

Trimeric Cyclamers: Hierarchical High Z' Crystal Engineering Based on Guest Structure and Basicity

Stuart R. Kennedy, Adeline Miquelot, Juan Aguilar-Malavia and Jonathan W. Steed*

Department of Chemistry, Durham University, University Science Laboratories, South Road, Durham, DH1 3LE. E-mail: jon.steed@durham.ac.uk; Fax: +44(0)191 384 4737; Tel: +44 (0)191 334 2085

Supplementary information

Synthesis of 5-ureidosalicylic acid (1).

A suspension of 5-aminosalicylic acid (3.00 g, 19.6 mmol) in acetonitrile (300 mL) was treated with 96% ethanol (4.5 mL) and trimethylamine (6 mL) under a dynamic nitrogen atmosphere. After stirring for 30 min at room temperature sodium cyanate (1.274 g, 19.6 mmol) was added and the mixture stirred at 95 °C for 48 h. The resulting pale precipitate was isolated by filtration and immediately added to aqueous hydrochloric acid (5 M). The suspension was sonicated for 25 min filtered to yield an off white precipitate. This material was air dried for 3 days and then further dried under vacuum at 110 °C to yield the product as an off white powder (1.72 g, 8.77 mmol, 57 %). ^1H NMR (400 MHz, DMSO- d_6): 13.81 (1H, br, s, COOH), 10.85 (1H, s, ArOH), 8.70 (1H, s, ArNH), 7.89 (1H, d, $J=2.8$ Hz, ArH), 7.47 (1H, dd, $J = 8.8$ & 2.8 Hz, ArH), 6.84 (1H, d, $J = 8.8$, ArH), 5.85 (2H, s, NH₂). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO- d_6): 172.4, 156.7, 156.2, 133.0, 126.9, 119.3, 117.4, 112.8. IR (solid, ν / cm^{-1}): 3460w (OH), 3323w, 3146w (NH), 1664s, 1654s (C=O), 1632m, 1560m (NH), 1493m (C=C), 1235m (CO). Anal. Calc. for C₈H₁₁N₂O₄·1.5H₂O: C, 42.93; H 4.05; N, 12.87 %. Found: C, 43.05; H, 4.97; N, 12.55 %.

Crystallographic data

Crystal data for **1**: C₈H₈N₂O₄, $M = 196.16$, colourless plate, $0.099 \times 0.077 \times 0.043$ mm³, triclinic, space group (No. 2), $a = 4.7242(12)$, $b = 12.369(3)$, $c = 13.831(3)$ Å, $\alpha = 90$, $\beta = 82.466(8)$, $\gamma = 90^\circ$, $V = 801.2(3)$ Å³, $Z = 4$, $D_c = 1.626$ g/cm³, $F_{000} = 408$, Bruker D8 Venture, MoK α radiation, $\lambda = 0.71073$ Å, $T = 173(2)$ K, $2\theta_{\text{max}} = 46.6^\circ$, 6579 reflections collected, 1154 unique ($R_{\text{int}} = 0.1669$). Final $\text{Goof} = 1.146$, $RI = 0.1138$, $wR2 = 0.1711$, R indices

based on 719 reflections with $I > 2\sigma(I)$ (refinement on F^2), parameters, restraints. Lp and absorption corrections applied, $\mu = 0.133 \text{ mm}^{-1}$. Poor precision and low resolution is because of the extremely small crystal size and hence weak diffraction.

Crystal data for **1**·THF: $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5$, $M = 268.27$, colourless block, $0.30 \times 0.25 \times 0.10 \text{ mm}^3$, monoclinic, space group $P2_1/c$ (No. 14), $a = 22.3090(19)$, $b = 19.1478(16)$, $c = 9.0100(8) \text{ \AA}$, $\beta = 91.398(3)^\circ$, $V = 3847.6(6) \text{ \AA}^3$, $Z = 12$, $D_c = 1.389 \text{ g/cm}^3$, $F_{000} = 1704$, Bruker D8 Venture, MoK α radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 120(2)\text{K}$, $2\theta_{\text{max}} = 49.7^\circ$, 43079 reflections collected, 6619 unique ($R_{\text{int}} = 0.0930$). Final $\text{Goof} = 0.989$, $RI = 0.0605$, $wR2 = 0.1375$, R indices based on 4236 reflections with $I > 2\sigma(I)$ (refinement on F^2), 514 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.109 \text{ mm}^{-1}$.

