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Diversity of felodipine solvates: structure and physicochemical properties

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Supporting Information

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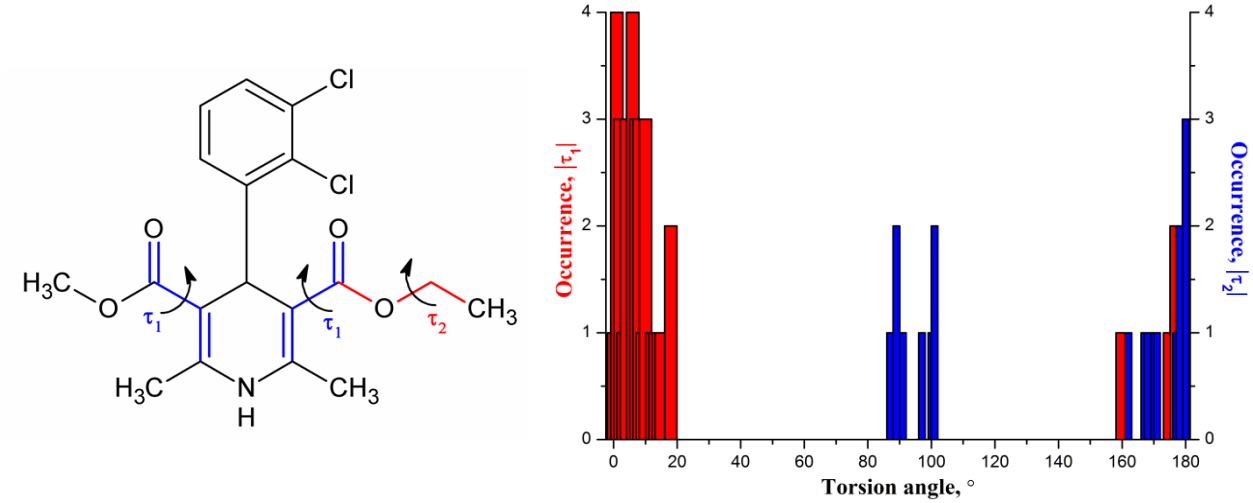
1. Conformational analysis

Analysis of the molecular conformation of felodipine shows that conformational changes are mainly due to the torsional flexibility of the methyl and ethyl ester groups, while the rest of the molecule remains virtually invariant. Therefore, all the felodipine conformations can be described by considering the two torsion angles τ_1 and τ_2 as shown in Fig. S1a. Fig. S1b shows the distributions of the torsion angles, τ_1 and τ_2, in all known crystal forms of felodipine.



(a) (b)

Fig. S1. (a) Flexible torsion angles in the felodipine molecule; (b) distributions of the torsion angle, $|\tau_1|$ (red), and the torsion angle, $|\tau_2|$ (blue), in all known crystal forms of **Fel**.

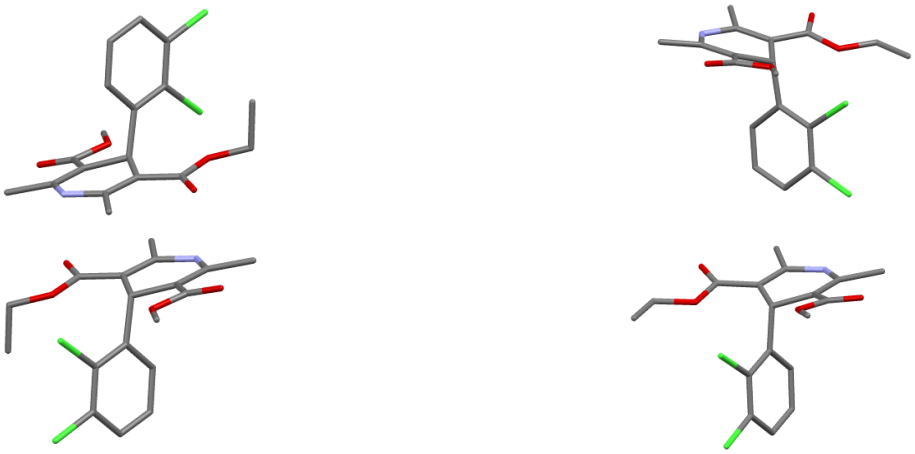
A value of $|\tau_1|$ close to 0 indicates that the C=O group points towards the Me group of the 1,4-dihydropyridine ring, while $|\tau_1|$ close to 180° indicates that it points away. A value of $|\tau_2| = 180°$ indicates that the entire ester group is essentially planar, while a value of $|\tau_2| = 90°$ indicates that the terminal CH_2–CH_3 bond lies perpendicular to the plane of the remainder of the group.

Apparently, most of the $|\tau_1|$ values are located in the low-angle region (84% of the total number), whereas only 16% of the values belong to the high-angle region. This distribution is consistent with the calculation results described in our previous work.[1] It has been shown that the molecules with $\tau_1 = 180°$ are relatively higher-energy conformers of felodipine compared to the molecules with $\tau_1 = 0°$. Moreover, all conformations with $|\tau_1|$ close to 180° are stabilized by either hydrogen bonds (Forms III and IV of pure **Fel**, [**Fel**+**N-MeFA**], [**Fel**+**FA**]) or intermolecular C-H…O interactions ([**Fel**+**APN**], [**Fel**+**TMU**]). In contrast to $|\tau_1|$, the $|\tau_2|$ values are distributed almost uniformly over two regions. About 42 % of the $|\tau_2|$ values are concentrated at 90°, and 58% of the values lie close to 180°.

