# **Supporting Information**

## A Combined NMR Crystallographic and PXRD Investigation of the Structure-Directing Role of Water Molecules in Orotic Acid and its Lithium and Magnesium Salts

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## S1. Synthesis of the Orotate Salts

Orotic acid, LiOH and Mg(OH)<sub>2</sub> were used as received from Sigma-Aldrich (Gilingham, U.K.) and this synthesis is based on the original procedure published by Schmidbaur and co-workers in 1990.<sup>[1]</sup>

Due to the better solubility of orotic acid in basic aqueous solutions, 0.103 g lithium hydroxide (4.31 mmol, 1 eq.) were dissolved in 20 mL  $H_2O$  and heated to 70 °C before 0.75 g orotic acid (4.31 mmol. 1 eq.) were slowly added. The clear solution was heated to 90 °C, stirred for 30 min and stored in the fridge for crystallization. After one weekend, a white microcrystalline material could be obtained. After filtration and drying, IR, NMR and PXRD analysis (presented in sections S2 and S4) showed the 0.38 g (2.12 mmol, 49 %) material to be lithium orotate hydrate with small impurities of starting material left.

For the synthesis of magnesium orotate and due to the low solubility of both magnesium hydroxide and orotic acid, 50 mL H<sub>2</sub>O were heated up to 70 °C. Half of the magnesium hydroxide (total: 0.125 g, 2.16 mmol, 1 eq.) was added to the warm solution. Subsequently, small amounts of both orotic acid (total: 0.75 g, 4.31 mmol, 2 eq.) and the remaining magnesium hydroxide were added alternatingly. After heating the solution to 90 °C and stirring it for 30 min, it was stored in the fridge for crystallization. After one weekend, 0.70 g (1.46 mmol, 68 %) of a white microcrystalline material could be obtained after filtration and drying. IR, NMR and PXRD analysis (presented in sections S2 and S4) confirmed the product to be magnesium orotate octahydrate.



Scheme S 1: Synthesis of the lithium and magnesium salt of orotic acid.

## S2. Verification of the Compound/Product Purity

#### S2.1 Powder X-ray diffraction experiments at ambient conditions

To ensure purity of the starting material as well as verify the synthesis of the two orotate salts, powder X-ray diffraction (PXRD) experiments were performed in the Bragg-Brentano mode. The two salts were dried under vacuum and then subjected to the measurements. The lithium orotate sample contains a small amount of starting material, which is in agreement with other data, e.g. TGA and NMR measurements (see Figures S3 and S11). For comparison, the experimental PXRD data is plotted in Figure S1 and S2 together with a simulated dataset based on the single crystal X-ray structure from the Cambridge Structural database (CSD codes OROTAC01, SIMZOD01 and SIMZUJ). The simulation was carried out using the program Mercury (Version 3.7, Cambridge Crystallographic Data Centre).



*Figure S 1:* Experimental PXRD data and corresponding simulated diffraction patterns for orotic acid monohydrate (1) and its lithium salt (2). The lithium data shows a small amount of remaining starting material.



*Figure S 2*: *Experimental PXRD data and corresponding simulated diffractions pattern for magnesium orotate octahydrate (3) after workup.* 

#### S2.2 Thermogravimetric Analysis (TGA)

Thermogravimetric Analysis (TGA) was performed for all three compounds. Orotic acid monohydrate was used as received from Sigma-Aldrich, while the synthesis products were dried under vacuum overnight and then subjected to the TGA measurements. In the case of magnesium orotate, a lower percentage of water molecules is observed compared to the theoretical expected loss of mass. This is due to the drying of the samples directly after synthesis and underlines the lability of this particular system.



*Figure S 3:* Thermogravimetric analysis of orotic acid monohydrate and its lithium and magnesium salt. In all three cases, the samples were heated from 25 to 500 °C at a constant heating rate of 10 °C per minute.

