**Electronic Supporting Information (ESI)†**
**for**

# Polymorph II of Hydroxyurea 150 years after its first synthesis

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## Table of Contents

## 1. List of Coformers

**Table S1.** List of coformers attempted for cocrystallization with hydroxyurea (HU) in water, methanol and ethanol solvents, and in some cases mixture of water and alcohol. Stoichiometry of HU:conformer was tried in 1:1, 1:2 and 2:1. In some cases ternary mixture was also tried in 1:1:1 ratio. Outcome is reported on the basis of cell parameter check by single crystal X-ray diffraction.

| S. No. | Coformer | S. No. | Coformer |
|---|---|---|---|
| 1. | Imidazole | 47. | 1,3,5-triazine |
| 2. | 2,3,5,6-Tetramethylpyrazine | 48. | Isonicotinic acid |
| 3. | 2,3-Diethyl-5-methylpyrazine | 49. | Isopropylamine |
| 4. | 2,3-Diethylpyrazine | 50. | Isoquinoline |
| 5. | 2,3-Dihydroxybenzoic acid | 51. | Isovaleric acid |
| 6. | 2,4-Dihydroxybenzoic acid | 52. | ketoprofen |
| 7. | 2,5-Dihydroxy-1,4-dithiane | 53. | Lactic acid |
| 8. | 2,5-Dihydroxybenzoic acid | 54. | L-Alanine |
| 9. | 2,5-Dimethylpyrazine | 55. | L-Aspartic acid |
| 10. | 2,6-Dihydroxybenzoic acid | 56. | L-Glutamine |
| 11. | 2,6-Dimethylpyrazine | 57. | L-Histidine |
| 12. | 2-Acetylpyridine | 58. | Malic acid |
| 13. | 2-Ethylpyrazine | 59. | Mefanamic acid |
| 14. | 2-Hydroxybenzoic acid | 60. | Myo-Inositol |
| 15. | 2-Picolinamide | 61. | n-Butylamine |
| 16. | 3,4-Dihydroxybenzoic acid | 62. | Niclosamide |
| 17. | 3-Hydroxybenzoic acid | 63. | Nicotinamide |
| 18. | 3-Methylcrotonic acid | 64. | Nicotinic acid |
| 19. | 4-Hydroxybenzoic acid | 65. | Niflumic acid |
| 20. | Acetamide | 66. | Nilotinib |
| 21. | Aconitic acid | 67. | Oxalic acid |
| 22. | Adipic acid | 68. | Oxoprosin |
| 23. | Albendazole | 69. | Panobinostat |
| 24. | Ascorbic acid | 70. | Pazopanib |
| 25. | Belinostat | 71. | Phenethylamine |
| 26. | Benzoic acid | 72. | Ponatinib |
| 27. | Benzamide | 73. | Propylamine |
| 28. | Butyric acid | 74. | Pyrazine |

| | | | |
|---|---|---|---|
| 29. | Isobutylamine | 75. | Pyrazine-2-carboxamide |
| 30. | Indole | 76. | Pyrazinoic acid |
| 31. | Ibuprofen | 77. | Pyridoxine |
| 32. | Caffeine | 78. | Pyruvic acid |
| 33. | Citric acid | 79. | Resorcinol |
| 34. | Dabrafenib | 80. | Sodium valproate |
| 35. | Dehydroacetic acid | 81. | Sorbic acid |
| 36. | Diclofenac | 82. | Succinic acid |
| 37. | Disodiumsuccinate hexahydrate | 83. | Tetrasodiumethylenediaminetetraacetate dihydrate |
| 38. | DL-Alanine | 84. | Thiolactic acid |
| 39. | Etodolac | 85. | Tolfenamic acid |
| 40. | Flufenamic acid | 86. | Trimethylamine |
| 41. | Flurbiprofen | 87. | Tripropylamine |
| 42. | Folic acid hydrate | 88. | Urea |
| 43. | Fumaric acid | 89. | Valproic acid |
| 44. | Hexylamine | 90. | Vanillic acid |
| 45. | Hydroquinone | 91. | Xanthine |
| 46. | Isobutyric acid | | |

## 2. Single Crystal X-ray Crystallography

Single crystal X-ray diffraction data was collected on a Bruker SMART APEX II single crystal X-ray CCD diffractometer having graphite monochromatized (Mo-Kα, λ = 0.71073 Å) radiation at low temperature(100K).[1] The X-ray generator was operated at 50 kV and 30 mA. The data reduction was performed using APEX-II software. Intensities were corrected for absorption using SADABS,[1] and the structure was solved and refined using SHELX97.[2]All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were geometrically fixed with thermal parameters equivalent to 1.2 times that of the atom to which they are bonded. Molecular diagram was prepared using ORTEP, and the packing diagrams were generated using Mercury version 3.10.[3] PLATON was used for the analysis of bond lengths, bond angles, and other geometrical parameters.[4] Crystallographic parameters are shown in Table S2.

