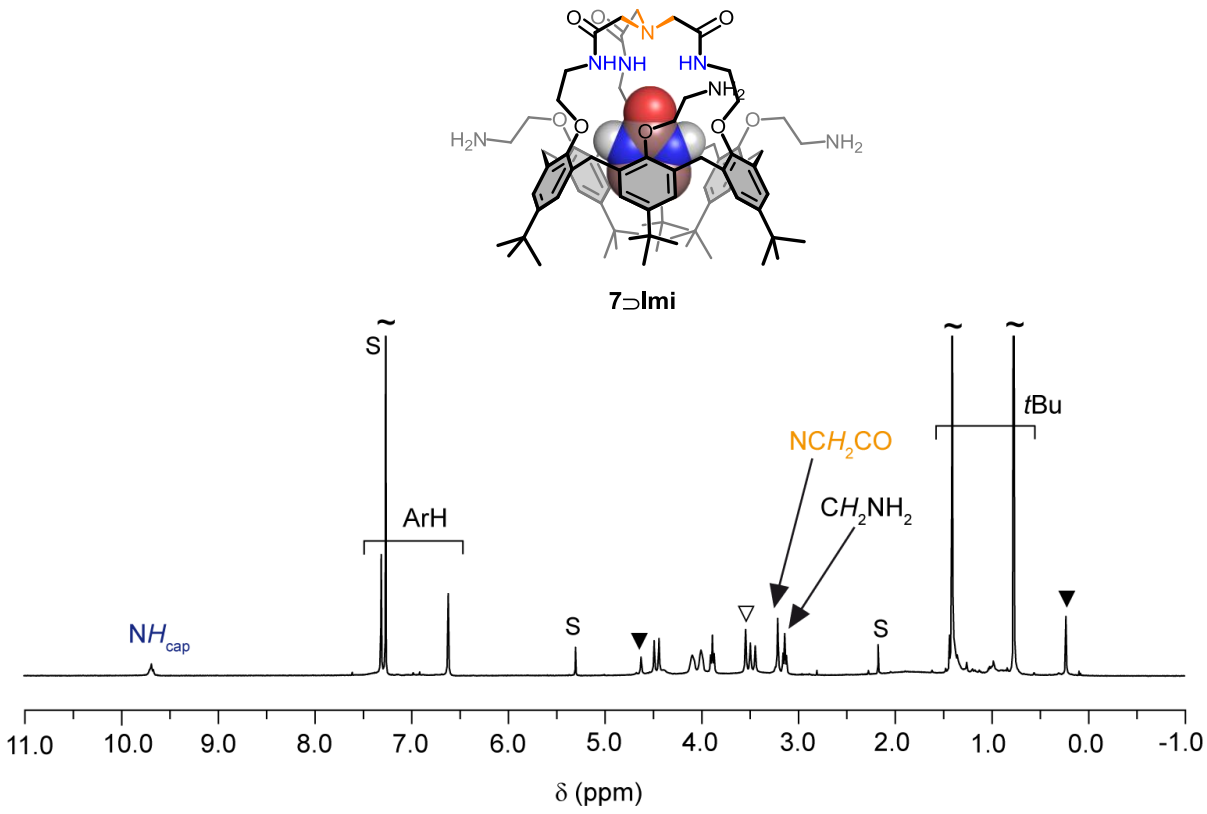
Edited-HSQC NMR (400MHz, 298K) spectrum of **6⊃Imi** in $CDCl_3$



8Hz-HMBC NMR (400MHz, 298K) spectrum of **6⊃Imi** in $CDCl_3$



^{1}H NMR (300MHz, 298K) spectrum of **7⊃Imi** in $CDCl_3$

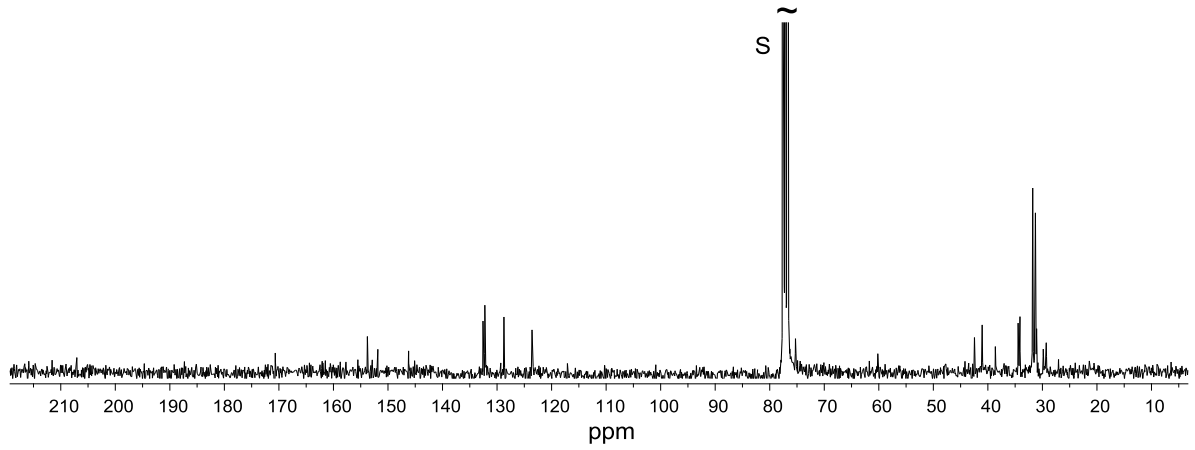


∇: free Imi; ▼: Imi included; S: solvent.

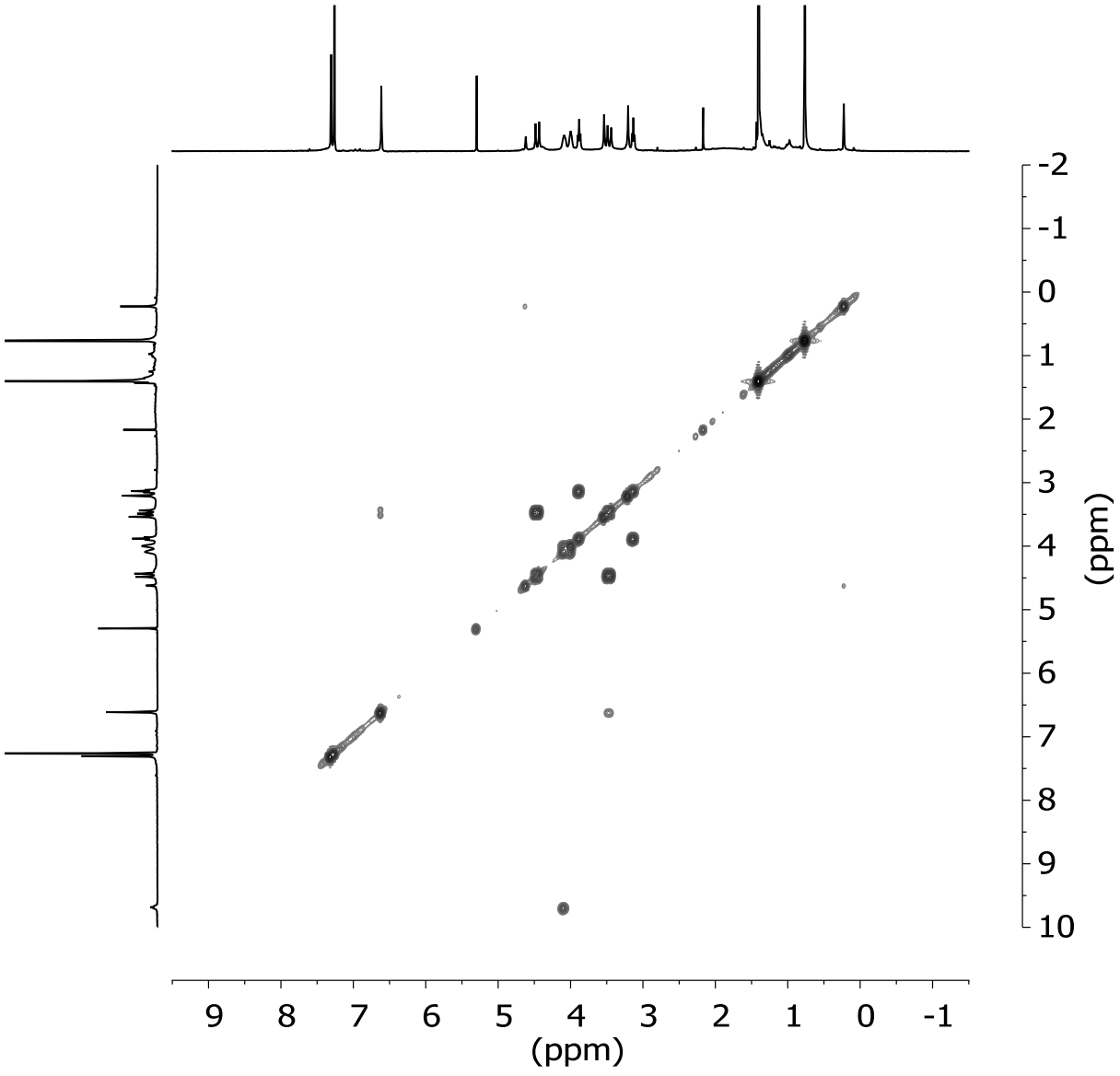
	δ (ppm) of **7⊃Imi**
CON*H* $_{cap}$	9.69 (s_b)
CH_2NH_2	nd
Ar*H* $_{out}$	7.31 (s)
Ar*H* $_{in}$	6.61(s)
Ar$CH_{2\ ax}$	4.45 (d, *J* = 15.1 Hz)
CH_2NHCO	4.09 (s_b)
$OCH_{2\ cap}$	4.00 (s_b)
$OCH_2CH_2NH_2$	3.88 (t_b, *J* = 5.6 Hz)
Ar$CH_{2\ eq}$	3.46 (d, *J* = 15.1 Hz)
NCH_2CONH	3.21 (s)
CH_2NH_2	3.13 (t_b, *J* = 5.6 Hz)
*t*Bu $_{out}$	1.40 (s)
*t*Bu $_{in}$	0.77 (s)
N*H* $_{Imi\ in}$	4.62 (s)
$CH_{2\ Imi\ in}$	0.23 (s)

