

# **Insights into the Crystallization and Structural Evolution of Glycine Dihydrate by In Situ Solid-State NMR Spectroscopy**

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German Edition: DOI: [10.1002/ange.201801114](http://dx.doi.org/10.1002/ange.201801114) Crystallization International Edition: DOI: [10.1002/anie.201801114](http://dx.doi.org/10.1002/anie.201801114) 1 1  $\frac{1}{2}$  Crystallization<br>3<br>3

#### Insights into the Crystallization and Structural Evolution of Glycine  $\frac{5}{6}$  Dihydrate by In Situ Solid-State NMR Spectroscopy  $3$  3  $3$  $4$  -Insights into the Crystallization and Structural Evolution of Glycine  $\qquad$  $\delta$  Dinyarate by in Situ Sond-State NMK Spectroscopy

<sup>7</sup> Paolo Cerreia Vioglio, Giulia Mollica, Marie Juramy, Colan E. Hughes, P. Andrew Williams,  $\frac{7}{8}$ 9 Fabio Ziarelli, Stéphane Viel, Pierre Thureau,\* and [Kenneth D. M. Harris\\*](http://orcid.org/0000-0001-7855-8598) New York Stephane 9  $8$  and Cerrell Vioglio, Guilla Motica, marie Jaramy, Colan E. Hagnes, T. Andrew Williams,  $\sim$  8

11 **Abstract:** In situ solid-state NMR spectroscopy is exploited to (e.g., L-lysine and L-arginine), the anhydrous solid form is 11 12 monitor the structural evolution of a glycine/water glass phase very hygroscopic and transforms readily to a hydrate phase 12 13 formed on flash cooling an aqueous solution of glycine, with under normal atmospheric conditions.<sup>[10]</sup> 13 elucidate structural properties of the solid phases present. The glycine/water glass is shown to crystallize into an intermediate phase, which then transforms to the  $\beta$  polymorph of glycine. first proposed only very recently.

ascribed to possible isomerism, his observations are now attributed to the existence of the  $\alpha$  and  $\beta$  polymorphs of 27 1954.<sup>[3]</sup> Except for three further polymorphs formed at high glycine with loss of water. 27 glycine, reported by Xu et al. in 2017.[5]

In general, crystallization of glycine from pure aqueous lization from water in nano-confined environments promotes



(e.g., l-lysine and l-arginine), the anhydrous solid form is very hygroscopic and transforms readily to a hydrate phase under normal atmospheric conditions.[10]

14 a range of modern solid-state NMR methods applied to The recent work<sup>[5]</sup> that proved the existence of glycine 14 18 Our in situ NMR results fully corroborate the identity of the quench frozen in liquid nitrogen to form a glycine/water glass 18 19 intermediate crystalline phase as glycine dihydrate, which was phase (frozen solution). When this glass phase is warmed to  $19$ Polymorphism in glycine was first observed, although not 22 22 23 fully understood, by Fischer in 1905.<sup>[1]</sup> Although originally diffractometer and determined the structure directly from 23 26 glycine.<sup>[2]</sup> A third polymorph ( $\gamma$  polymorph) was discovered in above 250 K, this phase transforms to the  $\beta$  polymorph of 26 The recent work $[5]$  that proved the existence of glycine 15 elucidate structural properties of the solid phases present. The dihydrate (GDH) relied on a preparation procedure reported 15 16 glycine/water glass is shown to crystallize into an intermediate by Pyne and Suryanarayanan<sup>[11]</sup> and later by Surovtsev 16  $17$  phase, which then transforms to the  $\beta$  polymorph of glycine. et al.<sup>[12]</sup> In this procedure, an aqueous solution of glycine is  $17$ quench frozen in liquid nitrogen to form a glycine/water glass phase (frozen solution). When this glass phase is warmed to 20 first proposed only very recently.  $\blacksquare$  around 209 K and held at this temperature, crystallization 20  $21$  occurs to give a new solid phase. Xu et al.<sup>[5]</sup> prepared the new 21 crystalline phase in situ in a synchrotron powder X-ray diffractometer and determined the structure directly from 24 ascribed to possible isomerism, his observations are now the powder XRD data, revealing that the new phase is  $24$ 25 attributed to the existence of the  $\alpha$  and  $\beta$  polymorphs of a dihydrate of glycine. It was also shown<sup>[5]</sup> that, on heating 25 above 250 K, this phase transforms to the  $\beta$  polymorph of glycine with loss of water.