**Table S2.** Crystallographic Parameters of HU form I and II.

| **Identification code** | **form I** | **form II** |
|---|---|---|
| CCDC no. | 2249768 | 1911362 |
| Empirical formula | $CH_4N_2O_2$ | $CH_4N_2O_2$ |
| Formula weight | 76.06 | 76.06 |
| Temperature/K | 100 | 100 |
| Crystal system | monoclinic | tetragonal |
| Space group | $P2_1/c$ | $I4_1/a$ |
| a/Å | 8.3422(10) | 9.19730(10) |
| b/Å | 4.8944(6) | 9.19730(10) |
| c/Å | 8.7962(10) | 14.6452(5) |
| α/° | 90 | 90 |
| β/° | 122.423(3) | 90 |
| γ/° | 90 | 90 |
| Volume/Å$^3$ | 303.16(6) | 1238.84(5) |
| Z | 4 | 16 |
| Z’ | 1 | 1 |
| $\rho_{calc}$g/cm$^3$ | 1.666 | 1.631 |
| μ/mm$^{-1}$ | 0.156 | 0.153 |
| F(000) | 160.0 | 640.0 |
| Radiation | MoKα (λ = 0.71073) | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 5.786 to 53.976 | 5.23 to 72.758 |
| Index ranges | $-10 \leq h \leq 10$, $-6 \leq k \leq 6$, $-11 \leq l \leq 11$ | $-12 \leq h \leq 15$, $-15 \leq k \leq 15$, $-24 \leq l \leq 24$ |
| Reflections collected | 7731 | 33045 |
| Independent reflections | 641 [$R_{int}$ = 0.0590, $R_{sigma}$ = 0.0269] | 1506 [$R_{int}$ = 0.0329, $R_{sigma}$ = 0.0113] |
| Data/restraints/parameters | 641/0/47 | 1506/0/47 |
| Goodness-of-fit on $F^2$ | 1.164 | 1.155 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0657, $wR_2$ = 0.1882 | $R_1$ = 0.0389, $wR_2$ = 0.1069 |
| Final R indexes [all data] | $R_1$ = 0.0662, $wR_2$ = 0.1885 | $R_1$ = 0.0436, $wR_2$ = 0.1120 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.62/-0.44 | 0.46/-0.29 |

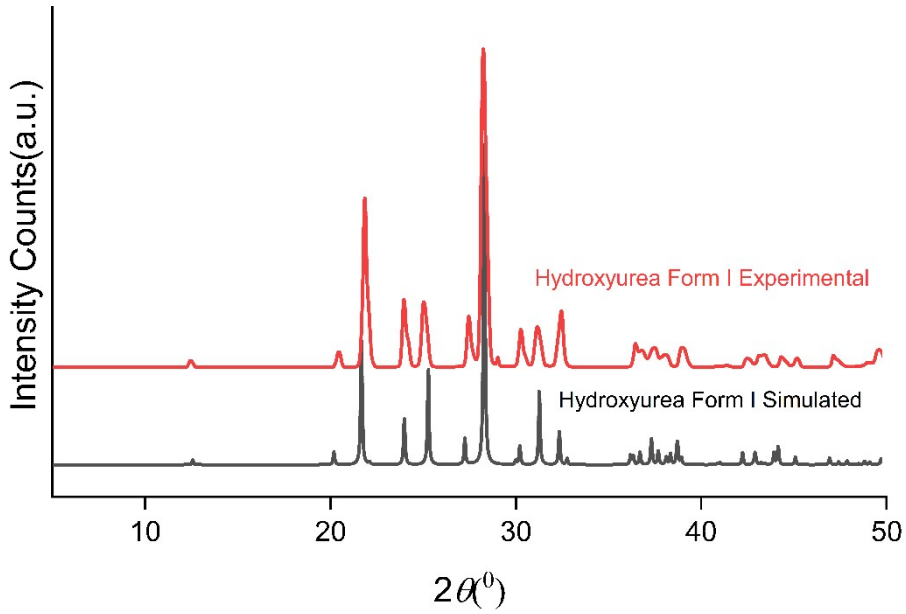



**Fig. S1** Overlay of experimental (for commercial HU) and calculated powder XRD lines from the crystal structures of HU from I.

