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A furosemide – isonicotinamide cocrystal: An investigation of properties and extensive structural disorder.

Supplementary Information

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IDR and solubility of the 2FS-INA cocrystal



Figure S1 Dissolution curve for pure FS and 2FS-INA over 6 hours. Note that FS data points are reproduced from Goud *et al., J. Pharm. Sci.*, 2012, **101**, 664 for the purposes of comparison.

Table S1 Summary of the IDR and solubility tests for known FS cocrystals. All values are given to two significant figures.

Cocrystal	Apparent solubility ^a / mg L ⁻¹	Coformer solubility / mg mL ⁻¹	IDR ^b / mg cm ⁻² min ⁻¹	Stability after solubility test
FSc	118		$44 imes10^{-3}$	Stable after 48 h
2FS-INA	660 (× 5.6)	200	$44 imes10^{-3}$ ($ imes$ 1.0)	Partially converted
FS-CAF ^c	720 (× 6.1)	22	$87 imes10^{-3}$ ($ imes$ 1.9)	Stable after 48 h
FS-URE ^c	630 (× 5.3)	1000	$83 imes10^{-3}$ (× 1.9)	Converted
FS-PABA ^c	370 (× 3.1)	5	$53 imes10^{-3}$ (× 1.2)	Converted
FS-ACT ^c	810 (× 6.9)	2000	$94 imes10^{-3}$ (× 2.1)	Converted
FS-NA ^c	1040 (× 8.8)	1000	$111 imes10^{-3}$ (× 2.5)	Converted
FS-INA ^c	860 (× 7.2)	190	$102 \times 10^{-3} (\times 2.3)$	Converted
FS-ADEN ^c	790 (× 6.7)	9	$91 imes 10^{-3}$ (× 2.1)	Stable after 48 h
FS-CYT ^c	1300 (× 10.7)	8	116×10^{-3} (× 2.6)	Stable after 48 h

^a After 24 hours

^b In water; enhancement compared to FS is shown in brackets

^c Taken from Goud *et al., J. Pharm. Sci.*, 2012, **101**, 664, with the average IDRs including the interval between t = 0 and the first measurement point. The same treatment of the 2FS-INA data set gives an IDR value of 56×10^{-3} (× 1.3)

Density Functional Theory

Fig. S2 shows the overlay of the four simulated disorder structures, which compare well with the experimental XRD structure given in Fig. 3 in the main text. Some "wobble" can be seen at the furan ring of **FS1**, which correlates with the furan ring disorder on **FS2**.



Figure S2 Overlay of four of the structures used in CASTEP calculations after full optimisation with H35 fixed in position in two cases. Note that the orientation of the asymmetric unit is the same as shown in Fig. 3 in the main text.





Figure S3 A magnified region of the ¹³C CPTOSS (bottom) and CPTOSS with non-quaternary suppression (top) spectra of 2FS-INA at 8 kHz MAS. The non-quaternary suppression experiment used a dipolar dephasing delay of 80 μs. Quaternary carbon peaks are labelled and residual peaks from dynamic carbon sites are in italic.



Figure S4 ¹H - ¹³C HETCOR at 9.5 kHz MAS with 200 µs contact time to allow only short-range correlations to be observed. Protonated carbon peaks and corresponding correlations are labelled.



Figure S5 ¹H - ¹³C HETCOR at 9.5 kHz MAS with 1 ms contact time to allow long-range correlations to be observed. Quaternary carbon correlations are labelled as well as the CH_2 correlations. The H11 peak was not observed.

It is noted that the intermolecular ¹H-¹³C distances between the furan ring and surrounding molecules are rather large (more than 3 Å) making it difficult to observe characteristic correlation peaks associated with the ring disorder.

