Supporting information for

"Calix[4]-box" cages promote the formation of amide bond in water in the absence of coupling reagents

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Materials: All the compounds were purchased from Sigma-Aldrich and were used without further purification.

NMR experiments: ^{1}H-NMR experiments were performed on an AVANCE 300 MHz Bruker spectrometer in D_2O and the chemical shifts (δ) are reported in ppm relative to the residual solvent (H_2O/HOD in D_2O) signal (δ = 4.7 ppm). Data for ^{1}H-NMR spectra are reported as follows: chemical shift (multiplicity, number of hydrogen atom and position of hydrogen atom). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). NMR experiments and 2D-NMR experiments were performed on 5 ml solution of 10 mg (**1**), (**2**), (**3**) or (**4**) dissolved in D_2O respectively.

2D-DOSY (Diffusion-Ordered Spectroscopy) NMR experiments were performed at 298 K with a Bruker Dual z-gradient probe head capable of producing gradients in the z direction with strength 55 G cm-1. The DOSY spectra were acquired with the ledbpgp2s pulse program (2D sequence for diffusion measurement using echo and led with bipolar gradient pulse. (*1S*) All spectra were recorded with 8 K time domain data points in the F2 Frequency axis and 32 experiments (F1). The gradient strength was logarithmically incremented in 32 steps from 2% up to 95% of the

maximum gradient strength. All measurements were performed with a diffusion delay D of 80 ms in order to keep the relaxation contribution to the signal attenuation constant for all samples. The gradient pulse length d was 5 ms in order to ensure full signal attenuation. The diffusion dimension of the 2D DOSY spectra was processed by means of the Bruker Topspin software (version 2.1).

X-ray Crystallography. Single crystals of **Calix[4]{1}**, **Calix[4]G{1}**, **Calix[4]{AG1}** and **Calix[4]{A_2G1}** of suitable dimensions were mounted onto thin glass fibers. All the intensity data were collected on an Agilent Technologies Gemini-S four-circle diffractometer using Mo-Kα radiation (λ = 0.71073 Å) and equipped with a Sapphire-3 detector at 175 K. The structures were solved using the ab initio iterative charge flipping method with parameters described elsewhere[2S] using the Superflip programme[3S] and they were refined using full-matrix least-squares procedures as implemented in CRYSTALS[4S] on all independent relections with I > 2σ (I), Crystallographic data for the structures (Table 1S) reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1553849-1553852.

Suitable crystals for all the structures were readily obtained in large quantities by slow evaporation of aqueous solutions below:

Calix[4]{1}: 41.6 mg, 0.05 mmol of 4-Sulfocalix[4]arene Sodium Salt, 6.5 mg, 0.05 mmol 6-aminohexanoic acid (**1**) and 50 μL HCl 37% in 1 mL H_2O. After 48 hours the crystals were filtered and dried under mild vacuum for 2 h.

Calix[4]G{1}: 41.6 mg, 0.05 mmol of 4-Sulfocalix[4]arene Sodium Salt, 9.5 mg, 0.1 mmol guanidinium, 6.5 mg, 0.05 mmol 6-aminohexanoic acid (**1**) and 50 μL HCl 37% in 1 mL H_2O. After 48 hours the crystals were filtered and dried under mild vacuum for 2 h.

Calix[4]{AG1}: 41.6 mg, 0.05 mmol of 4-Sulfocalix[4]arene Sodium Salt, 5.5 mg, 0.05 mmol aminoguanidinium, 6.5 mg, 0.05 mmol 6-aminohexanoic acid (**1**) and 50 μL HCl 37% in 1 mL H_2O. After 72 hours the crystals were filtered and dried under mild vacuum for 2 h.

Calix[4]{A_2G1}: 41.6 mg, 0.05 mmol of 4-Sulfocalix[4]arene Sodium Salt, 6.3 mg, 0.05 mmol 1,3-Diaminoguanidine, 6.5 mg, 0.05 mmol 6-aminohexanoic acid (**1**) and 50 μL HCl 37% in 1 mL H_2O. After 72 hours the crystals were filtered and dried under mild vacuum for 2 h.

Calix[4]$^{4-}$: ^{1}H-NMR (D_2O, 300 MHz): δ 7.538 (s, 10H, H^a), 3.990 (s, 10H, H^b).

