Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Selective recognition of quaternary ammonium ions and zwitterions by a biomimetic bis-calix[6]arene-based receptor

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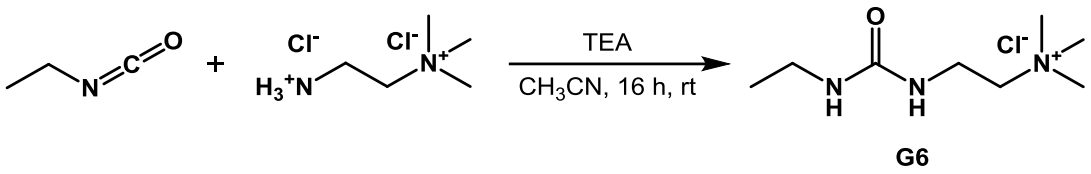
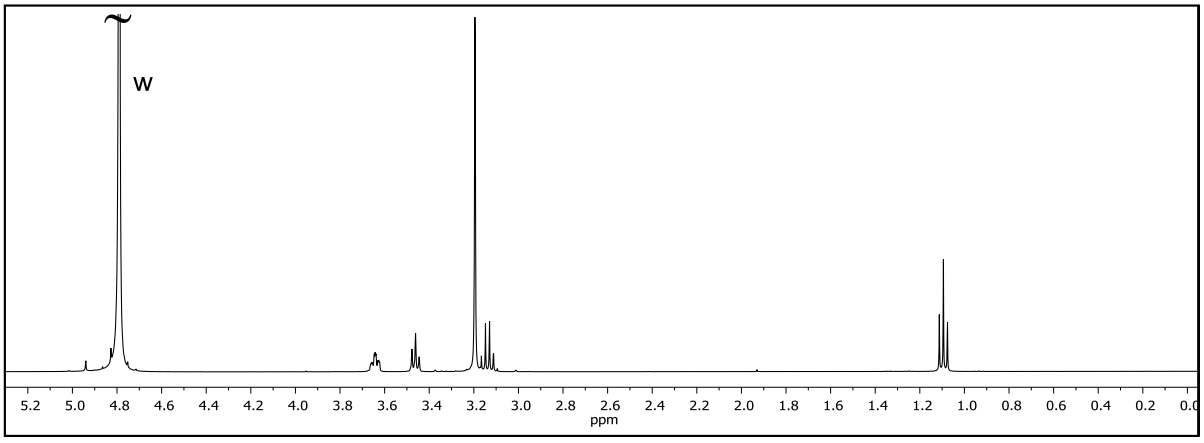
SI1. Synthesis of **G6**

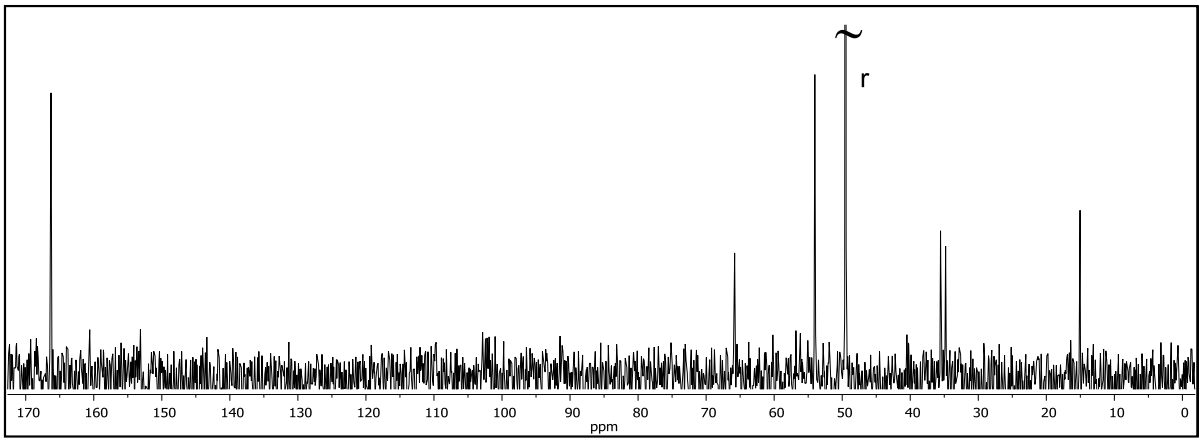


Ethyl isocyanate (226 µL, 2.86 mmol) was added to a solution of (2-aminoethyl)trimethylammonium chloride hydrochloride (50 mg, 0.286 mmol) and triethylamine (80 µL, 0.574 mmol) in acetonitrile (3 mL). The reaction mixture was stirred for 16 h at room temperature and then concentrated under reduced pressure. The solid was dissolved in methanol (3 mL). Then, dichloromethane (5 mL) was added to the solution and the mixture was sonicated and filtered to afford the desired ammonium **G6** as a white powder (56.1 mg, 94%).

^{1}H NMR (D_2O, 298 K, 400 MHz): δ (ppm) = 1.09 (t, ^{3}J = 7.2 Hz, 3H, NCH_2CH_3), 3.14 (q, ^{3}J = 7.2 Hz, 2H, NCH_2CH_3), 3.20 (s, 9H, $N^+(CH_3)_3$), 3.46 (t, ^{3}J = 6.8 Hz, 2H, $N^+CH_2CH_2$), 3.64 (t_b, ^{3}J = 6.8 Hz, 2H, $N^+CH_2CH_2$). ^{13}C NMR (D_2O, 298 K, 100 MHz, in presence of 5 µL of CH_3OH as internal reference): δ (ppm) = 15.04, 34.79, 35.54, 54.02, 65.80, 166.28. FTIR: ν (cm^{-1}): 2920, 1657, 1630, 1567, 1435, 1379. m.p.: > 260 °C.

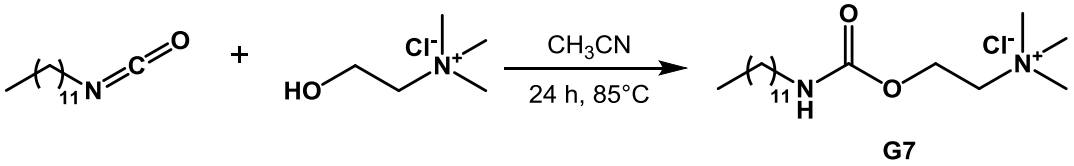


^{1}H NMR (298 K, 400 MHz) spectrum of **G6** in D_2O; W: Water.



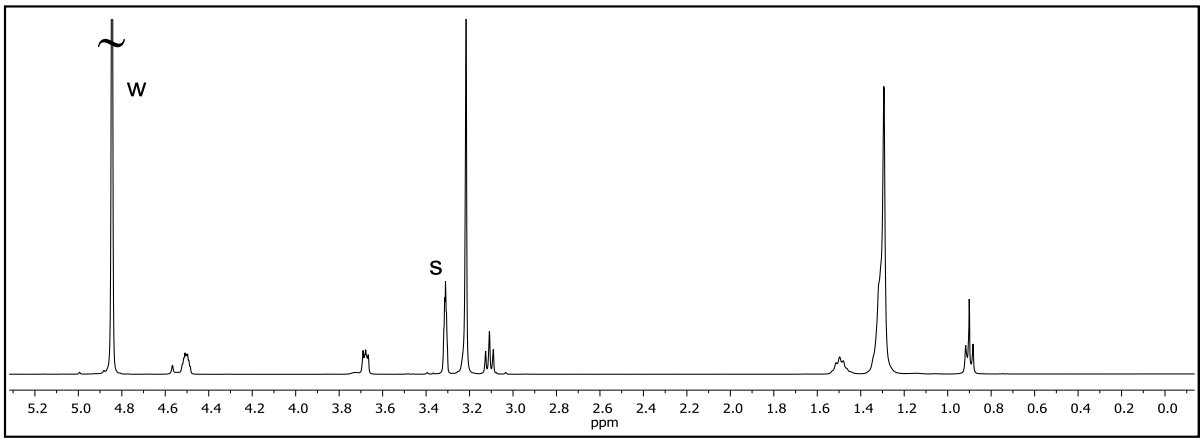
^{13}C NMR (298 K, 100 MHz) spectrum of **G6** in D_2O; r: reference (CH_3OH).

SI2. Synthesis of *N*-dodecylcarbamylcholine **G7**

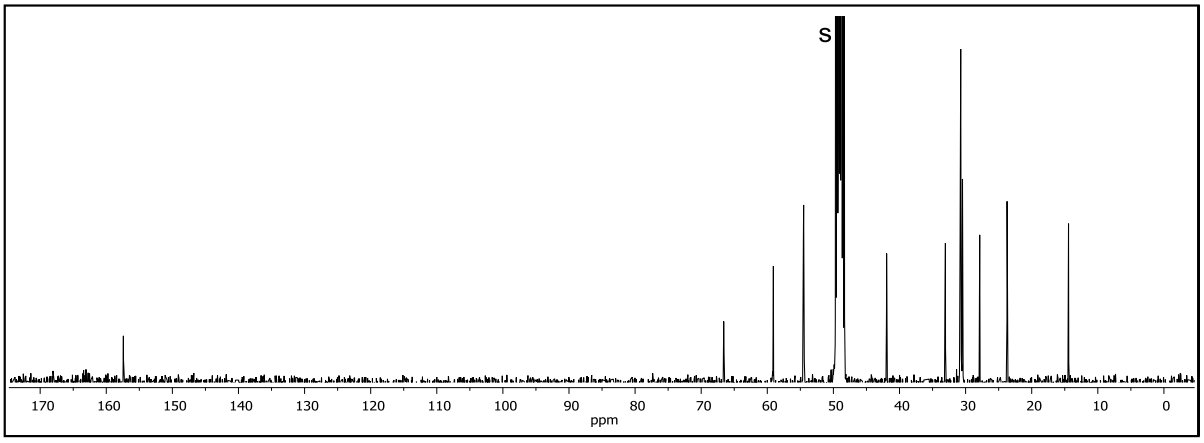


G7

Dodecyl isocyanate (400 µL, 1.66 mmol) was added to a solution of choline chloride (232 mg, 1.66 mmol) in anhydrous acetonitrile (25 mL). The reaction mixture was stirred for 24 h at 85°C. After cooling to room temperature, the precipitate was isolated by suction filtration and was washed with diethyl ether (15mL) to afford *N*-dodecylcarbamylcholine **G7** as a white powder (582 mg, quant).
^{1}H NMR (CD_3OD, 298 K, 400 MHz): δ (ppm) = 0.90 (t, ^{3}J = 6.8 Hz, 3H, CH_3), 1.29 (s_b, 18 H, $CH_3(CH_2)_9$), 1.50 (s_b, 2H, $NHCH_2CH_2$), 3.11 (t, ^{3}J = 7.0 Hz, 2H, $NHCH_2$), 3.22 (s, 9H, $N^+(CH_3)_3$), 3.68 (s_b, 2H, N^+CH_2), 4.50 (s_b, 2H, OCH_2). ^{13}C NMR (CD_3OD, 298 K, 100 MHz): δ (ppm) = 14.43, 23.72, 27.86, 30.45, 30.73 (m), 30.83, 33.06, 41.95, 54.50, 59.09, 66.59, 157.41. FTIR: ν (cm^{-1}): 2921, 2851, 1713, 1613, 1572, 1539, 1468, 1253, 1146. m.p.: 112 °C (dec).

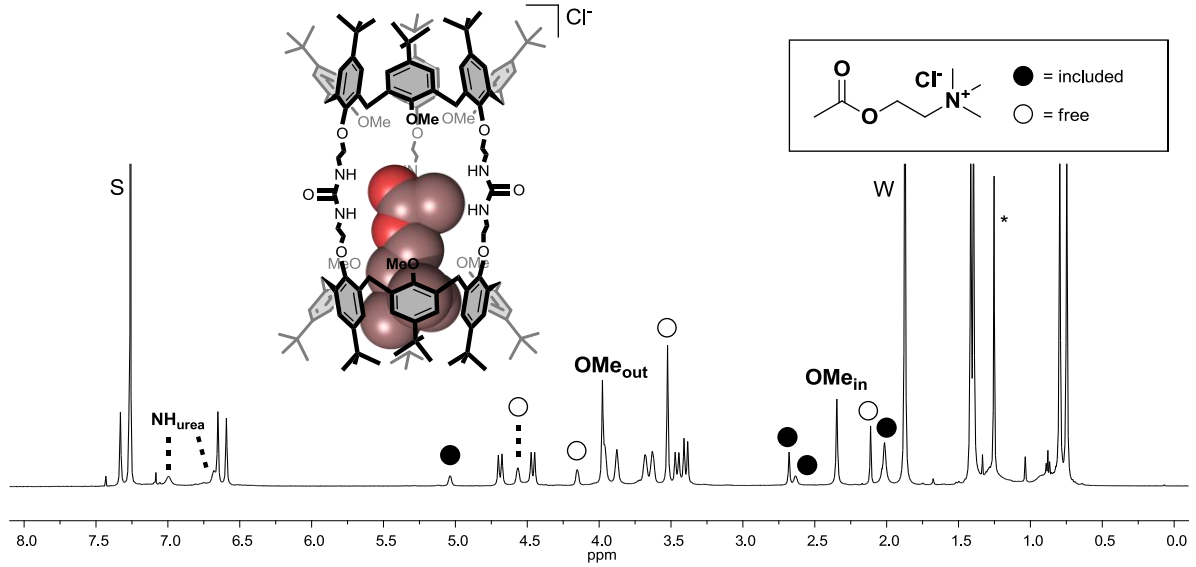


^{1}H NMR (298 K, 400 MHz) spectrum of **G7** in CD_3OD; S: Solvent; W: Water.

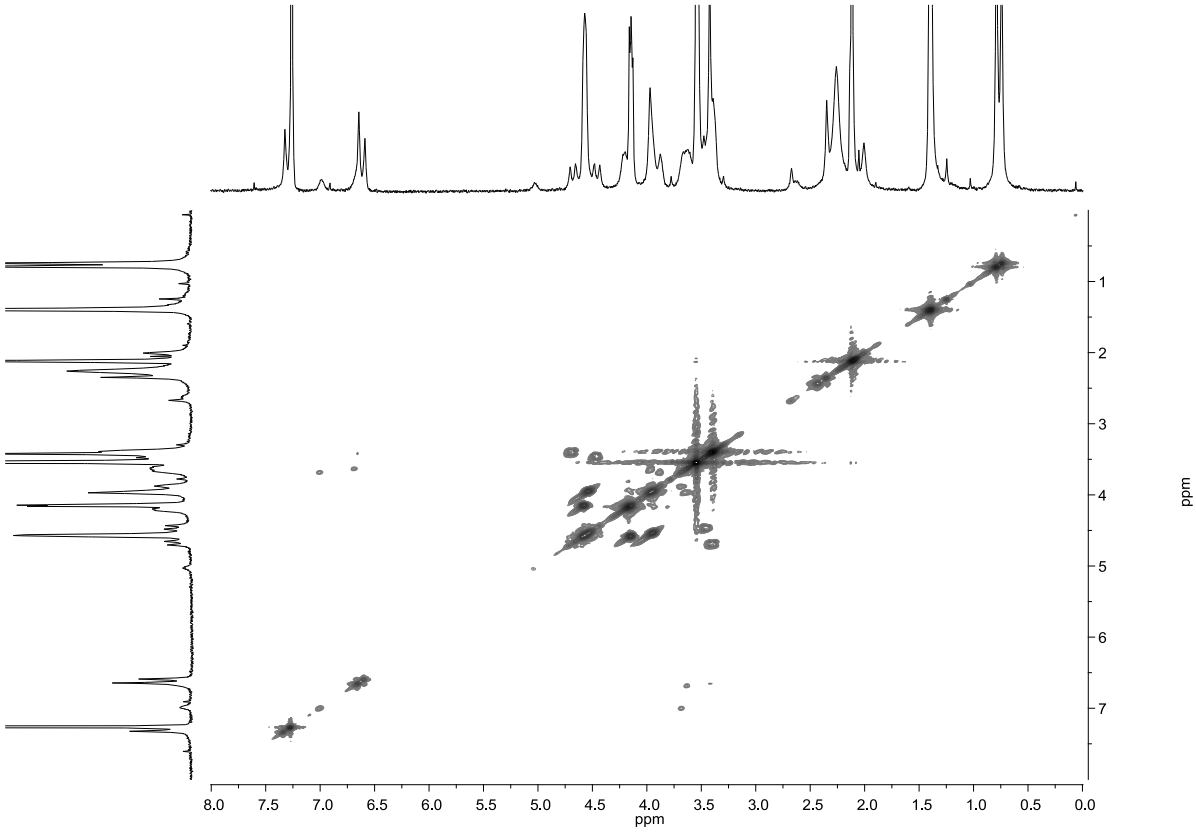


^{13}C NMR (298 K, 100 MHz) spectrum of **G7** in CD_3OD; S: Solvent.