nd: not detected

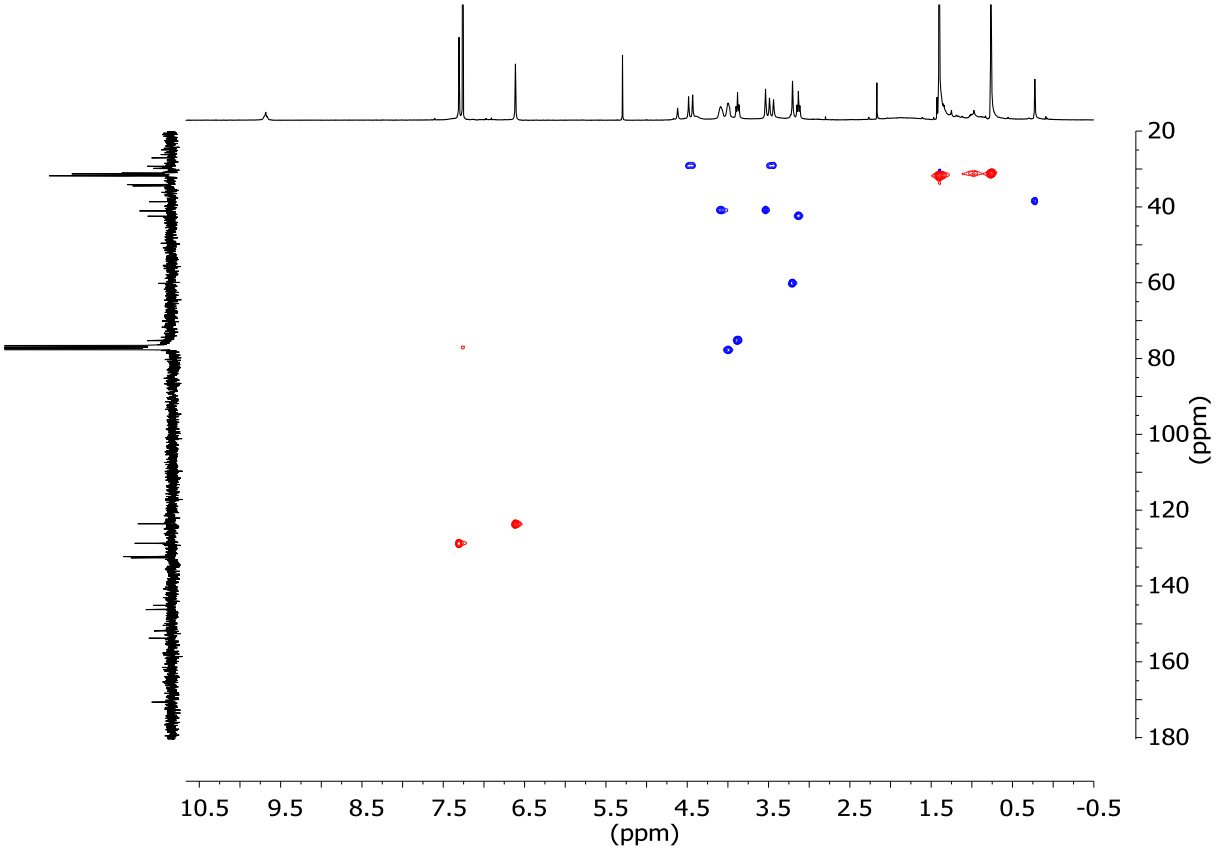
^{13}C NMR (75MHz, 298K) spectrum of **7⊃Imi** in $CDCl_3$



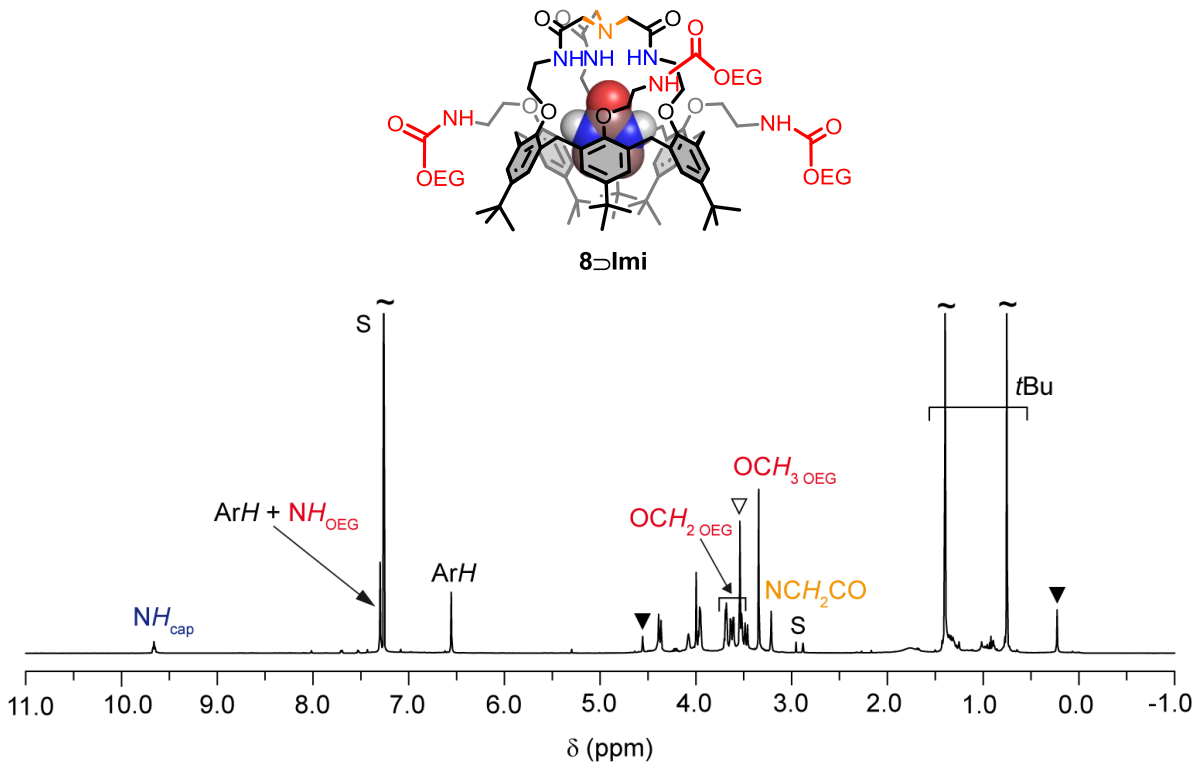
COSY NMR (300MHz, 298K) spectrum of **7⊃Imi** in $CDCl_3$



Edited-HSQC NMR (300MHz, 298K) spectrum of **7⊃Imi** in $CDCl_3$



^{1}H NMR (600MHz, 298K) spectrum of **8⊃Imi** in $CDCl_3$

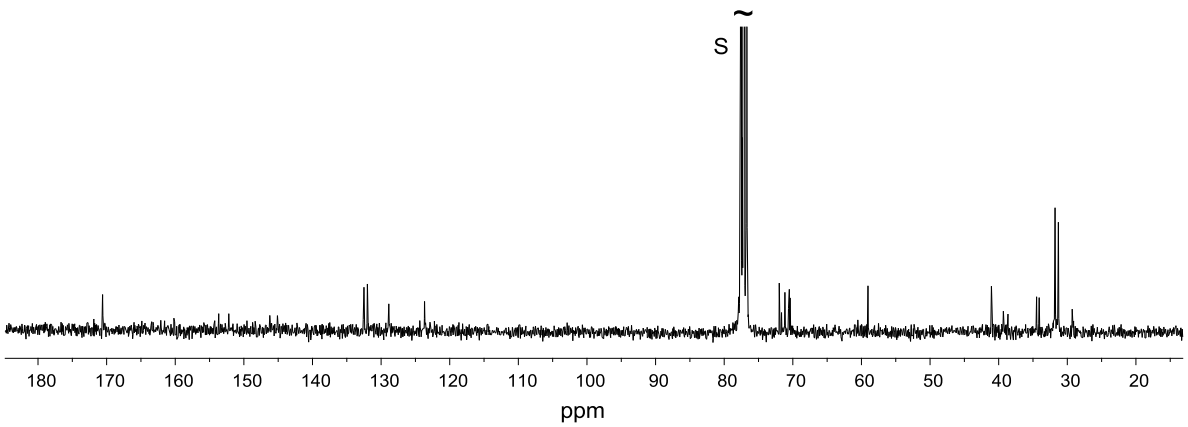


∇: free Imi; ▼: Imi included; S: solvent.

	δ (ppm) of **8⊃Imi**
CONH $_{cap}$	9.67 (t_b, J = 6.3 Hz)
CONH $_{OEG}$	7.30[a]
ArH $_{out}$	7.30 (s)
ArH $_{in}$	6.56 (s)
ArCH$_2$ $_{ax}$	4.38 (d, J = 15.1 Hz)
CH$_2$NHCO $_{cap}$	4.08 (s_b)
OCH$_2$CONH $_{OEG}$	4.00 (s)
ArOCH$_2$ $_{cap\ and\ OEG}$	3.93-3.98 (m)
CH$_2$NHCO $_{OEG}$ + OCH$_2$ $_{OEG}$	3.50-3.72 (m)
ArCH$_2$ $_{eq}$	3.47 (d, J = 15.1 Hz)
OCH$_3$ $_{OEG}$	3.34 (s)
NCH$_2$CONH	3.21 (s)
*t*Bu $_{out}$	1.40 (s)
*t*Bu $_{in}$	0.75 (s)
NH $_{Imi\ in}$	4.56 (s)
CH$_2$ $_{Imi\ in}$	0.23 (s)

