

Analysis of a New Hydrochloride Salt of the Common Pharmaceutical Metformin

Electronic Supplementary information

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A list of students from the Simon Langton Girls' Grammar School who were involved in this project are listed below. This list only includes the students who shared their consent for their name to be included. We also acknowledge those who did not share their consent to be named here.

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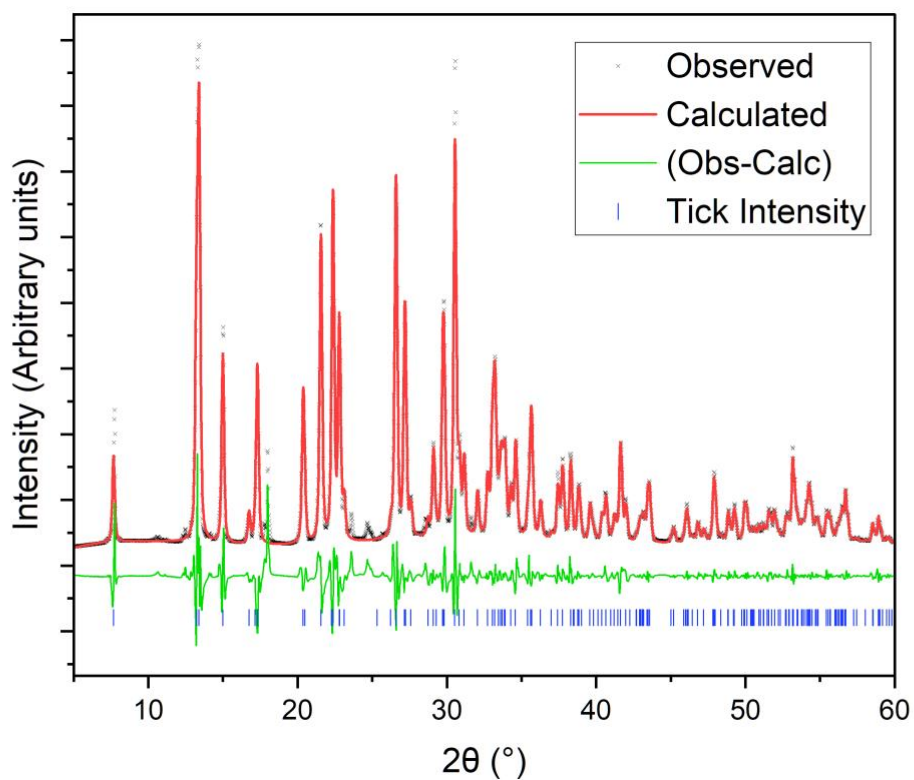


Figure S1: Powder X-ray diffraction pattern of metformin dihydrochloride fitted using the Le Bail method. The unfitted impurity peaks indicate the presence of a minor α -metformin hydrochloride impurity. Refined unit cells of $a = 7.1313(13) \text{ \AA}$, $b = 5.8049(6) \text{ \AA}$, $c = 12.553(3) \text{ \AA}$, $\beta = 105.112(5)^\circ$, with measures of fit $wR_2 = 11.94\%$, $R_1 = 7.38\%$ and $\chi^2 = 6.55$.

Table S1: Microanalysis results for the bulk metformin dihydrochloride sample

Atom	$C_4H_{11}N_5(HCl)_2$	$C_4H_{11}N_5(HCl)$	Found average
C	23.77%	29.01%	23.44%
H	6.48%	7.30%	6.31%
N	34.66%	42.28%	33.73%