## S2.3 Infrared Spectra



**Figure S 4**: Infrared spectra of orotic acid monohydrate as obtained from Sigma Aldrich (top), lithium orotate monohydrate (centre) and magnesium orotate octahydrate (bottom).

## **S3.** Additional Structural Details



**Figure S 5**: (a) Stacking arrangement of lithium orotate monohydrate (2), which contains layers that are interlinked by both lithium ions and water molecules; (b, c) a closer view on the coordination environment of the (b) lithium ion and (c) the water molecules (c) underlines their roles in forming intra- and inter-layer links.



*Figure S 6:* Representation of the layered arrangement found for magnesium orotate octahydrate (3) (top) and visualization of the channel environment for part of the water molecules along the c axis of the unit cell (bottom).

## S4. Characterization by Multinuclear NMR

For all characterizations (NMR and calculations), the following numbering scheme is used.



Figure S 7: Numbering Scheme for the analyzed orotic acid derivatives used throughout this paper.

For <sup>14</sup>N–<sup>1</sup>H HMQC<sup>[2]</sup> experiments, a 4-step nested phase cycle was used to select changes in coherence order  $\Delta p = \pm 1$  (on the first <sup>1</sup>H pulse, 2 steps) and  $\Delta p = \pm 1$  (on the last <sup>14</sup>N pulse, 2 steps).

<sup>15</sup>N NMR data was referenced using the lowest ppm resonance of <sup>15</sup>N-labelled Histidine·HCl·H<sub>2</sub>O (– 333.1 ppm, corresponding to liquid nitromethane as the primary reference). To convert to the corresponding <sup>15</sup>N chemical shift scale frequently used in protein NMR, where the reference is liquid ammonia at –50 °C, it is necessary to add 379.5 to the given values.<sup>[3]</sup>





*Figure S 8*: Experimental <sup>1</sup>H and <sup>1</sup>H-<sup>13</sup>C CP MAS NMR spectra of orotic acid monohydrate. <sup>1</sup>H and <sup>13</sup>C CP data was recorded at 14.1 T (56 kHz MAS, 1.3 mm) and 11.7 T (10 kHz, 4 mm), respectively. The stick spectra correspond to GIPAW (CASTEP) calculated chemical shifts.



**Figure S 9:** Experimental <sup>14</sup>N-<sup>1</sup>H HMQC and <sup>1</sup>H-<sup>15</sup>N CP NMR spectra of orotic acid monohydrate. <sup>14</sup>N and <sup>15</sup>N data was recorded at 14.1 T (59 kHz MAS, 1.3 mm) and 11.7 T (10 kHz, 4 mm), respectively. The stick spectra correspond to GIPAW (CASTEP) calculated chemical shifts.

#### S4.2 Orotic Acid Anhydrate

In order to transform orotic acid monohydrate into its anhydrate form, it was heated in an oven to 100 °C for 4 h and then subjected to NMR experiments at 30 kHz MAS (Figure S10). As can be seen from the dashed grey lines, the chemical shifts change compared to the monohydrate form. While the COOH resonance is shifted to a lower ppm value (indicating a slightly weaker hydrogen bond), the CH resonance is shifted to a higher ppm value. This is in agreement with <sup>1</sup>H data published by Braun and co-workers.<sup>[4]</sup> Interestingly, no line broadening is observed for the anhydrous structure confirming the COOH-water network to be the source of the observed dynamics for the monohydrate form.



**Figure S 10**: Experimental  ${}^{1}H(DQ) - {}^{1}H(SQ)$  MAS (30 kHz) NMR spectrum of orotic acid anhydrate recorded at 11.7 T using one rotor period of BABA recoupling. The grey vertical dashed lines represent the experimental chemical shifts observed for the monohydrate form.