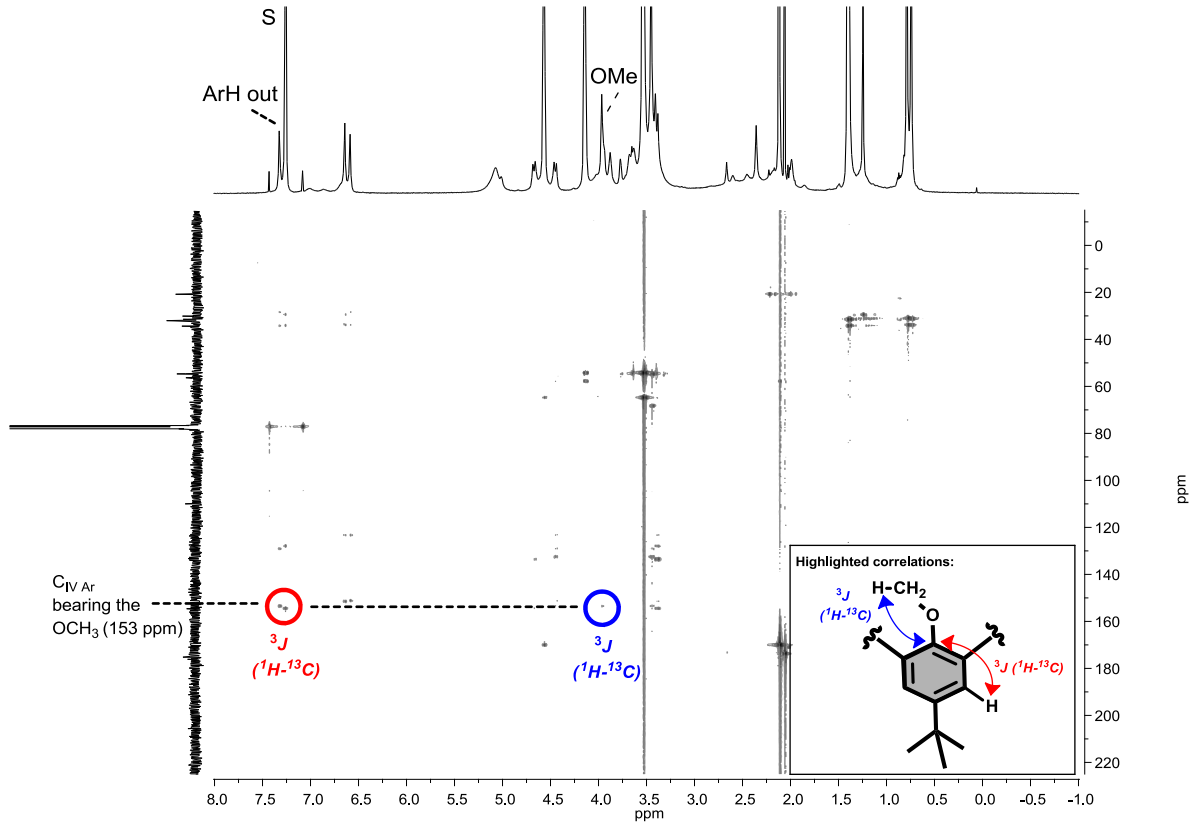
SI3. ^{1}H NMR, COSY NMR, HMBC NMR and ROESY NMR spectra of **1** with acetylcholine **G1** in $CDCl_3$



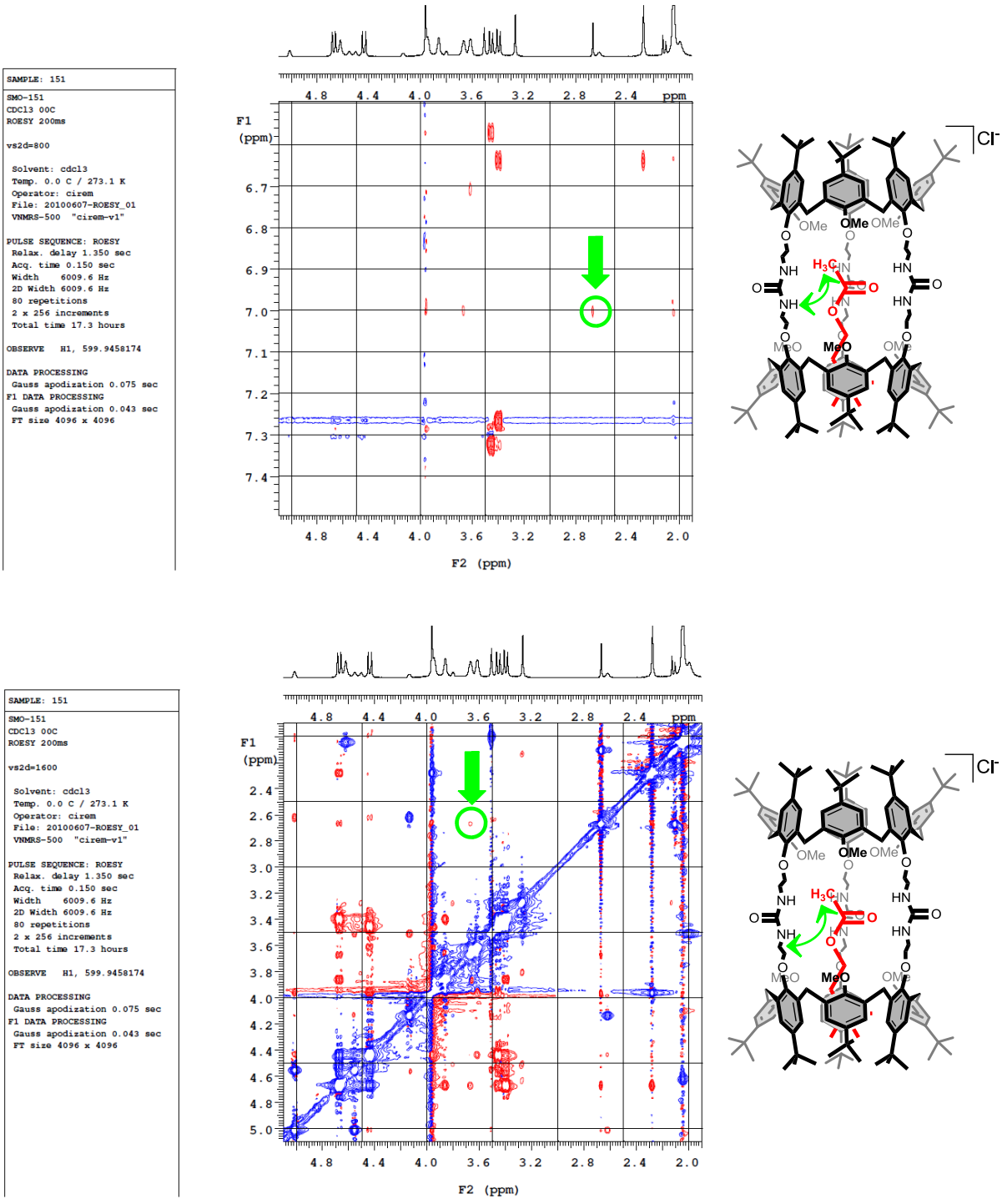
^{1}H NMR (298K, 600MHz) spectrum of **1⊃G1** in $CDCl_3$; S: Solvent; W: Water; ∗: residual grease.



COSY NMR (298K, 300MHz) spectrum of **1⊃G1** in $CDCl_3$.

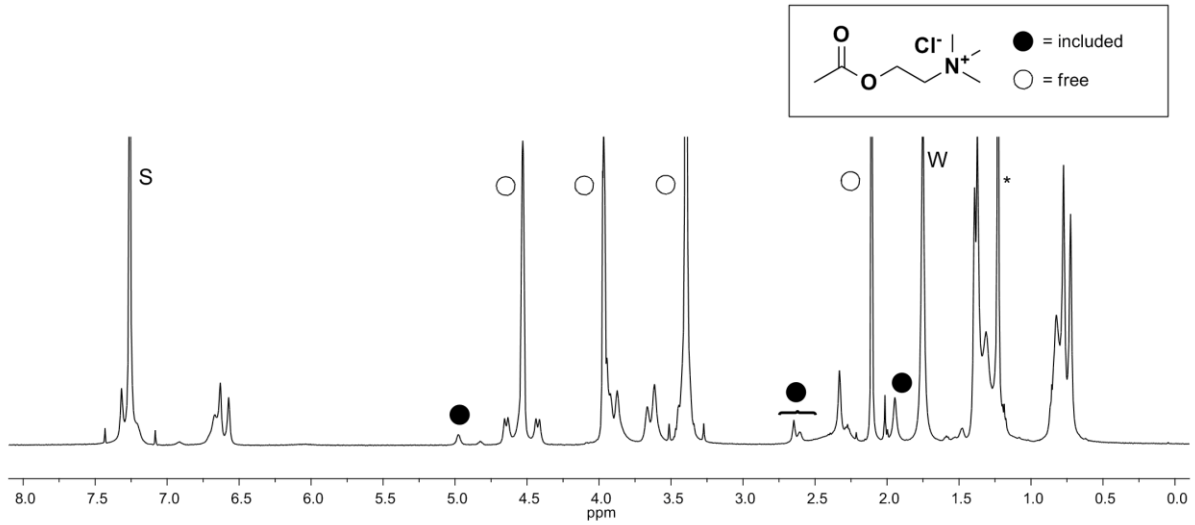


HMBC NMR (298K, 600MHz) spectrum of **1⊃G1** in $CDCl_3$.



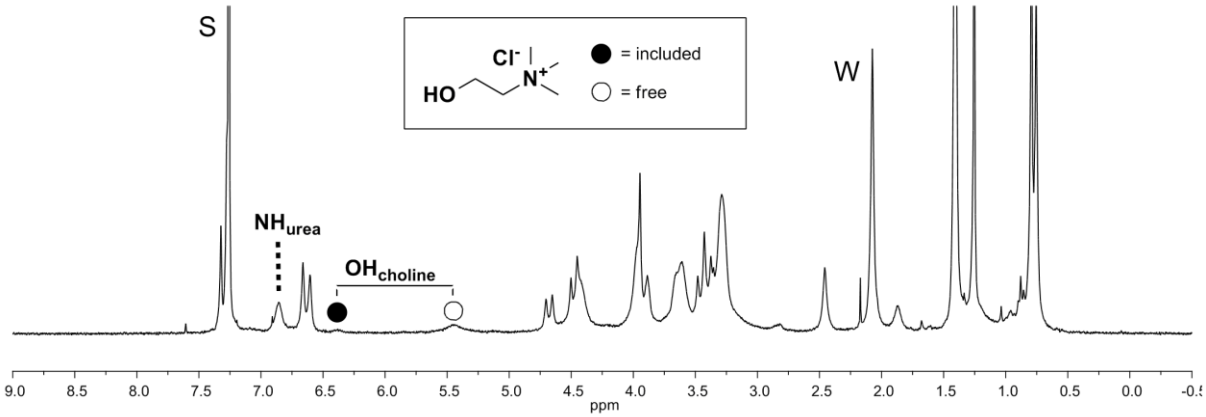
ROESY NMR (273K, 600MHz) spectra of **1⊃G1** in $CDCl_3$.

SI4. ^{1}H NMR spectrum of **1** with acetylcholine **G1** in $CD_3OD/CDCl_3$ (1:50)

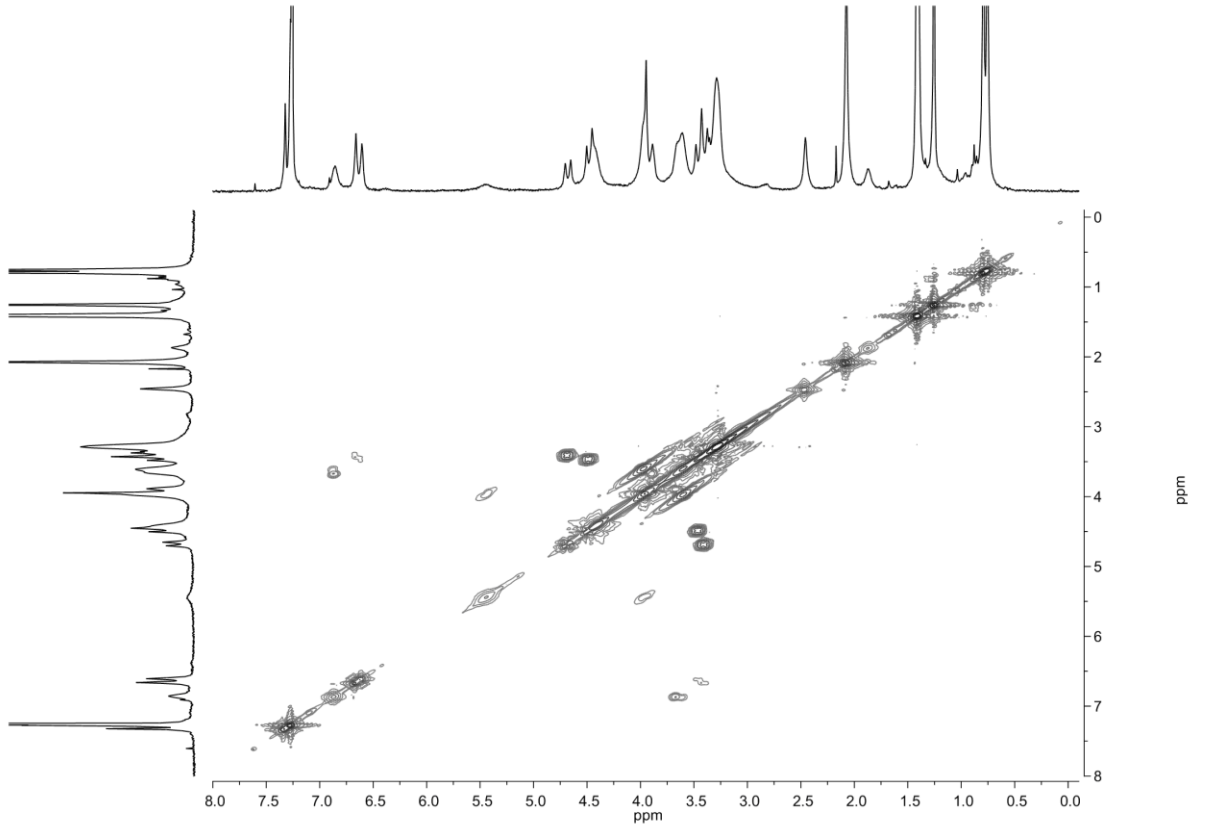


^{1}H NMR (298K, 300MHz) spectrum of **1** + 12 equiv. of acetylcholine **G1** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; ∗: residual grease.

SI5. ^{1}H NMR and COSY NMR spectra of **1** with choline **G2** in $CDCl_3$

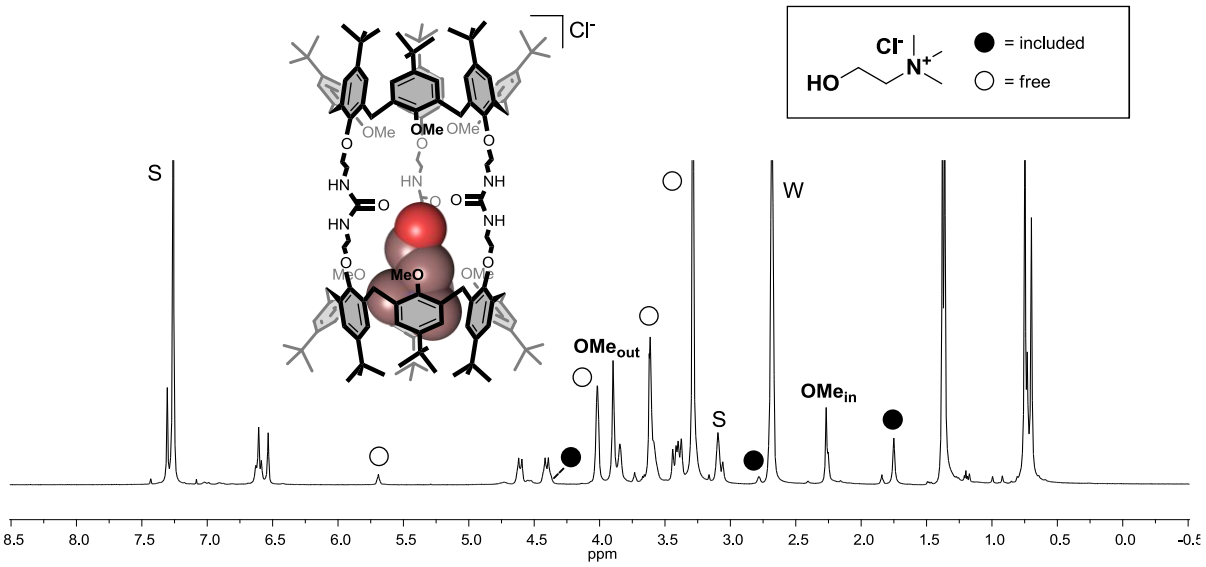


^{1}H NMR (298K, 300MHz) spectrum of **1⊃G2** in $CDCl_3$; S: Solvent; W: Water.

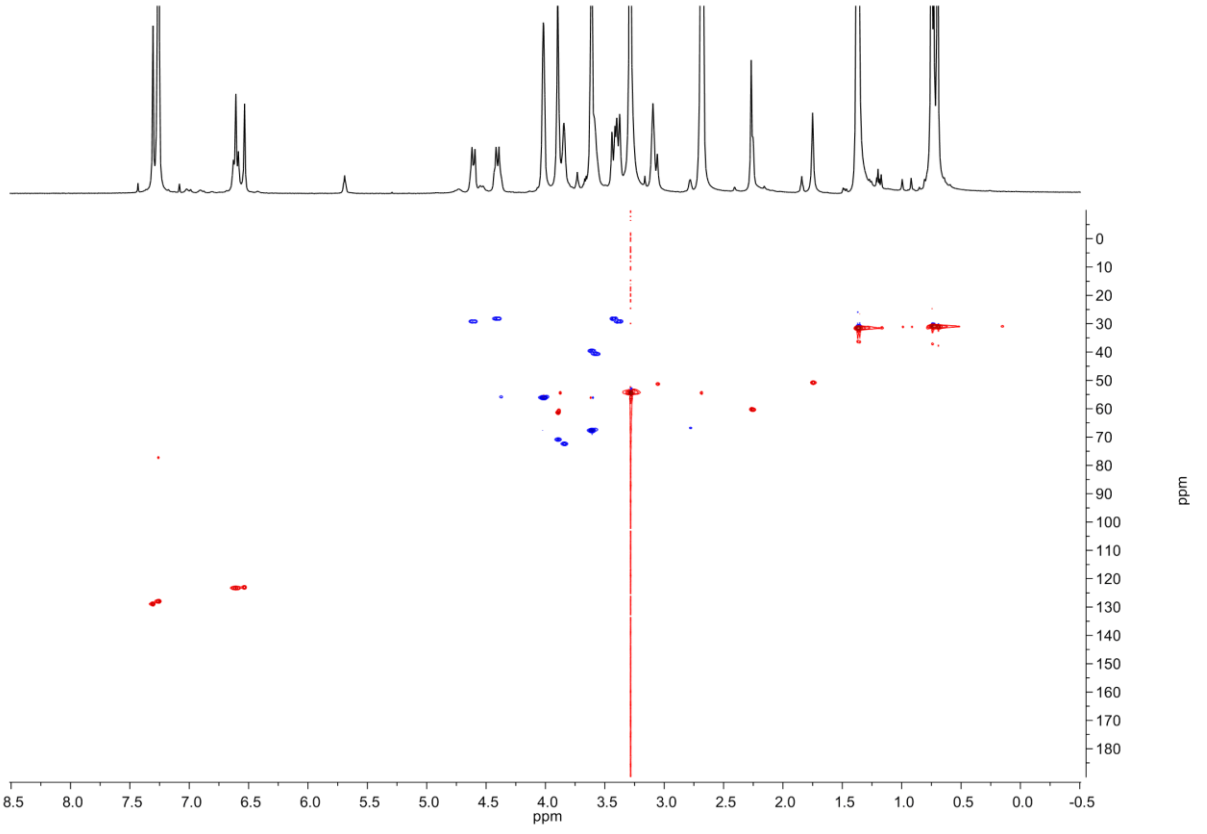


COSY NMR (298K, 300MHz) spectrum of **1⊃G2** in $CDCl_3$.

SI6. ^{1}H NMR and HSQC NMR spectra of **1** with choline **G2** in $CD_3OD/CDCl_3$ (1:50)

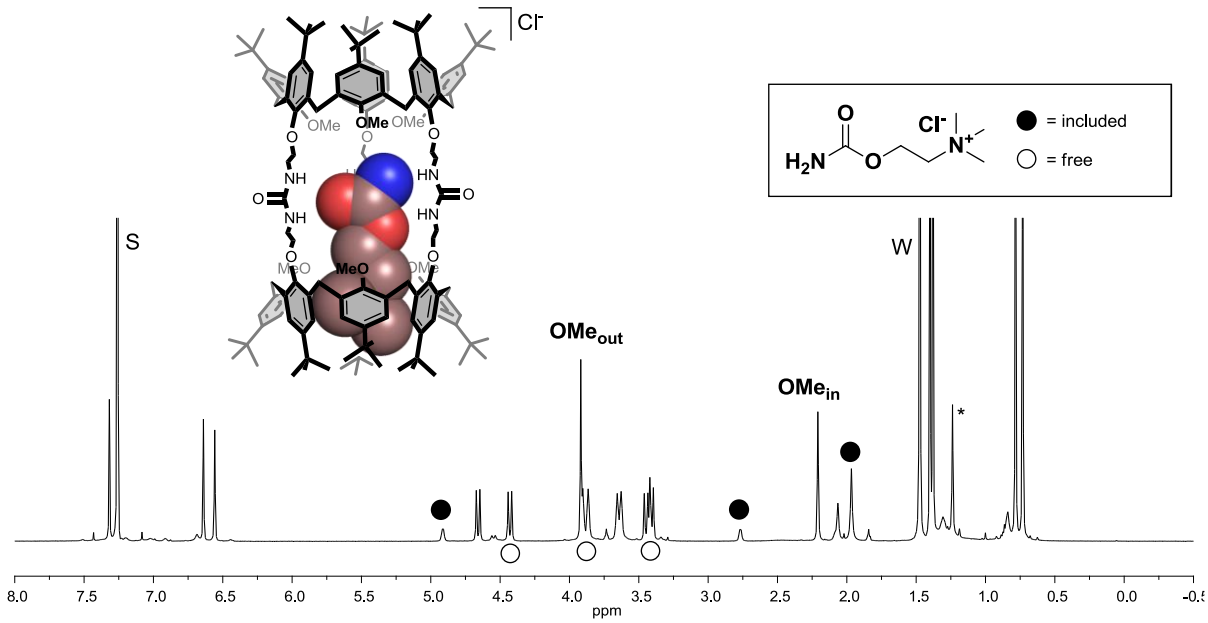


^{1}H NMR (263K, 600MHz) spectrum of **1** + 10 equiv. of choline **G2** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water.