28 pressure,<sup>[4]</sup> no new solid form of glycine was reported until In the present work, the procedure reported previ-29 over 60 years later, with the very exciting discovery and ously<sup>[5,11,12]</sup> has been carried out inside an NMR spectrometer, 29  $30$  structural characterization of a crystalline dihydrate of exploiting in situ solid-state NMR techniques to monitor the  $30$ 33 solution at neutral pH gives the  $\alpha$  polymorph,<sup>[6]</sup> which solution of glycine. In recent years, in situ NMR techniques 33 34 transforms to the stable  $\gamma$  polymorph over time.<sup>[7]</sup> Crystal- for monitoring crystallization processes have been applied to 34 36 the formation of the  $\beta$  polymorph.<sup>[8]</sup> In spite of extensive aqueous solution near ambient temperature.<sup>[13a,b]</sup> A signifi- 36  $37$  studies, no hydrated crystalline phase of glycine was reported cant advantage of solid-state NMR spectroscopy for in situ  $37$ 38 until the recent study by Xu et al.<sup>[5]</sup> In contrast, hydrate studies of such processes is that it allows the identification and 38  $39$  phases of several other amino acids are well known,<sup>[9]</sup> and characterization of both amorphous and crystalline phases.  $39$  $40$  interconversion processes between anhydrous and hydrate Thus, the institution solid-state NMR study presented here offers  $40$ 4 phases have been studied in detail.<sup>[9e, f]</sup> For certain amino acids the prospect of monitoring details of the structural evolution 4 In the present work, the procedure reported previously[5, 11, 12] has been carried out inside an NMR spectrometer, exploiting in situ solid-state NMR techniques to monitor the 31 glycine, reported by Xu et al. in 2017.<sup>[5]</sup> structural evolution, as a function of temperature and time, of 31 32 In general, crystallization of glycine from pure aqueous the glycine/water glass formed after flash cooling an aqueous 32 solution of glycine. In recent years, in situ NMR techniques for monitoring crystallization processes have been applied to 35 lization from water in nano-confined environments promotes a range of systems,<sup>[13]</sup> including crystallization of glycine from  $35$ aqueous solution near ambient temperature.<sup>[13a,b]</sup> A significant advantage of solid-state NMR spectroscopy for in situ studies of such processes is that it allows the identification and characterization of both amorphous and crystalline phases. Thus, the in situ solid-state NMR study presented here offers the prospect of monitoring details of the structural evolution **from the glycine/water glass phase to the dihydrate of glycine** 42 43  $\frac{1}{2}$  and then to the  $\beta$  polymorph of glycine. Furthermore, a range 43  $44$   $^{14}$   $^{17}$  F. Gerrela viogno, Dr. G. Monica, M. Juramy, Froi. 5. viei,<br>
of modern solid-state NMR techniques are exploited to  $44$  $\frac{45}{45}$  Aix Marseille Univ. CNRS. ICR elucidate specific structural aspects of the solid phases present  $\frac{45}{45}$ 

47 **E**-mail: pierre thureau@univ-amu fr **OUR** SULFER 13 COUR in situ solid-state <sup>13</sup>C NMR study used a sample of 47 48 Dr. C. E. Hughes, Dr. P. A. Williams, Prof. K. D. M. Harris glycine  $^{13}$ C-labelled in the carboxylate group (1-<sup>13</sup>C-glycine; 48 School of Chemistry, Cardiff University **1996** Scheme 1); thus, we focus on the carboxylate region of the 49

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1 prepared at ambient temperature was flash cooled in a few 1 2 seconds to ca. 145 K inside the NMR spectrometer. The  $\sim$  6  $\mu$   $\sim$  2 3 frozen glycine/water solution was then warmed slowly  $\frac{1}{222K}$  3  $4$  (2 Kmin<sup>-1</sup>) and <sup>1</sup>H $\rightarrow$ <sup>13</sup>C CPMAS NMR spectra were  $4$ recorded (MAS frequency, 8 kHz[14]) at several (fixed) 5 5 6 temperatures during warming (Figure 1). At lower temper-



215 K. The spectra were recorded at: (a) 165 K, (b) 175 K, (c) 210 K, (d) 211 K (recorded immediately on reaching this temperature), (e) 211 K (recorded after 3 min at this temperature) and (f) 215 K (recorded after 25 min at this temperature).