#### S4.3 Lithium Orotate Monohydrate



**Figure S 11**: Experimental <sup>1</sup>H and <sup>1</sup>H-<sup>13</sup>C CP NMR spectra of lithium orotate monohydrate. <sup>1</sup>H and <sup>13</sup>C data was recorded at 14.1 T (56 kHz MAS, 1.3 mm) and 11.7 T (10 kHz, 4 mm), respectively. The stick spectra correspond to GIPAW (CASTEP) calculated chemical shifts.



**Figure S 12**: Left: Experimental <sup>7</sup>Li MAS (10 kHz) NMR spectrum of **2** recorded at 11.7 T alongside a simulated (SIMPSON) spectrum using parameters calculated by the GIPAW (CASTEP) method. Right: Experimental  ${}^{1}H(DQ) - {}^{1}H(SQ)$  MAS (30 kHz) NMR spectrum recorded at 11.7 T using one rotor period of BABA recoupling.

Good agreement between experiment and simulation was achieved for a <sup>7</sup>Li MAS NMR spectrum (see Figure S12, left) – the simulation was performed using the program SIMPSON<sup>[5]</sup> based on the corresponding output option in MagresView<sup>[6]</sup> for a GIPAW (CASTEP) calculation. One strong resonance (with an isotropic chemical shift of 0.3 ppm referenced to LiCl) is observed, which agrees with the asymmetric unit from the crystal structure containing a single molecular unit. The effect of a second order quadrupolar shift of <sup>7</sup>Li on the calculated chemical shift was found to be below the experimental error in determining the peak position (see section S5.5).

#### SIMPSON INPUT:

```
spinsys {
    channels 7Li
    nuclei 7Li
    shift 1 -0.31806801p 2.44081206p 0.86239991 123.46762985 93.16104203 83.59935150
    quadrupole 1 2 -85323.83922225 0.92758826 -139.92800361 91.95079642 -91.51917229
}
# SIMPSON is extendable with other TCL packages
```

```
# we use these additional utilities for convenience
source ../util.tcl
par {
  method
                         gcompute freq
  proton frequency 500e6
  gamma angles
                        16
  spin_rate
                        10000
  start_operator
                        I1x
  detect_operator
                       I1p
                         8192
  np
  SW
                         0.5e6
  variable tsw
                         1.0e6/spin_rate/gamma_angles
  verbose
                         1101
}
proc pulseq {} {
  global par
  acq_block {
       delay $par(tsw)
  }
}
proc main {} {
  global par
# result is a spectrum directly
  set f [fsimpson]
  puts "Calc. time = [expr $par(tcalc)*1e-6] s"
# line-broadening is done in time domain
  fft $f -inv
  set z [findex $f 1]
  fsetindex $f 1 [expr [lindex $z 0]*0.5] [expr [lindex $z 1]*0.5]
  fft $f
# here we use custom Fsave function defined in ./utils.tcl
  set spename [Fsave $f $par(name)]
  puts "Saved files: $spename"
  funload $f
}
                                                                                         N1
                                                                              Ν2
                                                              100
                                                              100 0
14N shift [ppm]
                                                              200
                                                                                                  - 300
                                                                           - 200
                                                                                       - 250
             16
                    14
                           12
                                 10
                                        8
                                               6
                                                      4
                        <sup>1</sup>H chemical shift [ppm]
                                                                               <sup>15</sup>N chemical shift [ppm]
```

**Figure S 13:** Experimental <sup>14</sup>N-<sup>1</sup>H HMQC and <sup>1</sup>H-<sup>15</sup>N CP MAS NMR spectra of lithium orotate monohydrate. <sup>14</sup>N and <sup>15</sup>N data was recorded at 14.1 T (59 kHz MAS, 1.3 mm) and 11.7 T (10 kHz, 4 mm), respectively. The stick spectra correspond to GIPAW (CASTEP) calculated chemical shifts.