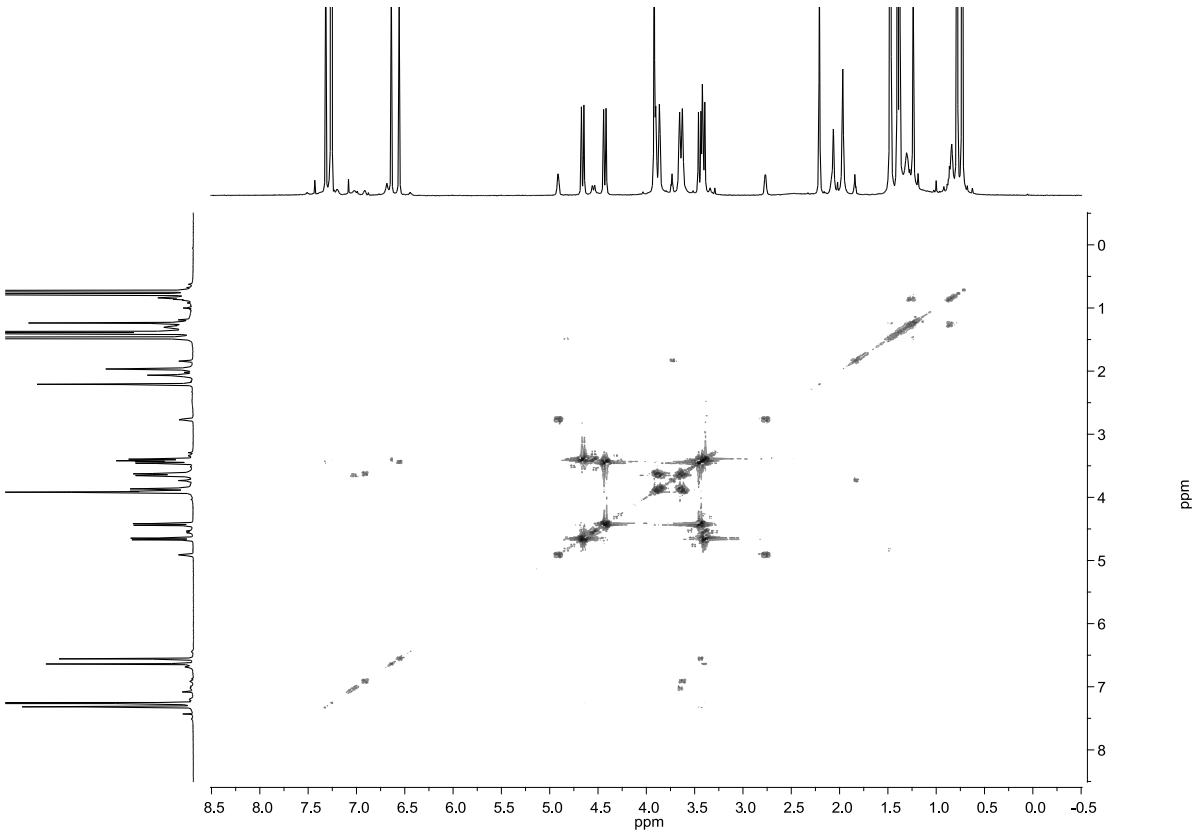


HSQC NMR (263K, 600MHz) spectrum of **1⊃G2** in $CD_3OD/CDCl_3$ (1:50).

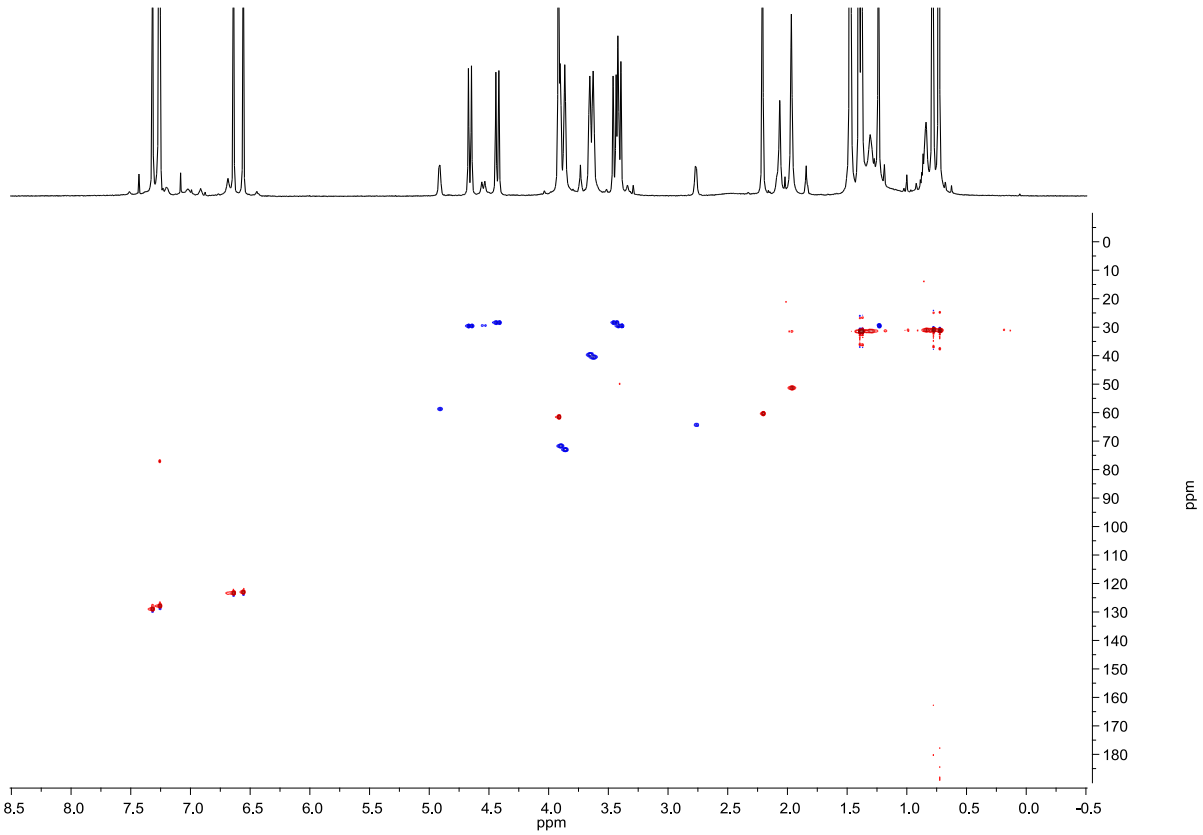
SI7. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with carbamylcholine **G3** in $CD_3OD/CDCl_3$ (1:50)



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G3** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; ∗: residual grease.

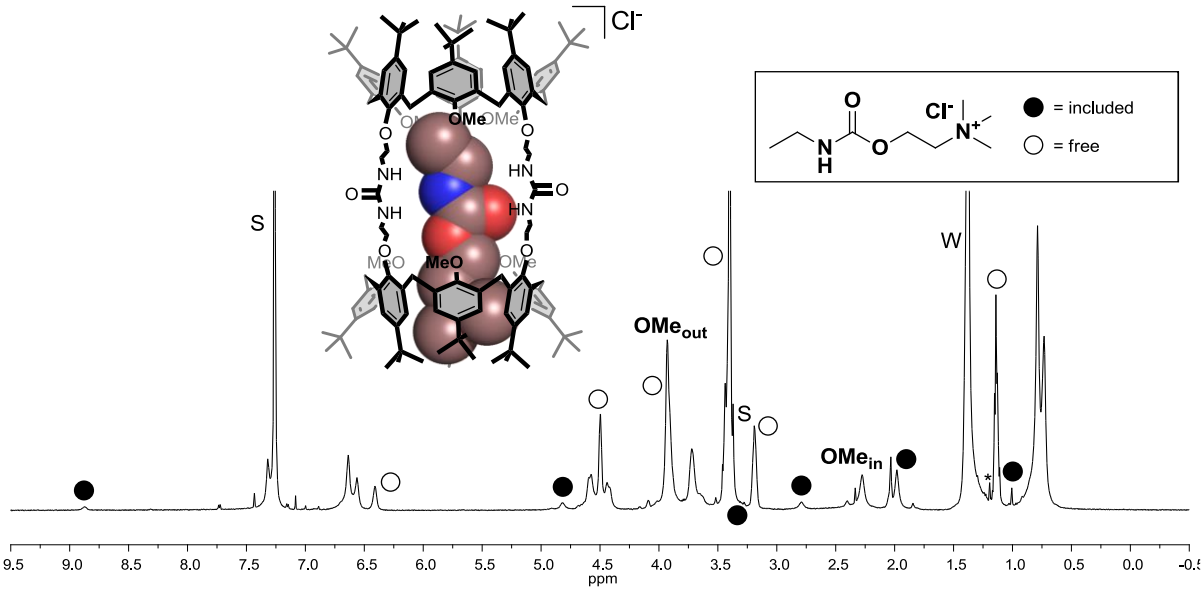


COSY NMR (298K, 600MHz) spectrum of **1⊃G3** in $CD_3OD/CDCl_3$ (1:50).

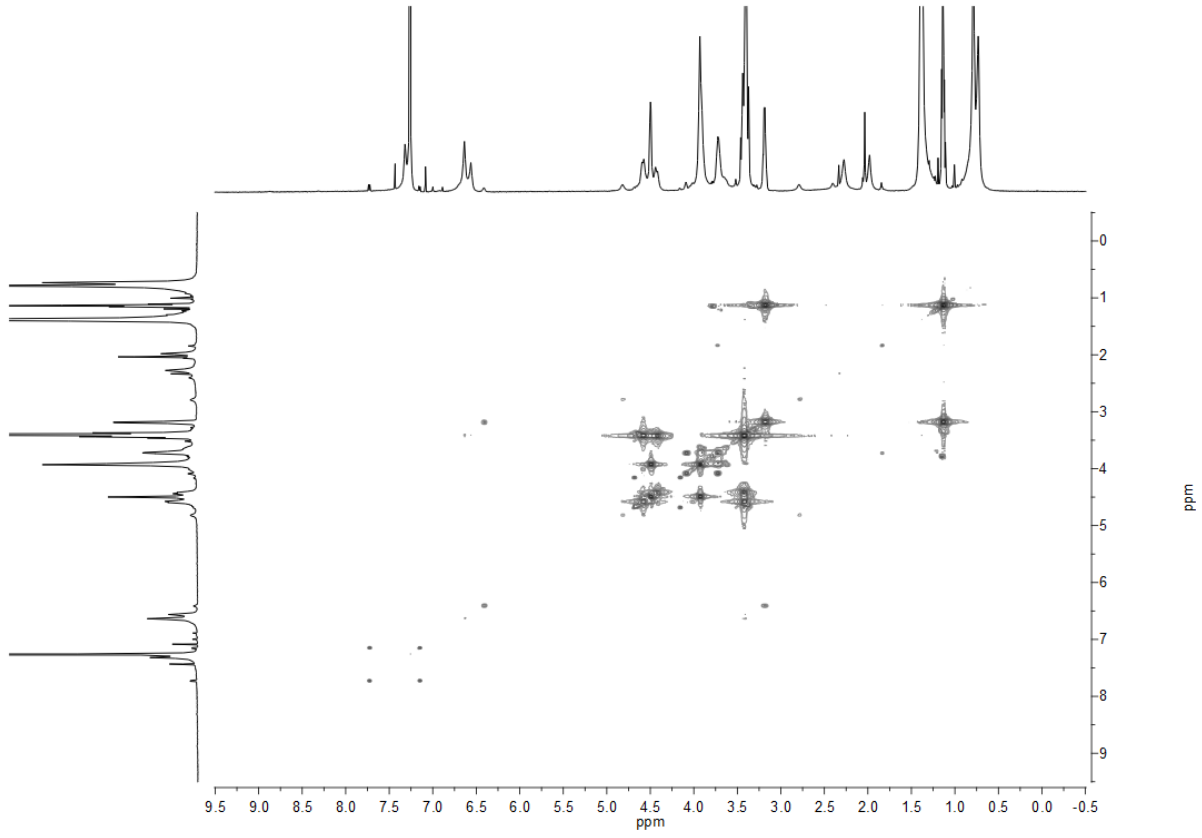


HSQC NMR (298K, 600MHz) spectrum of **1⊃G3** in $CD_3OD/CDCl_3$ (1:50).

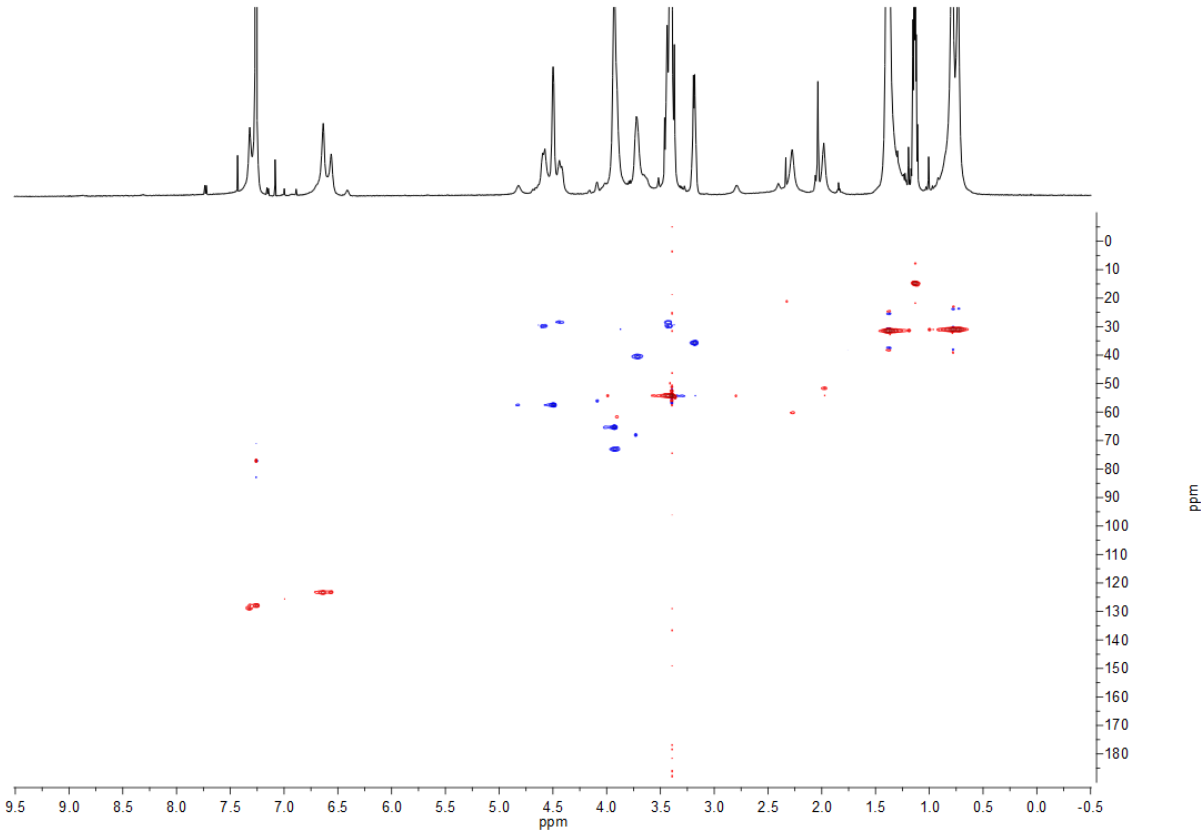
SI8. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with ethylcarbamylcholine **G4** in $CD_3OD/CDCl_3$ (1:50)



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G4** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; ∗: residual grease.

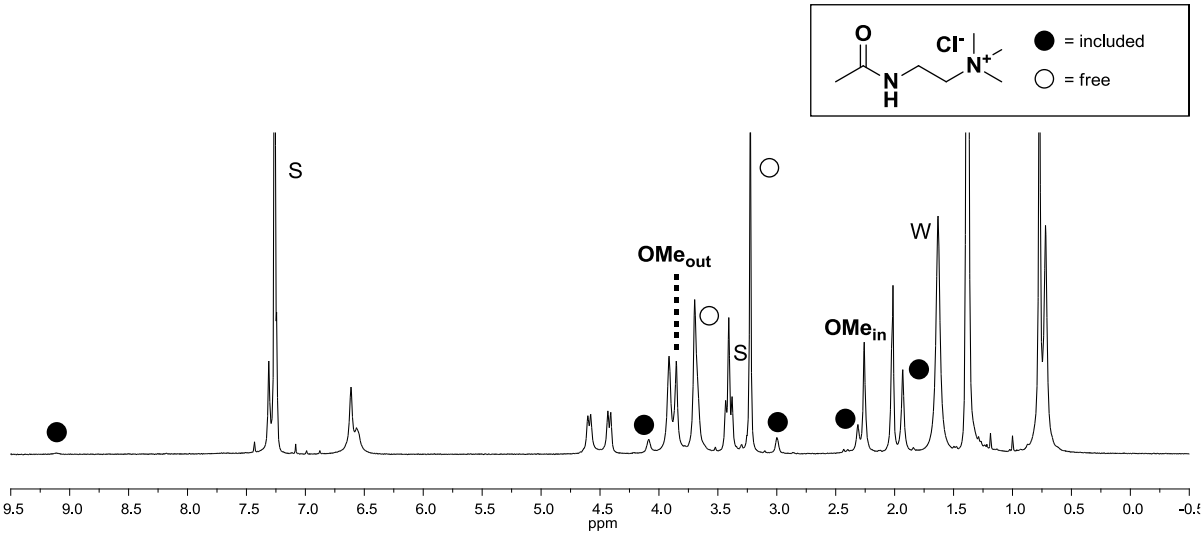


COSY NMR (298K, 600MHz) spectrum of **1⊃G4** in $CD_3OD/CDCl_3$ (1:50).