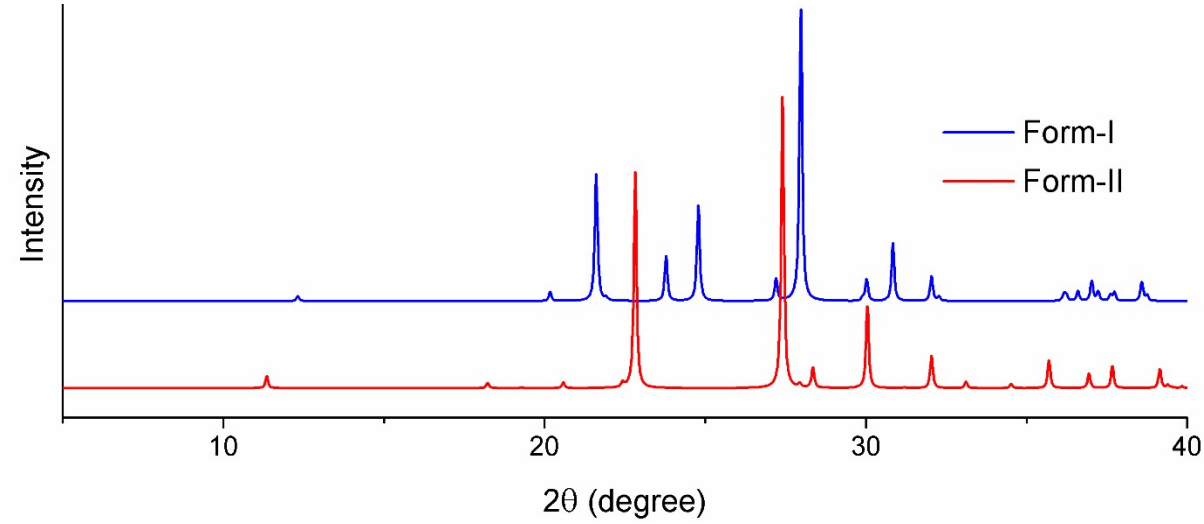



**Fig. S2** Overlay of calculated powder XRD lines from the crystal structures to show the difference between novel from II compared to the known form I (Refcode: UREAOH01).

### 3. Hirshfeld Surface Analysis

The Hirshfeld surface emerged from an attempt to define the space occupied by a molecule in a crystal for the purpose of partitioning the crystal electron density into molecular fragments. Graphical tools based on the Hirshfeld surface and the associated two-dimensional (2D) fingerprint plot offered considerable promise for exploring packing modes and intermolecular interactions in molecular crystals.[5] Calculations were performed using the Crystal Explorer package. The $d_{norm}$ and percentage contribution of various interactions in form I and form II

are shown in Fig. S3. Fingerprint plots and decomposed fingerprint plots are shown in Table S3.