#### S4.4 Magnesium Orotate



**Figure S 14**: Experimental <sup>13</sup>C (CP) MAS (10 kHz) NMR spectra recorded at 11.7 T of **3** after (left) drying in the lab and (right) after evacuation monitored by PXRD measurements (right).



**Figure S 15**: Experimental  ${}^{1}H(DQ) - {}^{1}H(SQ)$  MAS (30 kHz) NMR spectrum of **3** while undergoing change (due to MAS) measured at 11.7 T and 30 kHz using one rotor period of BABA recoupling. The orange crosses correspond to GIPAW calculated cross peaks, indicating the existence of an additional NH resonance corresponding to a second NH environment. As expected, the two signals at ~2 and 5 ppm assigned to "free"/supernatant water do not appear in this DQ filtered spectrum. The mobility of these molecules prevents effective recoupling.

## **S5. CASTEP calculations**

## S5.1 General Information on Version, Parameters and Conventions used

All calculations were run on the regional high performance computing facility Minerva (MidPlus) using the CASTEP code, academic release version 8.0. After geometry optimization, the NMR shieldings were calculated on the basis of the GIPAW method. The data thus obtained was loaded into MagresView<sup>[6]</sup> and output in tabulated form.

In this work, the chemical shielding tensors obtained by GIPAW (CASTEP) calculations are presented according to the *Haeberlen-Mehring-Spiess* convention:

The principal components of the chemical shielding tensor are  $\sigma_{xx}$ ,  $\sigma_{yy}$  and  $\sigma_{zz}$ , satisfying  $|\sigma_{zz} - \sigma_{iso}| \ge |\sigma_{xx} - \sigma_{iso}| \ge |\sigma_{yy} - \sigma_{iso}|$ . The isotropic chemical shielding is an average over the principal components:  $\sigma_{iso} = \frac{(\sigma_{xx} + \sigma_{yy} + \sigma_{zz})}{3}$  and the anisotropy is defined as  $\sigma_{aniso} = \sigma_{zz} - \sigma_{iso}$ . The asymmetry is obtained according to  $\eta_{asym} = \frac{\sigma_{yy} - \sigma_{xx}}{\sigma_{ansio}}$ , with  $\eta_{asym} = 0$  corresponding to axial symmetry.

To compare the calculated chemicals shieldings to experimental chemical shift data, referencing according to the following scheme is required:  $\delta_{iso} = \sigma_{ref} - \sigma_{iso}$ .<sup>[7]</sup> For the discussed nuclei <sup>1</sup>H, <sup>7</sup>Li, <sup>13</sup>C and <sup>14/15</sup>N, the references values and their origins are given below:

nucleus	σ <sub>ref</sub>	ref.
<sup>1</sup> H	29.5	[8]
<sup>7</sup> Li	89.7	LiCl set to -0.8, the experimental LiCl chemical shift
<sup>13</sup> C	170.9 for ( <b>1</b> ), 171.3 for ( <b>2</b> ), 171.2 for ( <b>3</b> )	exact value by plotting experimental chemical shifts and calculated shieldings (fixed slope at $-1$ ) <sup>[7-8]</sup>
<sup>14/15</sup> N	-166	corresponding to liquid CH <sub>3</sub> NO <sub>2</sub> as reference using a calculation for histidine HCl with experimental <sup>15</sup> N chemical shifts of –191.1, –204.4 and –333.1 ppm

**Table S 1:** Summary of the nuclei, for which NMR parameters were calculated using the GIPAW (CASTEP) approach and the corresponding references values used to convert chemical shieldings into chemical shifts.

A full set of calculated NMR parameters for orotic acid, lithium orotate and magnesium orotate can be found in the tables below. All molecules follow the same numbering scheme given in Figure S7.