Atom Label	Chemical shift / ppm	Notes ^{b,c}	Atom Label	Chemical shift / ppm	Notes ^{b,c}
C82	43.6	C, S, L H5: 2.16 Å, H3: 2.64 Å.	C32	140.9	C?,S.
C81	46.3	C, S, L H39: 2.16 Å, H38: 2.66 Å.	C52	140.9	C?, Q, broad due to proximity to Cl.
C111	111.6	C, S.	C51	141.6	C?, Q, broad due to proximity to Cl.
C21	114.2	Q?, L? H32: 2.13 Å, H39: 2.46 Å.	C72	147.6	C?, Q,? L? H5: 2.01 Å
C101	114.2	C, S.	C122	147.6	C?, S.
C102	116.4	C?, S.	C121	149.5	C, S.
C112	116.4	C?, S.	C71	149.5	C, Q?, L? H21: 1.99 Å, H51: 2.17 Å.
C22	117.4	Q?, L H16: 2.14 Å, H5: 2.54 Å.	C5'	150.6	C, S.
C62	118.0	C, S.	C1'	152.6	C, S.
C61	119.6	C, S.	C91	157.1	C, Q, L H40a,H40b: 2.14 Å, H45: 2.20 Å, H39: 2.50 Å.
C41	128.8	C, Q, L? H32: 2.14 Å.	C3′	158.8	C?, Q?, L? H4': 2.16 Å, H3': 2.18 Å, H1': 2.67 Å.
C42	130.3	C,Q.	C92	159.4	C?, Q?, L H6a,H6b: 2.13 Å, H103: 2.19 Å.
C2'	130.3	C, S.	C6'	173.7	C, Q, L H48a,H48b: 2.06 Å, H14: 2.52 Å, H54?: 2.70 Å.
C4'	130.3	C, S.	C11	176.5	C, Q.
C31	140.9	C?, S.	C12	177.3	C, Q, S, L H14: 1.93 Å, H5: 2.43 Å.

Table S2 List of all carbon atoms with assignments^a and comments.

^a From CPTOSS spectrum acquired at 125.67 MHz at ambient temperature.

^b Symbols used to indicate the basis of assignment: C = calculated ¹³C shielding from CASTEP, Q = ¹³C peak in non-quaternary suppression spectrum, S = cross peak visible in short contact time HETCOR experiment, L = cross peak visible in long contact time HETCOR experiment, ? = evidence is suggestive rather than definitive.

^c Distances to non-bonded hydrogen atoms are given up to 2.70 Å.

Atom		CASTEP Label	Predicted chemical shielding / ppm						
Label	CIF Label		r1s1	r1s2 ^a	r1s2-f	r2s1	r2s2ª	r2s2-f	
C52	C2	C1	28.11	26.5	27.92	28.71	26.91	28.31	
C62	C3	C2	55.11	54.49	54.9	55.83	55.78	55.7	
C72	C4	C3	16.67	17.01	16.91	17.16	17.32	17.08	
C82	C6	C4	134.17	134.34	134.17	133.14	133.35	133.06	
C92	C7	C5	12.44	12.46	11.69	16.94	16.72	16.41	
C22	C12	C6	60.53	61.52	60.77	59.93	60.93	60.07	
C12	C13	C7	-6.33	-6.54	-6.26	-6.63	-6.81	-6.63	
C32	C16	C8	33.62	33.47	33.28	32.57	32.58	32.55	
C42	C17	C9	42.36	41.1	41.61	42.03	40.96	41.25	
C122	C101	C10	26.17	25.16	26.93	20.28	20.82	20.58	
C102	C103	C11	57.5	57.71	57.35	54.7	54.2	55.09	
C112	C102	C12	55.67	57.33	55.93	62.18	62.09	63.29	
C51	C23	C13	31.05	29.14	28.16	31.69	29.66	28.35	
C41	C24	C14	43.3	44.35	42.75	43.31	44.33	43.2	
C31	C32	C15	34.71	32.22	32.96	34.42	31.99	32.67	
C21	C33	C16	57.62	56.62	60.45	57.59	56.67	60.05	
C11	C34	C17	-5.67	-6.28	-4.03	-5.63	-6.18	-3.86	
C71	C37	C18	16.74	17.85	18.05	16.97	17.81	18.15	
C61	C38	C19	53.64	53.37	53.57	52.79	53.17	52.77	
C81	C40	C20	130.73	130.24	130.34	130.43	130.23	130.21	
C91	C41	C21	15.06	14.55	15.37	14.29	14.13	14.95	
C121	C43	C22	21.34	21.26	21.15	20.87	20.86	20.38	
C111	C44	C23	56.46	56.73	55.83	57.06	57	56.44	
C101	C45	C24	60.46	61.86	61.25	61.16	61.87	61.36	
C6'	C47	C25	-1.62	-0.3	-1.05	-1.98	-0.31	-1.28	
C3'	C49	C26	25.66	23.32	25.71	24.91	23.13	25.24	
C2'	C50	C27	42.93	40.25	42.64	42.93	40.48	42.54	
C1′	C51	C28	17.92	21.06	18.14	18.19	21.21	18.14	
C5′	C53	C29	21.17	25.78	19.92	21.39	25.75	19.84	
C4'	C54	C30	43.05	41.89	42.95	43.45	42.05	43	