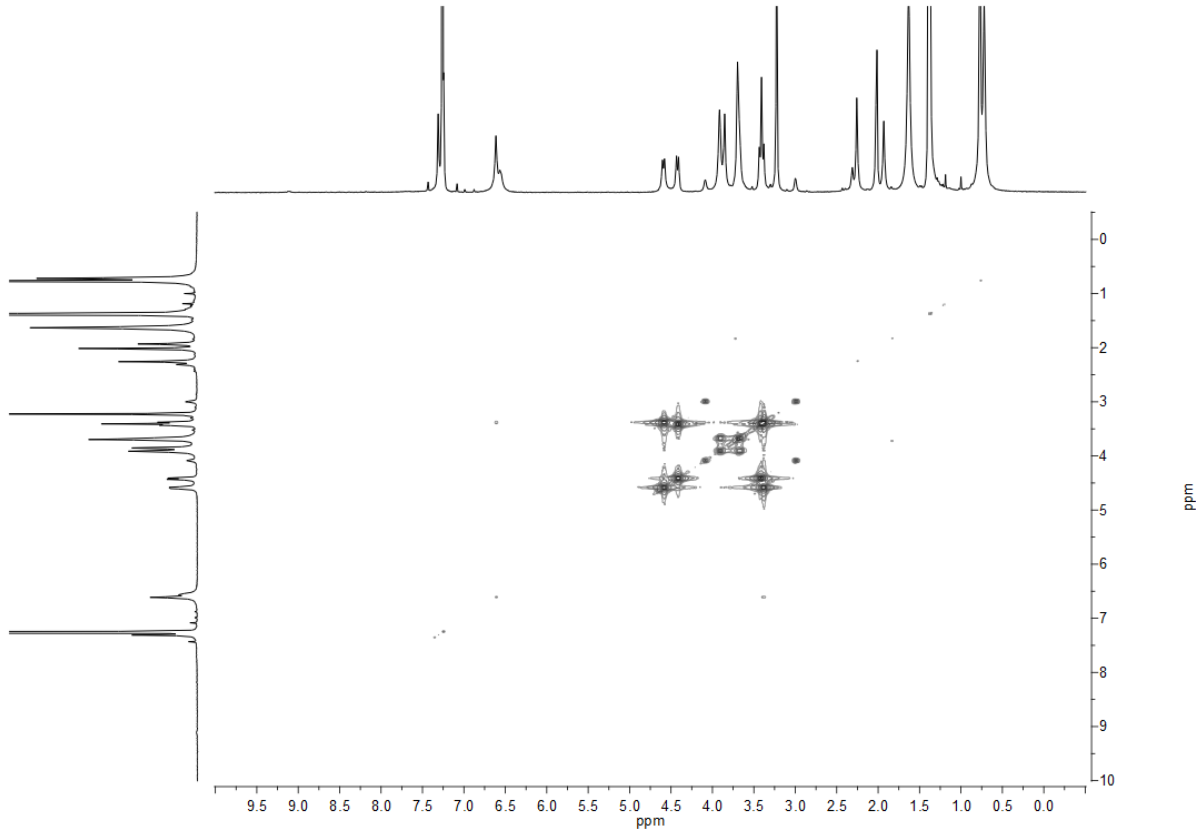


HSQC NMR (298K, 600MHz) spectrum of **1⊃G4** in $CD_3OD/CDCl_3$ (1:50).

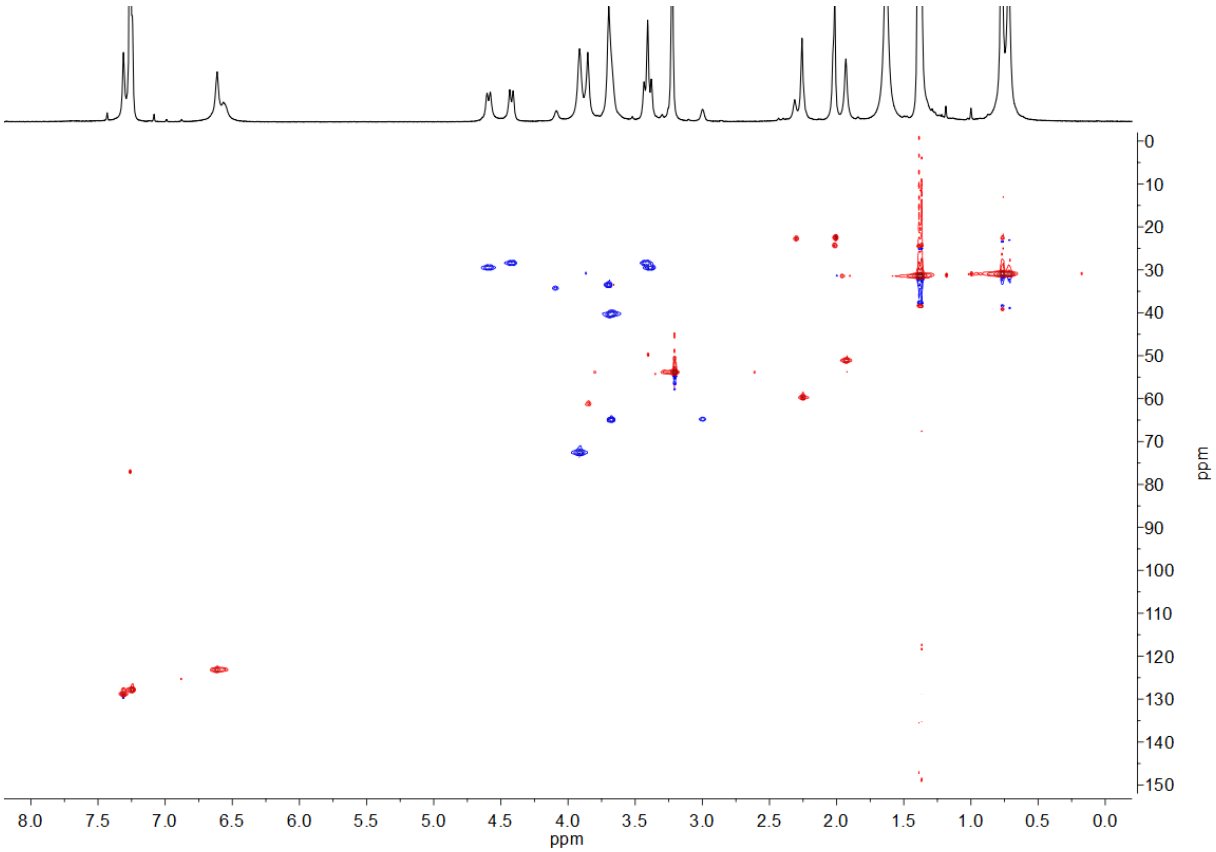
SI9. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with **G5** in $CD_3OD/CDCl_3$ (1:50)



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G5** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water.

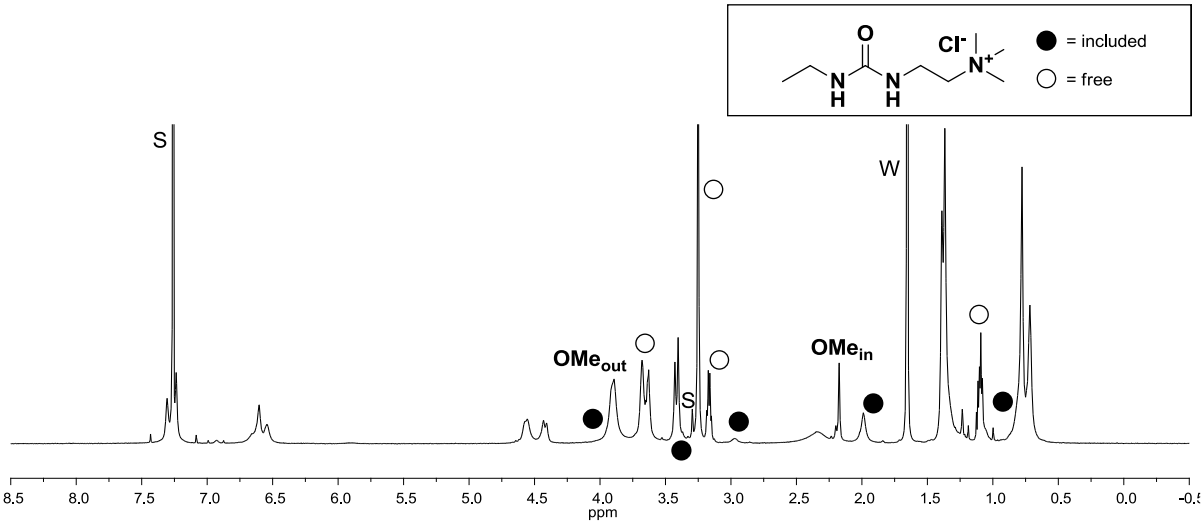


COSY NMR (298K, 600MHz) spectrum of **1⊃G5** in $CD_3OD/CDCl_3$ (1:50).

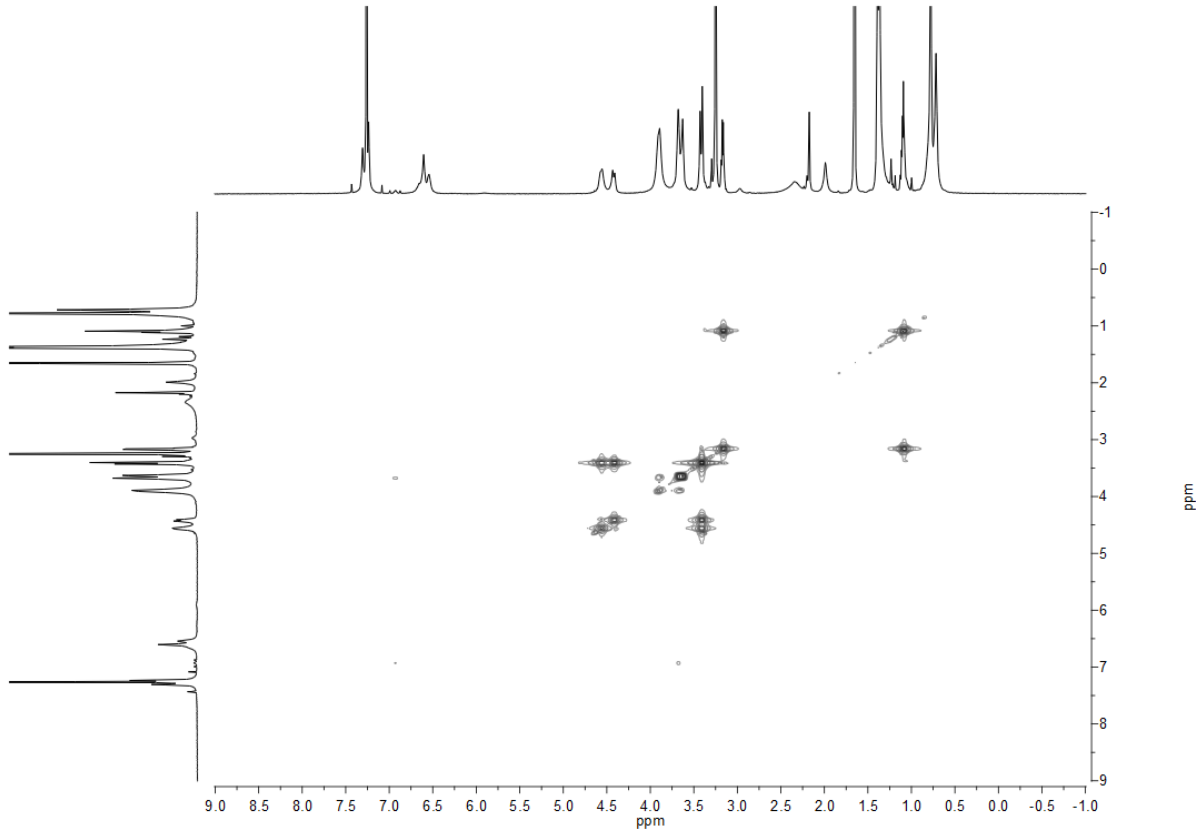


HSQC NMR (298K, 600MHz) spectrum of **1⊃G5** in $CD_3OD/CDCl_3$ (1:50).

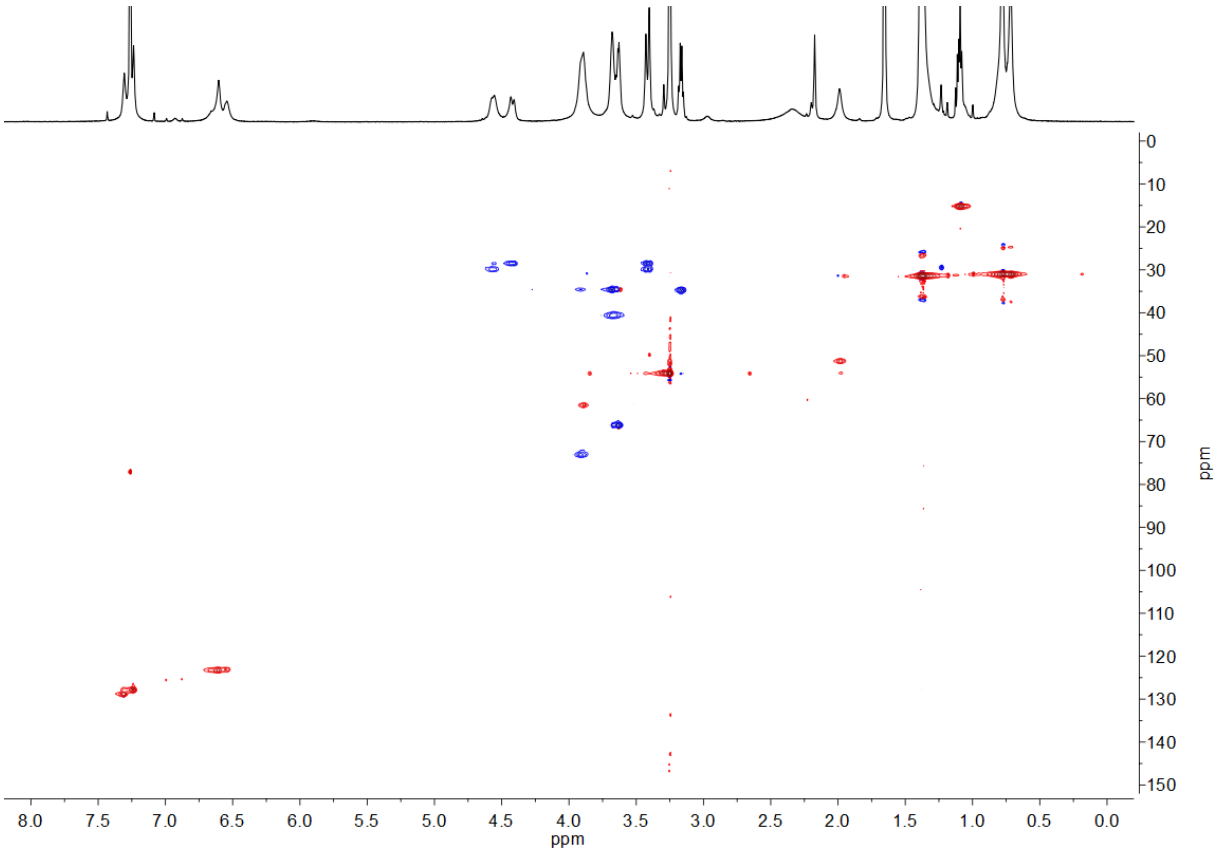
SI10. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with **G6** in $CD_3OD/CDCl_3$ (1:50)



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G6** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; ⁎: residual grease.

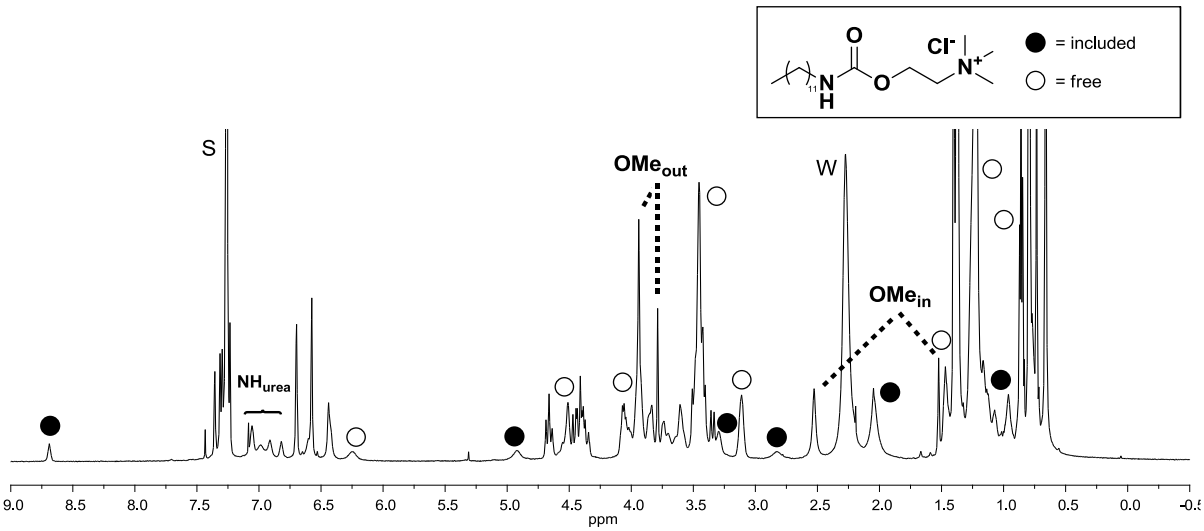


COSY NMR (298K, 600MHz) spectrum of **1⊃G6** in $CD_3OD/CDCl_3$ (1:50).

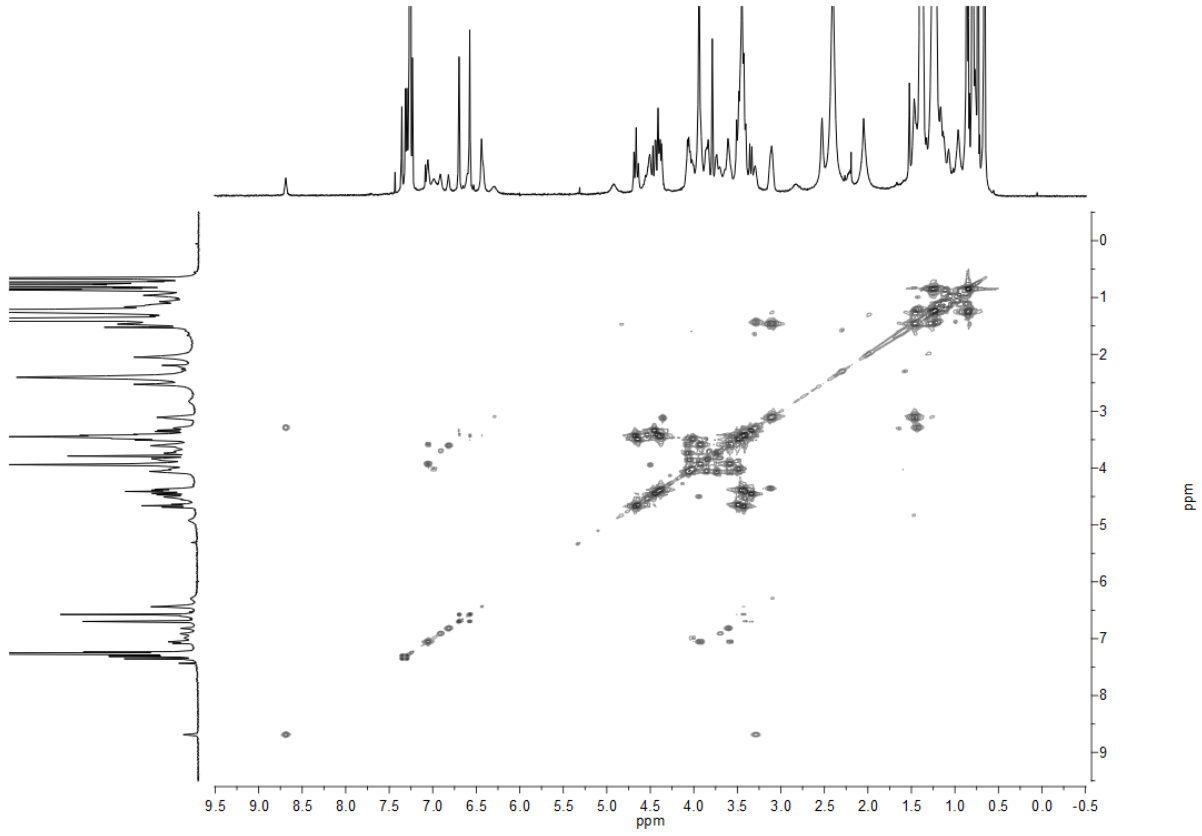


HSQC NMR (298K, 600MHz) spectrum of **1⊃G6** in $CD_3OD/CDCl_3$ (1:50).