Recently, molecular conformations of felodipine in dilute and saturated solution in DMSO have been investigated using NMR spectroscopy.[2] Therefore, it would be interesting to compare

conformations of **Fel** in the crystalline DMSO solvate and a DMSO solution. The authors claim that in the dilute DMSO solution, the dichlorophenyl fragment of the **Fel** molecule is rotated by approximately 180° compared to that in a crystal, so that the Cl atoms are oriented towards the NH group of the 1,4-dihydropyridine ring. This conformation of **Fel** is not observed in any of the felodipine crystal forms including the DMSO solvate. In the saturated solution, however, the fraction of this conformation decreases considerably, and the conformation corresponding to the crystal becomes dominant. Interestingly, according to Teberekidis and Sigalas, the conformation of **Fel** found in the dilute DMSO solution corresponds to the molecule's gas-phase minimum-energy conformation.[3] Moreover, the conformation of **Fel** in the crystal structure of Form I is calculated to be only *ca* 1.0 kJ mol^{-1} less stable. However, the energy required for rotation of the dichlorophenyl ring, which is expected to be much greater than 1.0 kJ mol^{-1}, has not been discussed in the paper. In fact, the situation remains unclear. There is no experimental evidence for the existence of a relatively lower-energy molecular conformation in any of the felodipine crystal forms, and a dilute DMSO solution seems to be the only reported example.

2. Description of "back-to-back", "side-on" and "face-to-face" contacts



(a) (b)

Figure S2. Illustration of (a) "back-to-back" and (b) "side-on" interactions in the crystal structures of the felodipine solvates.

A "back-to-back" interaction (Figure S2a) is a recurring motif in the structures of the polymorphs of pure felodipine and the solvates with formamide, *N*-methylformamide, acetone and DMSO. This type of interaction occurs between the 1,4-dihydropyridine rings of the centrosymmetric felodipine molecules, and it can be viewed as stacks of molecular pairs of felodipine in the crystal. A "side-on" notation implies a packing arrangement where the dichlorobenzene ring approaches the backside of the neighbouring 1,4-dihydropyridine ring. (Figure S2b) In this case, the structure does not contain discrete molecular pairs, while the felodipine molecules are arranged into chains or layers.

The "back-to-back" contacts can be characterized by the interplanar distances, i.e. distances between two least-squares planes of the 1,4-dihydropyridine rings of the neighbouring felodipine molecules (Figure S3). This parameter varies from 3.65 to 3.87 Å in felodipine polymorphs, but there are different degrees of lateral slip. In the solvates, the distance range is similar to that in the polymorphs (3.63-3.93).

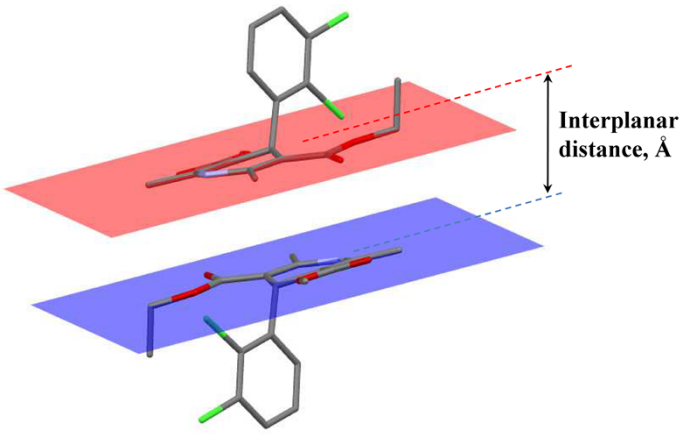
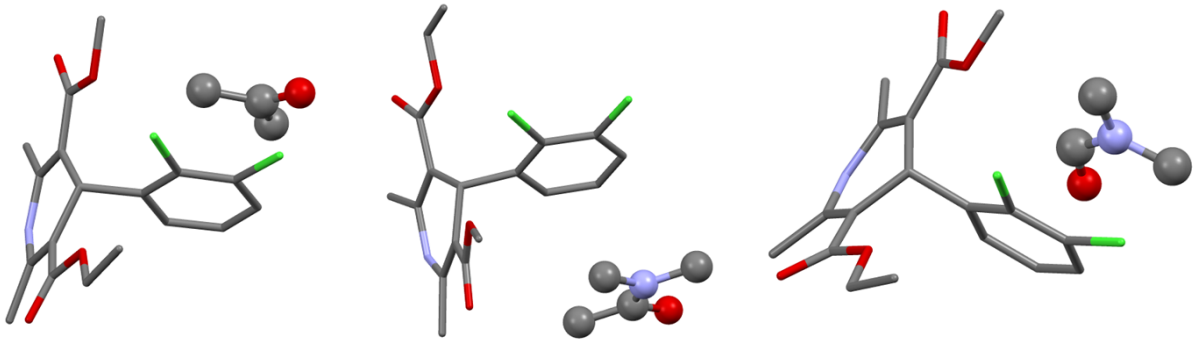


Figure S3. Illustration of the interplanar distance between two planes of the 1,4-dihydropyridine rings in the structures with "back-to-back" interactions.

If solvent molecule is flat, it can also form "face-to-face" interactions with the dichlorophenyl ring of felodipine. These interactions are clearly seen in the [**Fel**+**ATN**], [**Fel**+**DMF**] and [**Fel**+**DMAA**] solvates (Figure S4).