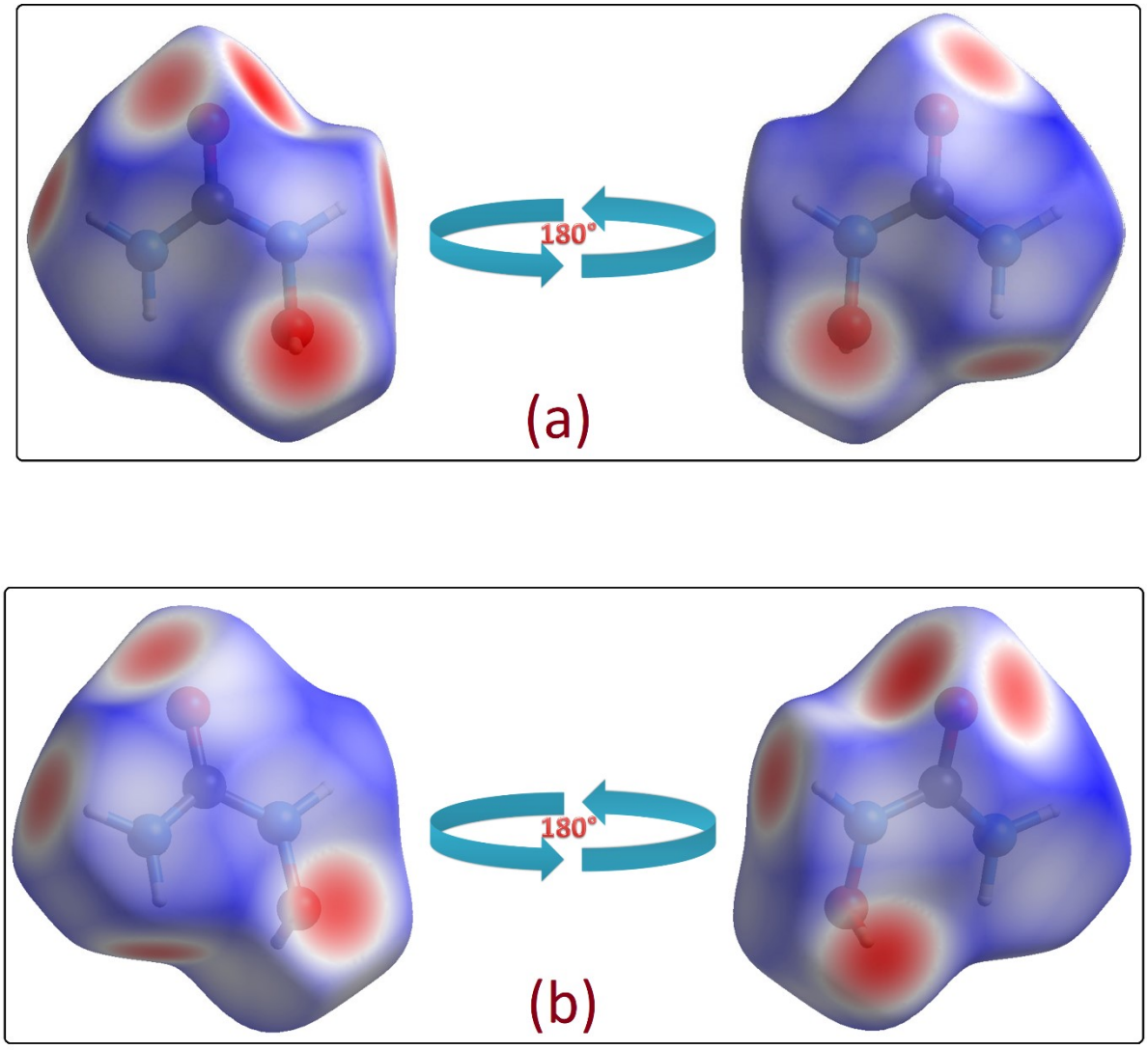
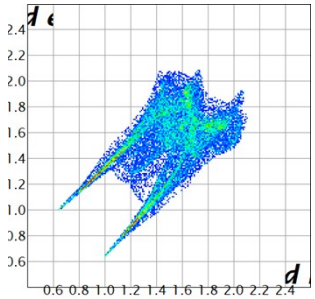
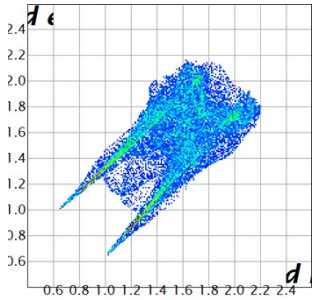
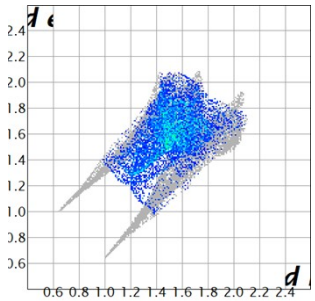
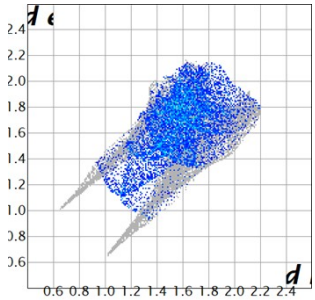
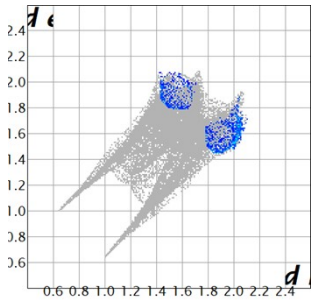
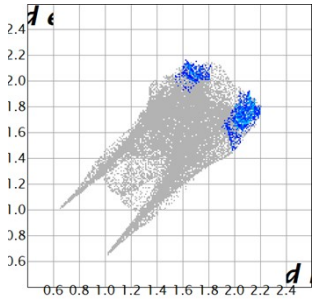
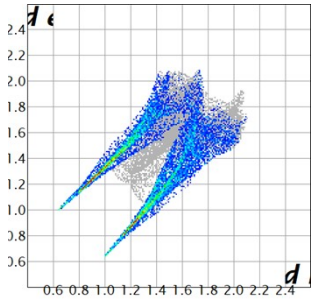
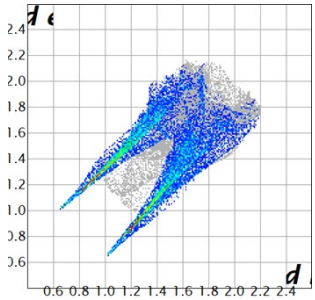
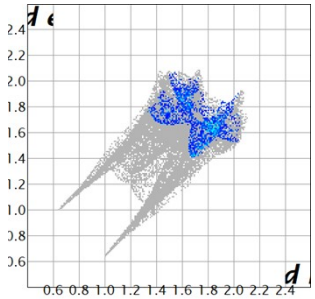
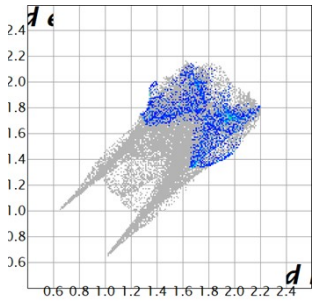