 $36$  173.9 ppm is observed and is attributed to the glycine/water determined from the powder XRD data as a dihydrate of  $36$  $37$  glass phase. However, on warming to 211 K, a significantly glycine (GDH). On further warming of the sample to 250 K,  $37$ 38 sharper peak appears at 173.5 ppm, with gradual loss of the the powder XRD pattern of GDH disappeared and was 38 broad peak due to the glass phase. The position of the sharp 40 peak does not match the <sup>13</sup>C NMR spectra of the  $\alpha$ ,  $\beta$ , or  $\gamma$  similarity between our results and those of Xu et al.<sup>[5]</sup> 40 polymorphs of glycine under similar operating conditions (see Figure S1 and Table S1; Supporting Information). 39 broad peak due to the glass phase. The position of the sharp replaced by that of the  $\beta$  polymorph of glycine.<sup>[5,16]</sup> Given the 39 4 polymorphs of glycine under similar operating conditions (see concerning the evolution of solid phases starting from the 4 42 Figure S1 and Table S1; Supporting Information). glycine/water glass phase, progressing to a new crystalline 42

Similar behavior is observed in in situ  ${}^{1}H \rightarrow {}^{15}N$  CPMAS 44 NMR spectra for an aqueous solution (1.8 m) of <sup>15</sup>N-labelled that the new crystalline phase giving the <sup>13</sup>C NMR signal at 44 glycine subjected to the same temperature schedule (Fig- $46$  ure S3). The isotropic <sup>15</sup>N chemical shift (30.3 ppm) of the GDH.  $46$  $47$  crystalline phase that emerges at 211 K is clearly distinct from We now consider specific structural aspects of GDH  $47$ 48 those of the  $\alpha$ ,  $\beta$  and  $\gamma$  polymorphs of glycine (Figure S2 and inferred from our in situ NMR studies and results from 48 Table S2).[15] 45 glycine subjected to the same temperature schedule (Fig- 173.5 ppm and the <sup>15</sup>N NMR signal at 30.3 ppm in our work is 45 A Table S2).<sup>[15]</sup> additional NMR experiments, which further support this 49

at a different set of temperatures are shown in Figure 2. After 52 flash cooling the aqueous solution of 1<sup>-13</sup>C-glycine and then molecule of glycine in the asymmetric unit  $(Z = 1)$ . Our solid-52 warming to 210 K, the sharp peak due to the new crystalline phase again appears at 173.5 ppm (Figure 2 a). However, after a total of 375 min at 210 K, a new peak emerges at 175.3 ppm, 56 characteristic of the  $\beta$  polymorph (Figure 2b). The trans-  $NH_3^+$  environments. 56  $57$  formation to the β polymorph continues even on reducing the Second, a significant feature of the reported crystal  $57$ 58 temperature to 205 K (Figure 2c,d) and continues more structure of GDH<sup>[5]</sup> is that glycine molecules are hydrogen- 58 5 at a different set of temperatures are shown in Figure 2. After First, the reported crystal structure of GDH<sup>[5]</sup> has one 5 53 warming to 210 K, the sharp peak due to the new crystalline state NMR results are fully consistent with this assignment, as 53 54 phase again appears at 173.5 ppm (Figure 2a). However, after the  ${}^{1}H\rightarrow {}^{13}C$  and  ${}^{1}H\rightarrow {}^{15}N$  CPMAS NMR spectra of GDH 54 55 a total of 375 min at 210 K, a new peak emerges at 175.3 ppm, contain only one isotropic peak for each of the  $CO_2^-$ , CH<sub>2</sub> and 55



Figure 2. <sup>1</sup>H<sup>13</sup>C CPMAS NMR spectra for an aqueous solution of 1<sup>-13</sup>C-20 **h h b**  $\frac{1}{20}$  **h h**  $\frac{1}{20}$  **h**  $\frac{1}{2$ 210 K. The spectra were recorded according to the following time/  $21$  $\frac{22}{}$  after 150 min at 210 K, (b) after a further  $\frac{22}{}$ 23 **a 2**  $\frac{1}{165 \text{ K}}$  **225** min at 210 K, (c) after 360 min at 205 K, (d) after a further 23  $\frac{24}{100}$  285 min at 205 K, (e) after 50 min at 210 K and then 50 min at 212 K, and (f) after 50 min at 222 K.