(a) (b) (c)

Figure S4. Illustration of "face-to-face" contacts between the solvent molecule and the dichlorophenyl ring of felodipine in the crystal structures of (a) [**Fel**+**ATN**], (b) [**Fel**+**DMF**] and (c) [**Fel**+**DMAA**].

3. Description of methods used to find a relationship between the solvent properties and the crystal packing arrangement of felodipine in the crystal

Different characteristics of the solvent molecules were analyzed in order to find a relationship between properties of the solvent and the crystal packing arrangement of the felodipine molecules. The ability of the solvent molecules to form donor-acceptor interactions with the host structure was tested by using the descriptors indicating the sum of all of H-bond acceptor factors in a molecule ($\sum C_a$) and the sum of H-bond donor factors ($\sum C_d$) as well as molecular polarizability (α). The descriptors were calculated by the program package HYBOT-PLUS (version of 2003) in Windows.[4] Unfortunately, we did not find any satisfactory correlation between none of those parameters and the packing arrangement of the solvates. As a next step, the topological similarity of the solvent molecules was estimated using Tanimoto similarity indices (Tc) obtained by means of the program MOLDIVS (MOLecular DIVersity & Similarity).[5] This approach, however, did not reveal any cluster of the solvent molecules with Tanimoto similarity coefficients within $0.5 < T_c < 1$ range (Tc=0: no similarity;Tc =1: identity). Therefore, the difference in the crystal packing does not seem to be due to topological reasons.

4. Crystal Packing Similarity analysis

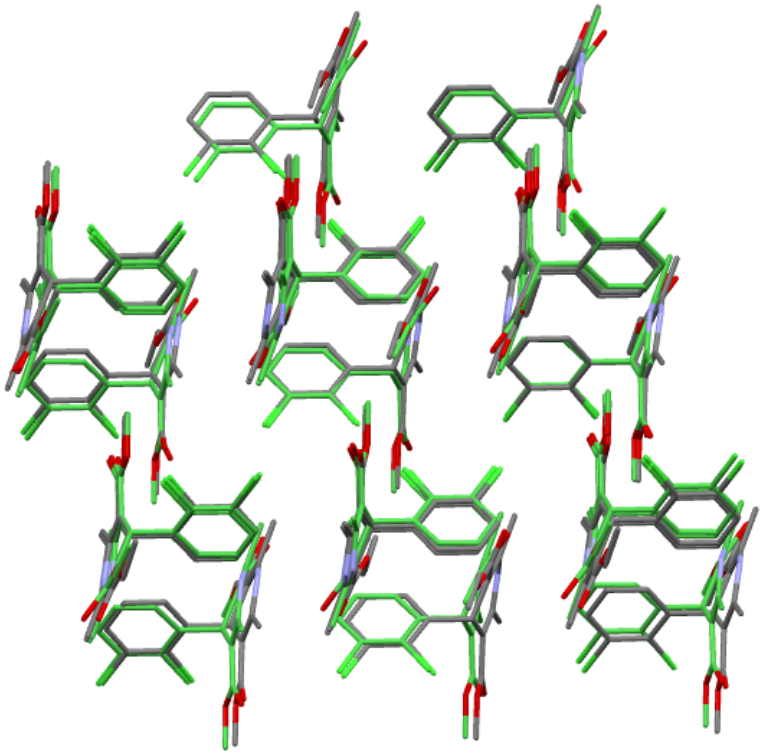


Fig. S5. Overlay of the [**Fel**+**DMAA**] crystal structure (gray) and [**Fel**+**DMF**] (green) (n=20, $rmsd_n$ = 0.350)

The crystal structures of the felodipine solvates were compared using the Crystal Packing Similarity module[6] implemented in Mercury.[7] The maximum number of molecules (*n*) that can be overlaid in two different structures is 20, when all non-H atom pairs are within a 20% distance tolerance and all corresponding angles within 20°. The smallest molecular components were ignored. The calculated $rmsd_n$ is the root-mean-square deviation of all non-H atom positions in the clusters of *n* molecules. The program allows for comparisons of crystal structures of different molecules with the $rmsd_n$ being calculated from only the common non-H atoms.