Crystal data for **1**·MeCN: $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_4$, $M = 237.22$, Colourless Block, $0.38 \times 0.32 \times 0.12 \text{ mm}^3$, triclinic, space group $P-1$ (No. 2), $a = 13.3689(18)$, $b = 15.143(2)$, $c = 18.786(3) \text{ \AA}$, $\alpha = 77.079(3)$, $\beta = 74.563(4)$, $\gamma = 63.839(3)^\circ$, $V = 3265.4(8) \text{ \AA}^3$, $Z = 12$, $D_c = 1.448 \text{ g/cm}^3$, $F_{000} = 1488$, Bruker D8 Venture, MoK α radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 120(2)\text{K}$, $2\theta_{\text{max}} = 46.7^\circ$, 26914 reflections collected, 9285 unique ($R_{\text{int}} = 0.1028$). Final $\text{Goof} = 1.034$, $RI = 0.0892$, $wR2 = 0.2027$, R indices based on 5891 reflections with $I > 2\sigma(I)$ (refinement on F^2), 925 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.114 \text{ mm}^{-1}$.

Crystal data for **1**·(CH₃)₂CO: $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_5$, $M = 254.24$, colourless block, $0.33 \times 0.11 \times 0.07 \text{ mm}^3$, monoclinic, space group $P2_1/n$ (No. 14), $a = 14.6759(9)$, $b = 31.2850(19)$, $c = 15.9269(10) \text{ \AA}$, $\beta = 99.324(2)^\circ$, $V = 7216.0(8) \text{ \AA}^3$, $Z = 24$, $D_c = 1.404 \text{ g/cm}^3$, $F_{000} = 3216$, Bruker D8 Venture, MoK α radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 120(2)\text{K}$, $2\theta_{\text{max}} = 44.14^\circ$, 63443 reflections collected, 8899 unique ($R_{\text{int}} = 0.1104$). Final $\text{Goof} = 1.055$, $RI = 0.0790$, $wR2 = 0.1799$, R indices based on 5728 reflections with $I > 2\sigma(I)$ (refinement on F^2), 985 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.112 \text{ mm}^{-1}$.

Crystal data for **1**·0.7C₆H₅NO₂: $\text{C}_{12.2} \text{H}_{11.5} \text{N}_{2.7} \text{O}_{5.4}$, $M = 282.34$, yellow needle, $0.100 \times 0.010 \times 0.001 \text{ mm}^3$, tetragonal, space group $P-42_1c$ (No. 114), $V = 2311.8(7) \text{ \AA}^3$, $Z = 8$, $D_c = 1.622 \text{ g/cm}^3$, $F_{000} = 1174$, Diamond I19, Synchrotron radiation, $\lambda = 0.6889 \text{ \AA}$, $T = 296(2)\text{K}$, $2\theta_{\text{max}} = 54.6^\circ$, 22865 reflections collected, 2853 unique ($R_{\text{int}} = 0.0559$). Final $\text{Goof} = 1.030$, $RI = 0.0749$, $wR2 = 0.1999$, R indices based on 2613 reflections with $I > 2\sigma(I)$ (refinement on F^2), 129 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.122 \text{ mm}^{-1}$. Absolute structure parameter = 0.7(3).

Crystal data for **1**·(4-picoline)₂: $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_4$, $M = 382.42$, colourless block, $1.15 \times 0.07 \times 0.07 \text{ mm}^3$, triclinic, space group $P-1$ (No. 2), $a = 4.5668(4)$, $b = 20.5310(16)$, $c = 20.9009(16) \text{ \AA}$, $\alpha = 76.149(2)$, $\beta = 88.228(3)$, $\gamma = 88.156(3)^\circ$, $V = 1901.2(3) \text{ \AA}^3$, $Z = 4$, $D_c = 1.336 \text{ g/cm}^3$, $F_{000} = 808$, Bruker D8 Venture, MoK α radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 120(2)\text{K}$, $2\theta_{\text{max}} = 49.6^\circ$, 21149 reflections collected, 6528 unique ($R_{\text{int}} = 0.0829$). Final $\text{Goof} = 0.996$, $RI = 0.0653$, $wR2 = 0.1367$, R indices based on 4312 reflections with $I > 2\sigma(I)$ (refinement on F^2), 509 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.095 \text{ mm}^{-1}$.