## S5.2<sup>14</sup>N quadrupolar effects

In contrast to its other NMR active isotope ( $^{15}N$ ),  $^{14}N$  is a quadrupolar nucleus with a spin *I* = 1. For  $^{14}N$ , the electric quadrupolar moment *Q* of the nucleus interacts with the electric field gradient (EFG), a

tensor with the principal components being  $V_{xx}$ ,  $V_{yy}$  and  $V_{zz}$ . Based on the quadrupolar coupling constant  $C_Q$  and the asymmetry parameter  $\eta_Q$ ,

$$C_Q = \frac{(V_{ZZ}eQ)}{h} = \frac{(e^2qQ)}{h} \quad \text{and} \quad \eta_Q = \frac{(V_{XX} - V_{YY})}{V_{ZZ}}$$
(Eq. S1)

the quadrupolar product can be defined as:

$$P_Q = C_Q \sqrt{\left[1 + \left(\frac{\eta_Q^2}{3}\right)\right]}.$$
 (Eq. S2)

The isotropic second order quadrupolar shift is given by:<sup>[2, 9]</sup>

$$\delta_{iso}^{Q} = -\left(\frac{3}{40}\right) \left(\frac{P_{Q}}{\nu_{0}}\right)^{2} \left[I(I+1) - 9m(m-1) - 3\right] / \left[I^{2}(2I-1)^{2}\right] \times 10^{6} .$$
 (Eq. S3)

In this particular case (I = 1 and m = 0), this can be simplified to

$$\delta_{iso}^Q = \left(\frac{3}{40}\right) \left(\frac{P_Q}{\nu_0}\right)^2 \times 10^6,\tag{Eq. S4}$$

where  $P_Q$  is the quadrupolar product and  $v_0$  the Larmor frequency, both in MHz.

### S5.3 Crystal vs. Molecule/ Fragment

To gain additional theoretical insight into the set of intermolecular interactions that are present for a particular form or packing arrangement, a second set of calculations was performed and the results compared to the "standard" GIPAW NMR chemical shift calculation for the full crystal. To do so, a single molecule from the fully geometry optimized structure is kept in the unit cell, which is also increased by ~5 Å in each direction. Thereby it is assured that this molecule is no longer in proximity to any neighbouring molecules. Subsequently, another set of NMR parameters can be calculated.

The thus obtained chemical shifts are then compared to the corresponding ones for the full crystal structure. This difference:

$$\Delta \delta = \delta \, ^{\text{crystal}} - \delta \, ^{\text{molecule}}$$

(Eq. S5)

then represents the change induced by the sum of all interactions the molecule is involved in. This can also be modified to analyse the effect of layers or particular fragments.

A positive difference between crystal and molecule chemical shifts is indicative of hydrogen bonding interactions, while a negative difference is observed if ring current effects are involved, e.g. for CH··· $\pi$  interactions.<sup>[10]</sup> As such an analysis can be carried out for all nuclei in a molecule, this procedure can be used to identify and illustrate a variety of different interactions with varying strength. In the particular case of lithium orotate, the procedure was slightly expanded as this complex is an extensive network. Therefore, a GIPAW calculation was carried out for the full crystal structure, the full crystal structure without any lithium atoms and the individual fragments, i.e., the orotate anion as well as the water molecule, inside an enlarged unit cell (charges were accounted for in the .param CASTEP file).

In the specific case of the "lithium-free crystal structure", the lithium atom was removed from the already geometry optimized crystal structure. As for the magnesium structure in general, the resulting structure is now charged. This charge was specified in the .param file:

TASK : MAGRES magres\_task : NMR CUT OFF ENERGY :800 eV opt\_strategy : speed #CONTINUATION=li NMR.check XC FUNCTIONAL : PBE grid scale : 2.0 charge: -1 WRITE\_CIF\_STRUCTURE=True WRITE\_CELL\_STRUCTURE=True

#### S5.4 GIPAW (CASTEP) calculations - Orotic Acid Monohydrate

**Table S 2**: Shielding and quadrupolar parameters of 1 calculated using the GIPAW (CASTEP) approach. The resulting chemicalshifts using the reference values in Table S1 are stated together with experimental data.