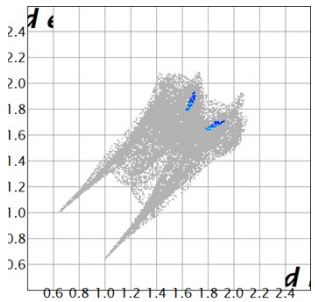
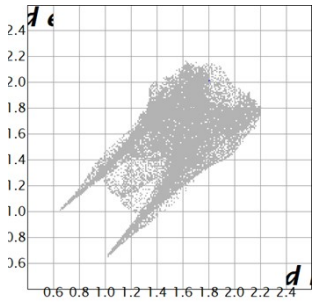
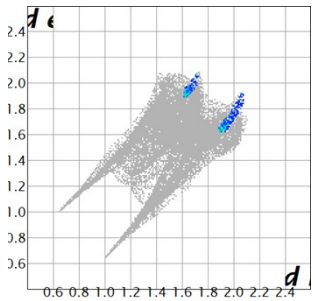
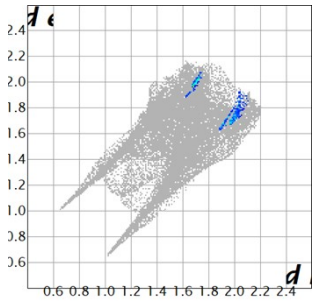
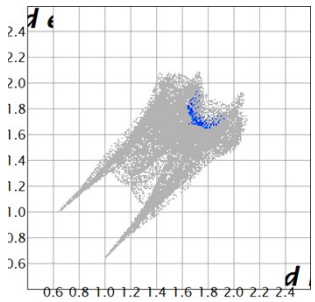
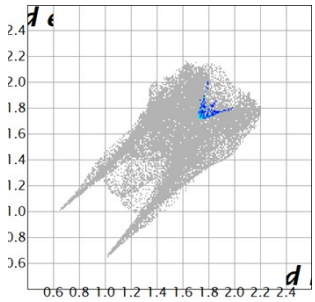
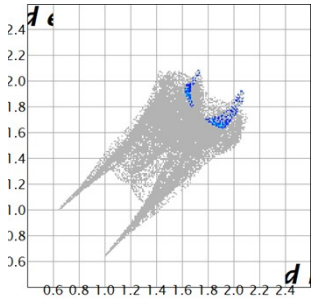
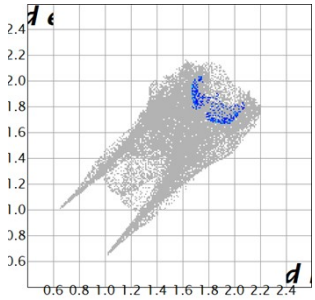
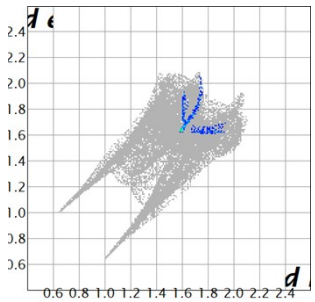
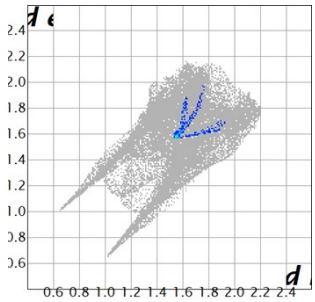