Crystal data for **1**·H₂O: $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_5$, $M = 214.18$, colourless plate, $0.184 \times 0.103 \times 0.054 \text{ mm}^3$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 4.5426(19)$, $b = 10.729(5)$, $c = 18.692(8) \text{ \AA}$, $V = 911.0(7) \text{ \AA}^3$, $Z = 4$, $D_c = 1.562 \text{ g/cm}^3$, $F_{000} = 448$, Bruker D8 Venture, MoK α radiation, $\lambda = 0.71073 \text{ \AA}$, $T = 153(2)\text{K}$, $2\theta_{\text{max}} = 49.7^\circ$, 9640 reflections collected,

1573 unique ($R_{\text{int}} = 0.1211$). Final $GooF = 1.042$, $RI = 0.0555$, $wR2 = 0.1122$, R indices based on 1138 reflections with $I > 2\sigma(I)$ (refinement on F^2), 165 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.132 \text{ mm}^{-1}$. Absolute structure parameter = 1.6(10).

DOSY NMR

The DOSY NMR spectrum of compound **1** in acetone- d_6 at 25°C in the presence of *o*-xylene as an internal reference is shown in Figure S1. This experiment yielded the following diffusion coefficients (D):

Compound **1**: $15.64 \pm 0.06 \text{ m}^2\text{s}^{-1}$

o-xylene: $32.0 \pm 0.2 \text{ m}^2\text{s}^{-1}$

Acetone: $41.7 \pm 0.3 \text{ m}^2\text{s}^{-1}$. A value of $41.5 \text{ m}^2\text{s}^{-1}$ has been reported by M. Holz, X. a. Mao, D. Seiferling and A. Sacco in *J. Chem. Phys.*, 1996, **104**, 669.

The pulse sequence used was the convection compensated DBPPSTE (Bipolar gradient pulses stimulated echo sequence). *J. Magn. Reson. Ser. A*, 115, 260-264 (1995) and *J. Magn. Reson.* 125, 372-375 (1997).

Based on this data the method of Morris and coworkers (R. Evans, Z. Deng, A. K. Rogerson, A. S. McLachlan, J. J. Richards, M. Nilsson and G. A. Morris, *Angew. Chem., Int. Ed.*, 2013, **52**, 3199.) was used to calculate the approximate molecular mass (MW) of each species in this medium using the equation given below. In addition to experimental D values this method requires knowledge of effective molecular density (ρ_{eff}), solvent viscosity (η) and temperature (T). MW_s is the molar mass of the solvent.

$$D = \frac{k_B T \left(\frac{3\alpha}{2} + \frac{1}{1+\alpha} \right)}{6\pi\eta \sqrt[3]{\frac{3MW}{4\rho_{\text{eff}}N_A}}}, \text{ where } \alpha = \sqrt[3]{\frac{MW_s}{MW}}$$

The viscosity of acetone- d_6 at 25 °C (0.326 cP) was taken from M. Holz, X. a. Mao, D. Seiferling and A. Sacco in *J. Chem. Phys.*, 1996, **104**, 669.

The density of acetone- d_6 (0.872 g/mL) was obtained from the manufacturer, Sigma-Aldrich <http://www.sigmaaldrich.com/catalog/product/aldrich/444855?lang=en®ion=GB>

This method yielded molecular masses of 55.5 – 57.0 g mol⁻¹, for acetone, 91.0 – 93.2 g mol⁻¹ for *o*-xylene, and 385.4 – 391.8 g mol⁻¹ for compound **1**. The molecular mass of the dimer is 392.4 g mol⁻¹ and that of the trimer is 588.6 g mol⁻¹.

These values compare to the actual molecular weight of acetone- d_6 : 64.1 g mol⁻¹, acetone- d_4 (the species actually observed in the NMR experiment): 62.1 g mol⁻¹ and *o*-xylene: 106 g mol⁻¹ implying an underestimation by a factor of 1.15. Correcting for this systematic under-estimation in the acetone and *o*-xylene masses would give an average value of 446.9 g mol⁻¹ for **1**.