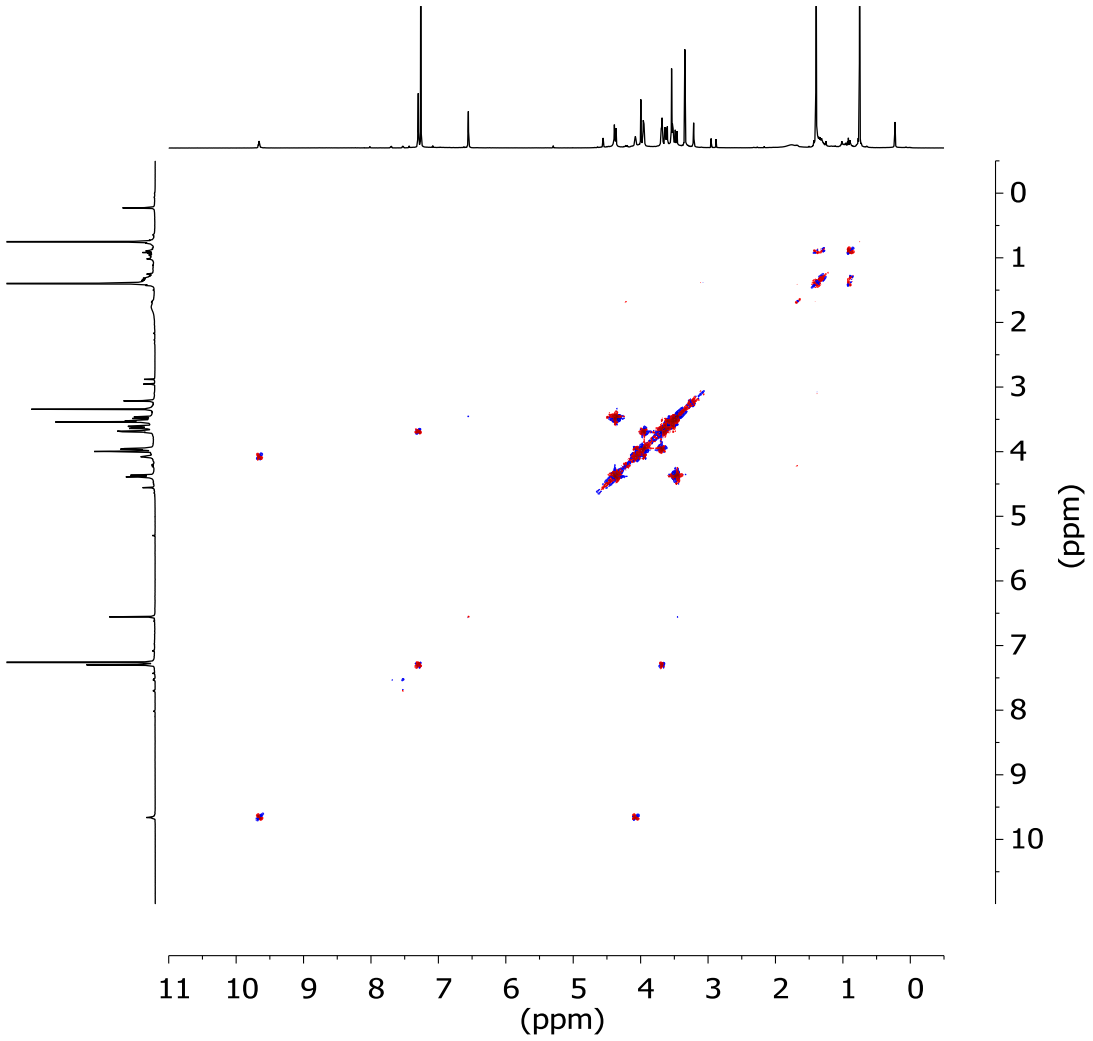
[a] identified through 2D NMR spectroscopy analysis

^{13}C NMR (75MHz, 298K) spectrum of **8⊃Imi** in $CDCl_3$

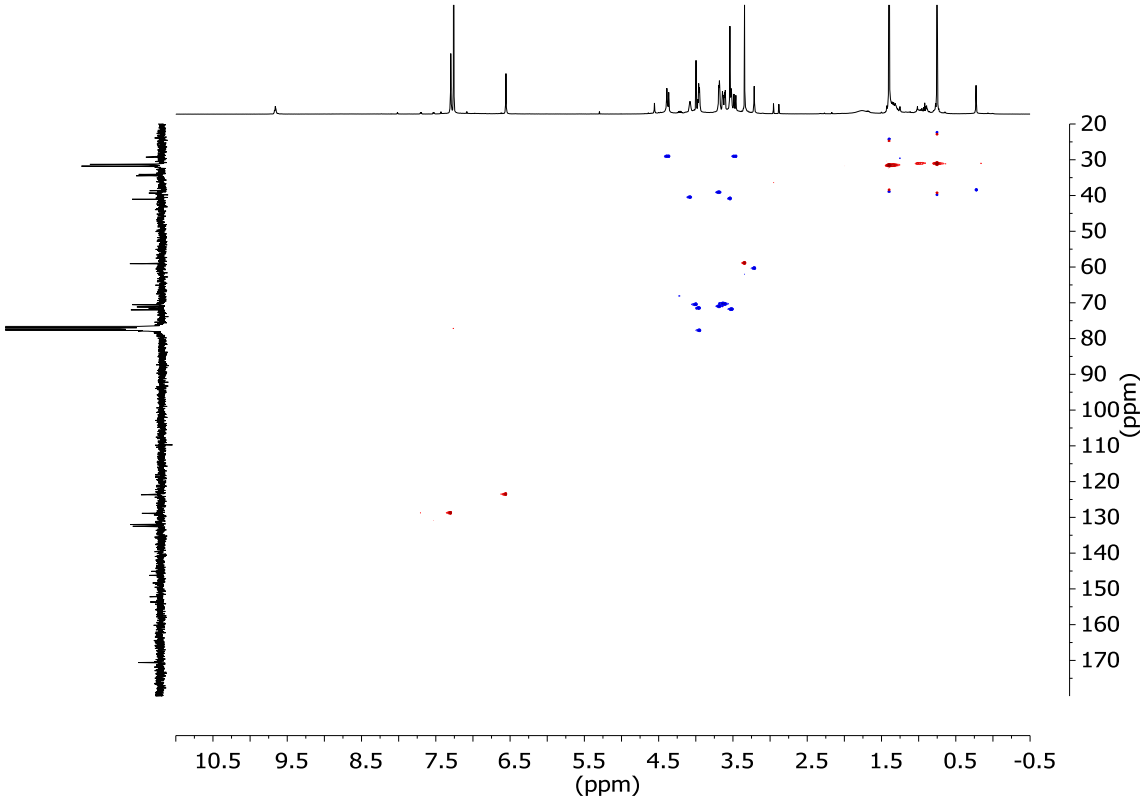


S: solvent.

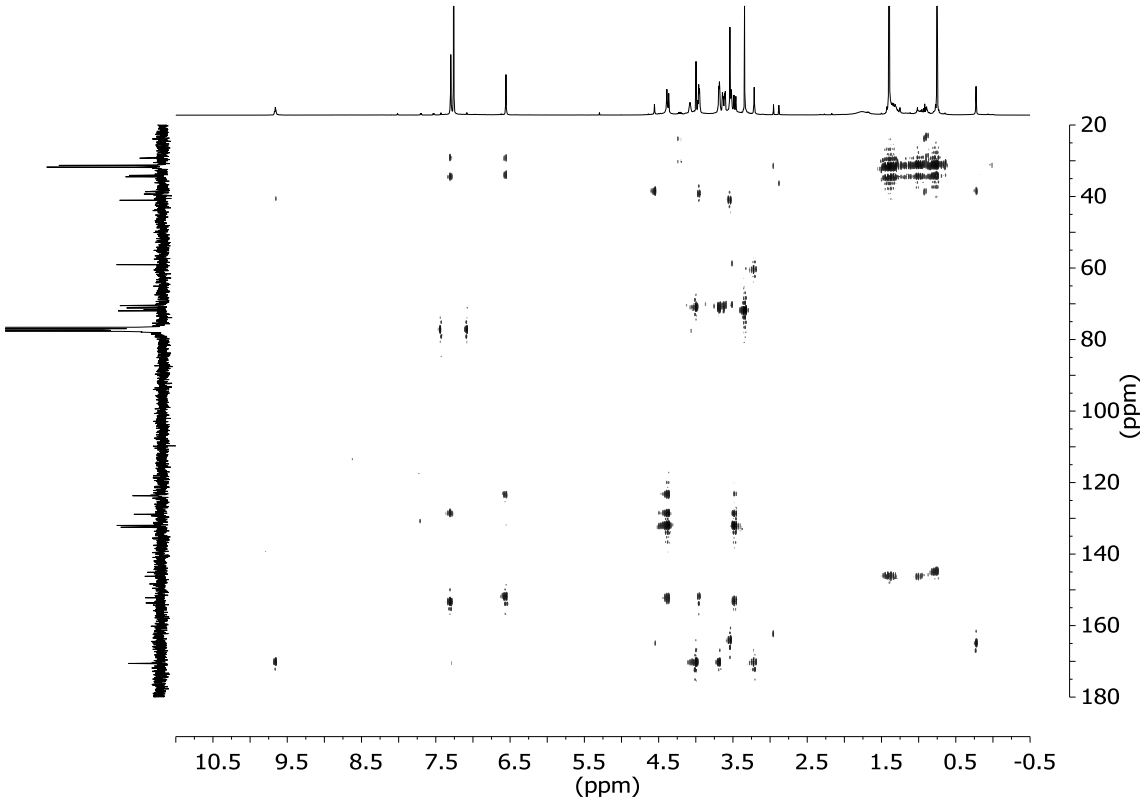
Symmetrized dqfCOSY NMR (600MHz, 298K) spectrum of **8⊃Imi** in $CDCl_3$



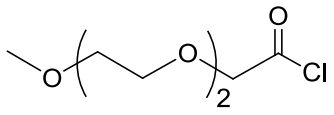
Edited-HSQC NMR (600MHz, 298K) spectrum of **8⊃Imi** in $CDCl_3$



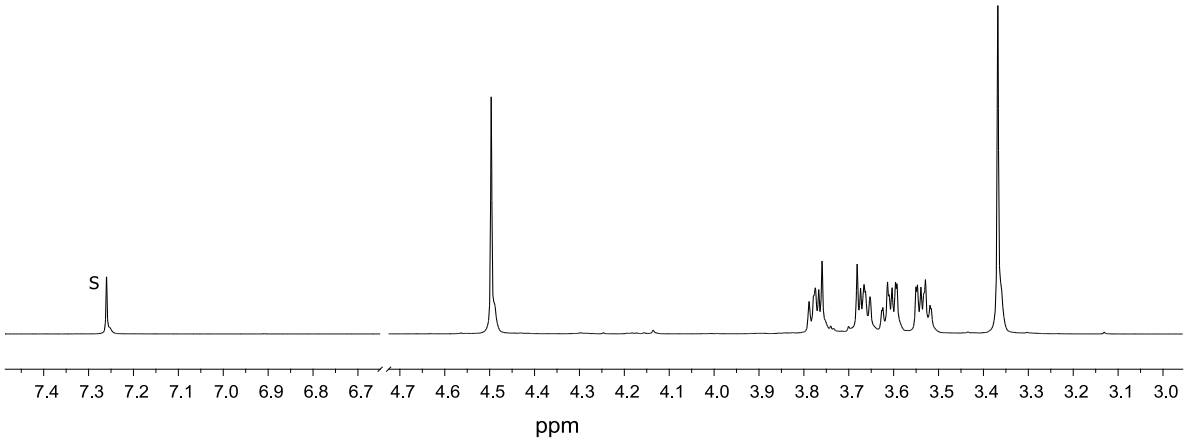
8Hz-HMBC NMR (600MHz, 298K) spectrum of **8⊃Imi** in $CDCl_3$