Table S2: Crystallographic details of reported structure

Empirical formula	C ₄ H ₁₃ Cl ₂ N ₅
Formula weight	202.09
Temperature/K	99.9(6)
Crystal system	monoclinic
Space group	<i>P</i> 2 ₁
<i>a</i> (Å)	7.0824(3)
<i>b</i> (Å)	5.7853(2)
<i>c</i> (Å)	12.4696(7)
β/°	105.262(5)
Volume/Å ³	492.90(4)
Z	2
ρ _{calc} /g/cm ³	1.362
μ/mm ⁻¹	0.612
F(000)	212.0
Crystal size/mm ³	0.171 × 0.109 × 0.089
Radiation	Mo Kα (λ = 0.71073)
2θ range for data collection/°	7.596 to 59.476
Index ranges	-9 ≤ <i>h</i> ≤ 9, -7 ≤ <i>k</i> ≤ 8, -15 ≤ <i>l</i> ≤ 15
Reflections collected	6044
Independent reflections	2364 [R _{int} = 0.0365, R _{sigma} = 0.0501]
Data/restraints/parameters	2364/1/102
Goodness-of-fit on F ²	1.065
Final R indexes [<i>I</i> ≥ 2σ (<i>I</i>)]	R ₁ = 0.0325, wR ₂ = 0.0700
Final R indexes [all data]	R ₁ = 0.0353, wR ₂ = 0.0721
Largest diff. peak/hole / e Å ⁻³	0.35/-0.28
Flack parameter	0.12(5)

Table S3: Thermal expansion coefficients calculated using PASCAL.³

Axes	α (MK ⁻¹)	<i>a</i>	<i>b</i>	<i>c</i>
X ₁	33.9(19)	0.8891	0.0	-0.4577
X ₂	47(4)	0.8569	-0.0	0.5155
X ₃	20.6(10)	-0.0	1.0	0.0
V	102(6)			

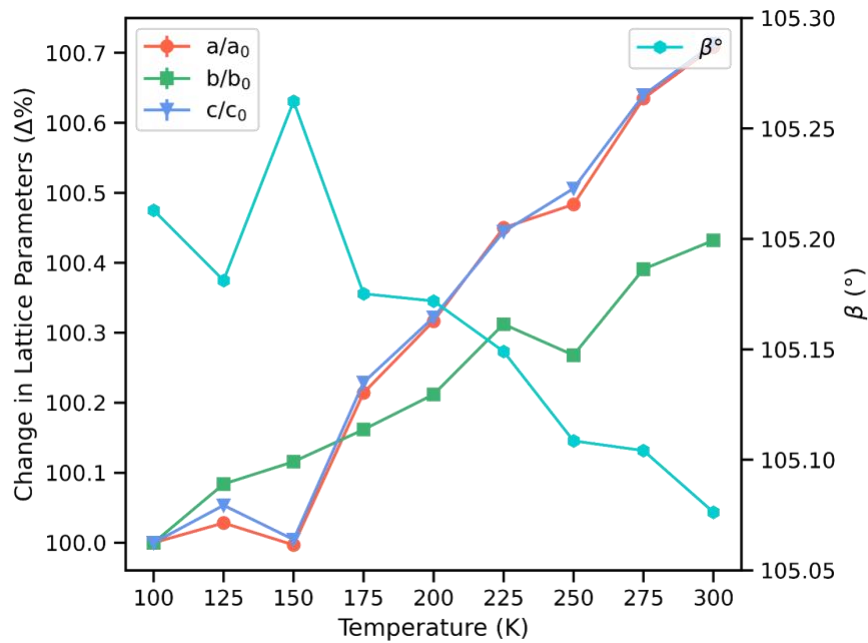


Figure S2: Evolution of lattice parameters for metformin dihydrochloride with temperature with reference to 100 K structure.

Table S4: Bond distances comparable across the metformin molecules in the monoprotic polymorphs and diprotic forms, all measured at 100 K. ^{1,2}

Atom	Atom	Bond Length (\AA)		
		Dihydrochloride	Monoprotic - α	Monoprotic β
N1	C1	1.318(4)	1.3407(4)	1.346(2)
N2	C1	1.306(4)	1.3398(3)	1.352(2)
N3	C1	1.365(4)	1.3332(3)	1.328(2)
N3	C2	1.389(4)	1.3545(4)	1.364(2)
N4	C2	1.306(4)	1.3372(4)	1.334(2)
N5	C2	1.320(4)	1.3376(4)	1.341(2)
N5	C3	1.462(4)	1.4566(5)	1.460(2)
N5	C4	1.466(4)	1.4590(4)	1.468(2)