1: ^{1}H-NMR (D_2O, 300 MHz): δ 2.883-2.933 (t, 2H, H^1), 2.080-2.128 (t, 2H, H^2), 1.560-1.636 (m, 2H, H^3), 1.450-1.534 (m, 2H, H^4), 1.231-1.333 (m, 2H, H^5).

Calix[4]{1}: ^{1}H-NMR (D_2O, 300 MHz): δ 7.560 (s, 10H, H^a), 4.010 (s, 10H, H^b), 2.039 (t, 2H, H^1), 1.644 (t, 2H, H^2), 0.394 (m, 4H, H^3+H^4), 0.041 (t, 2H, H^5).

Calix[4]G{1}: ^{1}H-NMR (D_2O, 300 MHz): δ 7.550 (s, 10H, H^a), 3.988 (s, 10H, H^b), 2.129 (t, 2H, H^1), 1.709 (t, 2H, H^2), 0.512 (m, 4H, H^3+H^4), 0.172 (t, 2H, H^5).

Calix[4]{AG1}: ^{1}H-NMR (D_2O, 300 MHz): δ 7.582 (s, 10H, H^a), 4.024 (s, 10H, H^b), 1.727 (t, 2H, H^1), 1.327 (t, 2H, H^2), 0.022 (t, 2H, H^3), -0.070 (t, 2H, H^4), -0.676 (t, 2H, H^5).

Calix[4]{A_2G1}: ^{1}H-NMR (D_2O, 300 MHz): δ 7.586 (s, 10H, H^a), 4.031 (s, 10H, H^b), 1.697 (t, 2H, H^1), 1.282 (t, 2H, H^2), -0.026 (t, 2H, H^3), -0.132 (t, 2H, H^4), -0.767 (t, 2H, H^5).