the experiment (at 222 K), the transformation to the  $\beta$ polymorph is virtually complete. 27 Figure 1.  $H \rightarrow B$  CPMAS NMR spectra for an aqueous solution of 1- the experiment (at 222 K), the transformation to the  $\beta$  27  $28$  <sup>13</sup>C-glycine following flash cooling to 145 K and then slow warming to polymorph is virtually complete.  $28$ 

35 atures (e.g., 165 K; Figure 1a), a broad signal centered at and the crystal structure of the new crystalline phase was  $35$ 29 215 K. The spectra were recorded at: (a) 165 K, (b) 175 K, (c) 210 K, The evolution of the solid crystalline phases observed in 29  $\frac{30}{18}$  (d) 211 K (recorded immediately on reaching this temperature), our in situ solid-state NMR studies mirrors the behavior  $\frac{30}{18}$  $\frac{1}{3}$  (e) 211 K (recorded after 3 min at this temperature) and (f) 215 K reported in the powder XRD study of Xu et al.<sup>[5]</sup> In their  $\frac{3}{1}$  $32$  (recorded and  $25$  mm at this temperature). work, using the same procedure<sup>[11,12]</sup> of flash cooling an  $32$ aqueous solution of glycine below 145 K followed by slow 33 34 warming to 209 K, a new powder XRD pattern was observed 34 and the crystal structure of the new crystalline phase was determined from the powder XRD data as a dihydrate of glycine (GDH). On further warming of the sample to 250 K, the powder XRD pattern of GDH disappeared and was similarity between our results and those of  $Xu$  et al.<sup>[5]</sup> 43 Similar behavior is observed in in situ  ${}^{1}H \rightarrow {}^{15}N$  CPMAS phase and then to the  $\beta$  polymorph of glycine, we conclude 43 that the new crystalline phase giving the  $^{13}$ C NMR signal at GDH.

50 The results from another in situ solid-state <sup>13</sup>C NMR study assignment. 50 We now consider specific structural aspects of GDH inferred from our in situ NMR studies and results from assignment.

> molecule of glycine in the asymmetric unit  $(Z' = 1)$ . Our solid- $NH<sub>3</sub><sup>+</sup>$  environments.

59 rapidly at higher temperatures (Figure 2e,f). By the end of bonded only to water molecules, with no direct glycine- 59 Second, a significant feature of the reported crystal structure of  $GDH^{[5]}$  is that glycine molecules are hydrogenbonded only to water molecules, with no direct glycine-

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glycine hydrogen-bonding. To investigate whether the mate-

 $\frac{1}{20}$  rigure 3. H. C. HETCOR spectrum recorded at 212 K after hash  $\frac{12}{10}$  and then slow  $\begin{array}{ccc}\n 20 & \text{cosmig at a question of 1} \\
 \hline\n 20 & \text{warming to 212 K. Homonuclear} \\
 \hline\n 31 & \text{cosmig to 212 K. Homonuclear} \\
 \end{array}$  H decoupling was applied during t<sub>1</sub> and a mixing time of 0.5 ms was used under Lee-Goldburg conditions.  $\frac{1}{2}$   $\frac{1}{2}$   $\frac{1}{2}$  21  $22$  This spectrum was recorded during the in situ study shown in Figure 2  $\frac{5}{2}$ 23 (corresponding to the period of 50 min at which the sample was at  $\Xi^{-0.2}$  and  $\Xi^{-0.2}$  and  $\cal N$  and  $\cal N$  and  $\cal N$  and  $\cal N$  $24$  212 K; see caption of Figure 2 e). Clearly some transformation of GDH  $\overline{a}$ 25 into the  $\beta$  polymorph occurred during measurement of this spectrum<br>  $\begin{array}{ccc}\n25 & 0.1\n\end{array}$ (as confirmed from  ${}^{1}H \rightarrow {}^{13}C$  CPMAS NMR spectra recorded before and after the <sup>1</sup>H-<sup>13</sup>C HETCOR experiment). The extracted <sup>1</sup>H NMR<br>26 and after the <sup>1</sup>H-<sup>13</sup>C HETCOR experiment). The extracted <sup>1</sup>H NMR  $\frac{27}{\text{spectra of GDH and the } \beta \text{ polymorph are shown at the right hand side}$   $\alpha \beta = 0.0$   $\beta \beta \gamma$  $\frac{28}{10}$  (<sup>1</sup>H chemical shifts of GDH: 2.5 ppm, CH<sub>2</sub>; 8 ppm, NH<sub>3</sub><sup>+</sup>; 5 ppm,  $\frac{1}{2}$  0.0 0.5 1.0 1.5 28  $H_2O$ ).