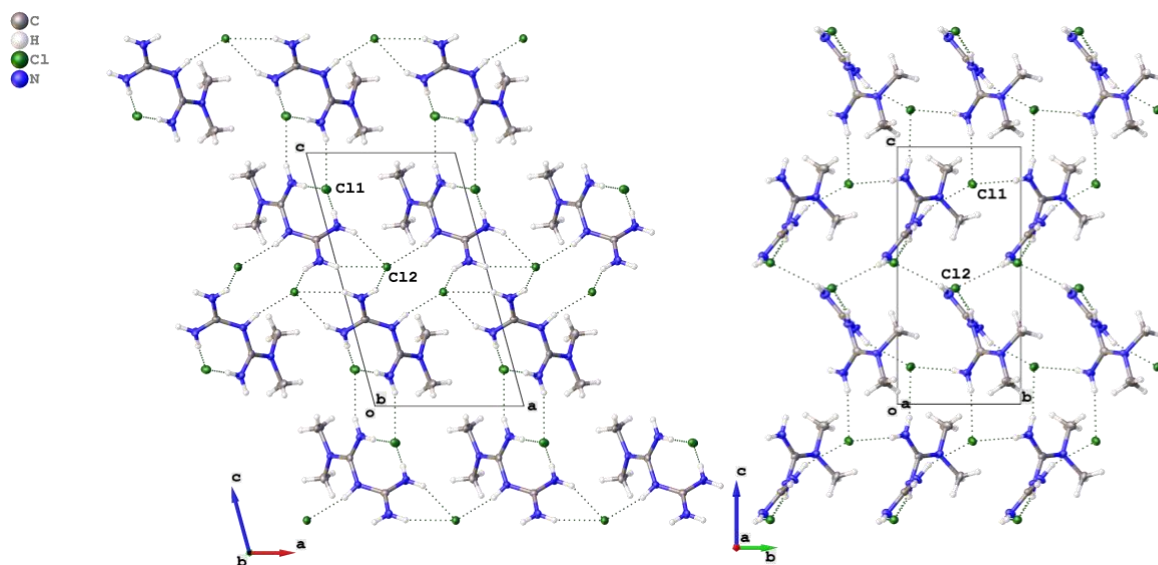


Figure S3: The packing of metformin dihydrochloride displayed along the *b*-axis (left) and the *a*-axis (right).

Table S5: Hydrogen bonding in metformin dihydrochloride at 100 K.

Hydrogen Bond (D-H...Cl)	Donor-Acceptor distance (Å)	Hydrogen bond angle (°)
N4-H4a...Cl1	3.135(2)	161.46(14)
N4-H4b...Cl1	3.200(3)	157.86(14)
N2-H2b...Cl1	3.180(2)	158.21(16)
N1-H1a...Cl2	3.227(2)	150.20(15)
N2-H2a...Cl2	3.233(2)	150.02(15)
N1-H1b...Cl2	3.210(2)	136.93(14)
N3-H3...Cl2	3.058(2)	161.94(16)

Table S6: Analysis of the hydrogen bonding in metformin dihydrochloride compared to published structures in the Cambridge Structural Database (CSD).

Distance									
Donor	Acceptor	D-A (Å)	Classification	Threshold	Hits	Mean	Std. dev.	Min	Max
N3 (sec_amine_1)	Cl2 (cl-)	3.06	Unusual	(3.08, 3.42)	437	3.23	0.11	3	3.73
N2 (acyclic_prim_amine)	Cl2 (cl-)	3.23	Not Unusual	(3.15, 3.45)	374	3.28	0.09	3.07	3.7
N1 (acyclic_prim_amine)	Cl2 (cl-)	3.21	Not Unusual	(3.15, 3.45)	374	3.28	0.09	3.07	3.7
N4 (iminium)	Cl1 (cl-)	3.21	Not Unusual	(3.12, 3.35)	251	3.22	0.08	3.03	3.7
N4 (iminium)	Cl1 (cl-)	3.13	Not Unusual	(3.12, 3.35)	251	3.22	0.08	3.03	3.7
N1 (iminium)	Cl2 (cl-)	3.23	Not Unusual	(3.12, 3.35)	251	3.22	0.08	3.03	3.7
N2 (iminium)	Cl1 (cl-)	3.19	Not Unusual	(3.12, 3.35)	251	3.22	0.08	3.03	3.7