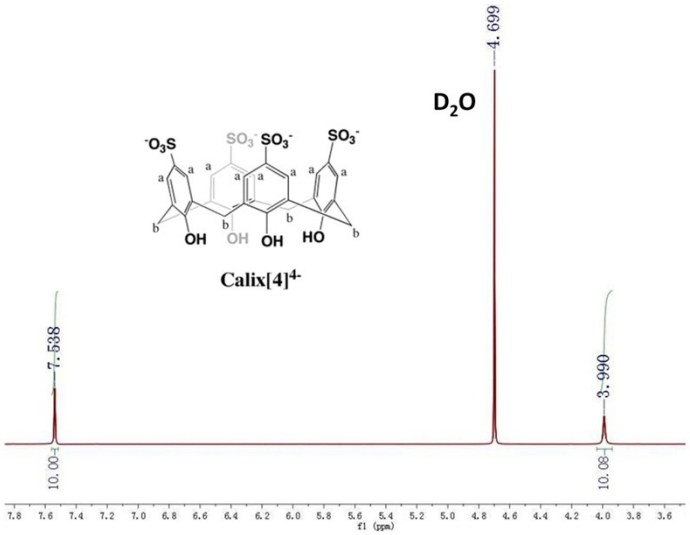

Figure 1s. ^{1}H-NMR (300 MHz, D_2O) of **Calix[4]$^{4-}$**

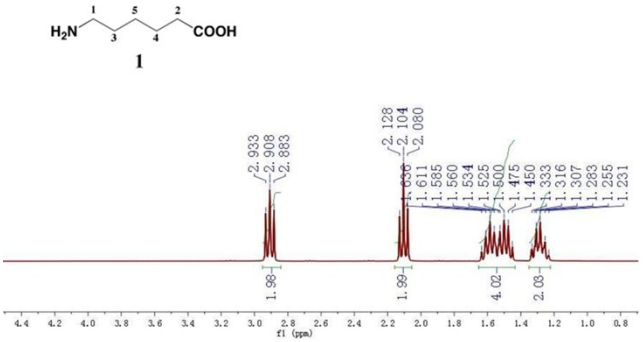

Figure 2s. ^{1}H-NMR (300 MHz, D_2O) of **1**

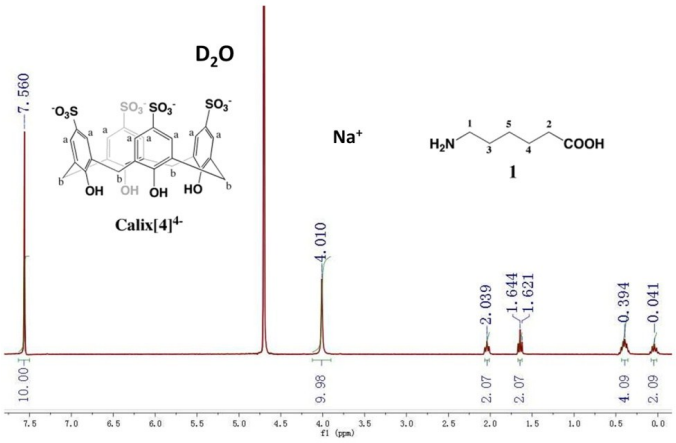

Figure 3s. ^{1}H-NMR (300 MHz, D_2O) of **Calix[4]{1}**

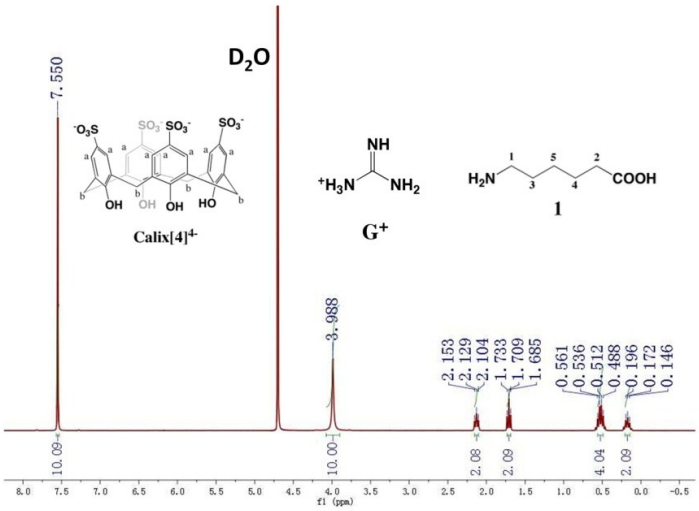

Figure 4s. ^{1}H-NMR (300 MHz, D_2O) of **Calix[4]G{1}**

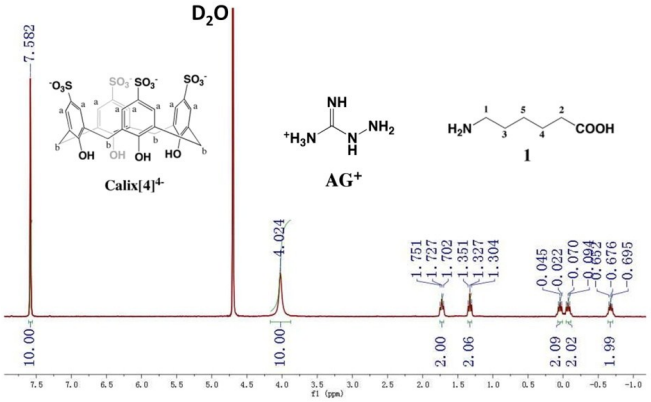

Figure 5s. ^{1}H-NMR (300 MHz, D_2O) of **Calix[4]AG{1}**

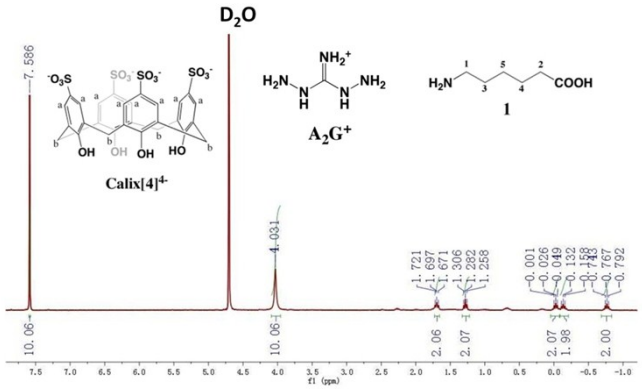

Figure 6s. ^{1}H-NMR (300 MHz, D_2O) of **Calix[4]A_2G{1}**

Table S1. Chemical shifts for **1, Calix[4]$^{4-}$, Calix[4]{1}, Calix[4]G{1}, Calix[4]{AG1}** and **Calix[4]{A_2G1}**