^{1}H NMR (300MHz, 298K) spectrum of **9** in $CDCl_3$

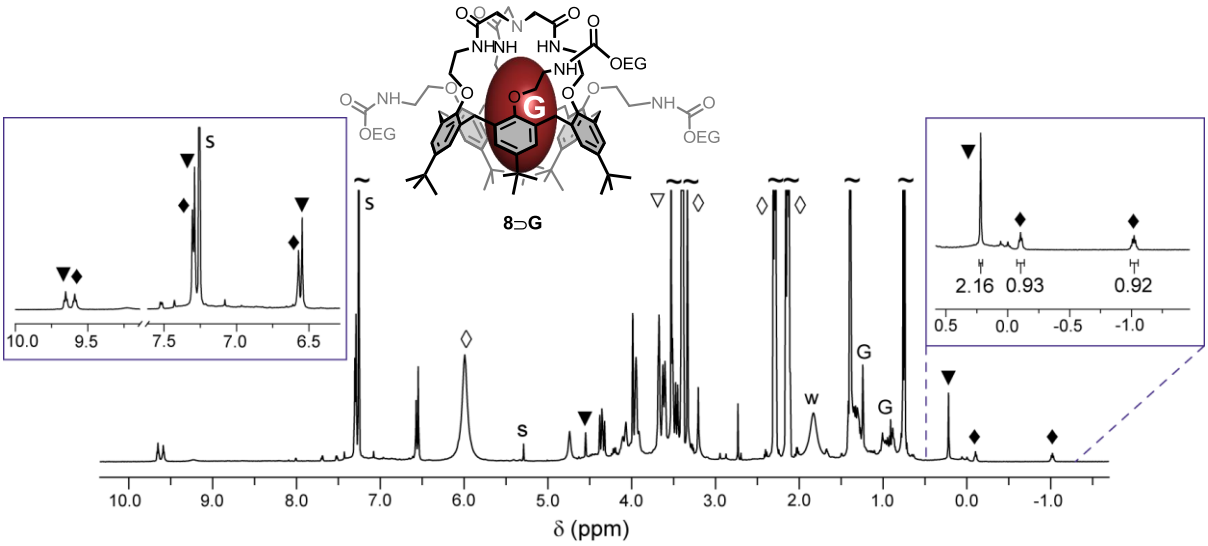


9



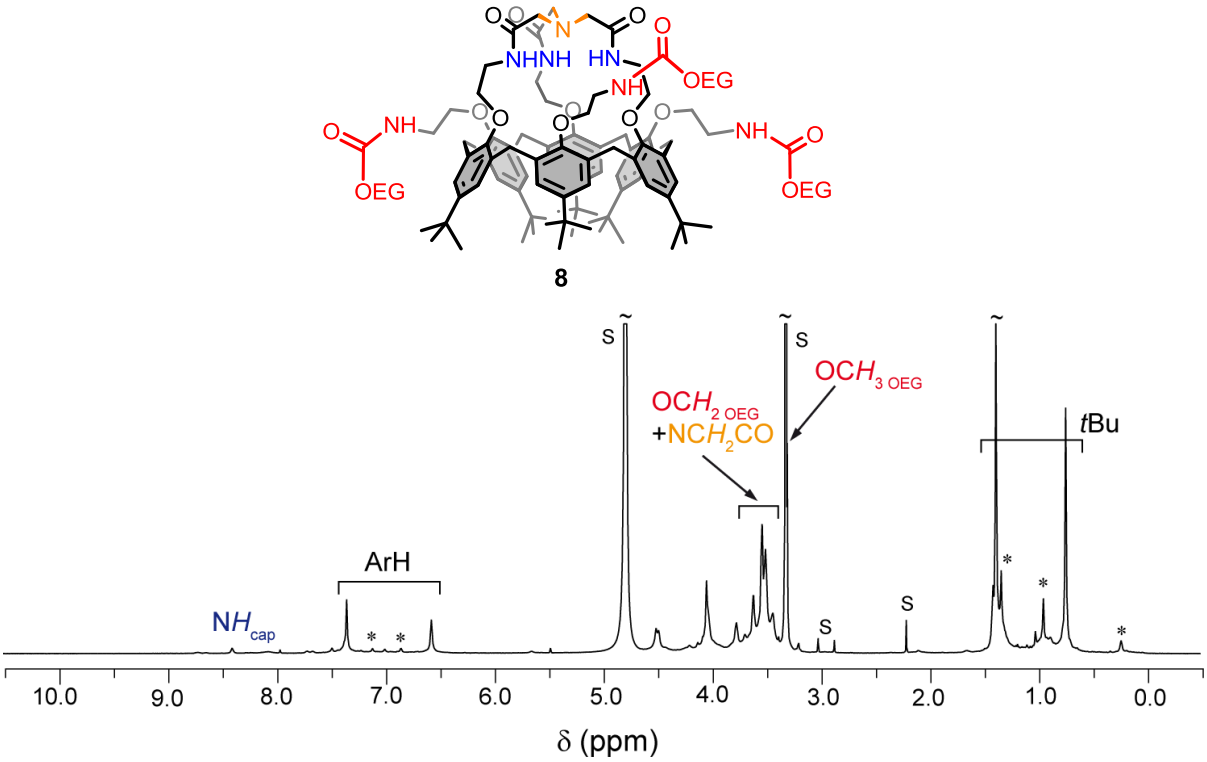
S: solvent.

Competitive binding study of **8** with Imi and Pyro in $CDCl_3$: ^1H NMR (600MHz, 298K) spectrum after addition of 48 equiv. of Pyro and 3.5 equiv. of Imi



▼: endo-complex **8⊃Imi**; ▽: free Imi; ♦: endo-complex **8⊃Pyro**; ◊: free Pyro; S: solvent; w: water; G: grease.

^{1}H NMR (600MHz, 298K) spectrum of **8** in D_2O/CD_3OD 1:2

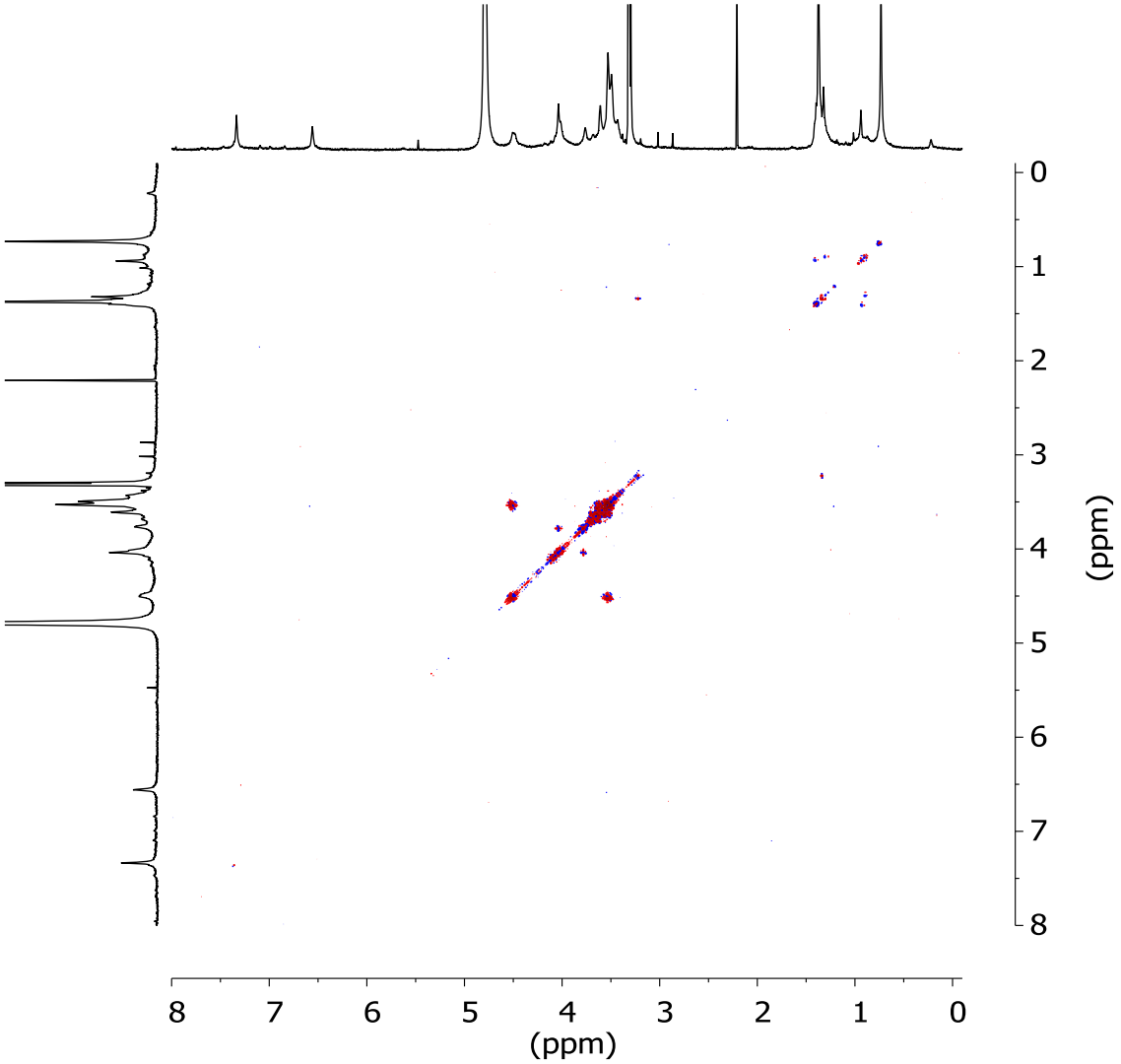


*: minor conformer; S: solvent.