Angle									
Donor	Acceptor	D-H...A (°)	Classification	Threshold	Hits	Mean	Std. dev.	Min	Max
N3 (sec_amine_1)	Cl2 (cl-)	161.02	Not Unusual	149.31	437	167.78	10.41	121.55	179.93
N2 (acyclic_prim_amine)	Cl2 (cl-)	150.34	Not Unusual	146.47	374	166.67	10.74	125.08	178.65
N1 (acyclic_prim_amine)	Cl2 (cl-)	137.26	Unusual	146.47	374	166.67	10.74	125.08	178.65
N4 (iminium)	Cl1 (cl-)	159.56	Not Unusual	144.29	251	166.22	11.27	125.62	179.97
N4 (iminium)	Cl1 (cl-)	162.23	Not Unusual	144.29	251	166.22	11.27	125.62	179.97
N1 (iminium)	Cl2 (cl-)	150.57	Not Unusual	144.29	251	166.22	11.27	125.62	179.97
N2 (iminium)	Cl1 (cl-)	158.2	Not Unusual	144.29	251	166.22	11.27	125.62	179.97

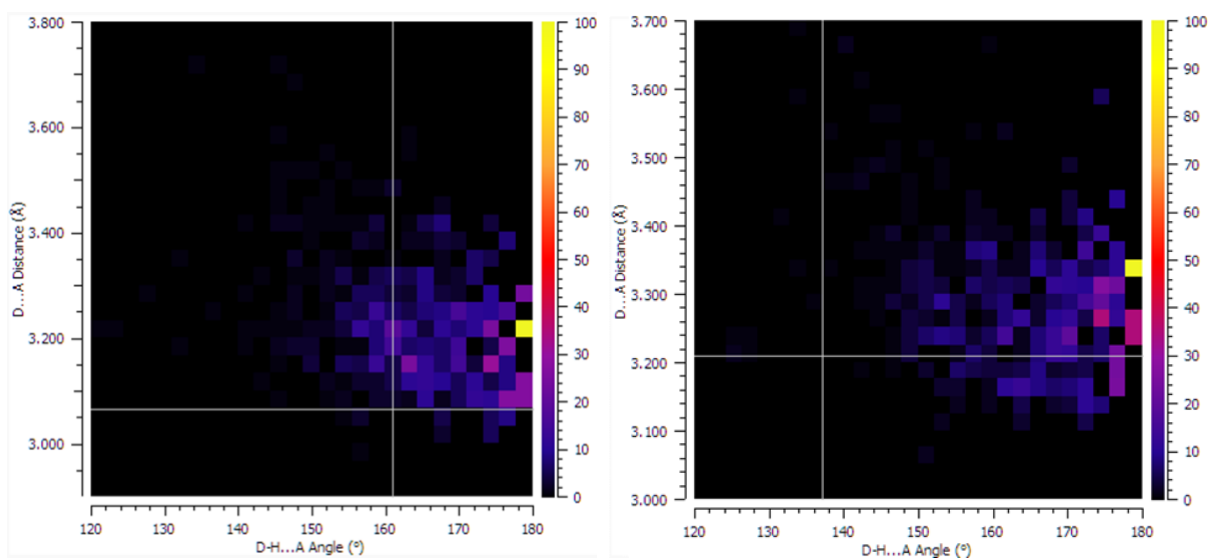


Figure S4: The distribution of distances and angles of hydrogen bond types from the CSD showing the context of the unusually short N3-H3...Cl2 (left) and nonlinear N1-H1b...Cl2 (right).