Name	Peak number/ Chemical shifts (ppm)
1	1 (2.908), 2 (2.104), 3 (1.585), 4 (1.500), 5 (1.283)
Calix[4]$^{4-}$	a (7.538), b (3.990)
Calix[4]{1}	a (7.560), b (4.010), 1 (2.039), 2 (1.644), 3 - 4 (0.394), 5 (0.041)
Calix[4]G{1}	a (7.550), b (3.988), 1 (2.129), 2 (1.709), 3 - 4 (0.536), 5 (0.172)
Calix[4]{AG1}	a (7.582), b (4.024), 1 (1.727), 2 (1.327), 3 (0.022), 4 (-0.070), 5 (-0.172)
Calix[4]{A_2G1}	a (7.586), b (4.031), 1 (1.697), 2 (1.282), 3 (-0.026), 4 (-0.158), 5 (-0.767)

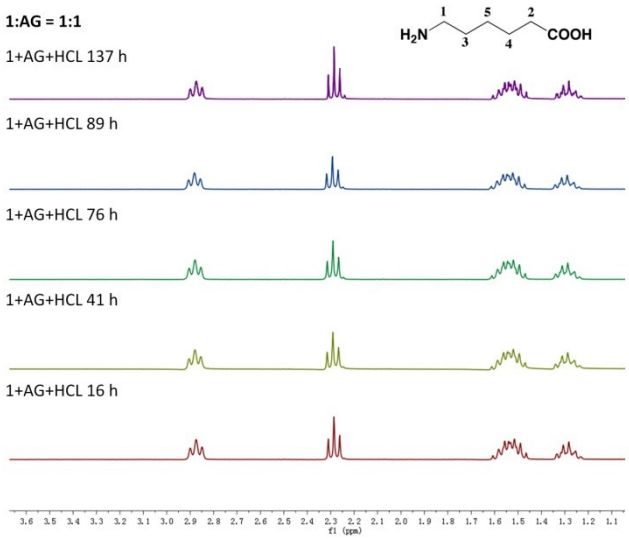

Figure 7S. Timely evolution of the ^{1}H-NMR (300 MHz, D_2O) of the aliphatic part of the spectra of equimolar mixture (0.025 mmol) of AG and **1** in the presence of 50 µL HCl 37% in 1 mL D_2O

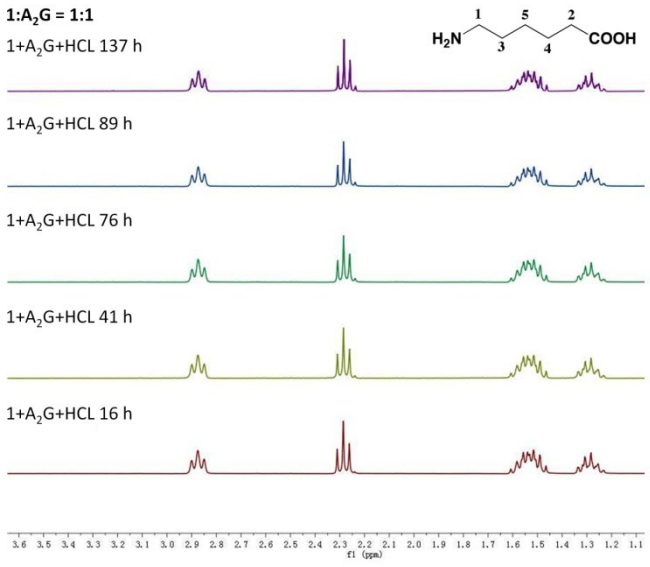

Figure 8S. Timely evolution of the ^{1}H-NMR (300 MHz, D_2O) of the aliphatic part of the spectra of equimolar mixture (0.025 mmol) of A_2G and 1 in the presence of 50 µL HCl 37% in 1 mL D_2O.