Both the measured and corrected values for **1** are closer to a dimer than a trimer but far from the mass of a monomer. This data can be interpreted as meaning that **1** is in essentially 100% dimer form in acetone at 25 °C. However this would imply a very high dimerization constant for **1** and would not explain the very broad nature of the OH and

NH protons in acetone (see Figure S2), which then sharpen on addition of DMSO. We interpret the observed molecular mass and other data results as implying that **1** is an equilibrating mixture of monomer, dimer and trimer under these conditions.

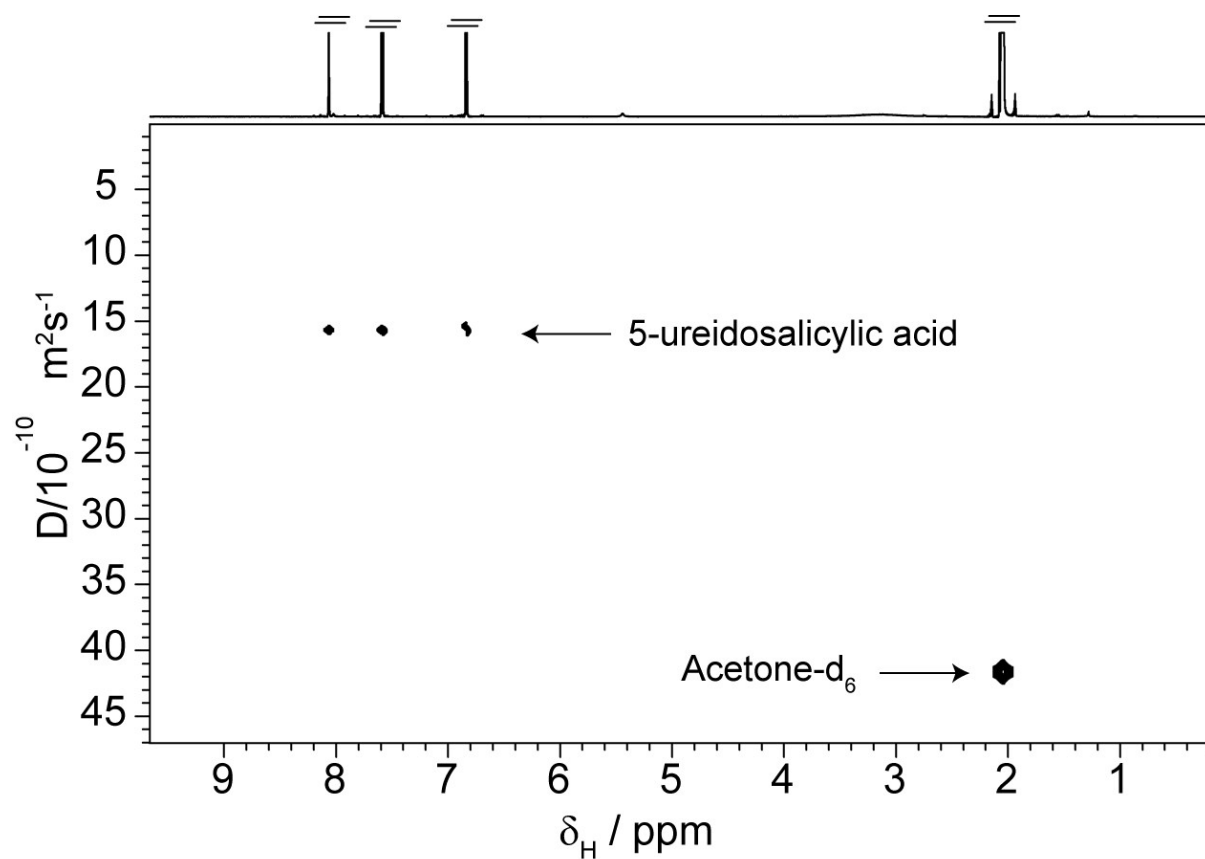


Figure S1. DOSY NMR spectrum of **1** in acetone- d_6 .