tively) on this material and the material (assigned as the  $\beta$  $\frac{1}{3}$  polymorph) to which it transforms over time. In the  ${}^{1}H^{-13}C$  (b), in each case containing its set of the line o  $\frac{34}{24}$  HETCOR spectrum (Figure 3), a strong correlation peak is  $\frac{1}{2}$  (regular band line) and the q polymerph (black line) are also shown 35 observed between the  $CO_2^-$  group of glycine (<sup>13</sup>C) and water  $36$  molecules ( $^1$ H), consistent with glycine and water molecules  $36$  $37$  in intimate proximity in a crystalline phase. In contrast, for build-up curve for GDH (containing 1-<sup>13</sup>C-glycine). The  $37$ the phase  $(\beta$  polymorph) into which GDH transforms over time, no correlation peak is observed between the carboxylate 40 group of glycine (<sup>13</sup>C) and water molecules (<sup>1</sup>H), fully between labelled  ${}^{13}CO_2^-$  sites in this material, which depend 40 4 consistent with the assignment that this phase is not a hydrate on the intermolecular  ${}^{13}$ C ${}^{...}{}^{13}$ C distances between carboxylate 4  $1$ phase of glycine. Together with the other evidence presented 43 above, these observations are fully consistent with the assign- GDH, calculated from the intermolecular  ${}^{13}$ C ${}^{13}$ C distances 43 ment that the initially formed crystalline phase is GDH, which 45 transforms over time to the (anhydrous)  $\beta$  polymorph of Figure 4. The agreement between experimental and calcu- 45 46 glycine. We note that, for the  $\beta$  polymorph, no correlation lated dipolar build-up curves is excellent, giving strong 46 47 peak is observed between <sup>1</sup>H in the NH<sub>3</sub><sup>+</sup> group and <sup>13</sup>C in the corroboration that the hydrated crystalline phase of glycine 47 48  $CO_2^-$  group as a consequence of rotational motion of the observed in our in situ NMR study is indeed GDH. 48  $49$  NH<sub>3</sub><sup>+</sup> group. As discussed in SI, three resonances are To illustrate that the <sup>13</sup>C-<sup>13</sup>C dipolar build-up curve is 49 50 observed for the NH<sub>3</sub><sup>+</sup> group in the <sup>1</sup>H NMR spectrum of sensitive to structural properties, Figure 4 also shows exper- 50 5 the β polymorph at 200 K, but coalescence occurs in the imental and calculated <sup>13</sup>C-<sup>13</sup>C dipolar build-up curves for 1-51 52 temperature regime around 212 K due to rotation of the NH<sub>3</sub><sup>+ 13</sup>C-glycine in a different material (the  $\alpha$  polymorph). 52 53 group, producing a very broad peak that is not seen in the Again, good agreement is observed between experimental  $53$ 54 contour plot in Figure 3. We note that rotational dynamics of and calculated data. The fact that the DQF/ZQF curve builds  $54$  $NH<sub>3</sub><sup>+</sup>$  groups has been observed for several amino acids in the 56 solid state,<sup>[17]</sup> including the  $\alpha$  and  $\gamma$  polymorphs of glyci-consistent with the intermolecular <sup>13</sup>C<sup>...13</sup>C distances being 56 ne.[17a, d] 38 the phase ( $\beta$  polymorph) into which GDH transforms over dependence of the <sup>13</sup>C-<sup>13</sup>C dipolar build-up curve on the 38 39 time, no correlation peak is observed between the carboxylate recoupling time  $\tau_{DQ}$  depends only on the <sup>13</sup>C-<sup>13</sup>C couplings 39 42 phase of glycine. Together with the other evidence presented groups. The theoretical <sup>13</sup>C-<sup>13</sup>C dipolar build-up curve for 42 44 ment that the initially formed crystalline phase is GDH, which in the reported crystal structure of GDH,<sup>[5]</sup> is also shown in 44  $55$  NH<sub>3</sub><sup>+</sup> groups has been observed for several amino acids in the up more slowly for GDH than for the  $\alpha$  polymorph is 55  $57$  ne.<sup>[17a,d]</sup> higher in GDH, as the glycine molecules are separated by  $57$ S2 tively) on this material and the material (assigned as the  $\beta$  ted against recoupling time  $\tau_{DQ}$  for GDH ( $\bullet$ ) and the  $\alpha$  polymorph 32<br>33 spolymorph) to which it transforms over time. In the <sup>1</sup>H-<sup>13</sup>C-( $\bullet$ ), i