5. Hot stage microscopy experiments

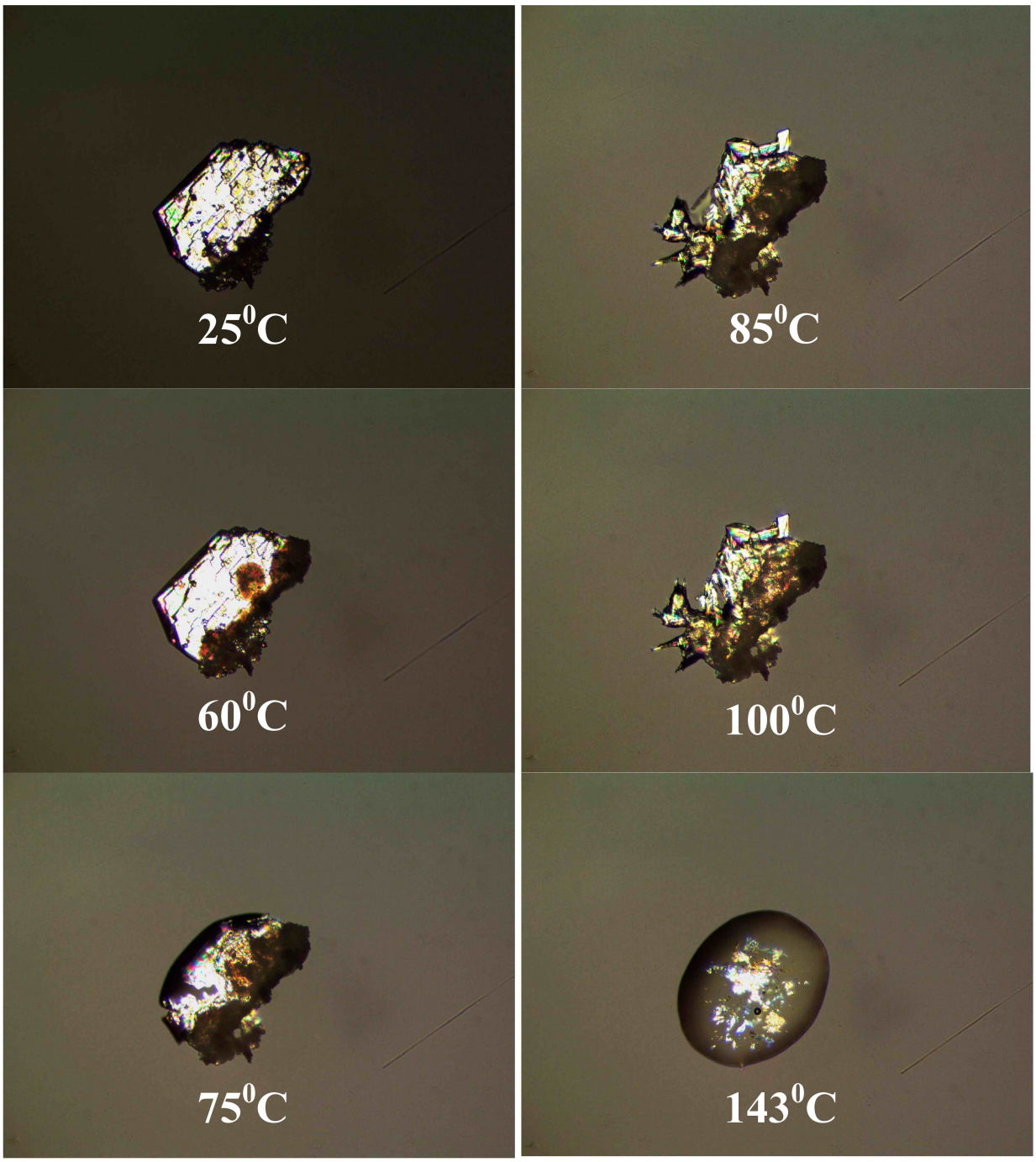


Fig. S6. Photomicrographs of **[FeI+DMSO]** showing thermal decomposition of the solvate.