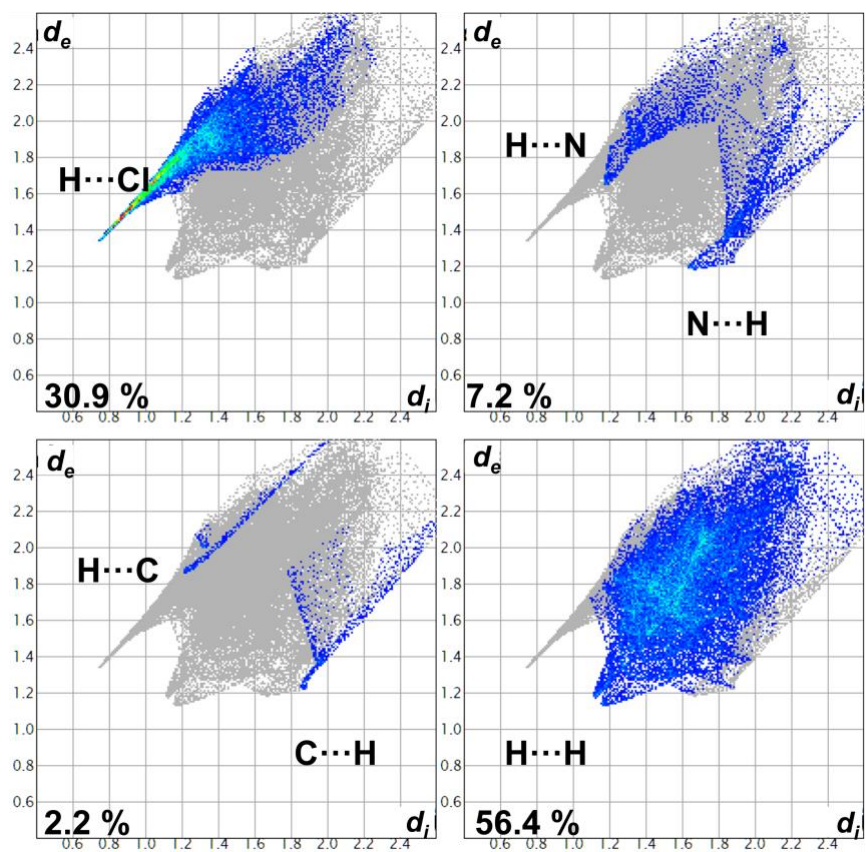


Figure S5: Filtered Hirschfeld analysis fingerprint plots for metformin dihydrochloride.

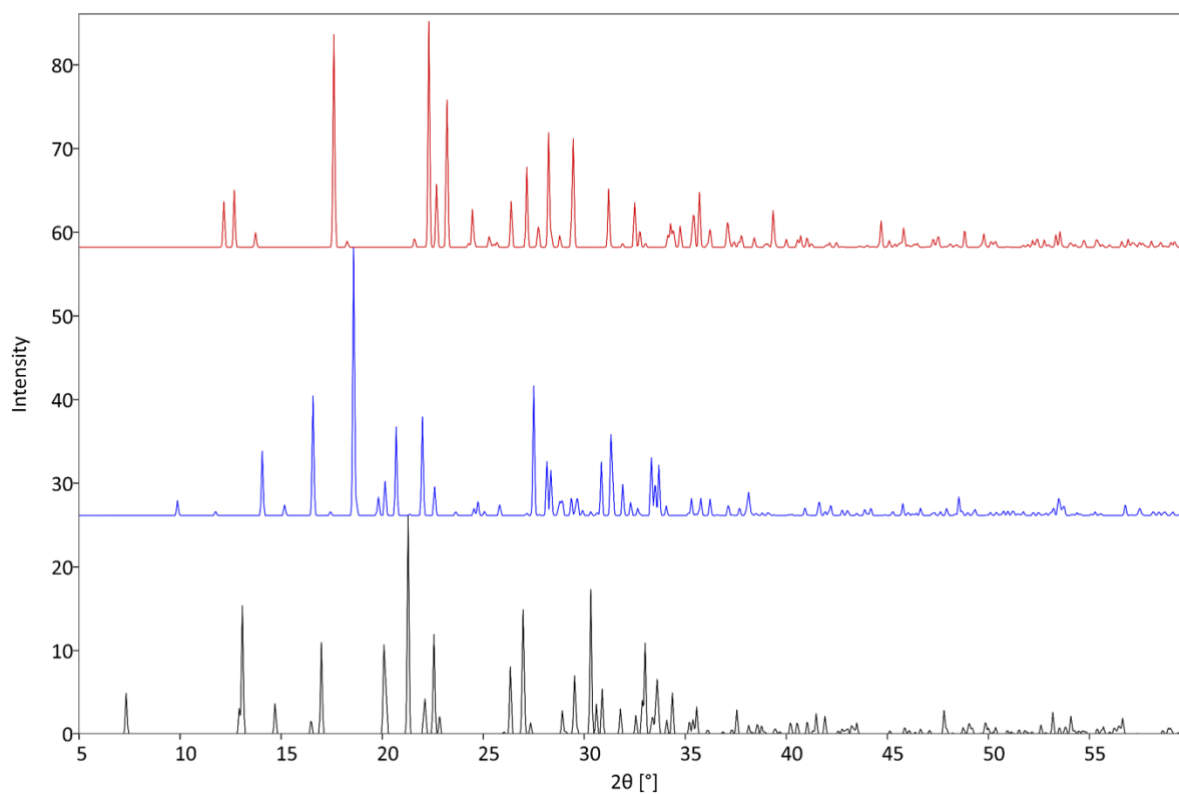


Figure S6: Simulated patterns for α -metformin hydrochloride (red), β -metformin hydrochloride (blue) and metformin dihydrochloride (black), showing these phases are distinguishable by powder diffraction, with minimal peak overlap between systems.