**Fig. S3** Hirshfeld surfaces of (a) form I and (b) form II, generated over $d_{norm}$, where, selected values are min = -0.737, mean = 0.249 Å, and max = 0.891 Å.

**Table S3.** Fingerprint plots and decomposed fingerprint plots of form I and form II.

| Interaction Type | form I | form II |
|---|---|---|
| **Fingerprint** |  |  |
| **H···H** |  32.3% |  30.2% |
| **C···H** |  4.5% |  4.9% |
| **O···H** |  48.2% |  50.5% |

| | | |
|---|---|---|
| **N···H** |  8.4% |  8.7% |
| **C···N** |  0.7% |  0.0% |
| **C···O** |  2.3% |  1.9% |
| **N···N** |  0.8% |  1.0% |

| | | |
|---|---|---|
| **N···O** |  0.9% |  1.4% |
| **O···O** |  1.5% |  1.3% |

## 4. Images of Hot Stage Microscopy (HSM)

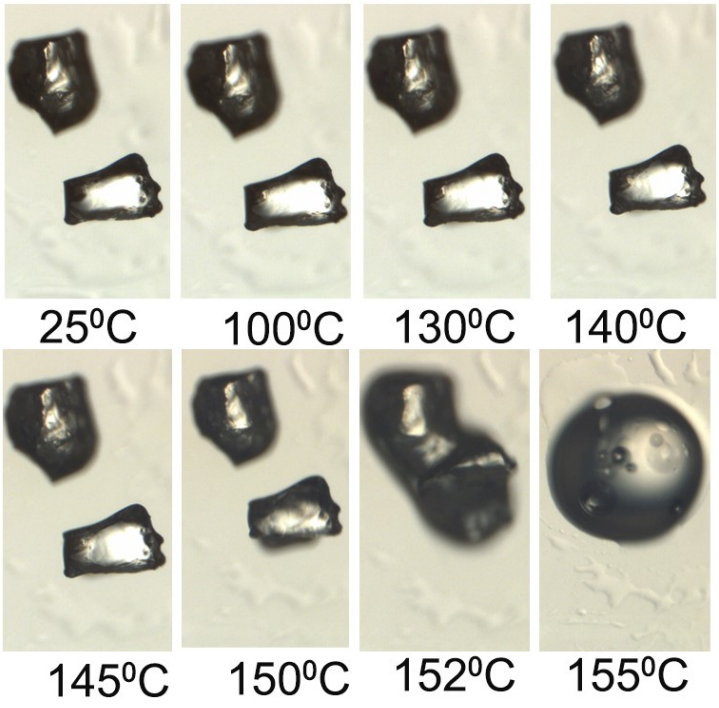



**Fig. S4** HSM images of form I upon heating at different temperature points.

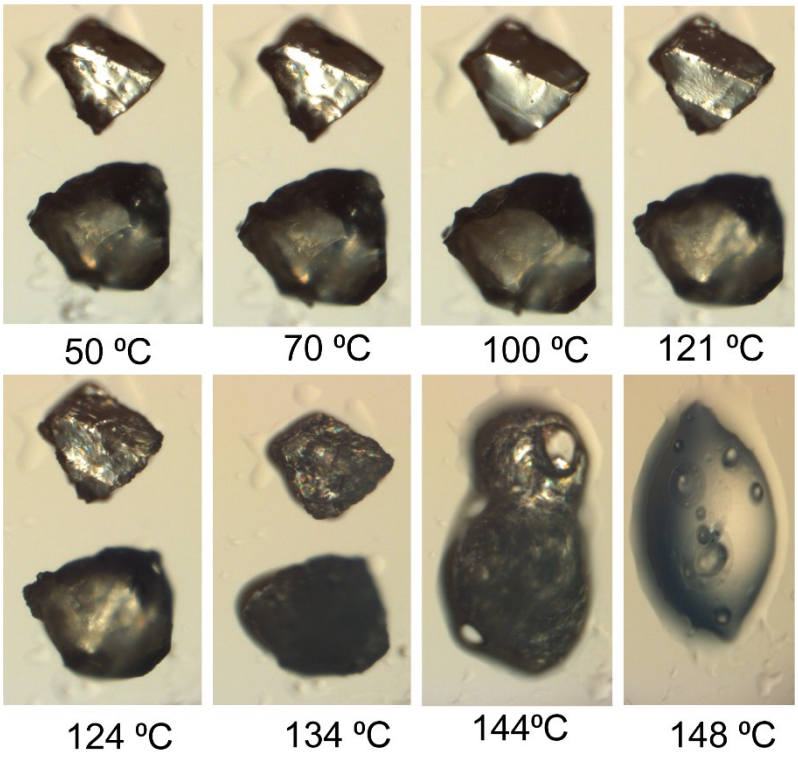