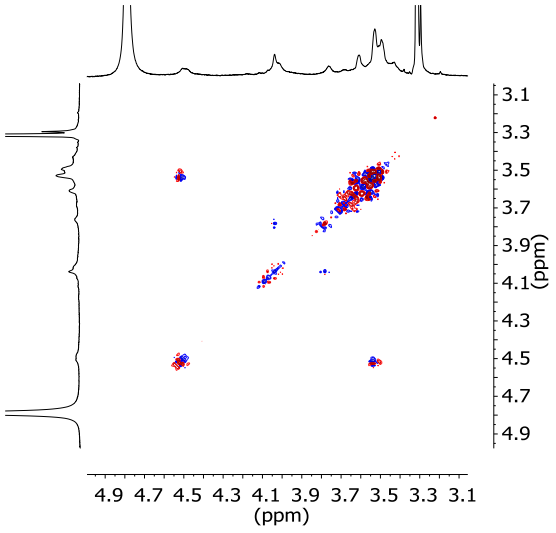
	δ (ppm) of **8**
CONH $_{cap}$	8.39 (s_b)
CONH $_{OEG}$	nd
ArH $_{out}$	7.33 (s)
ArH $_{in}$	6.55 (s)
ArCH$_{2\ ax}$	4.50 (m)
OCH$_2$CONH $_{OEG}$ ArOCH$_{2\ cap\ and\ OEG}$	3.97-4.09 (m)
CH$_2$NHCO $_{cap\ and\ OEG}$ + OCH$_{2\ OEG}$	3.39-3.81 (m)
ArCH$_{2\ eq}$	3.52 (m)
NCH$_2$CO	3.50 (m)
OCH$_{3\ OEG}$	3.29 (s)
*t*Bu $_{out}$	1.37(s)
*t*Bu $_{in}$	0.73(s)

nd: not detected

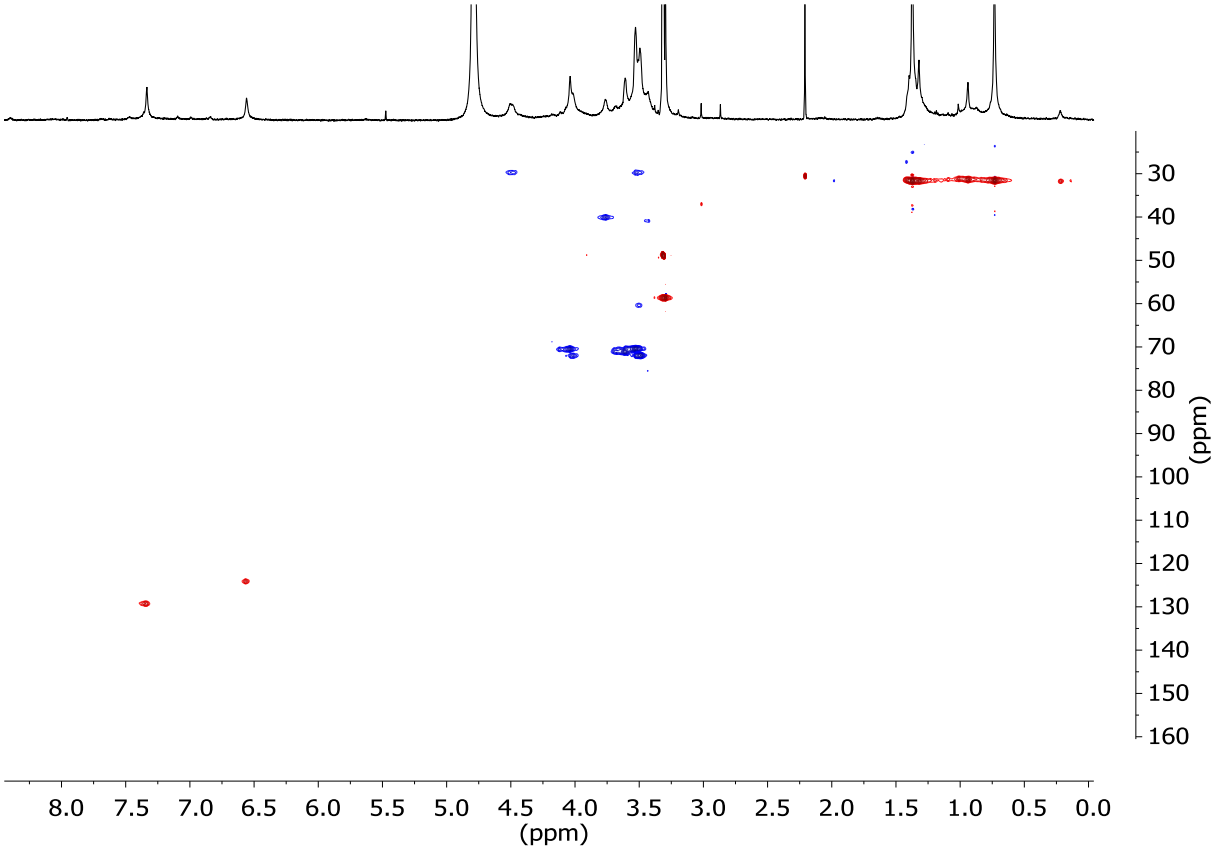
Symmetrized dqfCOSY NMR (600MHz, 298K) spectrum of **8** in D_2O/CD_3OD 1:2



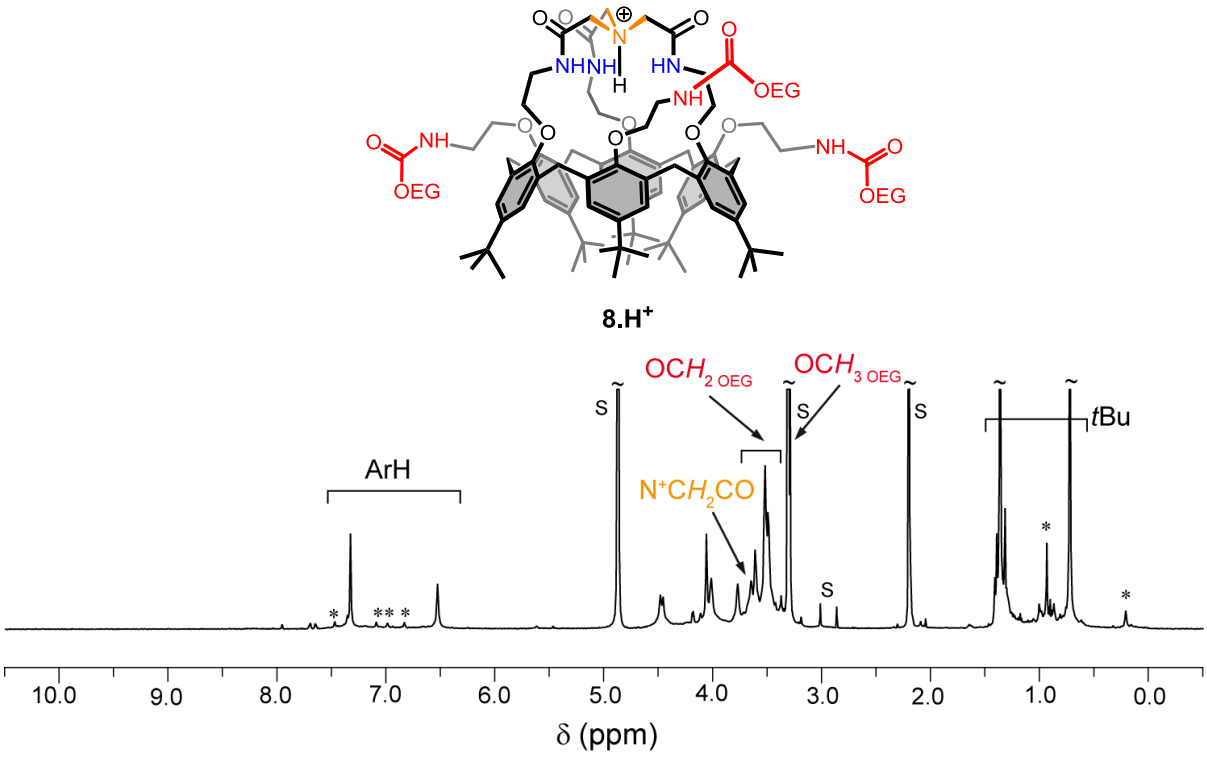
Selected region of the symmetrized dqfCOSY NMR (600MHz, 298K) spectrum of **8** in D_2O/CD_3OD 1:2



Edited-HSQC NMR (600MHz, 298K) spectrum of **8** in D_2O/CD_3OD 1:2



^{1}H NMR (600MHz, 298K) spectrum of **8.H$^+$** in D_2O/CD_3OD 1:2

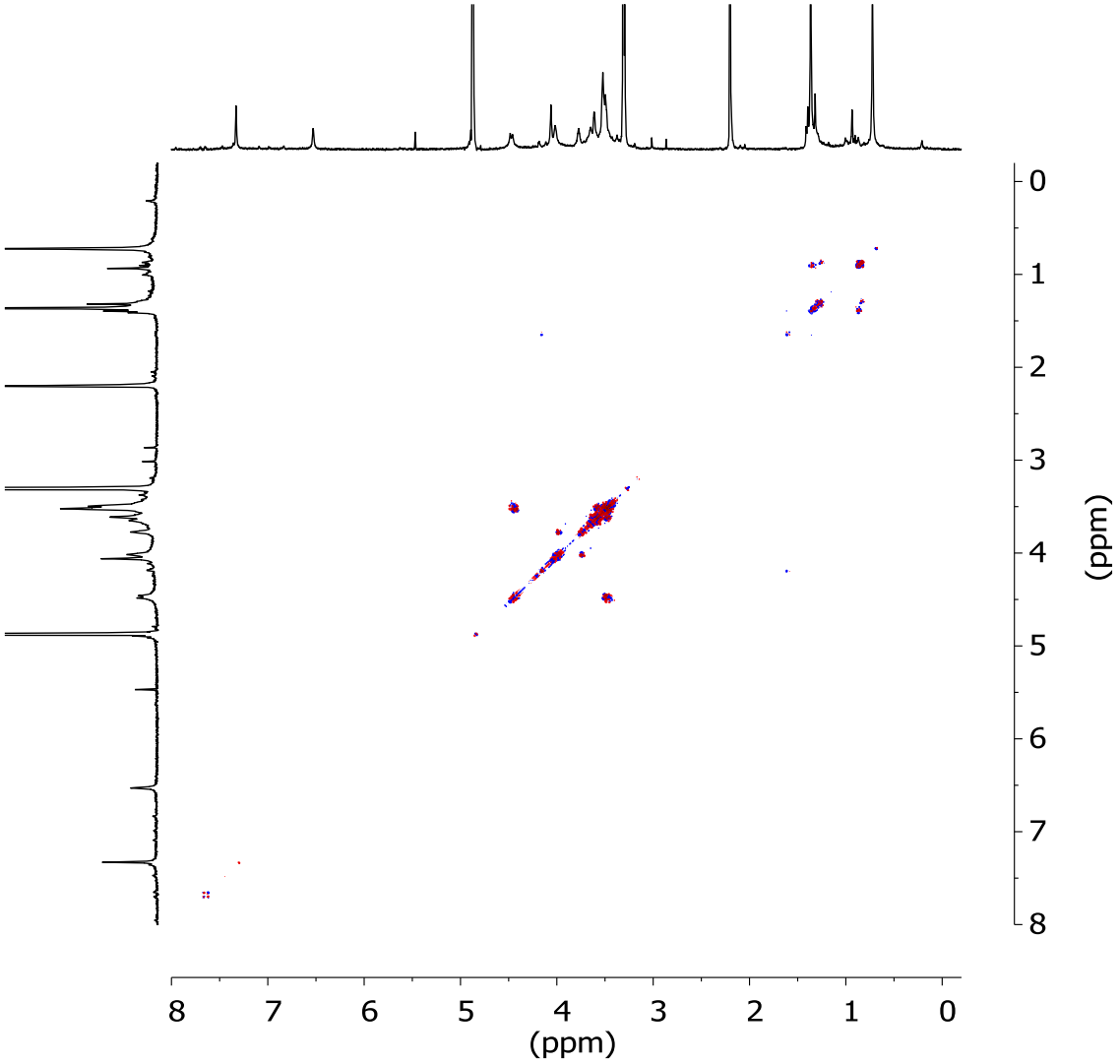


*: minor conformer; S: solvent.