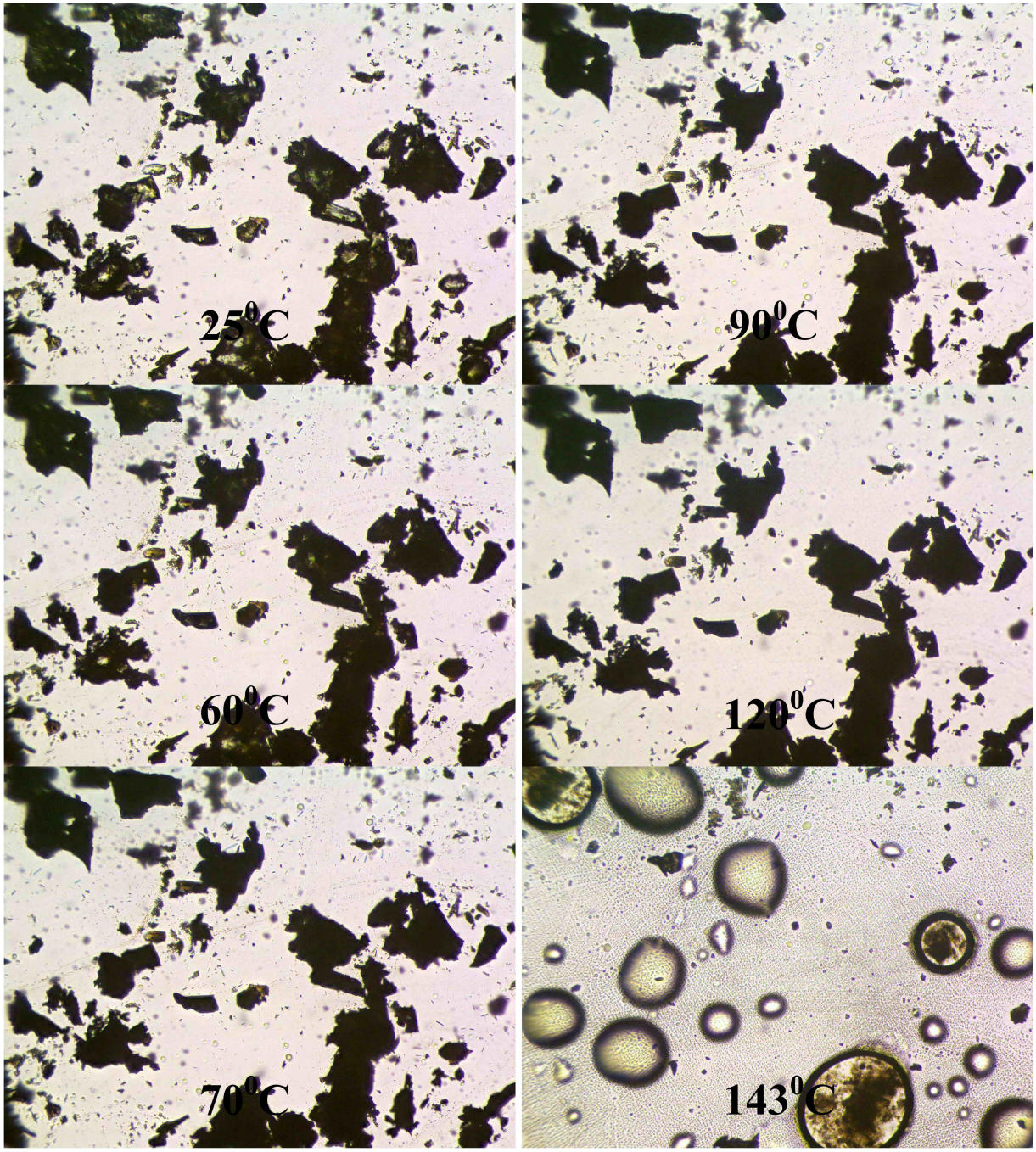


Fig. S7. Photomicrographs of **[Fel+ATN]** showing thermal decomposition of the solvate.

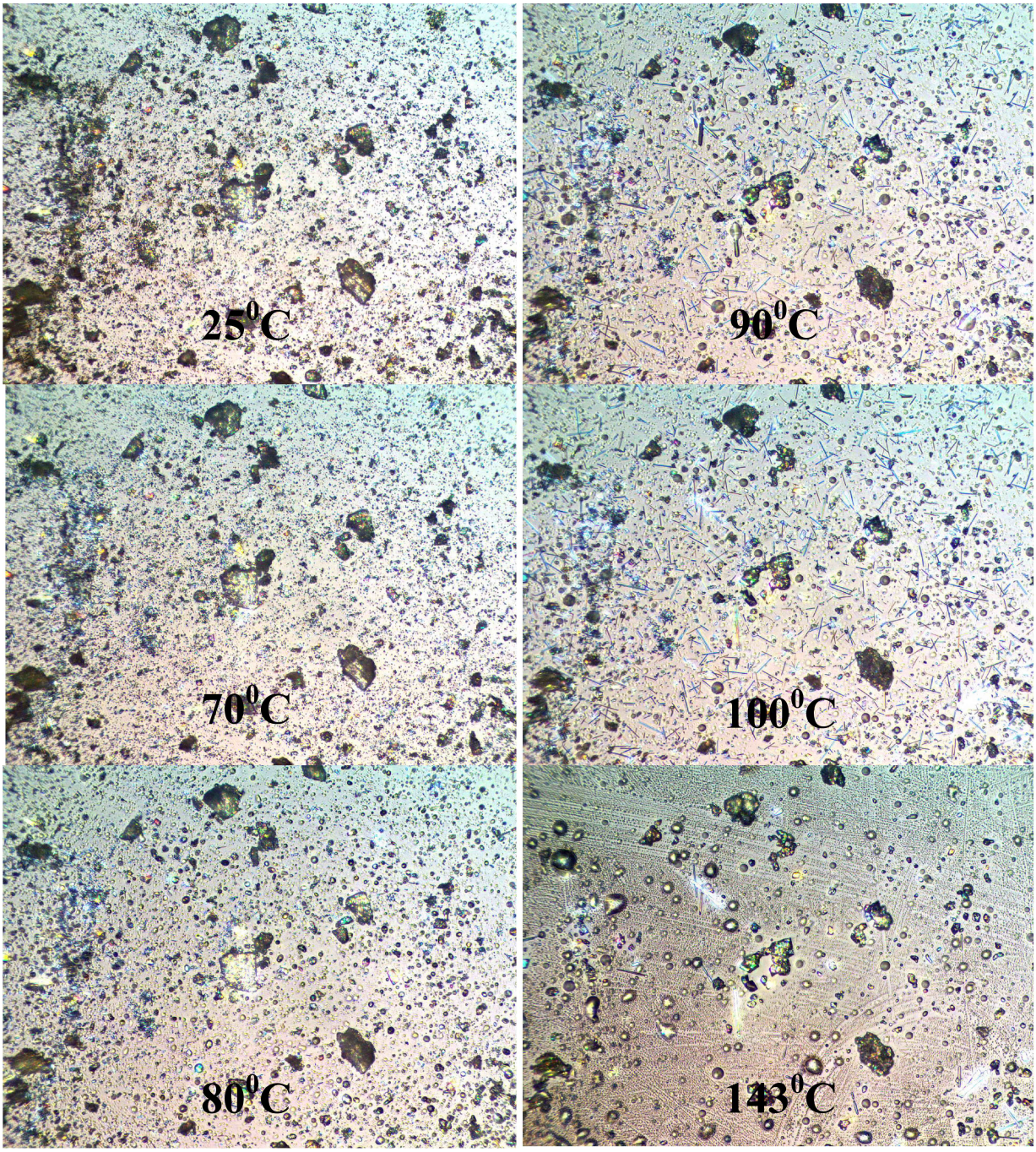


Fig. S8. Photomicrographs of **[Fel+APN]** showing thermal decomposition of the solvate.