**Fig. S5** HSM images of form II upon heating at different temperature points.

## 5. Computational Studies

In order to investigate the intermolecular interaction in various synthons (Fig S3), computational studies were performed using the DFT-D method (Grimme's D2 dispersion model) equipped in Gaussian 09.[6] An appropriate density functional theory ωB97X-D/aug-cc-PVTZ/def2-TZV was used. Interaction energies (ΔE) were calculated by subtracting the energy of the two monomers using the formula [$\Delta E = (E_{Dimer}) - 2(E_{Monomer})$]. Further, dimer energies were corrected for basis set superposition error by the use of the counterpoise method.

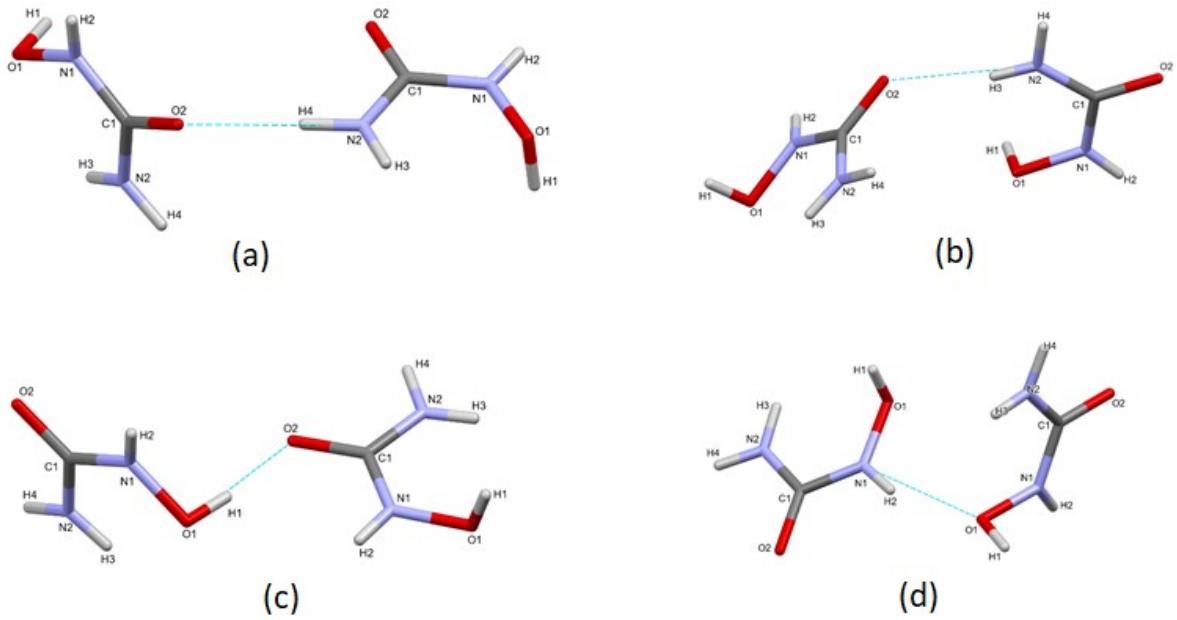



**Fig. S6** Representation of synthons used for the calculation of intermolecular interactions energy in form I (Refcode: UREAOH01) and II. These interactions are (a) N2–H4···O2, (b) N2–H3···O2, (c) O1–H1···O2, and (d) N1–H2···O1.