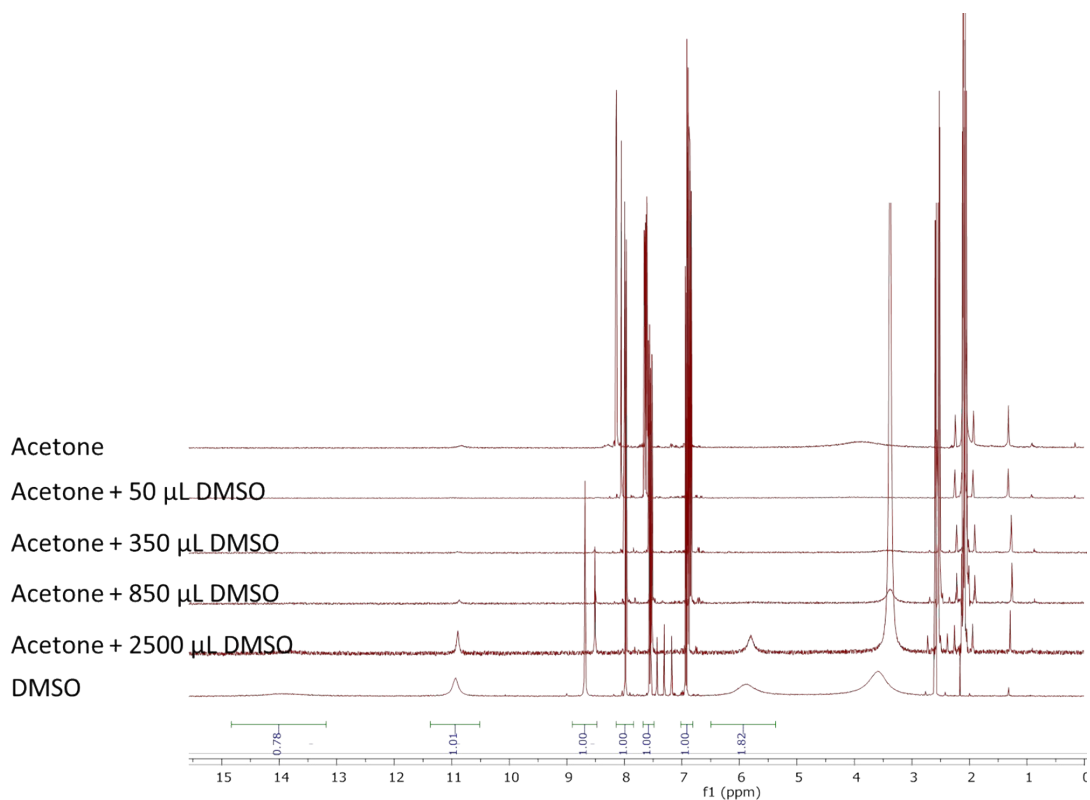


Figure S2. Addition of DMSO to an acetone- d_6 solution of **1** showing the gradual appearance of the NH and OH resonances.

ESI-MS

A075p, ESI - no column MeOH (TQD), RT 0.2349 mins, Scan# 27, NL 2.185E7, 21/01/2015 15:19, m/z [100.5-1997.7]

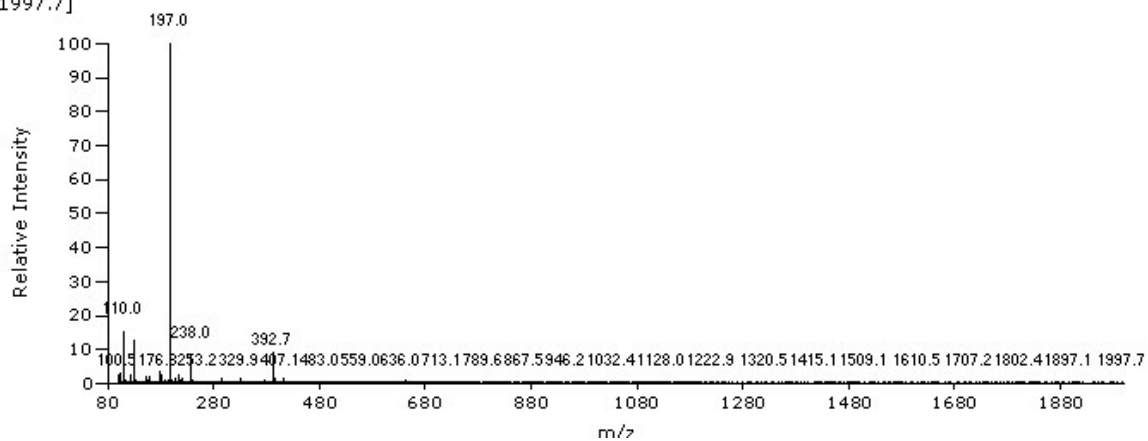


Figure S2 ESI mass spectrum of **1** ($197 \text{ M}+\text{H}^+$) showing a peak at m/z 392.7 assigned to a dimer of **1** $2\text{M}+\text{H}^+$.