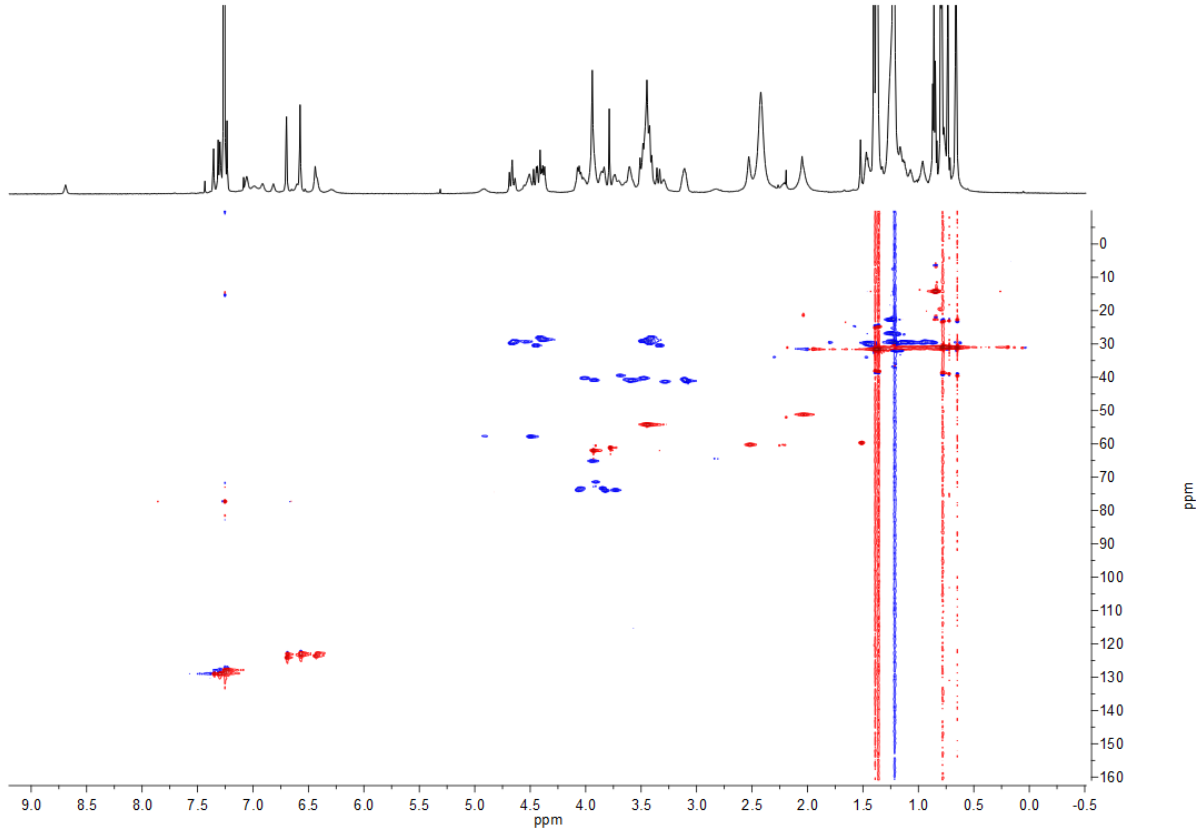
SI11. ^{1}H NMR, COSY NMR, HSQC NMR and ROESY NMR spectra of **1** with dodecylcarbamylcholine **G7** in $CDCl_3$



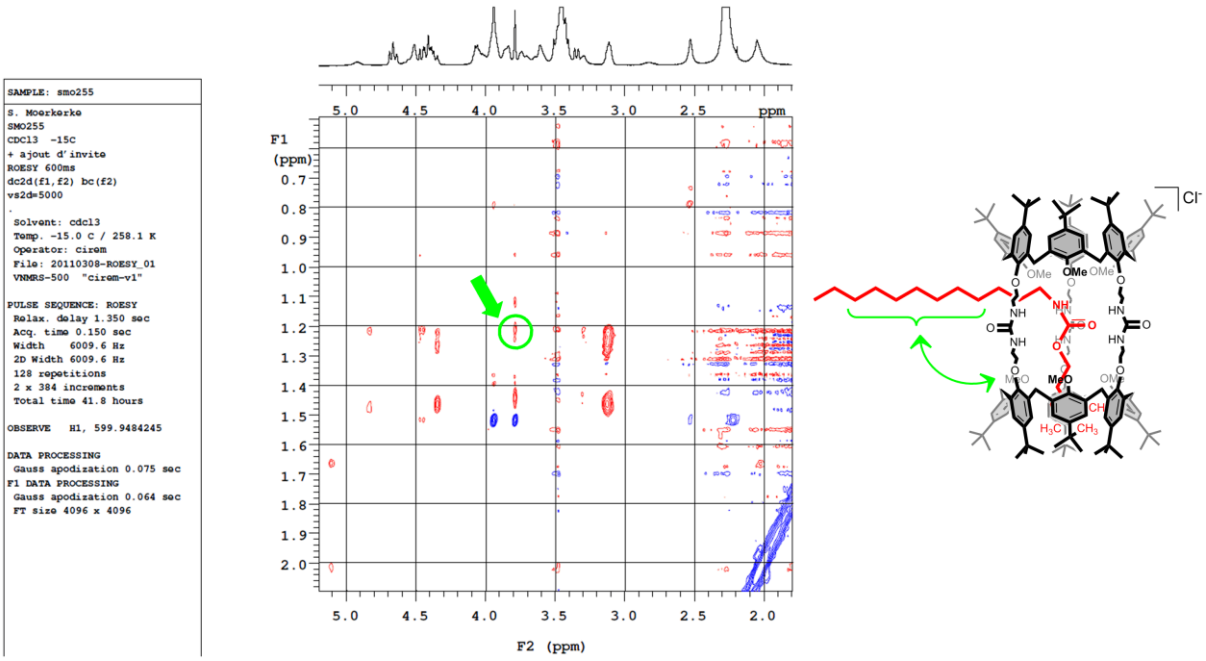
^{1}H NMR (258K, 600MHz) spectrum of **1⊃G7** in $CDCl_3$; S: Solvent; W: Water.



COSY NMR (258K, 600MHz) spectrum of **1⊃G7** in $CDCl_3$.

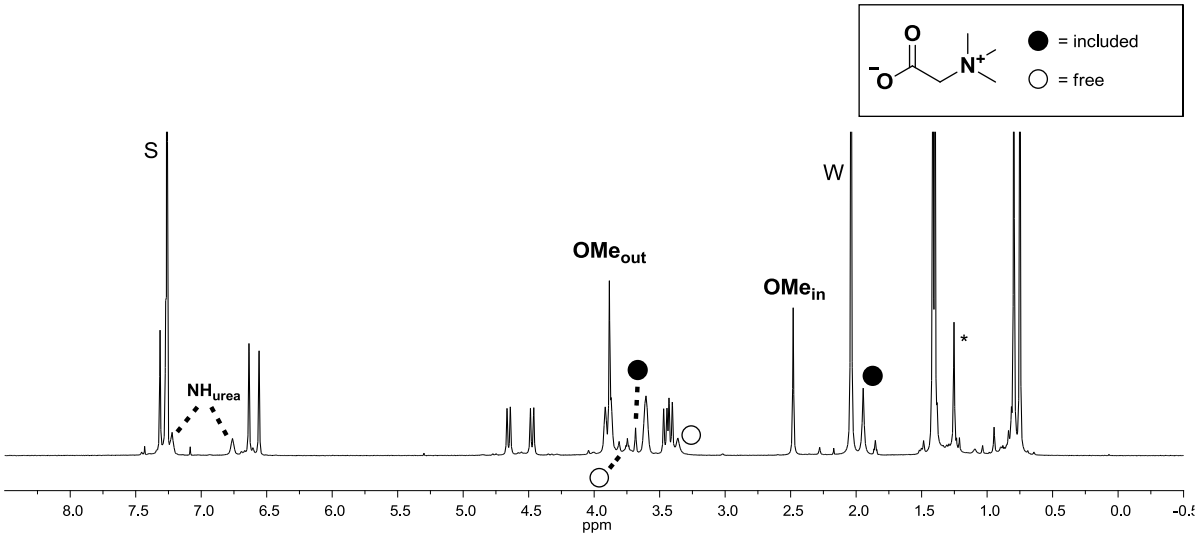


HSQC NMR (298K, 600MHz) spectrum of **1⊃G7** in $CDCl_3$.

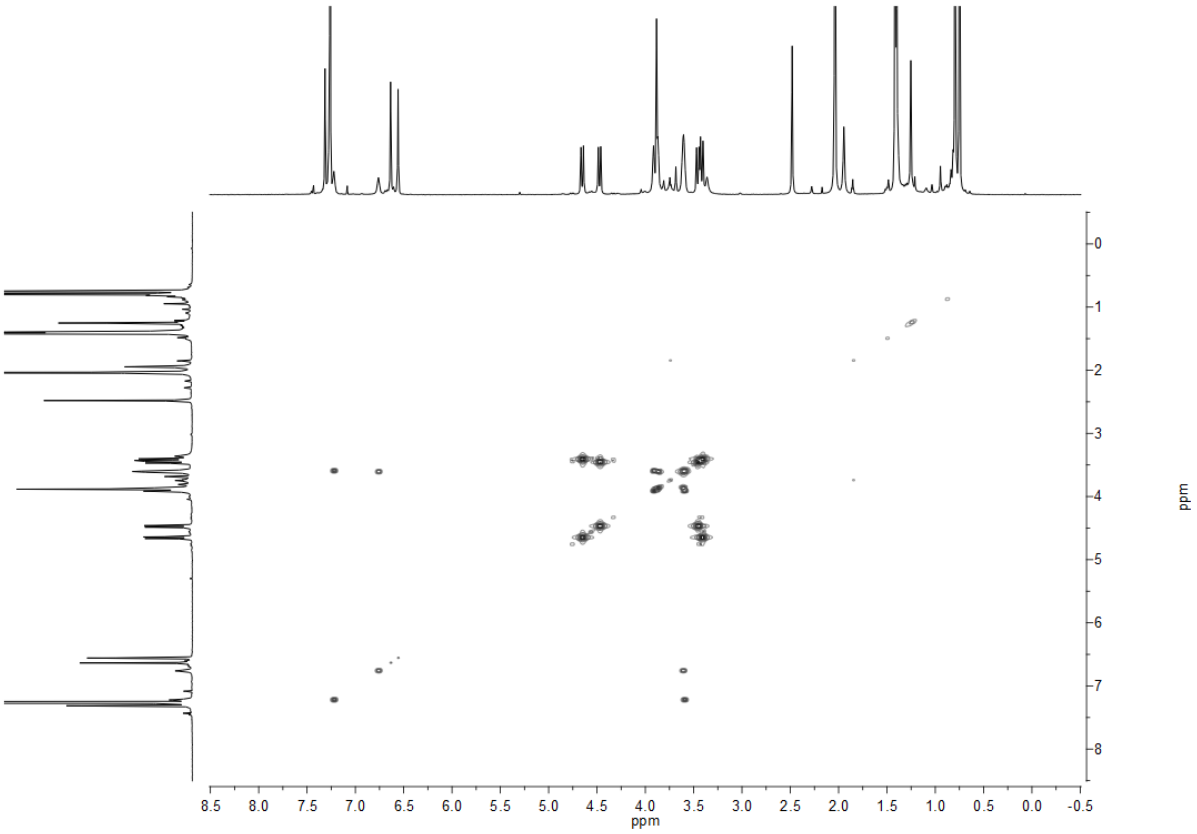


ROESY NMR (258K, 600MHz) spectrum of **1⊃G7** in $CDCl_3$.

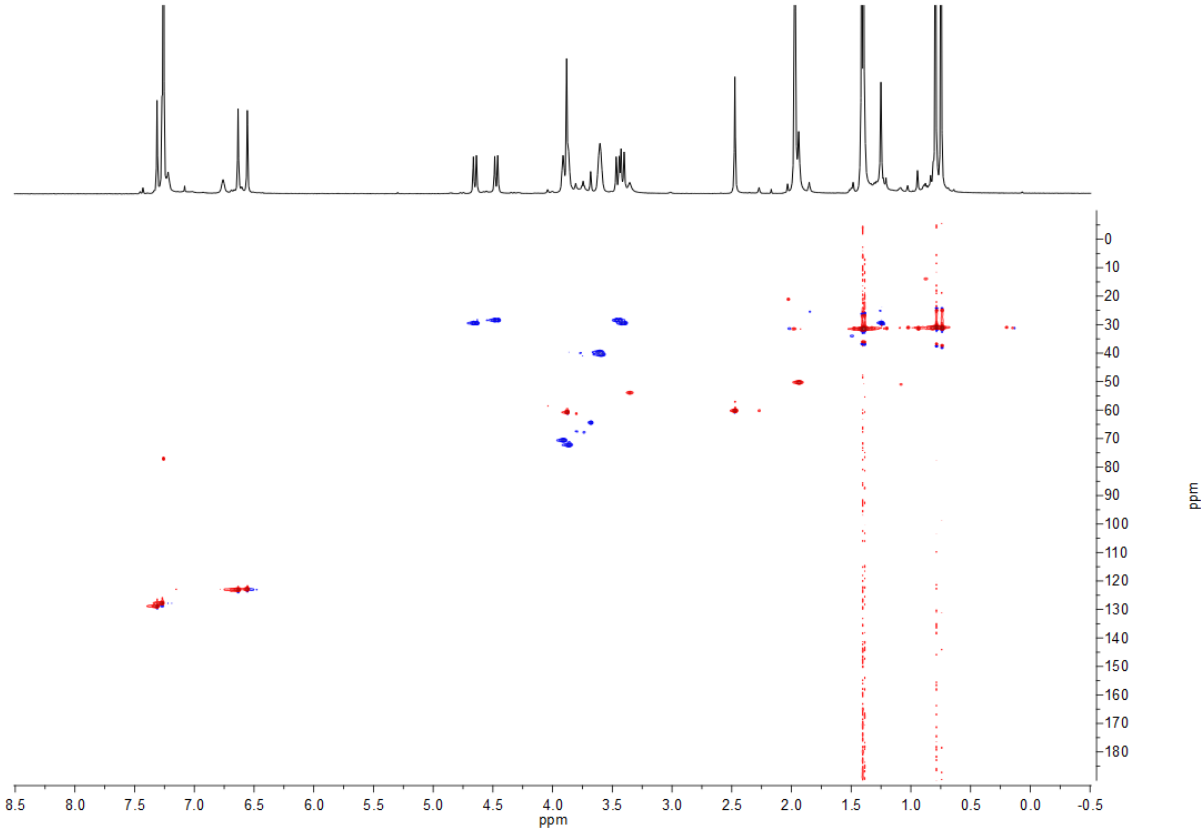
SI12. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with trimethylglycine **G11** in $CDCl_3$



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G11** in $CDCl_3$; S: Solvent; W: Water; *: residual grease.

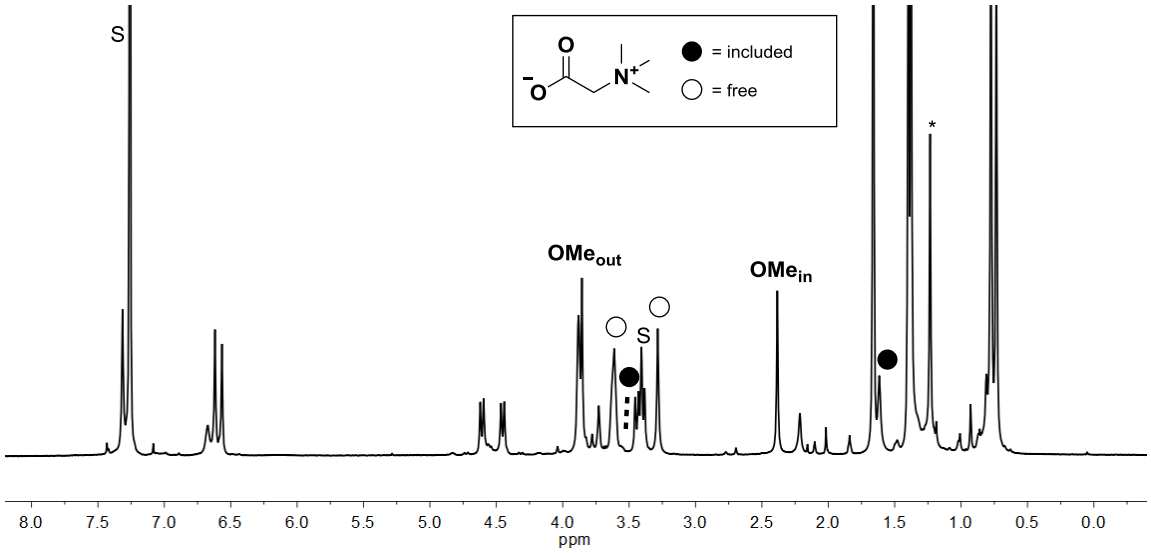


COSY NMR (298K, 600MHz) spectrum of **1⊃G11** in $CDCl_3$.



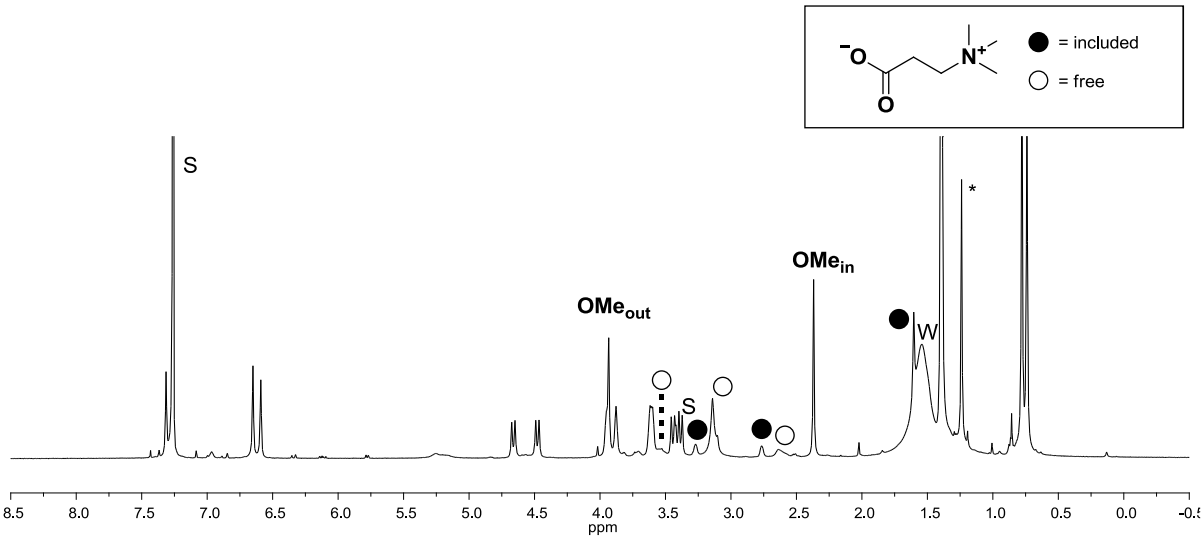
HSQC NMR (298K, 600MHz) spectrum of **1⊃G11** in $CDCl_3$.