The corresponding  ${}^{1}H-{}^{15}N$  HETCOR spectrum (Fig-

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2 rial assigned as GDH in our in situ NMR study is consistent supporting our assignment that the initially formed crystalline  $2$ 3 with this feature, we have carried out 2D  $^1H^{-13}C$  and  $^1H^{-15}N$  phase contains glycine and water molecules in intimate 3 4 HETCOR experiments at 212 K (Figures 3 and S4, respec-<br>proximity and consistent with the assignment of this phase 4 <sup>1</sup> glycine hydrogen-bonding. To investigate whether the mate-<br>group of glycine  $(^{15}N)$  and water molecules  $(^{1}H)$ , further supporting our assignment that the initially formed crystalline phase contains glycine and water molecules in intimate proximity and consistent with the assignment of this phase

as GDH.



 $\frac{1}{31}$  Figure 4. Experimental <sup>13</sup>C-<sup>13</sup>C DQF/ZQF dipolar build-up curves plot-  $\frac{1}{31}$ ted against recoupling time  $\tau_\text{DQ}$  for GDH ( $\bullet$ ) and the  $\alpha$  polymorph dipolar build-up curves calculated for the crystal structures of GDH (grey dashed line) and the  $\alpha$  polymorph (black line) are also shown.

build-up curve for GDH (containing  $1<sup>-13</sup>C$ -glycine). The between labelled  ${}^{13}CO_2^-$  sites in this material, which depend on the intermolecular  ${}^{13}$ C···<sup>13</sup>C distances between carboxylate GDH, calculated from the intermolecular  ${}^{13}$ C ${}^{...13}$ C distances Figure 4. The agreement between experimental and calculated dipolar build-up curves is excellent, giving strong corroboration that the hydrated crystalline phase of glycine observed in our in situ NMR study is indeed GDH.

59 ure S4) also shows a correlation peak between the NH<sub>3</sub><sup>+</sup> distance:  $\alpha$  polymorph, 3.10 Å; GDH, 3.81 Å). 59 To illustrate that the  ${}^{13}C_{1}{}^{13}C_{1}$  dipolar build-up curve is sensitive to structural properties, Figure 4 also shows experimental and calculated  ${}^{13}C_{1}{}^{13}C_{1}$  dipolar build-up curves for 1-<sup>13</sup>C-glycine in a different material (the  $\alpha$  polymorph). Again, good agreement is observed between experimental and calculated data. The fact that the DQF/ZQF curve builds consistent with the intermolecular  ${}^{13}$ C···<sup>13</sup>C distances being 58 The corresponding  ${}^{1}H {}^{15}N$  HETCOR spectrum (Fig- intervening water molecules (shortest internuclear  ${}^{13}C {}^{...13}C$  58 distance:  $\alpha$  polymorph, 3.10 Å; GDH, 3.81 Å).