Atom	$\sigma_{iso}{}^{calc}$	σ <sub>xx</sub> /ppm	σ <sub>yy</sub> /ppm	σ <sub>zz</sub> /ppm	δ <sub>iso</sub> <sup>calc</sup> /ppm	δ <sub>iso</sub> <sup>exp</sup> /ppm
C_1	6.67	66.24	33.44	-79.66	164.2	162.2
C_2	25.24	120.9	30.18	-75.36	145.6	144.4
C_3	68.45	-5.96	58.17	153.15	102.4	102.7
C_4	1.73	-70.19	-10.27	85.66	169.1	169.9
C_5	20.35	76.47	43.18	-58.60	150.5	152.6
H_1	13.38	0.94	2.82	36.38	16.1	15.5
H_2	24.80	23.8	24.28	26.30	4.7	5.8
H_3	16.89	9.57	13.30	27.80	12.6	12.1
H_4	18.43	11.75	16.22	27.31	11.1	11.4
H_a	24.83	16.66	17.1	40.72	4.7	151
H_b	24.64	16.49	17.09	40.34	4.9	} 3.1
<sup>15</sup> N_1	79.94	-11.54	71.35	180.00	-245.9	-247.9
<sup>15</sup> N_2	55.63	-27.48	52.14	142.24	-221.6	-219.9

	( <sup>14</sup> N) Electric field gradient data (symmetric component)								
Atom	Chi(Hz)	asym	v_1(Hz)	v_2(Hz)	v_3(Hz)	δ <sup>Q</sup> iso <sup>calc</sup> /ppm <sup>a</sup>	δ <sup>14N</sup> iso <sup>calc</sup> /ppm <sup>b</sup>	δ <sup>Q</sup> <sub>iso</sub> <sup>exp</sup> /ppm	
<sup>14</sup> N_1	-2504901	0.67	-275391	-1394542	-1669934	260.4	14.5	10	
<sup>14</sup> N_2	-2430524	0.68	-257962	-1362386	-1620349	246.1	24.5	30	

°Calculated according to equation S4 with a scaling of  $P_Q$  by 95%.  ${}^b\delta_{iso}{}^{calc}({}^{15}N) + \delta^{Q}_{iso}{}^{calc}$ 

#### S5.5 GIPAW (CASTEP) calculations - Lithium Orotate Monohydrate

**Table S 3**: Shielding and quadrupolar parameters of **2** calculated using the GIPAW (CASTEP) approach. The resulting chemical shifts using the reference values in Table S1 are stated together with experimental data.

Atom	$\sigma_{iso}^{calc}$	σ <sub>xx</sub> /ppm	σ <sub>yy</sub> /ppm	σ <sub>zz</sub> /ppm	δ <sub>iso</sub> <sup>calc</sup> /ppm	δ <sub>iso</sub> <sup>exp</sup> /ppm
C_1	5.85	64.20	27.70	-74.34	165.4	162.2
C_2	21.74	120.56	22.88	-78.21	149.5	144.4
C_3	68.50	-5.80	58.95	152.34	102.8	102.6
C_4	2.72	-72.65	-5.78	86.58	168.6	169.8
C_5	20.25	78.03	34.59	-51.88	151.0	152.6
H_2	24.81	23.52	24.12	26.80	4.7	5.5
H_3	18.02	13.14	13.79	27.13	11.5	11.1
H_4	18.33	11.70	14.97	28.33	11.2	10.8
H_a	25.48	15.42	20.08	40.94	4.0	< 4.9 (BABA)
H_b	23.63	12.77	15.40	42.71	5.9	5.7 (BABA)
<sup>7</sup> Li	89.39	91.66	89.56	86.95	0.3	0.4
<sup>15</sup> N_1	75.77	-13.81	67.96	173.16	-242.8	-244.6
<sup>15</sup> N_2	54.69	-26.27	51.20	139.12	-221.7	-219.9