6. Thermogravimetric analysis

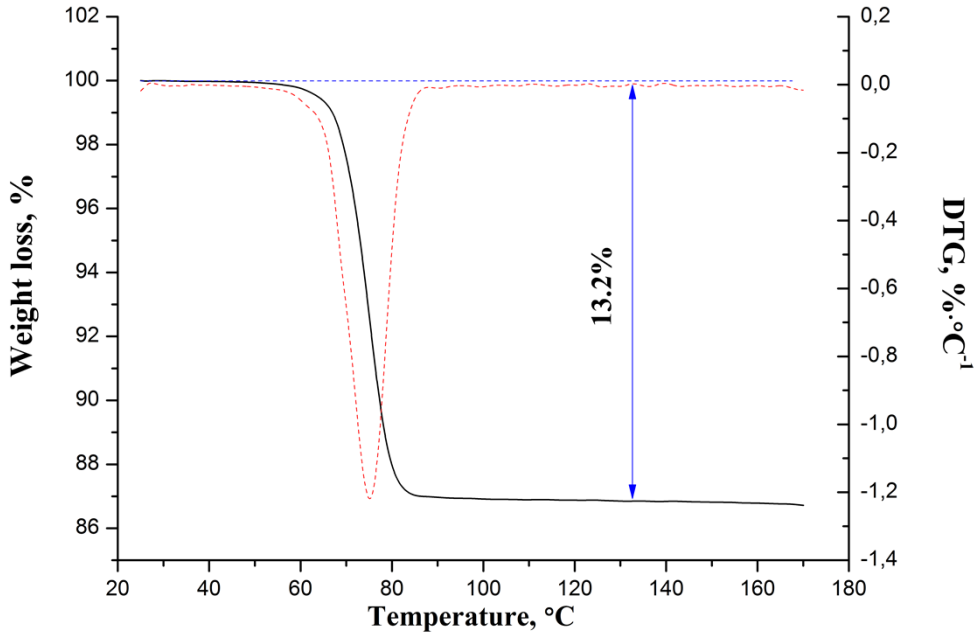


Fig. S9. TGA trace of **[Fel+ATN]** solvate

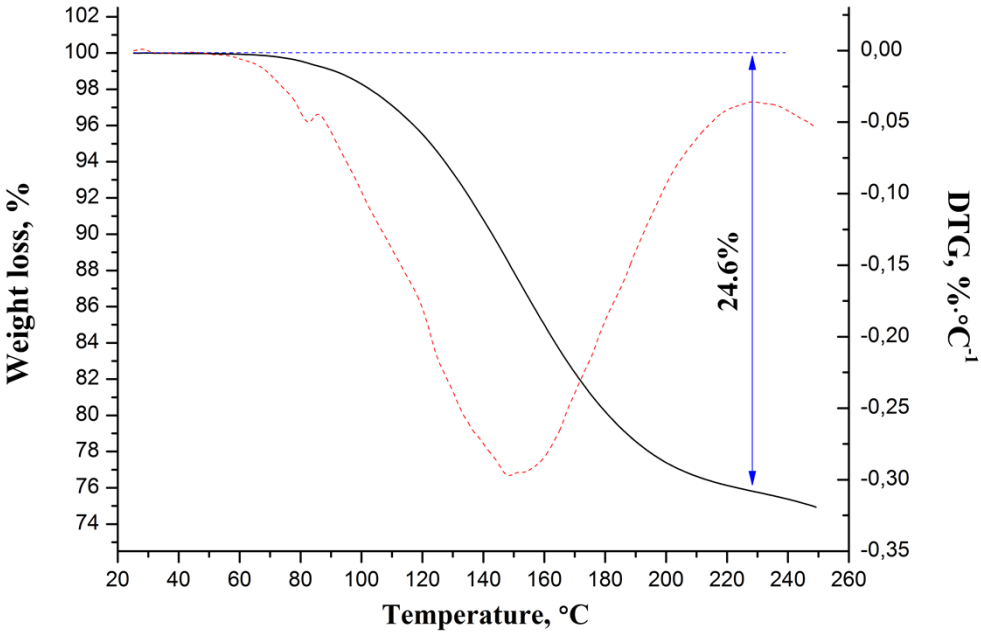


Fig. S10. TGA trace of **[Fel+APN]** solvate

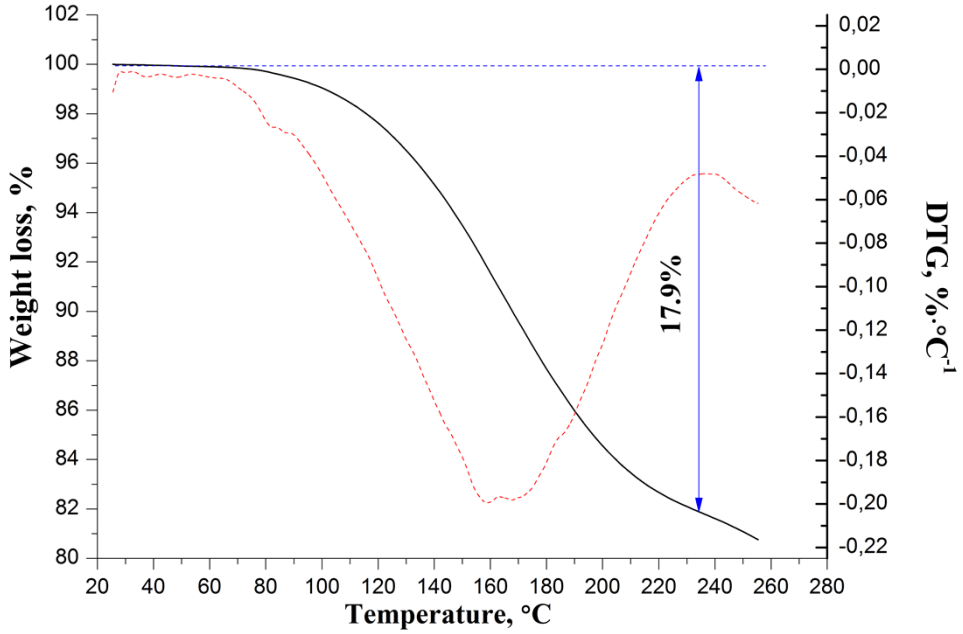
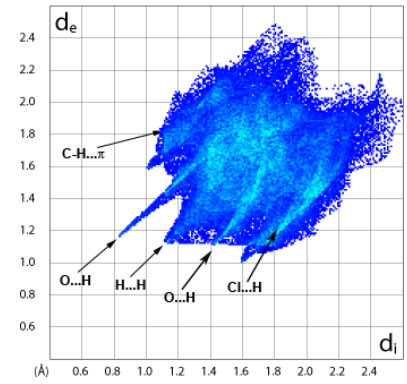
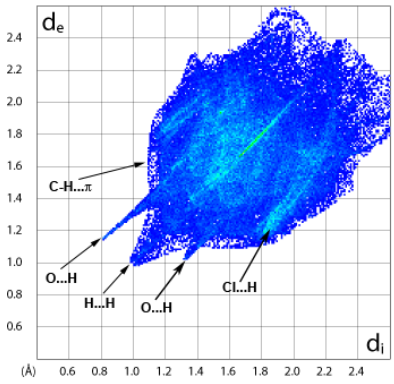


Fig. S11. TGA trace of **[Fel+DMSO]** solvate