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1 Our results demonstrate the advantages of exploiting [8] B.D. Hamilton, M. A. Hillmyer, M. D. Ward, Cryst. Growth Des. 1 2 in situ solid-state NMR techniques to elucidate details of  $2008, 8, 3368 - 3375$ . 3 structural evolution during crystallization processes, reporting  $[9]$  a) G. Kartha, A. de Vries, Nature 1961, 192, 862–863; b) I.L. 4 the first application of such techniques to explore crystalli-<br>  $\frac{\text{Karte, J. Karte, Acta Crystallogr. 1964, 17, 835-841; C) M. N.}}{\text{EVAL}}$  $\frac{1}{2}$  zation of an organic material within a glass phase ("frozen  $\frac{1}{2}$ " mustelless Red P. 200 274, 200 274, 200 35 Supplementally in the Pedmont of Decking  $\frac{1}{2}$  $\frac{1}{2}$  solution") formed on flash cooling a liquid solution. Impor-<br>  $\frac{1}{2}$  abban. M. Viiavan I Biomal Struct Dyn 1994. Il 1425  $\frac{1}{435}$  and  $\frac{1}{435}$  and  $\frac{1}{435}$  and  $\frac{1}{435}$  and  $\frac{1}{435}$  existence of GDH as  $\frac{1}{435}$  existence of GDH 8 a crystalline intermediate on the transformation pathway Gaisford, K.D.M. Harris, J. Phys. Chem. C 2013, 117, 12136 -  $8$  $\degree$  from the glycine/water glass phase to the β polymorph, and 12145; f) P. A. Williams, C. E. Hughes, J. Martin, E. Courvoisier,  $\degree$ 10 highlight the complementarity between our in situ solid-state A.B.M. Buanz, S. Gaisford, K.D.M. Harris, J. Phys. Chem. C 10 11 NMR strategy<sup>[21]</sup> and the in situ powder XRD approach that  $\frac{2016}{2016}$ ,  $\frac{120}{385}$  –9392. 2 was first used to identify this new solid phase of glycine very  $\frac{100 \text{ a}}{25}$ . Courvoisier, P.A. Williams,  $\frac{0.026 \text{ a}}{25}$ ,  $\frac{0.026 \text{ a}}{25}$ ,  $\frac{0.026 \text{ a}}{25}$ ,  $\frac{0.026 \text{ a}}{25}$ ,  $\frac{0.026 \text{ a}}{25}$ 13 recently.<sup>[5]</sup> Clearly, a major objective is now to establish  $\frac{N.D. M. Harris, *Chem. Commun. 2012, 46, 2/01-2/03*; 0) P.A.$ 14 whether GDH serves any role in mechanistic pathways for the  $\frac{14}{2015}$  54.3973-3977; Angely Chem. 2015 127 4045-4049  $\frac{15}{2}$  crystallization of glycine from aqueous solution under ambi-<br>1111 A. Pyne. R. Survanaravanan. *Pharm. Res* 2001. 18. 1448–1454. ent conditions. This paper reported DSC measurements on a quenched glycine/ 16

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2. We thank Bruker SAS for access to the solid-state NMR  $\frac{p}{121 \text{ N.V}}$  suppresents of  $\frac{p}{N}$  at interior  $\frac{N}{N}$  Melineurly, A.C. 2.1 22 spectrometer used here and Dr F. Aussenac and Dr P. Dorffer  $\frac{1+2}{1+2}$  in the spectrometer of  $\frac{1+2}{1+2}$  in the spectrometer of  $\frac{1+2}{1+2}$  in the spectrometer of  $\frac{1}{2}$  and  $\frac{1}{2}$ 23 for experimental assistance. This work was supported by the  $\overline{A} \cdot S$  Yunoshev E.V. Boldvreva *J. Chem. Phys.* 2012 137 23 24 French National Research Agency grant ANR-13-JS080001 665103. 24 and by Cardiff University. K.D.M.H. is grateful to Dr Tony 25 and by Cardiff University. K.D.M.H. is grateful to Dr Tony [13] a) C. E. Hughes, K. D. M. Harris, [J. Phys. Chem. A](https://doi.org/10.1021/jp805182v) 2008, 112, 25

### Conflict of interest

Keywords: crystallization · glycine · polymorphism · solid-state NMR spectroscopy · structural transformation

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 $\frac{5}{2}$  [21] We note that in situ solid-state NMR allows direct observation (in an isotope-specific manner) of the crystalline and amorphous Manuscript received: January 26, 2018 phases present in the system as a function of time, yielding Revised manuscript received: March 1, 2018 8 information on specific structural and dynamic aspects of these Accepted manuscript online: April 6, 2018 phases. By focusing on in situ <sup>13</sup>C and <sup>15</sup>N NMR, our measure-<br>  $\sqrt{ }$  Version of record online:  $\blacksquare \blacksquare \blacksquare$ ,  $\blacksquare \blacksquare \blacksquare$ 

ments selectively detect only the phases that contain glycine. Thus, our results are not complicated by the fact that pure ice phases may be present in significant amounts during the processes studied here.

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## **Communications**



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Insights into the Crystallization and by In Situ Solid-State NMR Spectroscopy



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#### Kristallisation

P. Cerreia Vioglio, G. Mollica, M. Juramy, C. E. Hughes, P. A. Williams, F. Ziarelli, S. Viel, P. Thureau,\* K. D. M. Harris\* **\_\_\_\_\_\_\_\_\_\_\_ |||||-||||** 

Insights into the Crystallization and Structural Evolution of Glycine Dihydrate by In Situ Solid-State NMR Spectroscopy



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