SI13. ^{1}H NMR spectrum of **1** with trimethylglycine **G11** in $CD_3OD/CDCl_3$ (1:50)

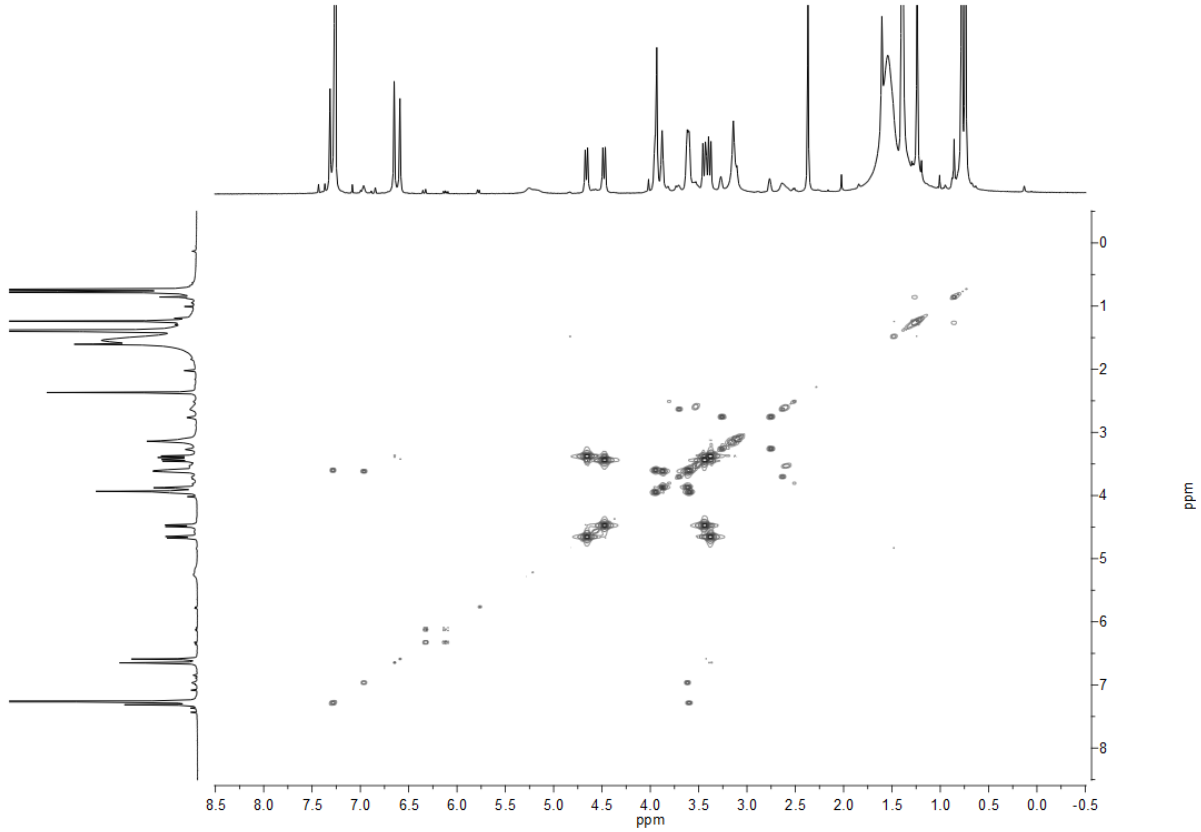


^{1}H NMR (298K, 600MHz) spectrum of **1⊃G11** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; *: residual grease.

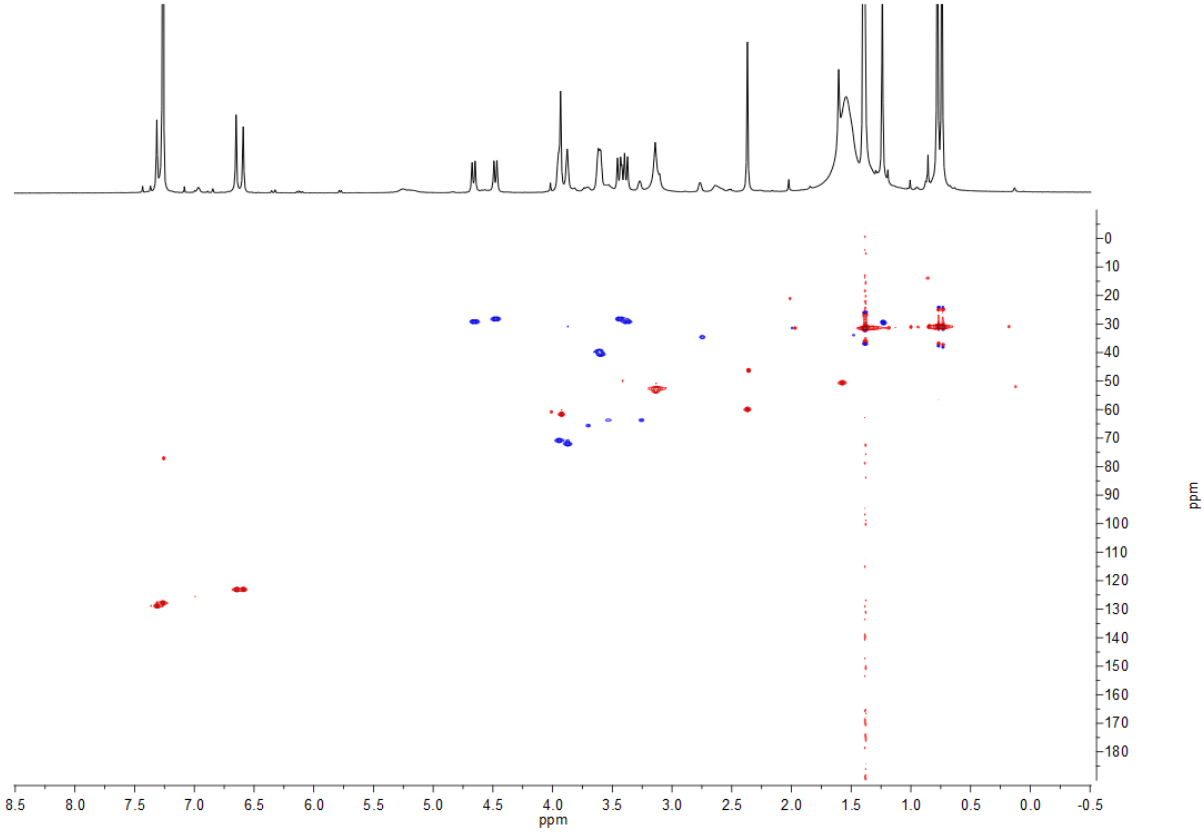
SI14. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with *β*-alanine betaine **G12** in $CD_3OD/CDCl_3$ (1:50)



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G12** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; ⁎: residual grease.

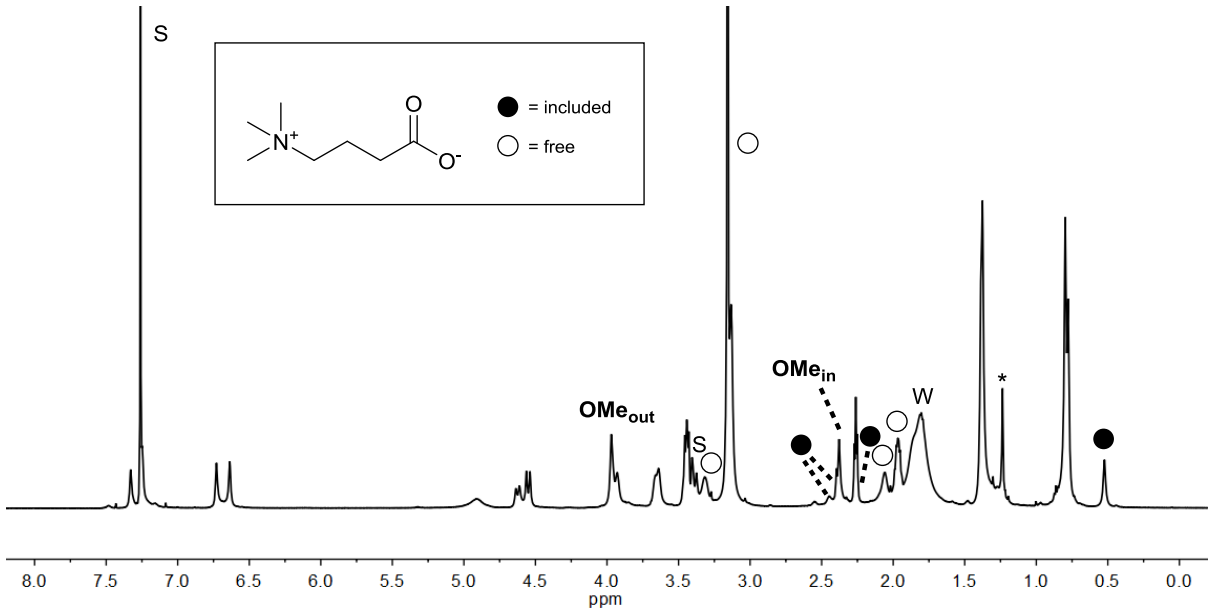


COSY NMR (298K, 600MHz) spectrum of **1⊃G12** in $CD_3OD/CDCl_3$ (1:50).

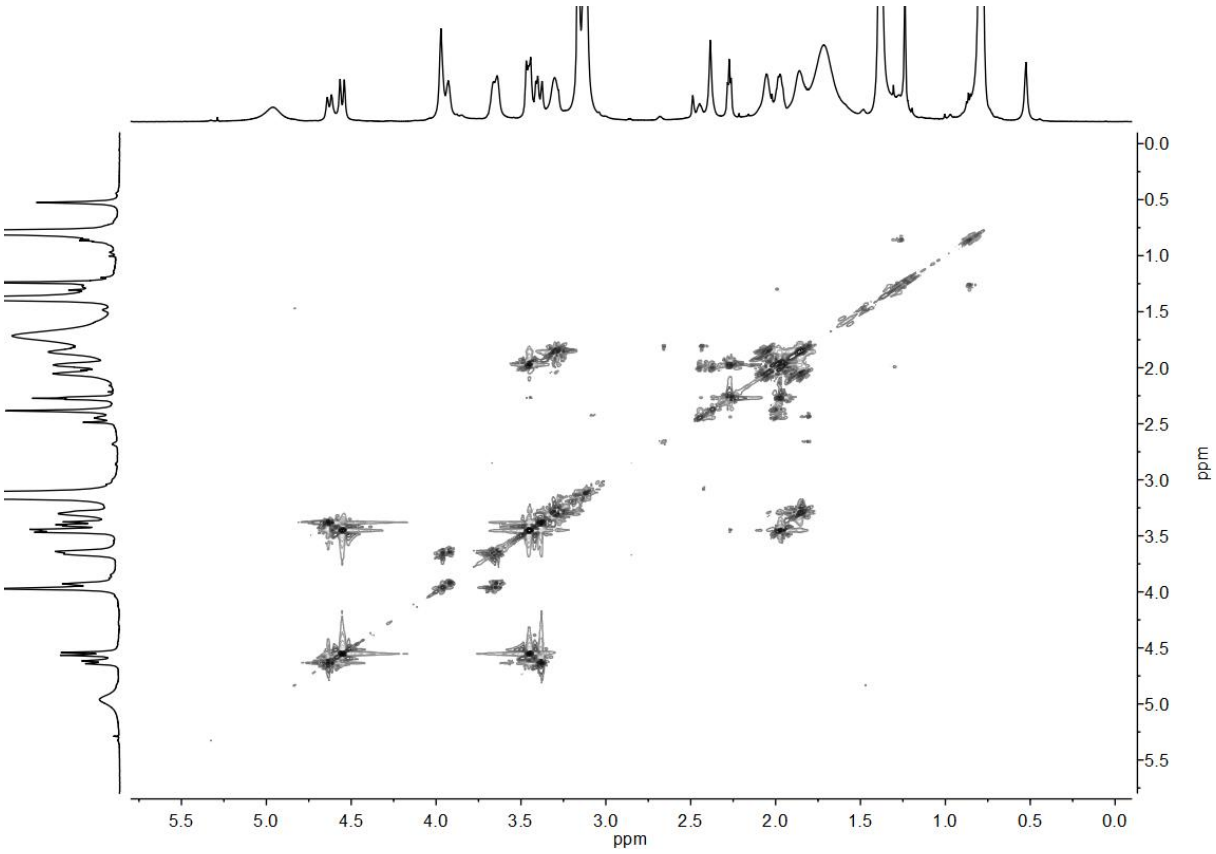


HSQC NMR (298K, 600MHz) spectrum of **1⊃G12** in $CD_3OD/CDCl_3$ (1:50).

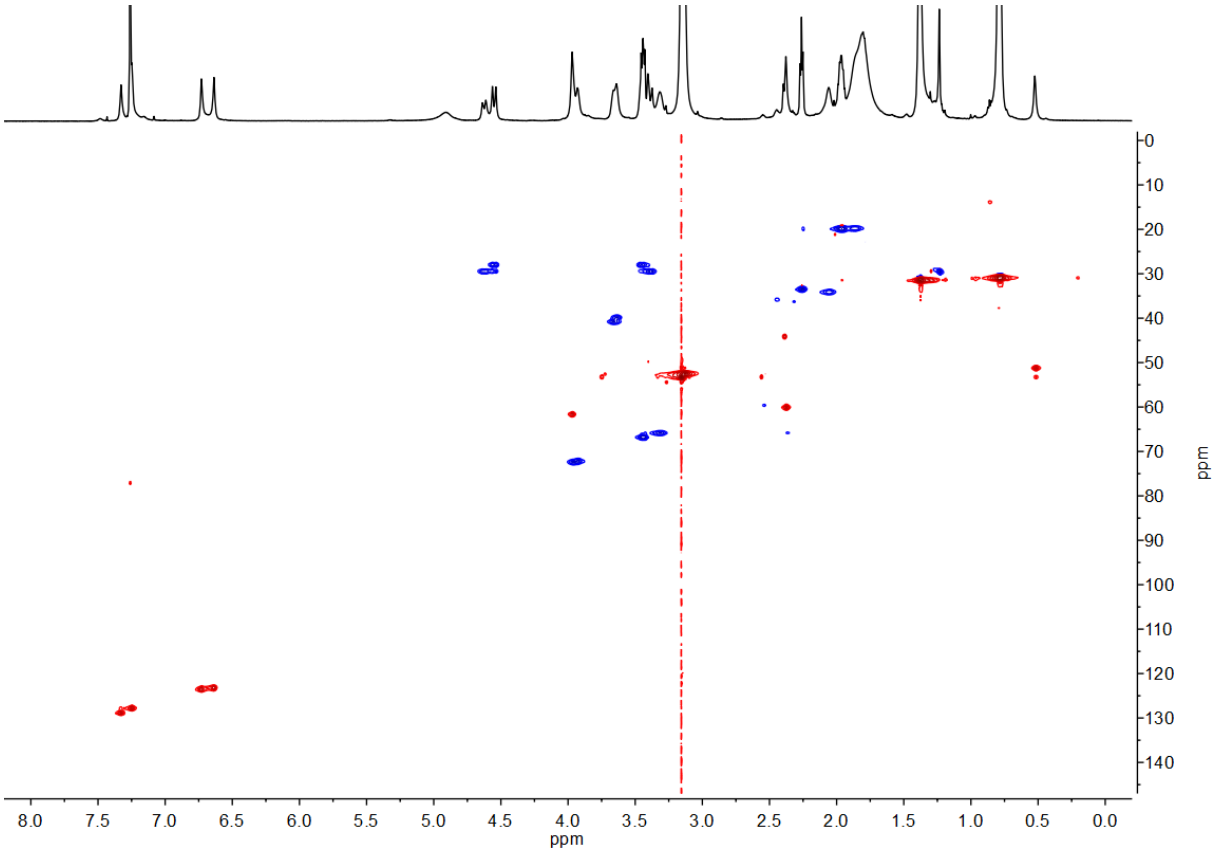
SI15. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with deoxycarnitine **G13** in $CD_3OD/CDCl_3$ (1:50)



^{1}H NMR (298K, 600MHz) spectrum of **1⊃G13** in $CD_3OD/CDCl_3$ (1:50); S: Solvent; W: Water; ⁎: residual grease.

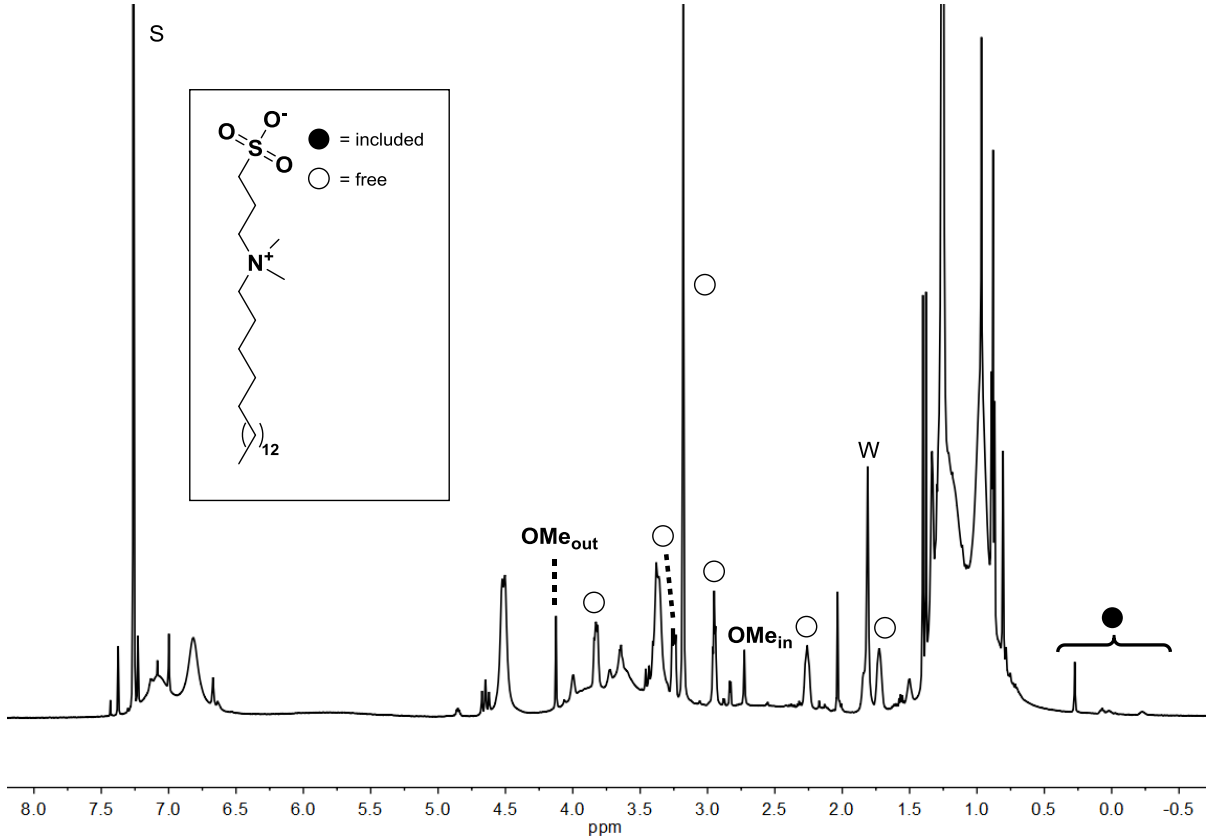


COSY NMR (298K, 600MHz) spectrum of **1⊃G13** in $CD_3OD/CDCl_3$ (1:50).