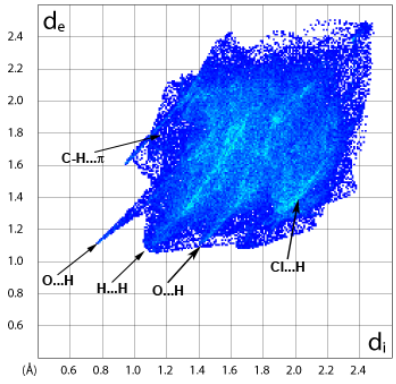
7. The 2-D fingerprint plots



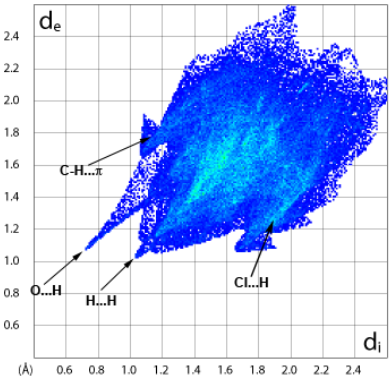
[Fel+ATN]



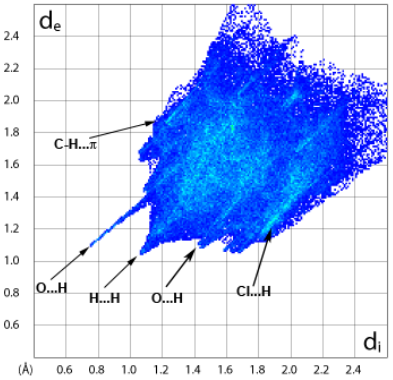
[Fel+APN]



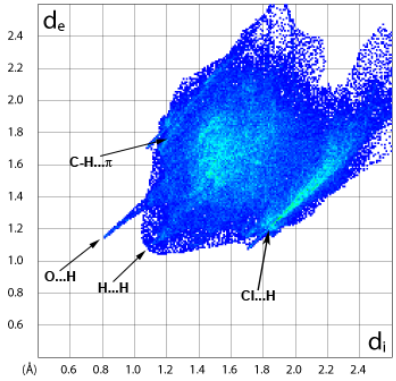
[Fel+DMSO]



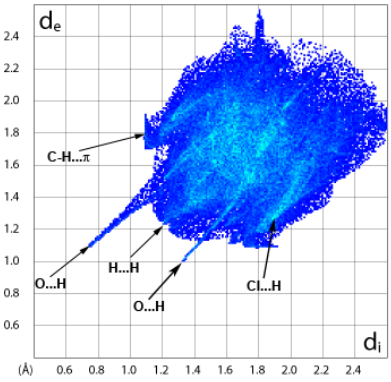
[Fel+DMAA]



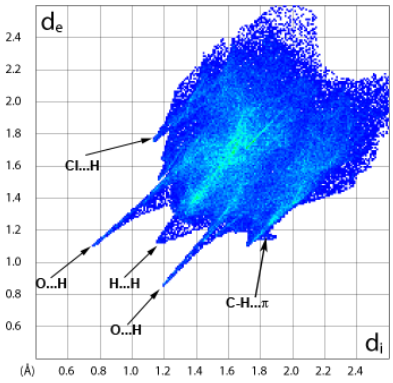
[Fel+DMEU]



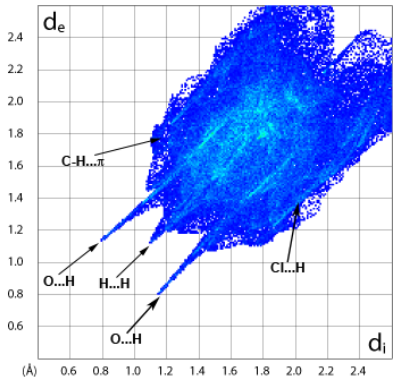
[Fel+TMU]