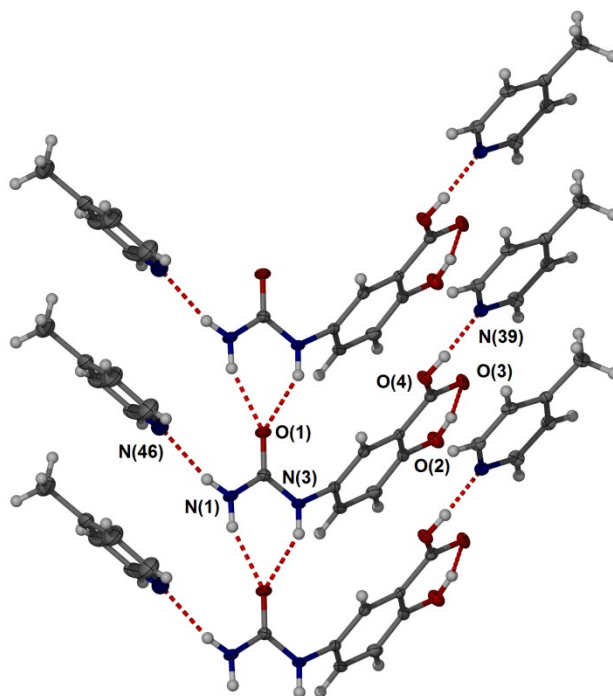


Figure S3. the picoline capped urea α -tape in $1 \cdot 2(4\text{-picoline})$. Selected hydrogen bond distances (\AA): N1 \cdots N46 2.973(4), N1 \cdots O1 2.843(3), O2 \cdots O3 2.544(3), N3 \cdots O1 2.868(3), O4 \cdots N39 2.546(3).

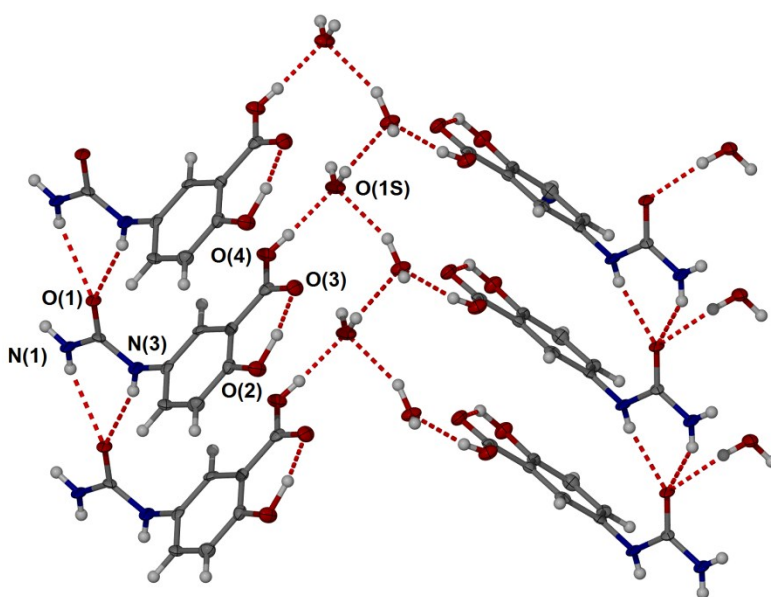


Figure S4. Crystal packing in the monohydrate $1 \cdot \text{H}_2\text{O}$. Selected intermolecular interactions (\AA): N3 \cdots O1 2.812(6), N1 \cdots O3 2.925(7), N1 \cdots O1 2.938(6), O1S \cdots O1S 2.881(5), O1S \cdots O1 2.757(6), O2 \cdots O3 2.610(5), O4 \cdots O1S 2.660(6).