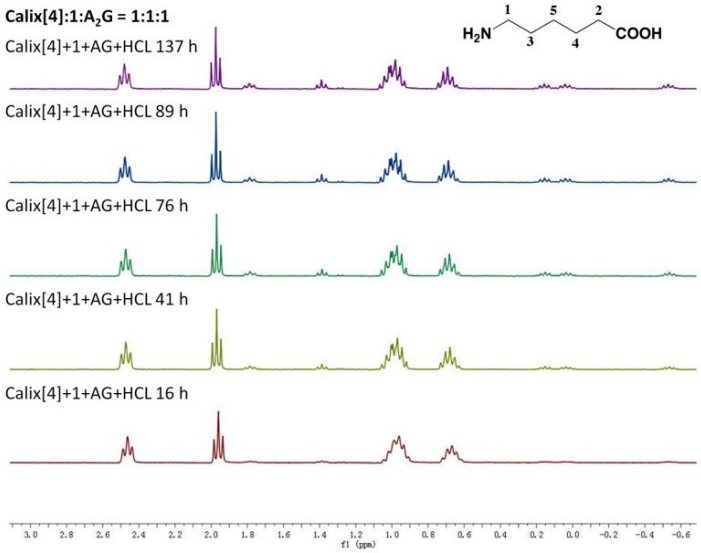

Figure 9S. Timely evolution of the ^{1}H-NMR (300 MHz, D_2O) of the aliphatic part of the spectra of 1:1:1 mixture (0.025 mmol) of Calix[4], AG and 1 in the presence of 50 µL HCl 37% in 1 mL D_2O.

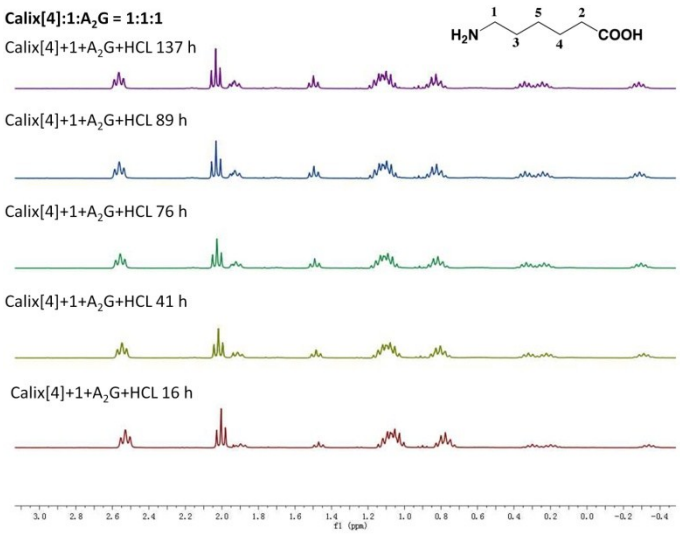

Figure 10S. Timely evolution of the ^{1}H-NMR (300 MHz, D_2O) of the aliphatic part of the spectra of 1:1:1 mixture (0.025 mmol) of Calix[4], A_2G and 1 in the presence of 50 µL HCl 37% in 1 mL D_2O.