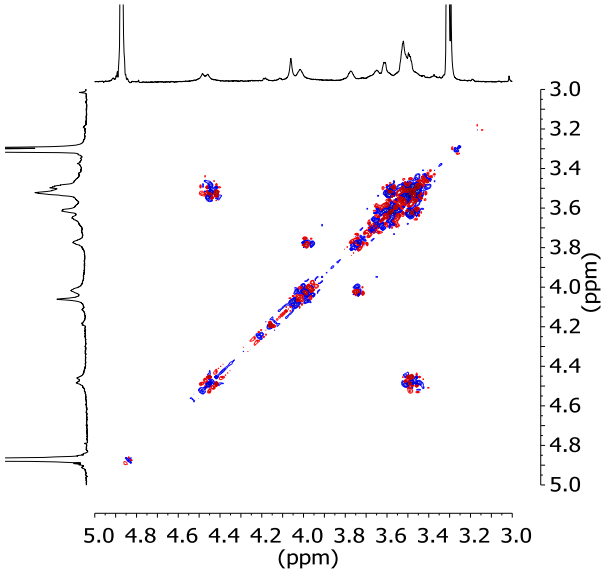
	δ (ppm) of **8.H$^+$**
CON*H* $_{cap}$	nd
CON*H* $_{OEG}$	nd
Ar*H* $_{out}$	7.33 (s)
Ar*H* $_{in}$	6.53 (s)
ArC*H*$_{2\ ax}$	4.47 (d_b, *J* =15.1 Hz)
OC*H*$_2$CONH $_{OEG}$ ArOC*H*$_{2\ cap\ and\ OEG}$	3.98-4.09 (m)
C*H*$_2$NHCO $_{cap\ and\ OEG}$ + OC*H*$_{2\ OEG}$	3.44-3.81 (m)
ArC*H*$_{2\ eq}$	3.51 (m)
HN$^+$C*H*$_2$CO	3.65 (m)
OC*H*$_{3\ OEG}$	3.29 (s)
*t*Bu $_{out}$	1.37 (s)
*t*Bu $_{in}$	0.72 (s)

nd: not detected

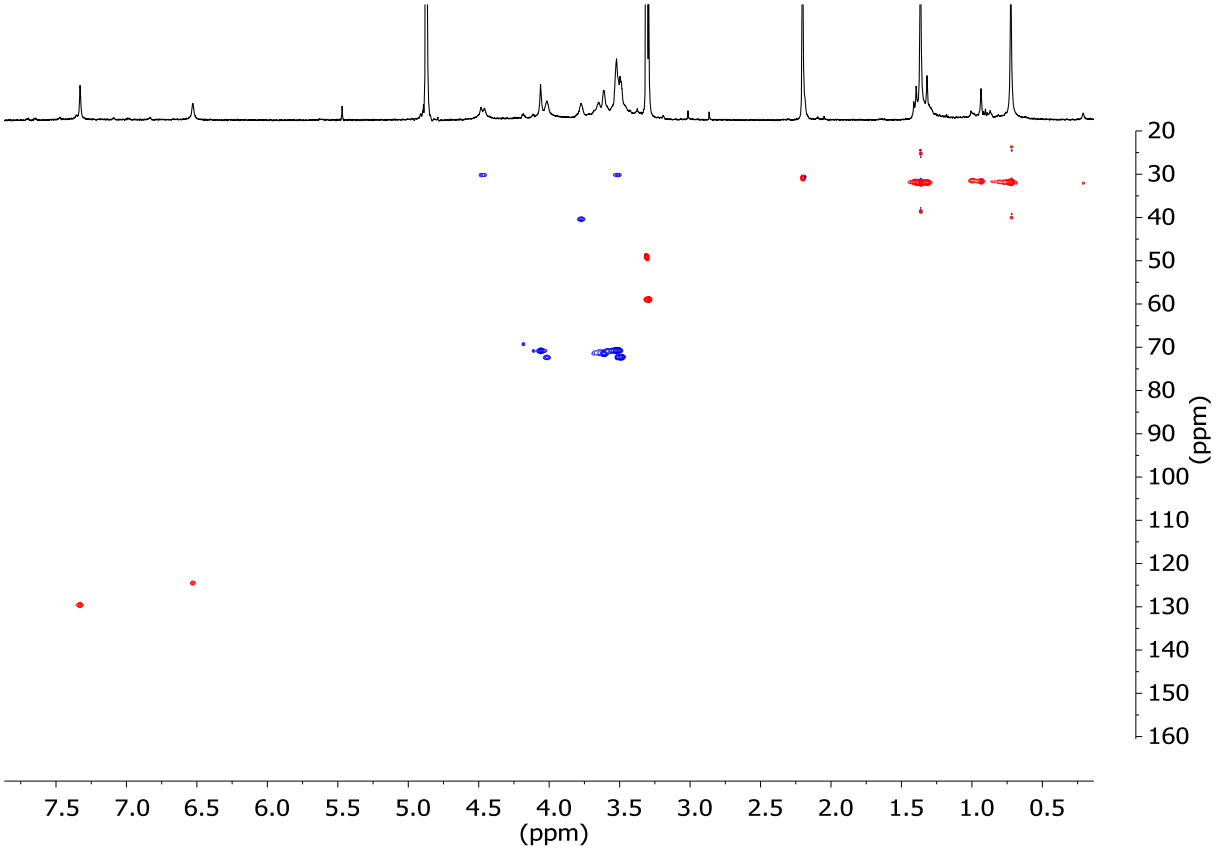
Symmetrized dqfCOSY NMR (600MHz, 298K) spectrum of **8.H**$^+$ in D_2O/CD_3OD 1:2



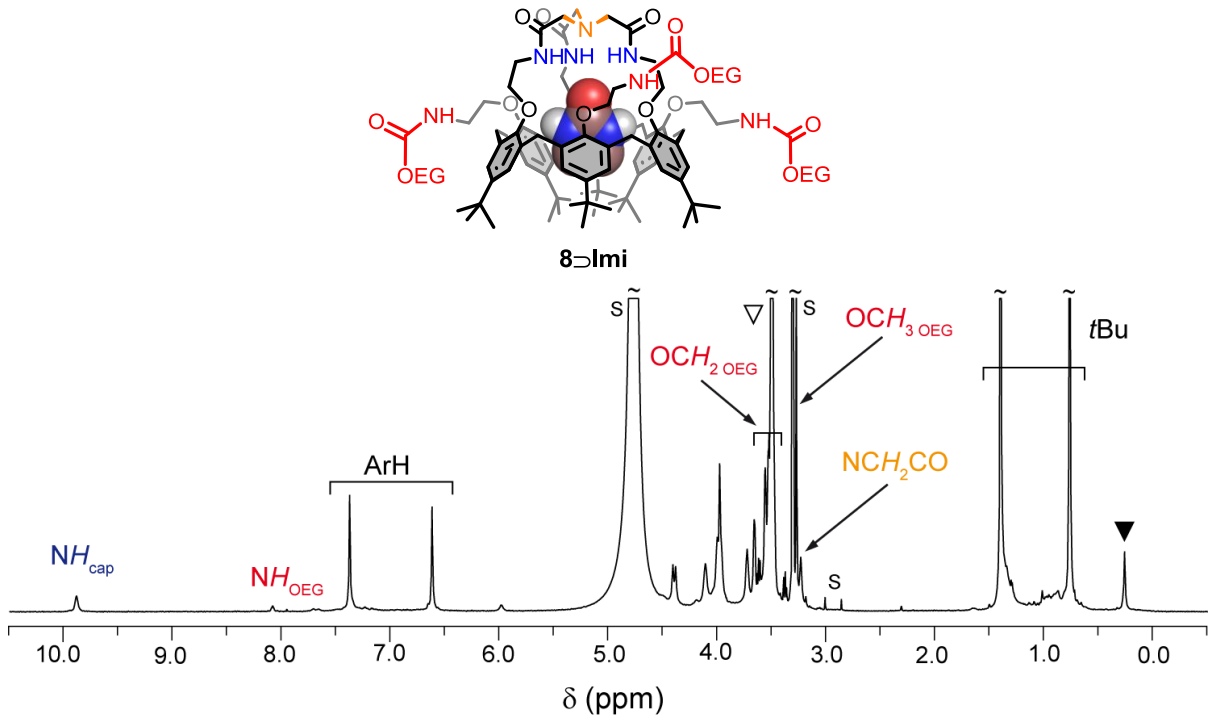
Selected region of the symmetrized dqfCOSY NMR (600MHz, 298K) spectrum of **8.H**$^+$ in D_2O/CD_3OD 1:2