( <sup>14</sup> N) Electric field gradient data (symmetric component)									
Atom	Chi(Hz)	asym	v_1(Hz)	v_2(Hz)	v_3(Hz)	δ <sup>Q</sup> iso <sup>calc</sup> /ppm <sup>a</sup>	δ <sup>14N</sup> iso <sup>calc</sup> /ppm <sup>b</sup>	δ <sup>Q</sup> <sub>iso</sub> <sup>exp</sup> /ppm	
<sup>14</sup> N_1	-2457182	0.67	-271500	-1366621	-1638121	250.6	7.8	1 20	
<sup>14</sup> N_2	-2532330	0.57	-365324	-1322895	-1688220	256.6	34.9	} 20	
<sup>Q</sup> Calculato	d according to	oquation (	A with a scaling	of D. by 05%		•			

<sup>a</sup>Calculated according to equation S4 with a scaling of  $P_Q$  by 95%. <sup>b</sup> $\delta_{iso}$ <sup>calc</sup>(<sup>15</sup>N) +  $\delta^{Q}_{iso}$ <sup>calc</sup>

Second order quadrupolar shifts were calculated for the spin 3/2 nucleus <sup>7</sup>Li as well. However, with values for this compound found to be smaller than 0.02 ppm, they were not included in this section.

#### **S5.6 Magnesium Orotate Octahydrate**

**Table S 4**: Shielding and quadrupolar parameters of **3** calculated using the GIPAW (CASTEP) approach. The resulting chemicalshifts using the reference values in Table S1 are stated together with experimental data.

Atom	$\sigma_{iso}^{calc}$	σ <sub>xx</sub> /ppm	σ <sub>γγ</sub> /ppm	σ₂₂/ppm	δ <sub>iso</sub> <sup>calc</sup> /ppm	δ <sub>iso</sub> <sup>exp</sup> /ppm
C_1	5.88	66.81	20.86	-70.02	165.3	
C_2	23.84	121.33	27.57	-77.39	147.3	
C_3	66.36	-8.99	54.26	153.82	104.8	
C_4	3.51	85.41	4.45	-79.32	167.6	
C_5	21.07	77.13	43.42	-57.33	150.1	
H_2	20.33	15.89	19.03	26.06	9.7	4-7
H_3	19.76	15.89	16.81	26.57	10.2	10.0
H_4	24.28	22.41	24.05	26.37	5.7	} 9.8
H_a	25.69	16.20	18.30	42.57	4.3	
H_b	24.53	14.83	17.61	41.15	5.5	} 4-7
	23.52	12.04	16.64	41.87	6.5	
	22.53	10.87	13.95	42.77	7.5	
$M_{\alpha}(1, 0)$	23.20	12.23	14.36	43.00	6.8	
WIg(H <sub>2</sub> U)	23.74	13.21	16.44	41.56	6.3	} 4-7
	23.71	12.58	15.93	42.62	6.3	
	24.35	14.80	16.4	41.86	5.6	
<sup>15</sup> N_1	85.77	171.67	86.36	-0.73	-251.8	
<sup>15</sup> N_2	60.63	133.17	68.33	-19.61	-226.6	

Due to the magnesium orotate sample changing upon MAS, no <sup>13</sup>C and <sup>15</sup>N experimental data was obtained for the initial composition.



**Figure S 16**: Crystal vs. molecule GIPAW NMR shielding calculation for magnesium orotate octahydrate, **3**. The differences plotted are obtained from one calculation for the full crystalline environment and one for a single molecule only (separately for the orotate anion, the crystal water and the  $[Mg(H_2O)_6]^{2+}$  fragment).