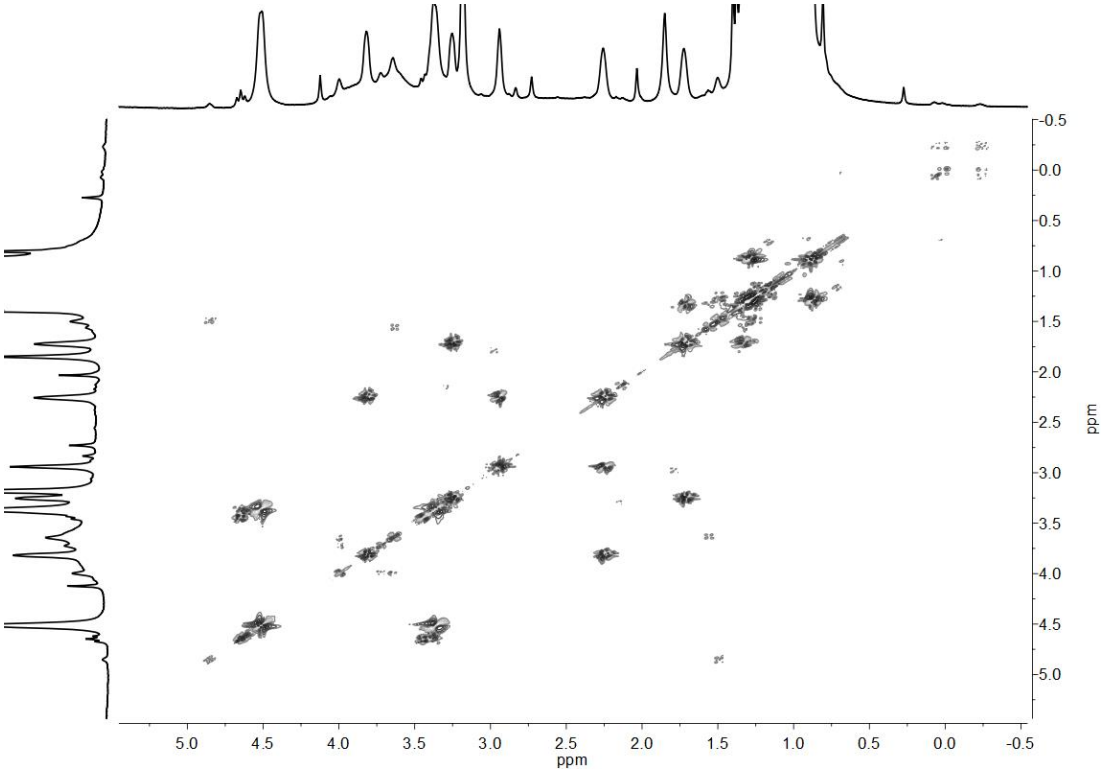


HSQC NMR (298K, 600MHz) spectrum of **1⊃G13** in $CD_3OD/CDCl_3$ (1:50).

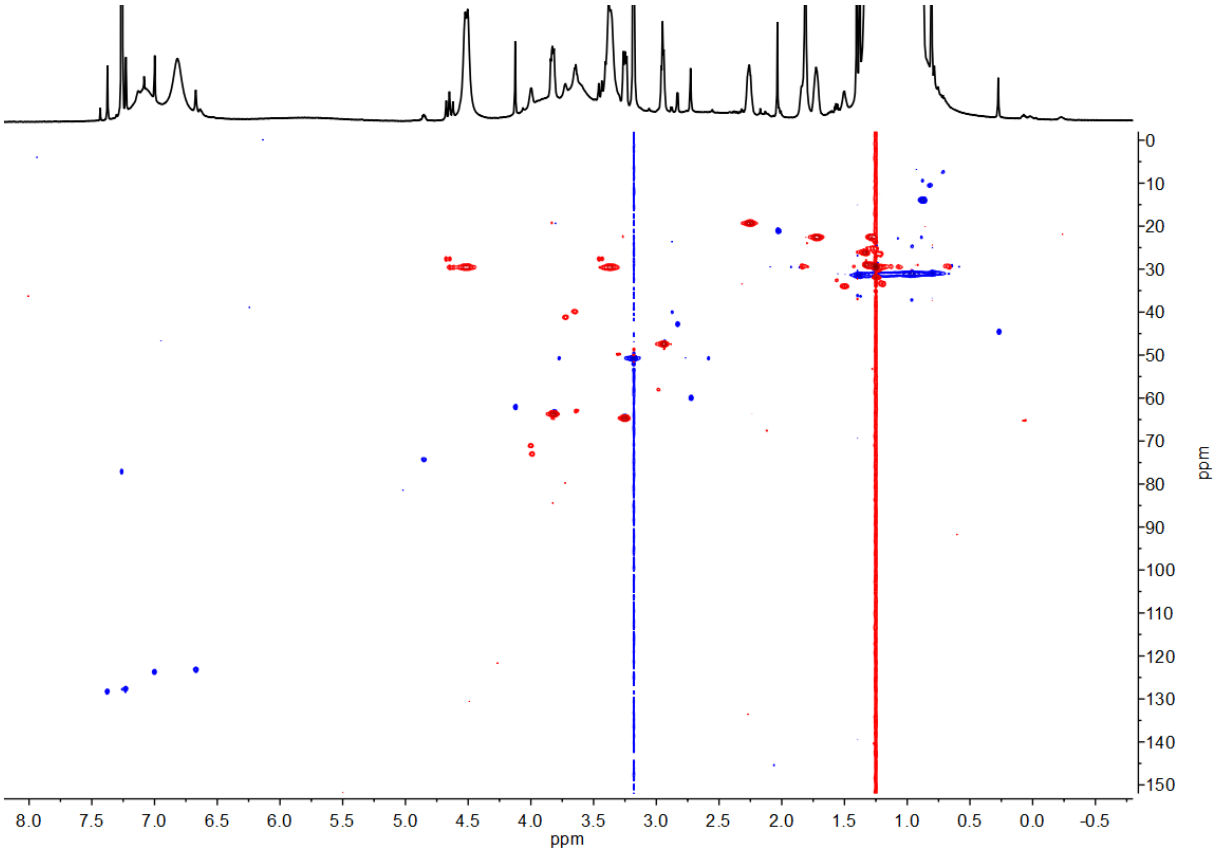
SI16. ^{1}H NMR, COSY NMR and HSQC NMR spectra of **1** with sulfobetaïne-18 **G14** in $CDCl_3$



^{1}H NMR (298K, 600MHz) spectrum of **1** + 1.9 equiv. of **G14** in $CDCl_3$; S: Solvent; W: Water.

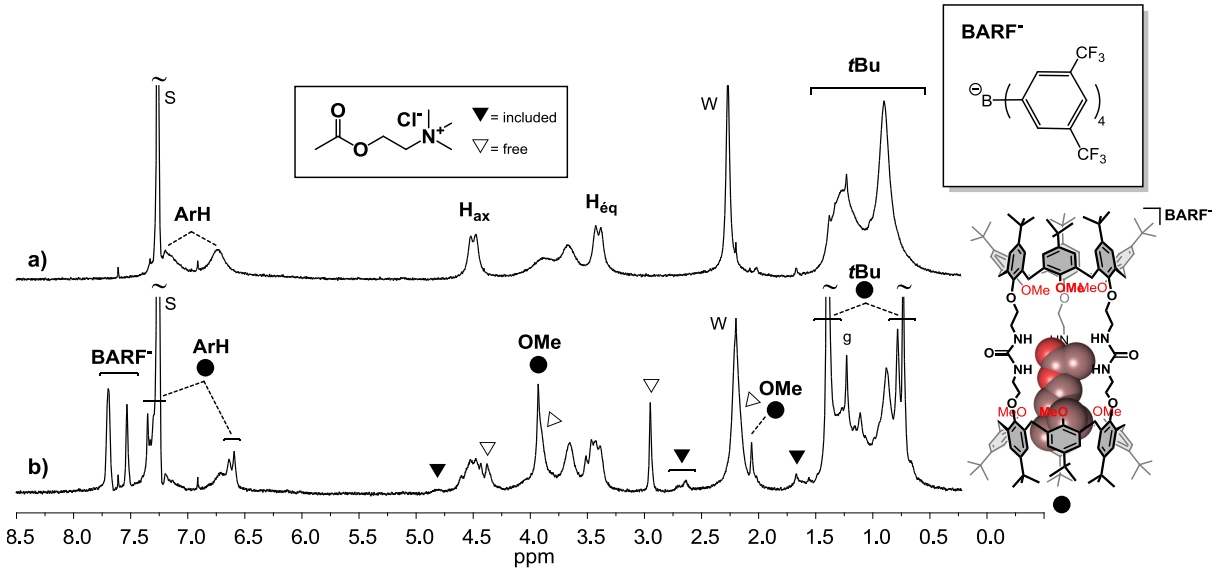


COSY NMR (298K, 600MHz) spectrum of **1⊃G14** in $CDCl_3$.



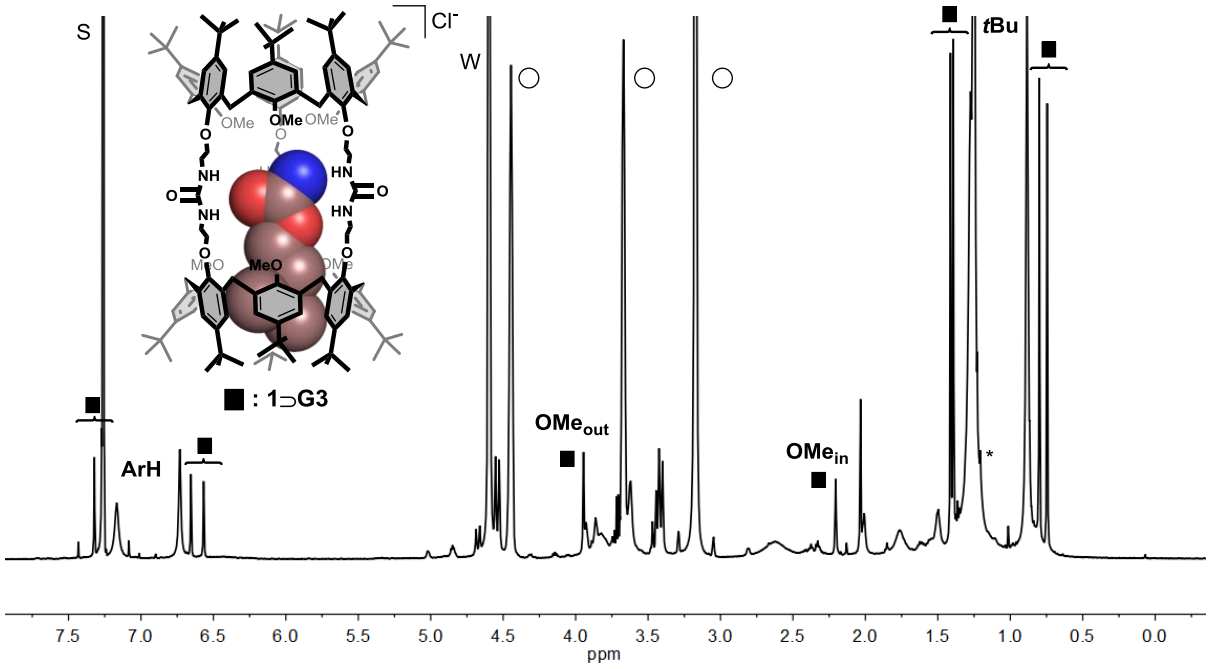
HSQC NMR (298K, 600MHz) spectrum of **1⊃G14** in $CDCl_3$.

SI17. ^{1}H NMR spectra of **1** with acetylcholine^{+}BARF^{-} in $CDCl_3$



^{1}H NMR ($CDCl_3$, 258K, 300MHz) spectra of: a) **1**, b) **1** + 0.8 equiv. of acetylcholine^{+}BARF^{-}; S: Solvent; W: Water; ∗: residual grease.

SI18. ^{1}H NMR (298K, 600MHz) spectrum of **1** with carbamylcholine **G3** in $CDCl_3/D_2O$ (5:1).



^{1}H NMR (298K, 600MHz) spectrum of **1** with **G3** in $CDCl_3/D_2O$ (5/1) obtained after 24h of stirring; ○: Signals corresponding to free **G3** which is solubilized in the water phase; S: Solvent; W: Water; ∗: residual grease.

SI19. Theoretic model for the determination of the kinetic association constant k_{on}

Complexation of sulfobetaines (G) by bis-calix[6]arene **1** proceeds with a 1 + 1 stoichiometry. This is an equilibrium process. Kinetic association and dissociation constants can be described respectively as k_{on} and k_{out}. The kinetics of complex **1⊃G** formation depends on those two concurrent processes. It can be described as:

$$\frac{d[\mathbf{1}\supset\mathbf{G}]}{d\tau} = k_{on}[\mathbf{1}][\mathbf{G}] - k_{out}[\mathbf{1}\supset\mathbf{G}] \tag{1}$$

The dissociation kinetic constant can be defined as:

$$k_{out} = \frac{k_{on}}{K_a} \tag{2}$$

The studies were conducted with a large excess of the sulfobetaines G so their concentration remained almost unchanged, while the calix[6]arene **1** is partially consumed. Therefore, the concentration of active species can be expressed as:

$$[\mathbf{1}] = [\mathbf{1}]_\mathbf{0} - [\mathbf{1}\supset\mathbf{G}]; \qquad [\mathbf{G}] \approx const = [\mathbf{G}]_0 \tag{3}$$

Using the equations (1), (2) and (3), the kinetics of complex **1⊃G** formation can be written as:

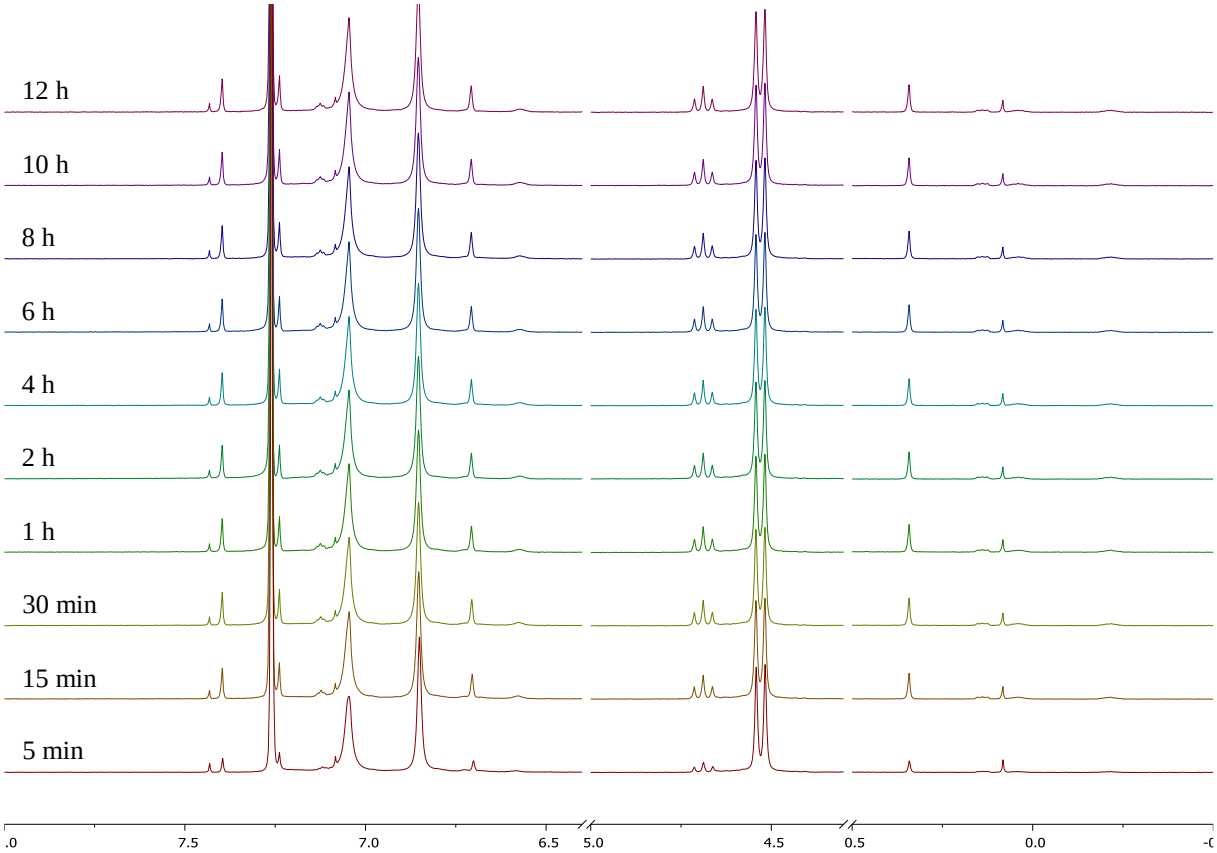
$$\begin{aligned}\frac{d[\mathbf{1}\supset\mathbf{G}]}{d\tau} &= k_{on}([\mathbf{1}]_\mathbf{0} - [\mathbf{1}\supset\mathbf{G}])[\mathbf{G}]_0 - \frac{k_{on}}{K_a}[\mathbf{1}\supset\mathbf{G}] \\ &= -k_{on}\left([\mathbf{G}]_0 + \frac{1}{K_a}\right)[\mathbf{1}\supset\mathbf{G}] + k_{on}[\mathbf{1}]_\mathbf{0}[\mathbf{G}]_0\end{aligned} \tag{4}$$

Given that at $\tau = 0$ the complex is absent, i.e. $[\mathbf{1}\supset\mathbf{G}]_\mathbf{0} = 0$, the solution of this differential equation can be written as:

$$\begin{aligned}[\mathbf{1}\supset\mathbf{G}] &= \frac{[\mathbf{1}]_\mathbf{0}[\mathbf{G}]_0}{\left([\mathbf{G}]_0 + \frac{1}{K_a}\right)} - \frac{[\mathbf{1}]_\mathbf{0}[\mathbf{G}]_0}{\left([\mathbf{G}]_0 + \frac{1}{K_a}\right)} e^{-k_{on}\left([\mathbf{G}]_0 + \frac{1}{K_a}\right)\tau} \\ \frac{[\mathbf{1}\supset\mathbf{G}]}{[\mathbf{1}]_\mathbf{0}} &= \frac{1}{\left(1 + \frac{1}{K_a[\mathbf{G}]_0}\right)} - \frac{\mathbf{1}}{\left(1 + \frac{1}{K_a[\mathbf{G}]_0}\right)} e^{-k_{on}\left([\mathbf{G}]_0 + \frac{1}{K_a}\right)\tau}\end{aligned} \tag{5}$$

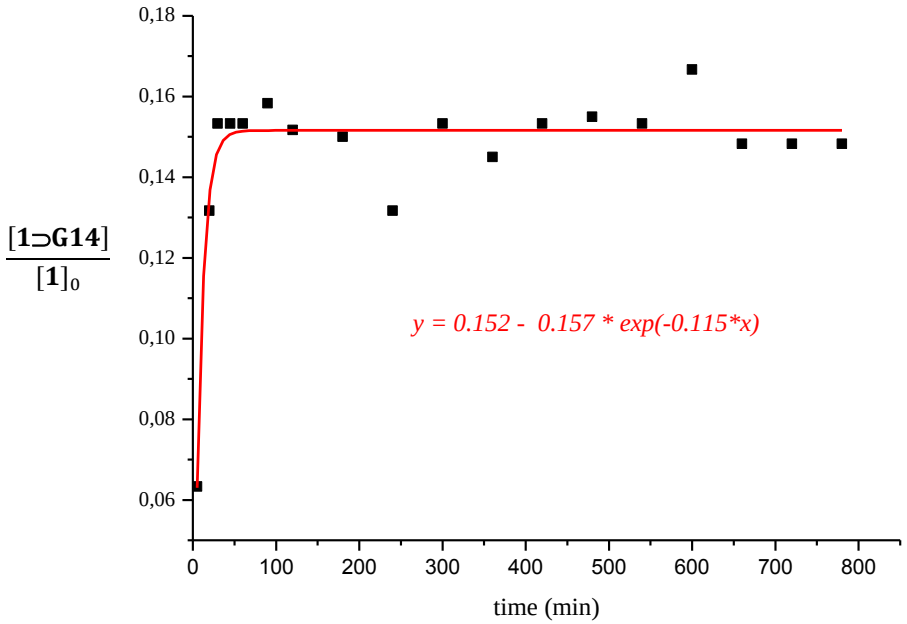
Thus, the kinetic constant k_{on} can be determined from an exponential fit of the **1⊃G** concentration over the reaction time.