Edited-HSQC NMR (600MHz, 298K) spectrum of **8.H**$^+$ in D_2O/CD_3OD 1:2



^{1}H NMR (600MHz, 298K) spectrum of **8⊃Imi** in D_2O/CD_3OD 1:2

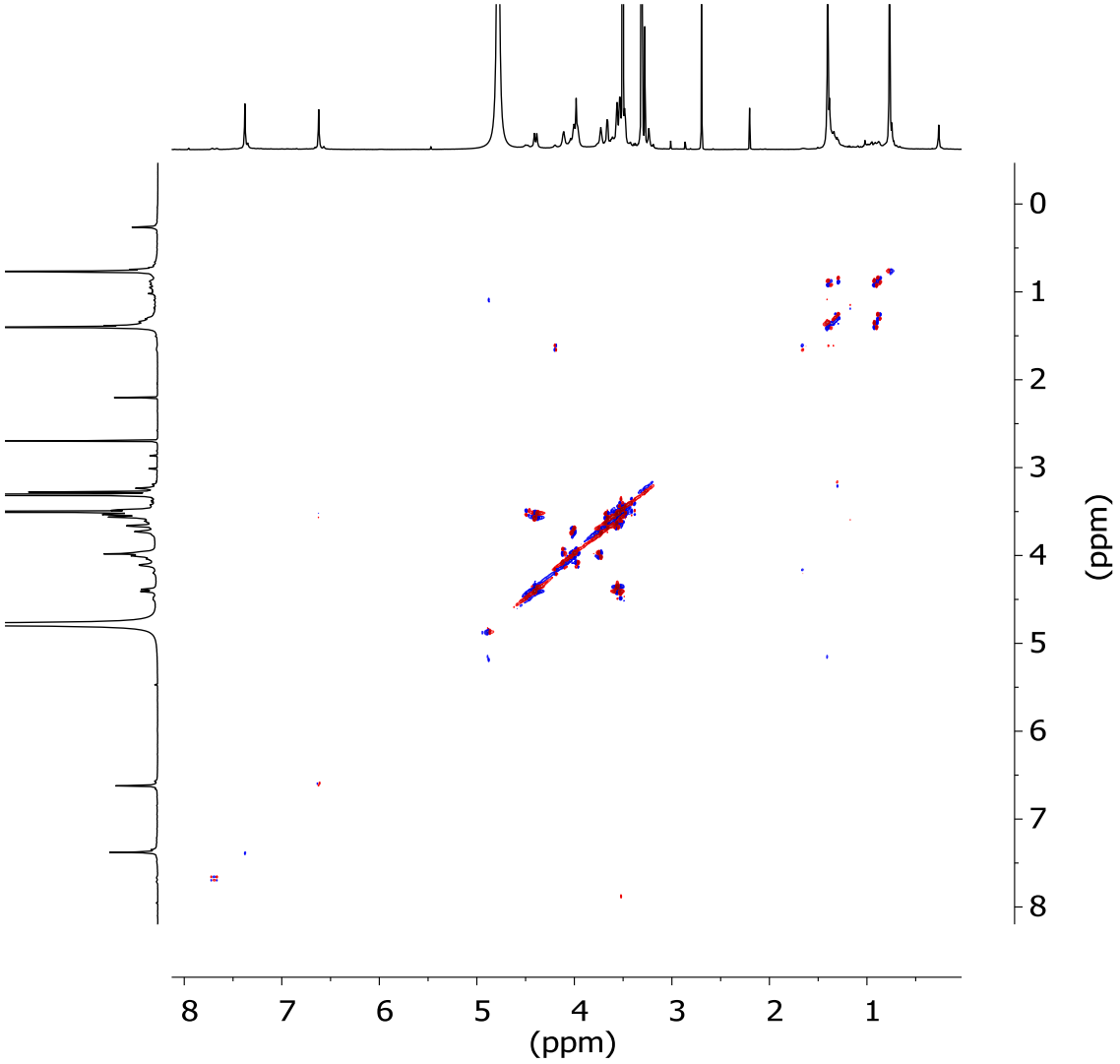


▽: free Imi; ▼: Imi included; S: solvent.

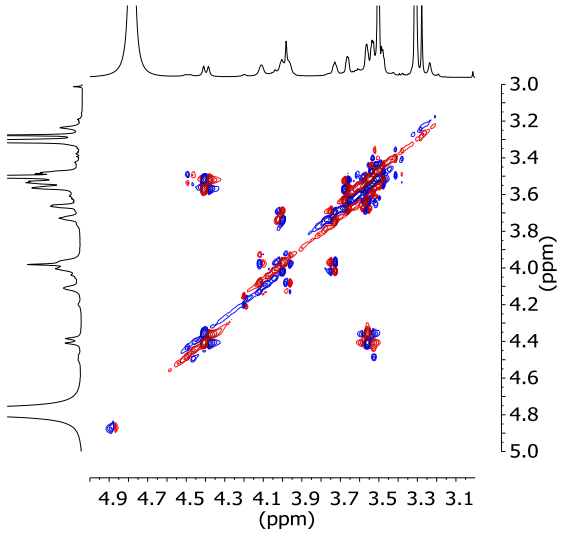
	δ (ppm) of **8⊃Imi**
CONH $_{cap}$	9.90 (s_b)
CONH $_{OEG}$	8.08 (s_b)
ArH $_{out}$	7.38 (s)
ArH $_{in}$	6.62 (s)
ArCH$_{2\ ax}$	4.39 (d, *J* =15.1 Hz)
CH$_2$NHCO $_{cap}$	4.11 (s_b)
OCH$_2$CONH $_{OEG}$	3.98 (s_b)
ArOCH$_{2\ cap\ and\ OEG}$	3.94-4.02 (m)
CH$_2$NHCO $_{OEG}$	3.73 (s_b)
ArCH$_{2\ eq}$+ OCH$_{2\ OEG}$	3.45-3.68 (m)
OCH$_{3\ OEG}$	3.28 (s)
NCH$_2$CO	3.24 (s_b)
*t*Bu $_{out}$	1.40 (s)
*t*Bu $_{in}$	0.77 (s)
NH $_{Imi\ in}$	nd
CH$_{2\ Imi\ in}$	0.26 (s)

nd: not detected

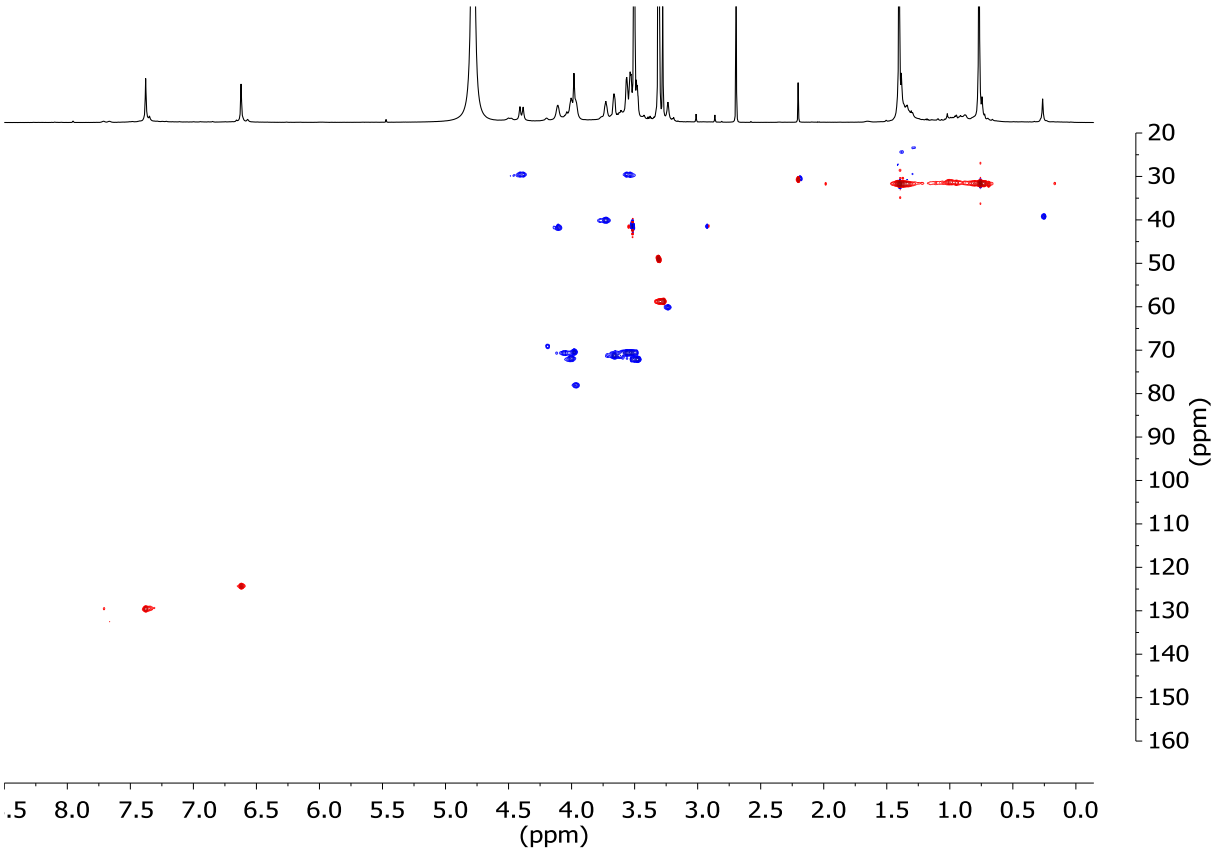
dqfCOSY NMR (600MHz, 298K) spectrum of **8⊃Imi** in D_2O/CD_3OD 1:2