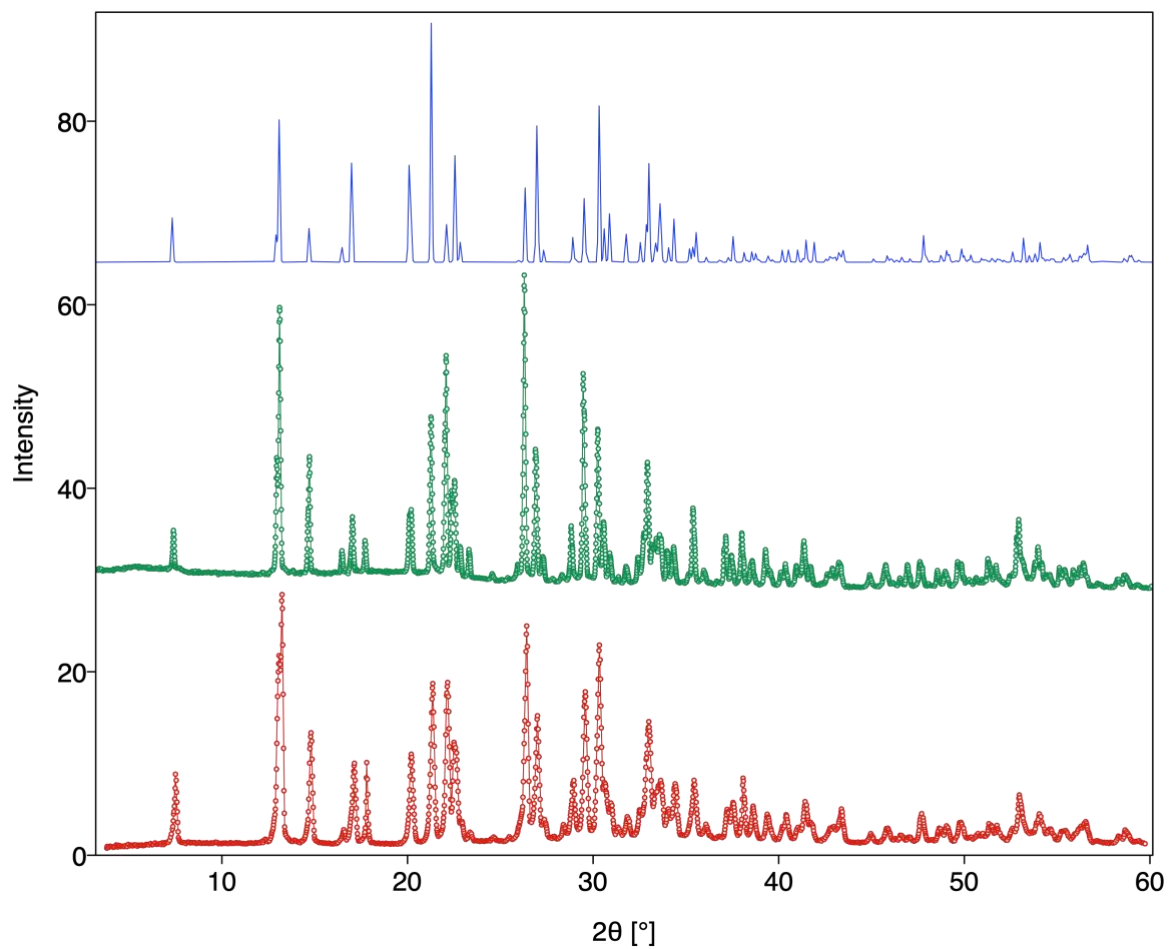


Figure S7: Diffraction patterns of freshly synthesised α -metformin hydrochloride (red) and the same sample after aging for two years (green). A pattern calculated from the structure determined during this study is shown above in blue for reference.