## S6. Powder X-ray diffraction data

### S6.1 Experiments at ambient conditions

As the magnesium orotate octahydrate structure changed upon magic angle spinning in the solid-state NMR experiments, the sample was dried further and the PXRD data was re-measured. For comparison, the experimental data is plotted together with a simulated dataset based on the single crystal X-ray structure from the Cambridge Structural database (CSD code SIMZUJ). The simulation was carried out using the program Mercury.





## **S7.** Further Calculations / structure generation

## S7.1 TGA after evacuation

For different numbers of water molecules, the percentage with respect to the total molecular weight was calculated showing that the 10.2% weight loss observed in the TGA corresponds to two water molecules within the structural unit. The molecular weight is always calculated from one magnesium ion, two orotate units and the amount of water present.

**Table S 5**: Calculation of the molecular weight percentages corresponding to the different number of water molecules in the structure. The general weight is calculated based on one Mg, two orotate units and the particular amount of water present.

x H <sub>2</sub> O	8	7	6	5	4	3	2	1	0
MW	478.09	460.08	442.07	424.06	406.05	388.04	370.03	352.02	334.01
$MW\SigmaH_2O$	144.08	126.07	108.06	90.05	72.04	54.03	36.02	18.01	0
% of MW	30.14	27.40	24.44	21.24	17.74	13.92	9.73	5.12	0

#### **S7.2 CASTEP Calculations of potential arrangements**

To gain further insight into possible (dehydrate) structures, GIPAW (CASTEP) calculations with dispersion correction and varying unit cell parameters were performed. Based on the TGA data after evacuation, a set of structures with two H<sub>2</sub>O molecules per magnesium unit was generated. These structures varied between how water molecules were deleted from the channels and/or from the [Mg(H<sub>2</sub>O)<sub>6</sub>]<sup>2+</sup> octahedral sites.





**Figure S 18**: Experimental (blue) <sup>1</sup>H MAS (60 kHz) NMR (14.1 T) spectrum of **3** after evacuation in the powder X-ray diffractometer and GIPAW (CASTEP) calculated <sup>1</sup>H NMR spectra (with 360 Hz of line broadening applied) spectra for two structures produced by DFT geometry optimization corresponding to an asymmetric (red) or symmetric (green) arrangement of two water molecules per magnesium atom.

**Table S 6**: Comparison of the GIPAW (CASTEP) calculated chemical shifts for three different structural magnesium orotate hydrate structures: the initial single crystal X-ray structure SIMZUJ and a symmetric as well as an asymmetric dihydrate structure. H\_a and H\_b correspond to channel water in the initial structure. In the structures with only two water molecules left, both molecules are coordinated to the magnesium ion.

Atom	δ <sub>iso</sub> <sup>calc</sup> /ppm SIMZUJ	$\delta_{iso}^{calc}$ /ppm symmetric	δ <sub>iso</sub> <sup>calc</sup> /ppm assymmetric
C_1	165.3	174.5	164.7 & 163.0
C_2	147.3	148.9	149.5 &147.8
C_3	104.8	107.3	106.6 & 109.9
C_4	167.6	168.3	165.9 & 169.2
C_5	150.1	148.1	149.8 & 154.7
H_2	9.7	11.4	10.9 & 11.3
H_3	10.2	12.1	11.2 & 12.5
H_4	5.7	5.4	5.6 & 6.2
H_a	4.3	х	x
H_b	5.5	х	х
Mg(H <sub>2</sub> O)	6.5, 7.4, 7.0, 6.3, 6.2, 5.6	2.7, 6.2	3.3, 5.0, 6.7, 7.8
<sup>15</sup> N_1	-251.8	-251.4	-246.0 & -251.0
<sup>15</sup> N_2	-226.6	-223.6	-221.4 & -222.7



**Figure S 19**: Comparison between the experimental PXRD pattern of **3** after evacuation in the diffractometer and the simulated PXRD patterns for the initial octahydrate crystal structure (SIMZUJ) as well as the symmetric and asymmetric dihydrate structures.

## **S8.** References

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