**Table S4.** Single point energy (E) of Hydroxyurea (HU) and its dimers calculated at ωB97X-D/aug-cc-PVTZ/def2-TZV level of theory for form I (Refcode: UREAOH01) and II. Dimer interaction energies are represented by ΔE.

| S. No. | Interaction | form I | | form II | |
|---|---|---|---|---|---|
| | | E (kJ/mol) | ΔE(kJ/mol) | E (kJ/mol) | ΔE(kJ/mol) |
| | HU | -788769.35 | | -788636.14 | |
| 1 | N2–H4···O2 | -1577576.57 | -37.86 | -1577300.64 | -28.41 |
| 2 | N2–H3···O2 | -1577559.29 | -20.54 | -1577299.22 | -26.95 |
| 3 | O1–H1···O2 | -1577594.56 | -55.86 | -1577313.86 | -41.59 |
| 4 | N1–H2···O1 | -1577548.92 | -10.21 | -1577281.77 | -9.50 |

**Table S5.** Total energy of HU after optimization of H atoms' only and its dimers calculated at ωB97X-D/aug-cc-PVTZ/def2-TZV level of theory for form I (Refcode: UREAOH01) and II. Dimer interaction energies are represented by ΔE.

| S. No. | interaction | form I | | form II | |
|---|---|---|---|---|---|
| | | E (kJ/mol) | ΔE(kJ/mol) | E (kJ/mol) | ΔE(kJ/mol) |
| | HU | -788845.67 | | -788844.83 | |
| 1 | N2–H4···O2 | -1577720.54 | -29.20 | -1577720.92 | -31.25 |
| 2 | N2–H3···O2 | -1577718.99 | -27.61 | -1577719.83 | -30.17 |
| 3 | O1–H1···O2 | -1577733.55 | -42.22 | -1577731.72 | -42.09 |
| 4 | N1–H2···O1 | -1577708.99 | -17.61 | -1577702.38 | -12.72 |

**Periodic DFT Calculations**

Periodic DFT calculations were performed using the plane-wave DFT code CASTEP.[7] Crystal structures of the two polymorphs were converted into CASTEP input format using the program cif2cell.[8] The structures were geometry-optimized using each of the following methods: PBE+MBD*, PBE+D2 and LDA. The plane wave basis set was truncated at 800 eV plane-wave cutoff, the 1st electronic Brillouin zone was sampled with 2πx0.05 $Å^{-1}$ k-point spacing. Geometry optimization was deemed converged upon satisfying the following convergence criteria: maximum energy change: $2x10^{-5}$ eV/atom; maximum atomic force: 0.05 eV/Å; maximum atomic displacement: $10^{-3}$ Å, maximum residual stress: 0.1 GPa.

**Table S6.** Total energies of the two polymorphs of HU after periodic DFT geometry optimization.

| Polymorph | Calculated energies per formula unit /eV | | |
|---|---|---|---|
| | PBE+MBD* | PBE+D2 | LDA |
| **form I** | -1654.1957 | -1654.1576 | -1653.4135 |
| **form II** | -1654.1949 | -1654.1591 | -1653.4100 |

## 6. References


**1.** Bruker (2016). APEX3, SAINT and SADABS.Bruker AXS Inc., Madison, Wisconsin, USA.

**2.** Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *ActaCrystallogr.*,*Sect. C*: *Struct. Chem.***2015**, *71*, 3−8.

**3.** Farrugia, L. J. WinGX and ORTEP for Windows: an update. *J. Appl. Crystallogr.***2012**, *45(4)*, 849-854.

**4.** Spek, A. L. Structure Validation in Chemical Crystallography. *ActaCryst.***2009**, *D65*, 148-155.

**5.** McKinnon, J. J.; Spackman, M. A.; Mitchell, A. S. ActaCrystallogr., Sect. B 2004, 60, 627−668.

**6.** Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.;Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci,B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H.P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.;Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima,T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.;Peralta, J. E.; Ogliaro, F.; Bearpark,

M.; Heyd, J. J.; Brothers, E.; Kudin,K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.;Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega,N.; Millam, M. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.;Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.;Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.;Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.;Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.;Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc.:Wallingford, CT, 2009.

**7.** S. J. Clark, M. D. Segall, C. J. Pickard, P. J. Hasnip, M. I. J. Probert, K. Refson and M. C. Payne, *Zeitschrift für Krist. - Cryst. Mater.*, 2005, **220**, 567–570.

**8.** T. Björkman, *Comput. Phys. Commun.*, 2011, **182**, 1183–1186.