SI20. Selected ^{1}H NMR spectra of **1** with sulfobetaine-8 **G14** in $CDCl_3$ and determination of k_{on}



Selected ^{1}H NMR (333K, 600MHz) spectra of **1** with **G14** in $CDCl_3$ at different times. Only aromatic, axial ArC$\underline{H_2}$Ar and high field signals are shown for clarity. Starting concentrations of bis-calix[6]arene **1** and sulfobetaine-8 **G14** are 1 mM and 9.4 mM respectively.

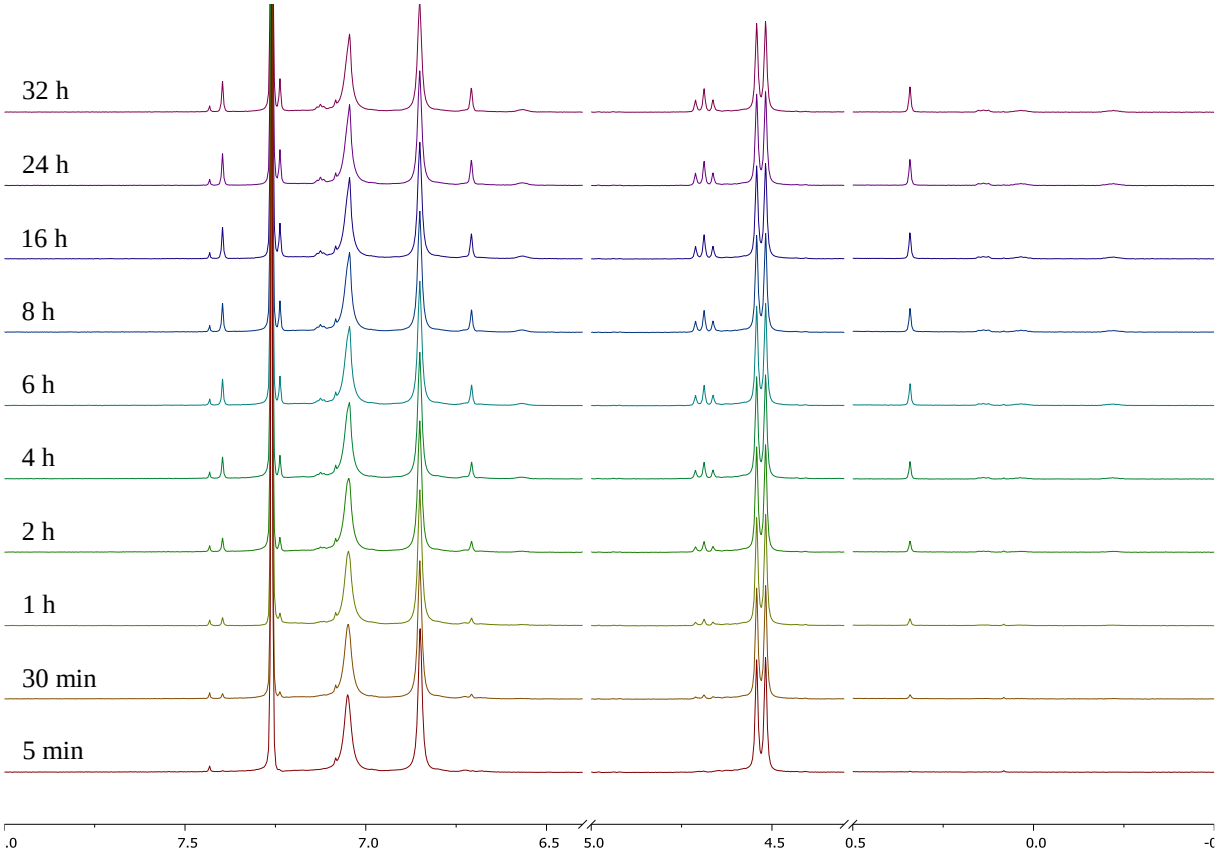
Singlet at 0.34 ppm corresponds to α-CH_3 protons of the guest included into the calixarene cavity. It was used to estimate the concentration of the complex **1⊃G14**. Peaks in the 4.3-4.8 ppm region correspond to signals of axial ArC$\underline{H_2}$Ar protons of free host **1** (*d* at 4.51 ppm) and of the complex **1⊃G14** (2 *d* at 4.68 ppm and 4.70 ppm). Based on integration of those signals, the **1⊃G14** concentration – time dependence was estimated as shown on figure below.



Relative **1⊃G14** concentration over time and fitted exponential grow.

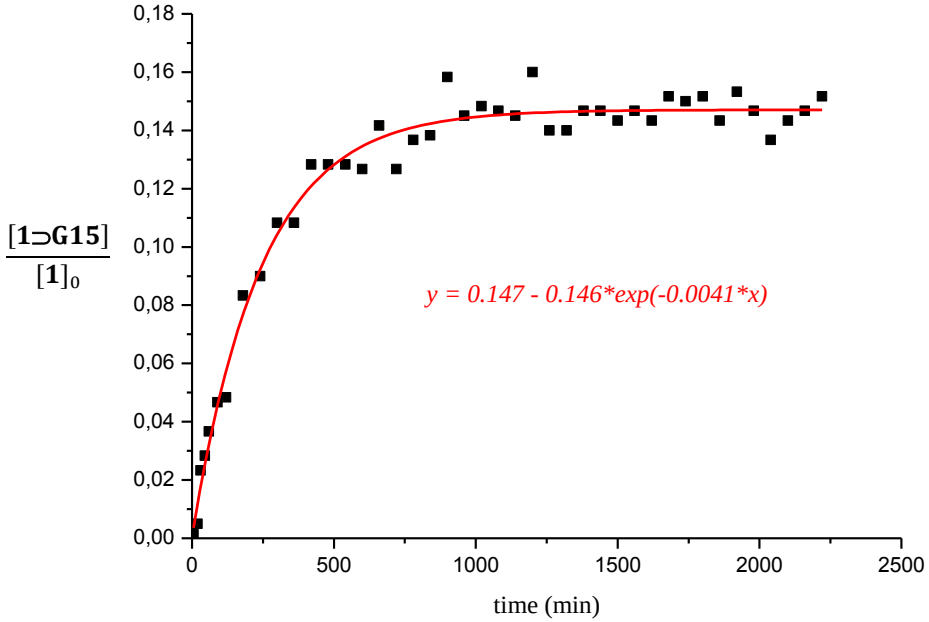
Using founded fitting parameters, the kinetic constant k_{on} was calculated accordingly to equation (5), giving a value of 1.86 $M^{-1} \cdot min^{-1}$ = $3.1 \cdot 10^{-2}$ $M^{-1} \cdot s^{-1}$.

SI21. Selected ^{1}H NMR spectra of **1** with sulfobetaine-10 **G15** in $CDCl_3$ and determination of k_{on}



Selected ^{1}H NMR (333K, 600MHz) spectra of **1** with **G15** in $CDCl_3$ at different times. Only aromatic, axial ArC$\underline{H_2}$Ar and high field signals are shown for clarity. Starting concentrations of bis-calix[6]arene **1** and sulfobetaine-10 **G15** are 1 mM and 9.9 mM respectively.

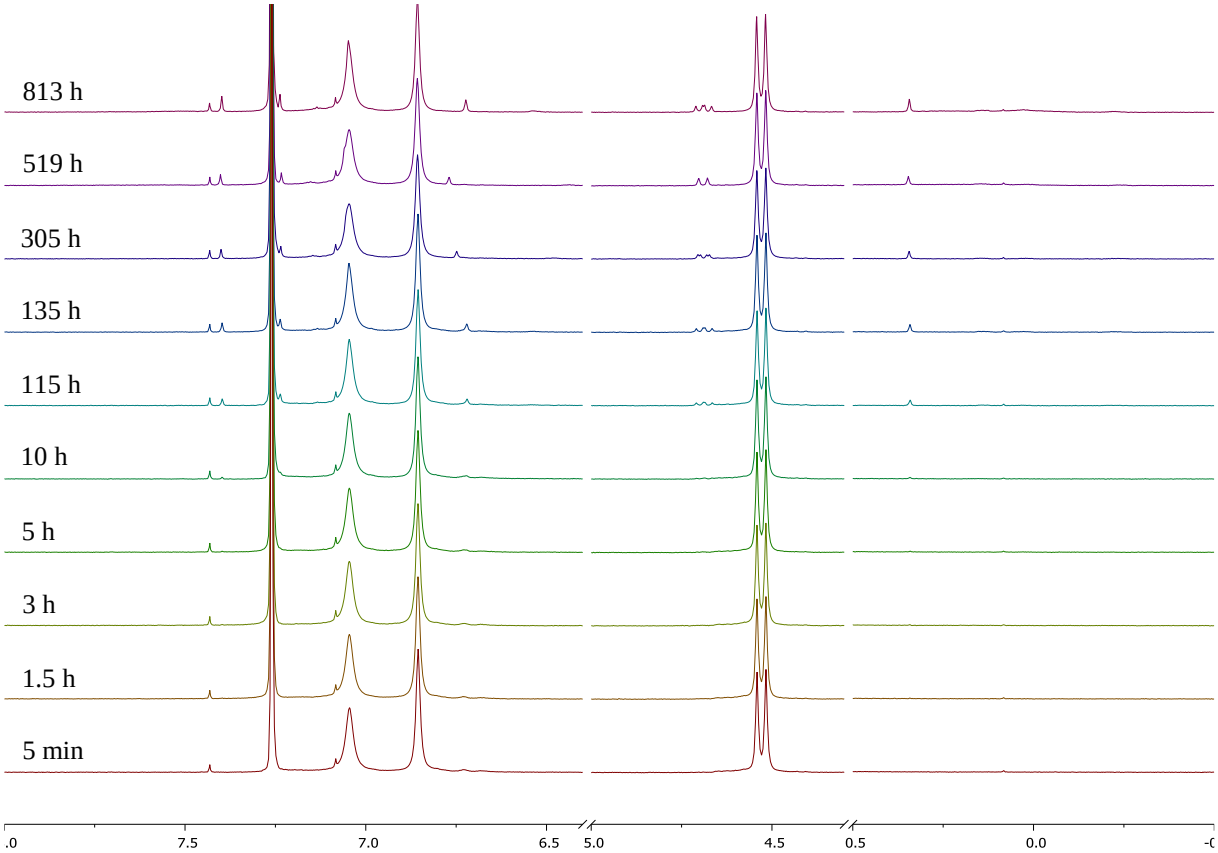
Similarly to the case of sulfobetaine-8 **G14** (*vide supra*), based on NMR peaks integration (regions 0.30-0.38 ppm and 4.30-4.80 ppm), the **1⊃G15** concentration – time dependence was estimated as shown on figure below.



Relative **1⊃G15** concentration over time and fitted exponential grow.

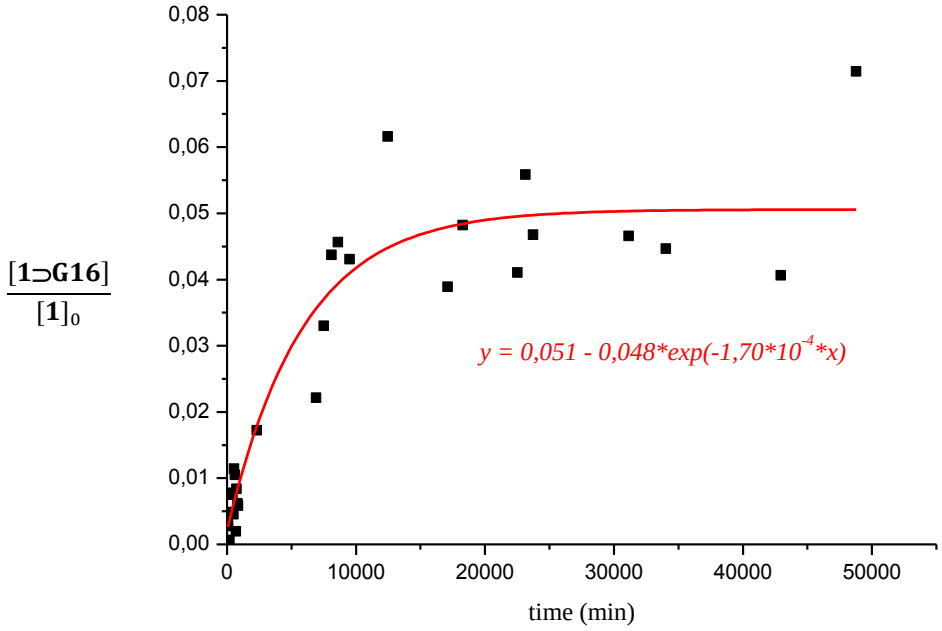
Using founded fitting parameters, the kinetic constant k_{on} was calculated accordingly to equation (5) giving a value of 0.0609 $M^{-1} \cdot min^{-1}$ = $1.02 \cdot 10^{-3}$ $M^{-1} \cdot s^{-1}$.

SI22. Selected ^{1}H NMR spectra of **1** with sulfobetaine-18 **G16** in $CDCl_3$ and determination of k_{on}



Selected ^{1}H NMR (333K, 600MHz) spectra of **1** with **G16** in $CDCl_3$ at different times. Only aromatic, axial ArC$\underline{H_2}$Ar and high field signals are shown for clarity. Starting concentrations of bis-calix[6]arene **1** and sulfobetaine-18 **G16** are 1 mM and 10.9 mM respectively.

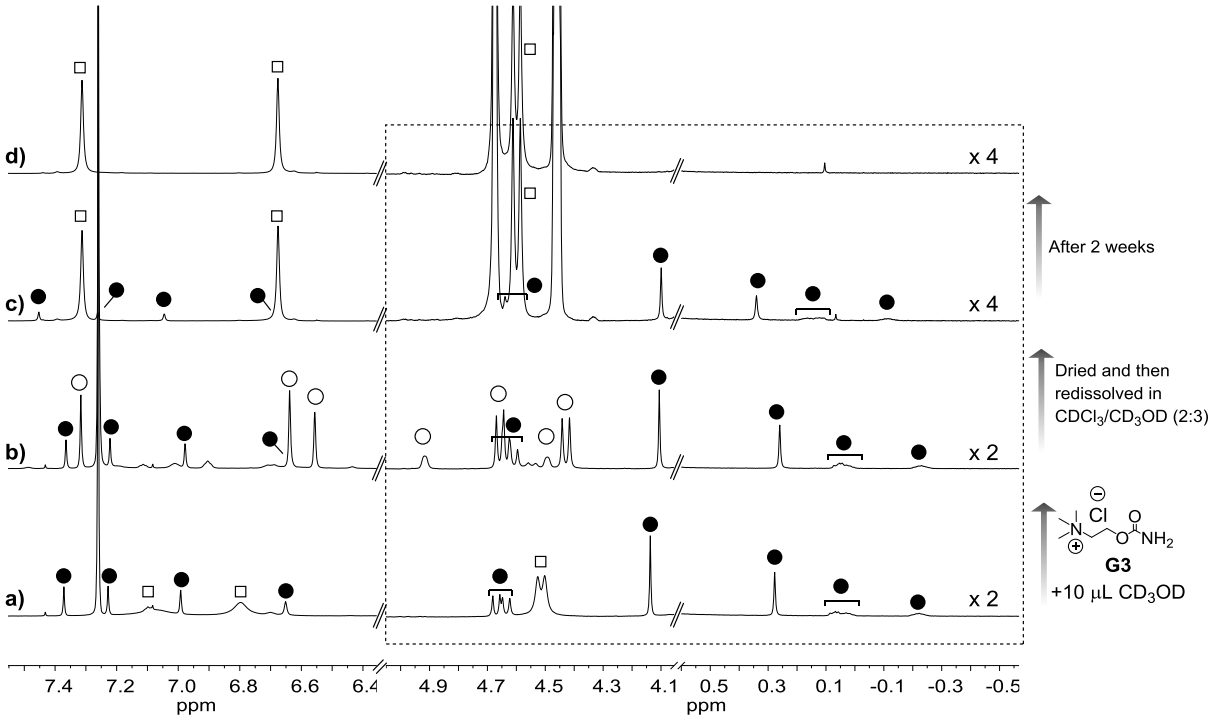
Similarly to the case of sulfobetaine **G14** (*vide supra*), based on NMR peaks integration (regions 0.30-0.38 ppm and 4.30-4.80 ppm), the **1⊃G16** concentration – time dependence was estimated as shown on figure below.



Relative **1⊃G16** concentration over time and fitted exponential grow.

Using founded fitting parameters, the kinetic constant k_{on} was calculated accordingly to equation (5) giving a value of 0.000795 $M^{-1} \cdot min^{-1}$ = $1.33 \cdot 10^{-5}$ $M^{-1} \cdot s^{-1}$.

SI23. ^{1}H NMR spectra of the complex **1⊃G15** in presence of a competing guest **G3** and in a polar environment



^{1}H NMR (298 K, 600MHz) spectra of: (a) **1** with *ca.* 9 equiv. of **G15** in $CDCl_3$; (b) 16h after addition of *ca.* 9 equiv. of **G3** (in 10 µL of CD_3OD); (c) after evaporation and dissolution in $CDCl_3/CD_3OD$ (2:3); (d) after 2 weeks at room temperature; ●: signals corresponding to complex **1⊃G15**; ○: signals corresponding to complex **1⊃G3**; □: signals corresponding to free receptor **1**. Only selected regions are shown for clarity. The intensity of the high field signals as well as those of the Ar$C\underline{H}_2$Ar protons are adjusted as indicated at the right side of spectra.