Dichloride Salt

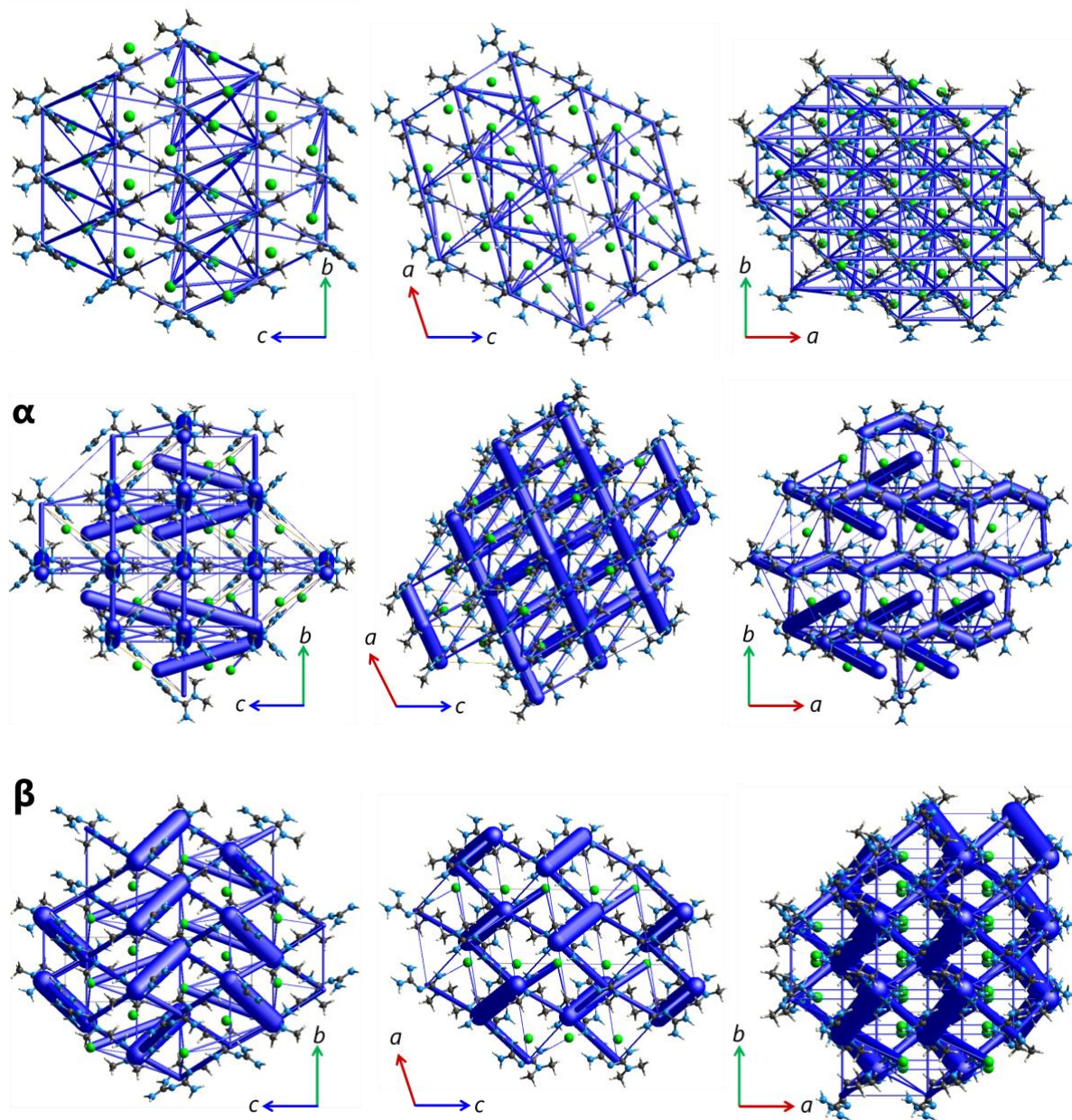


Figure S8: Total energy frameworks visualised as blue cylinders with the thickness indicative of the strength of interaction between centroids of molecular pairs.

References

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