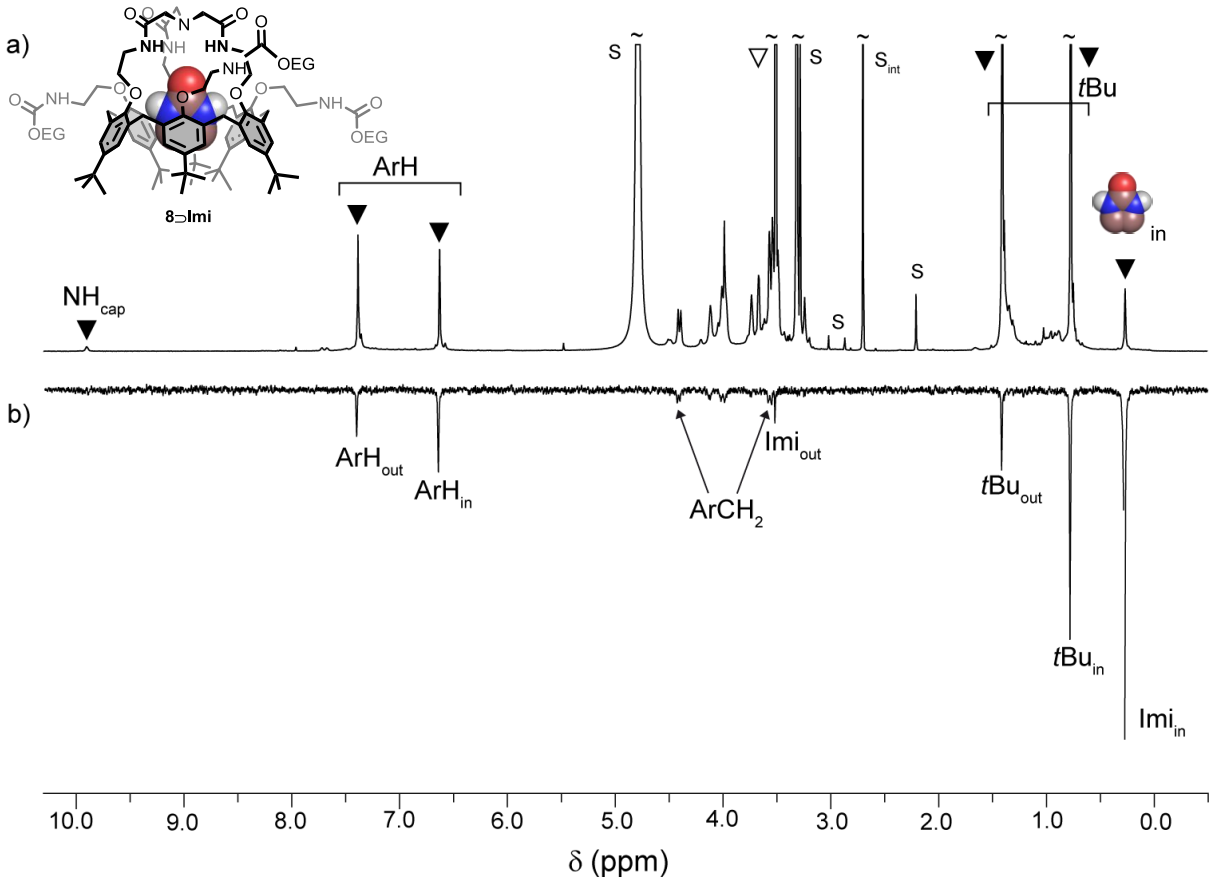
Selected region of the dqfCOSY NMR (600MHz, 298K) spectrum of **8⊃Imi** in D_2O/CD_3OD 1:2



Edited-HSQC NMR (600MHz, 298K) spectrum of **8⊃Imi** in D_2O/CD_3OD 1:2

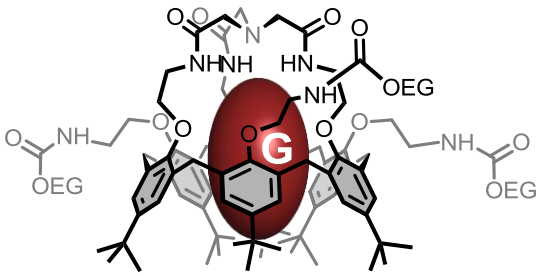


1D NOESY (600MHz, 298K) experiment on **8⊃Imi** in D_2O/CD_3OD 1:2

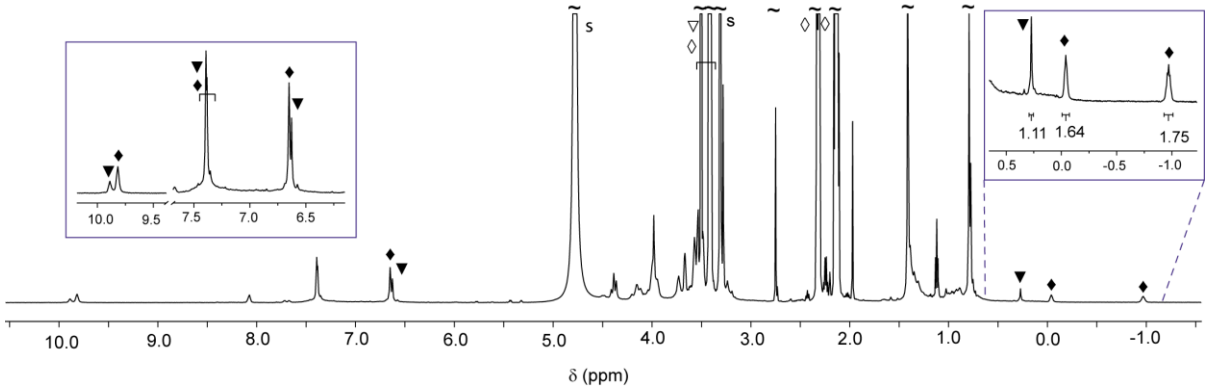


a) ^{1}H NMR spectrum; b) 1D NOESY spectrum recorded with selective excitation at 0.23 ppm (Imi_{in}) and a mixing time of 1100 ms; The signal of Imi_{out} is due to the in-out exchange of the guest (EXSY-type signal). It is rather weak, suggesting that the residence time of Imi included in the cavity of **8** is significantly longer than the mixing time. ▽: free Imi; ▼: **8⊃Imi**; S: solvent; S_{int}: internal standard (DMSO).

Competitive binding study of **8** with Imi and Pyro in D_2O/CD_3OD 1:2: ^1H NMR (600MHz, 298K) spectrum after addition of 115 equiv. of Pyro and 13.5 equiv. of Imi

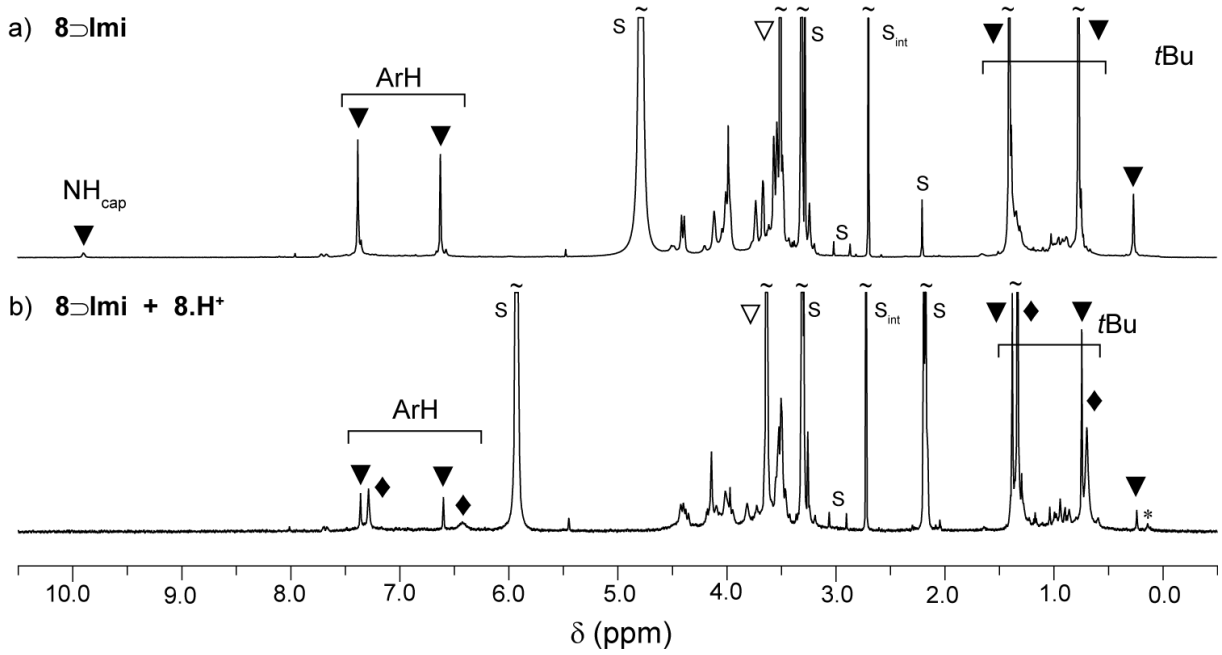


8⊃G



▼: endo-complex **8⊃Imi**; ▽: free Imi; ♦: endo-complex **8⊃Pyro**; ◊: free Pyro; S: solvent.

Acid-triggered release of Imi in an aqueous medium: ^{1}H NMR (600MHz, 298K) spectra in D_2O/CD_3OD 1:2



a) **8** after addition of 18 equiv. of Imi; b) after the subsequent addition of 450 equiv. of D_2SO_4 (>96%). ▼: **8⊃Imi**; ▽: free Imi; ♦: **8.H**$^+$; *: minor conformer; S: solvent; S_{int}: internal standard (DMSO).

X-ray Crystallography

X-ray data were collected on a Nonius KappaCCD diffractometer equipped with a Bruker APEXII detector at T = 123.0(1) K using graphite-monochromatized Mo-$K\alpha$ radiation (λ = 0.71073 Å). Collect[1] software package was used for data collection, DENZO-SMN[2] was used for integration and reduction, and the multiscan absorption correction was applied using SADABS2008.[3]

The structures were solved with SHELXS-97[4] (**1⊃Imi** chloroform/pentane solvate) or Superflip[5] (**1⊃Imi** chloroform/diisopropyl ether solvate) and refined by full-matrix least-squares using SHELXL-2014/7[6] within WinGX[7] package. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were calculated and refined as riding on the parent carbon or oxygen atoms with U_H = 1.2 U_C. Geometrical restraints were applied to the 1,2- and 1,3-distances in case of solvent molecules and the guest molecule **Imi** to enforce the expected symmetry, in such a way that the parameters were allowed to refine freely. The occupancies of the disordered moieties were also allowed to refine freely. The guest molecule, **Imi**, was modelled as partially disordered, with the two components related by a non-crystallographic two-fold symmetry axis. Anisotropic displacement parameters were also restrained. Certain erroneous reflections were omitted.

Further refinement details for **1⊃Imi** chloroform/pentane solvate (1_Imi_CHCl3_pent):

One of three chloroform molecules in the crystal structure was modelled as disordered, with a pentane molecule partially occupying the same position. Its 1,2- and 1,3-distances were restrained to be equal to the ordered chloroform molecules, while the expected geometry of the pentane molecule was also enforced by appropriate restraints. Their occupancy ratio was finally allowed to refine freely.

Further refinement details for **1⊃Imi** chloroform/diisopropyl ether solvate (1_Imi_CHCl3_iPr2O):

Two out of three chloroform molecules were modelled as disordered, one of them as disordered over two positions and the other as disordered over two positions and partially substituted by a diisopropyl ether molecule occupying the same position. The 1,2- and 1,3-distances were restrained to be equal for all, either fully or partially occupied, chloroform molecule positions, and the expected geometry of the diisopropyl molecule was enforced by appropriate restraints. Their occupancy ratios were finally allowed to refine freely, with the occupancies summing up to 100% in case of the two-fold disorder and 60% in the case of position partially substituted with diisopropyl ether.

A minor twin component was found, with the transformation matrix [1 0 0.078 0 −1 0 0 0 −1] and the batch scale factor converging to 0.0104(7).

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