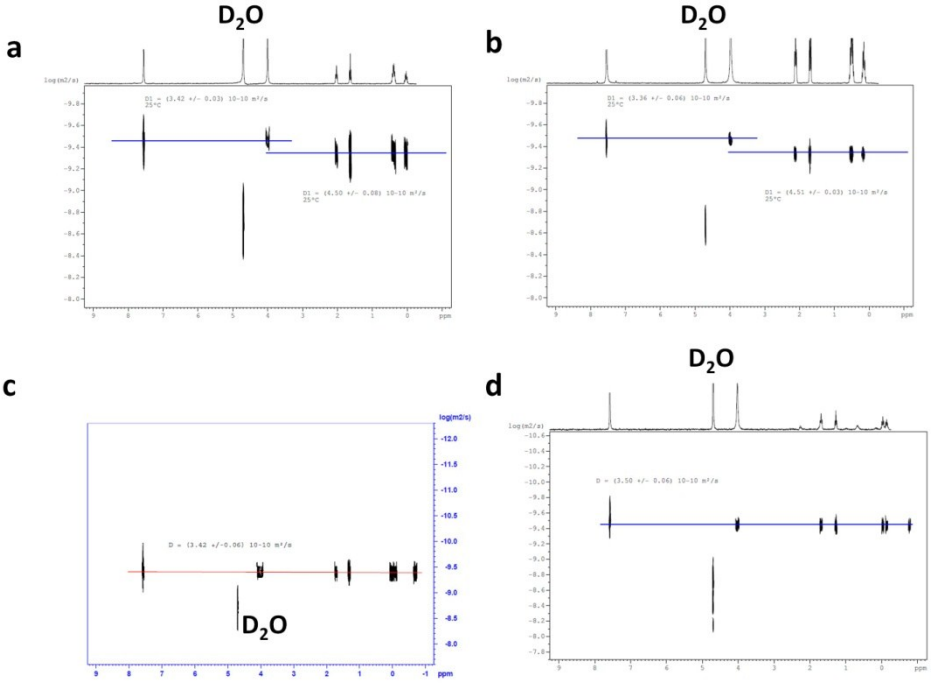

Figure 11s. DOSY spectral of a) Calix[4]{1}, b) Calix[4]G{1} c) Calix[4]AG{1} and d) Calix[4]A_2G{1}

Table S2. DOSY diffusion coefficients for **Calix[4]$^{4-}$** and **1**, **AG1** or **A_2G1** in HOD at room temperature.

samples	Complex diffusion coeff. (m^2s^{-1})	
Calix[4]{1}	3.42×10^{-10} (**Calix[4]$^{4-}$**)	4.50×10^{-10} (**1**)
Calix[4]G{1}	3.36×10^{-10}(**Calix[4]$^{4-}$**)	4.51×10^{-10} (**1**)
Calix[4]{AG1}	3.42×10^{-10}(**Calix[4]$^{4-}$**)	3.42×10^{-10}(**AG1**)
Calix[4]{A_2G1}	3.50×10^{-10}(**Calix[4]$^{4-}$**)	3.50×10^{-10}(**A_2G1**)

Table S3. Crystallographic information on data collection and structure refinement.

	Calix[4]Na{1}	**Calix[4]G{1}**	**Calix[4]AG{1}**	**Calix[4]A_2G{1}**
Formula	$C_{68}H_{92}N_2NaO_{48}S_8$	$C_{35}H_{39}N_4NaO_{18}S_4$ (Solvent)	$C_{68}H_{92}N_2NaO_{48}S_8$ (Solvent)	$C_{35}H_{49}N_6NaO_{21}S_4$
Crystal Class	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space Group	Pn	P-1	P2(1)/n	P2(1)/n
a (Å)	11.9054(4)	12.2682(7)	11.5859(5)	11.7762(2)
b (Å)	29.1876(9)	13.7258(9)	31.7590(13)	31.6823(5)
c (Å)	12.3389(3)	14.1574(8)	12.3239(5)	12.3285(2)
α (°)	89.996(2)	70.256(5)	90.008(3)	90.00
β (°)	90.743(2)	83.703(4)	90.620(3)	92.99(16)
γ (°)	90.004(2)	84.488(5)	90.030(3)	90.00
Volume (Å3)	4287.3(2)	2225.85(12)	4534.4(3)	4593.43(9)
Z	2	2	2	4
Radiation type	Mo-*K*α	Mo-*K*α	Mo-*K*α	Mo-*K*α
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
ρ (mg/cm^{-3})	1.538	1.602	1.454	
Temperature (K)	175	175	175	175
Diffractometer type	Gemini	Gemini	Gemini	Gemini
Scan type	ω	ω	ω	ω
Reflections measured	37233	8669	10022	10955
Independent reflec.	16839	6957	6649	9026
R_{int}	0.04	0.035	0.062	0.034
Average size (mm)	0.45x0.38x0.21	0.35x0.35x0.05	0.40x0.25x0.10	0.60x0.45x0.10
Refinement on	F	F	F	F
R_1(I>2σ(I))	0.088	0.044	0.0971	0.1003
$wR_2(I>2\sigma(I))$	0.096	0.043	0.0876	0.1081
*R*1 (all data)	0.095	0.061	0.1394	0.1142
wR_2 (all data)	0.102	0.048	0.1072	0.1136
Number of parameters	1190	559	578	673
Goodness of fit	1.107	1.117	1.256	1.033

References

[1S] D. Wu, A. Chen & C.S. Johnson Jr., *J. Magn. Reson*. A **1995**, *115*, 260-264.

[2S] A. Van der Lee, *J. Appl. Cryst.* **2013**, *46*, 1306-1315.

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