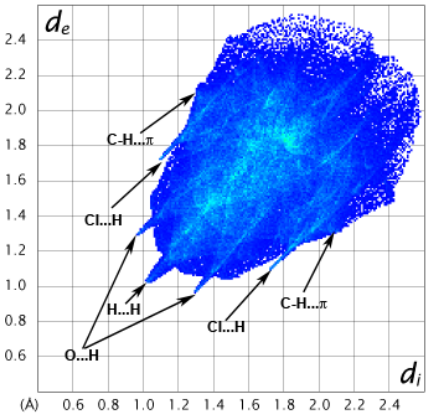
[Fel+DMF]



[Fel+N-MeFA]



[Fel+FA]



Fel form I

Fig. S12. 2D fingerprint plots of the felodipine solvates and Fel form I.

8. Solution calorimetry data

Table S1. The weight, g (mg), solution concentrations, m (mol kg^{-1}), and solution enthalpies, ΔH^0_{sol} (kJ·mol^{-1}), of felodipine and its solvates in respective solvents at 298 K.

Dimethyl sulfoxide (DMSO)					
Felodipine			[Fel+DMSO]		
mg	m·10^{-3}	ΔH^0_{sol}	mg	m·10^{-3}	ΔH^0_{sol}
23.6	1.26	15.2	10.6	0.46	31.7
33.6	1.79	15.2	17.7	0.77	30.4
34.2	1.83	15.2	16.1	0.67	31.0
23.4	1.25	15.1	15.3	0.64	30.2
	$\Delta H^{m,298}_{sol}$	=15.2 ± 0.1		$\Delta H^{m,298}_{sol}$	=30.8 ± 0.3
Acetophenone (ATN)					
Felodipine			[Fel+APN]		
mg	m·10^{-3}	ΔH^0_{sol}	mg	m·10^{-3}	ΔH^0_{sol}
15.1	0.77	11.7	14.9	0.62	27.1
15.1	0.77	10.8	15.1	0.63	27.3
15.1	0.86	11.0	15.0	0.62	27.7
15.1	0.86	11.1	15.0	0.62	27.0
			15.0	0.62	26.5
	$\Delta H^{m,298}_{sol}$	=11.1 ± 0.2		$\Delta H^{m,298}_{sol}$	=27.1 ± 0.2

9. Crystallographic data of the felodipine solvates

Table S2. Crystallographic data for the felodipine solvates reported in the literature.

Compound reference	**[Fel+FA]**	**[Fel+DMF]**	**[Fel+ N-MeFA]**	**[Fel+DMAA]**	**[Fel+DMEU]**	**[Fel+TMU]**
Chemical formula	$C_{18}H_{19}Cl_2NO_4$•CH_3NO	$C_{18}H_{19}Cl_2NO_4$•C_3H_7NO	$C_{18}H_{19}Cl_2NO_4$•C_2H_5NO	$C_{18}H_{19}Cl_2NO_4$•C_4H_9NO	$C_{18}H_{19}Cl_2NO_4$•$C_5H_{10}N_2O$	$C_{18}H_{19}Cl_2NO_4$•$C_5H_{12}N_2O$
Formula Mass	429.29	434.24	443.31	471.36	498.39	500.41
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic
a/Å	9.6360(19)	8.8600(10)	9.5850(19)	9.1075(4)	28.6544(12)	16.3261(18)
b/Å	11.335(2)	16.008(3)	10.799(2)	15.7970(7)	11.4450(5)	11.4866(11)
c/Å	11.685(2)	16.657(4)	11.388(2)	16.6894(7)	14.5730(6)	14.7468(17)
a/Å	100.99(3)	90.00	74.70(3)	90.00	90.00	90.00
β/°	112.09(3)	103.560(10)	88.60(3)	105.699(1)	90.715(1)	111.959(3)
γ/°	107.52(3)	90.00	74.08(3)	90.00	90.00	90.00
Unit cell volume/Å^3	1058.9(4)	2296.6(7)	1091.9(4)	2311.55(17)	4778.8(3)	2564.9(5)
Temperature/K	295(2)	293(2)	293(2)	150(2)	150(2)	220(2)
Space group	*P***Error!**	*P*21/*c*	*P***Error!**	*P*21/*n*	*C*2/*c*	*P*21/*c*
No. of formula units per unit cell, *Z*	2	4	2	4	8	4
No. of reflections measured	8620	5265	4557	30341	36365	21211
No. of independent reflections	4547	4045	4262	5576	5967	5566
R_{int}	0.0157	0.0315	0.1243	0.0271	0.0242	0.0626
Final R_1 values ($I > 2\sigma(I)$)	0.0627	0.0543	0.0630	0.0475	0.0469	0.0563
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1872	0.1319	0.1647	0.1343	0.1202	0.1420
Final R_1 values (all data)	0.0692	0.1039	0.1718	0.0578	0.0540	0.1033
Final $wR(F^2)$ values (all data)	0.1978	0.1545	0.1943	0.1422	0.1248	0.1579
Goodness of fit on F^2	1.078	1.026	0.899	1.070	1.084	0.959
Ref. code	COXGOM	[8]	[8]	BICNEI	BICNAE	BICMUX

10. References

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