 Table S3 Predicted ¹³C chemical shielding values for the 6 simulated disorder structures of 2FS-INA.

^a These structures showed (incorrectly) transfer of the H11 across the SSHB.





Figure S6 Variable temperature ¹³C CPTOSS spectra. Dashed lines are guides for the eye centred on 20 °C peaks that show temperature-dependant behaviour. All spectral changes were fully reversible. The spinning rate was 8 kHz except at -50 °C where the sample was spun at 5 kHz.

No significant drift or broadening is observed at the peaks assigned as C102-C122, but some changes occur in the region assigned to C101 and C21 as the temperature was lowered indicating that there is some dynamics. C1' and C5' of the phenyl ring of INA can be seen to remain as distinct peaks meaning no flipping of the phenyl ring occurs, although all lines broadened at -50 °C. Variable temperature CRAMPS spectra were also obtained but no changes were observed over the range -25 °C to 60 °C due to the broad and strongly overlapped nature of the ¹H signals.



Figure S7 Batch 1 (bottom) and batch 2 (top) deuterated 2FS-INA by the " D_2O shake" method. The centre-bands are magnified on the right.

The D_2O shake method was not a reliable way of reproducibly deuterating the cocrystal; the longer the sample was suspended in D_2O the more degradation was seen to occur, as shown by the large number of peaks visible in the centre band of batch 2 in Fig. S7. These extra peaks are assumed to be degradation products of the cocrystal breaking up into a mixture of the cocrystal and the starting materials.



Figure S8: An example of the fitting of the ²H quadrupolar parameters of 2FS-INA with the simulated spectrum shown above the experimental spectrum at -50 °C.

	r1	ls1	r1	Ls2 ^a	r1	.s2-f	r:	2s1	r2	s2 ^a	r2s	52-f
Site	C _Q / kHz	η	<i>C_Q /</i> kHz	η	C _Q / kHz	η	C _Q / kHz	η	<i>C_Q /</i> kHz	η	C _Q / kHz	η
H41a ^b and <i>H41b</i> ^b	233	0.15	196	0.18	210	0.18	234	0.14	196	0.18	212	0.18
H42 ^b	225	0.17	227	0.15	229	0.15	224	0.17	227	0.15	230	0.15
H1' ^b	208	0.15	203	0.15	207	0.15	205	0.15	203	0.15	206	0.15
H21 and H22	191	0.21	194	0.20	196	0.21	194	0.20	194	0.12	199	0.20
H12	134	0.16	143	0.16	140	0.16	134	0.15	144	0.14	143	0.15
H11	33	0.60	55	0.37	67	0.37	27	0.73	53	0.39	63	0.39

Table S4 CASTEP-calculated quadrupolar parameters for all exchangeable proton sites.

^a These structures showed (incorrectly) transfer of the H11 across the SSHB.

^b The values of the two deuterium sites are very similar and so the values given are averaged.



Figure S9 Variation in the linewidth of the disordered sulphonamide ²H centre band with temperature.

The linewidth of the disordered sulphonamide peak in Fig. 6 of the main text was measured at different temperatures by deconvolution in GSim. The line of best fit has a gradient of 1143 K corresponding to an activation barrier of 9.5 kJ mol⁻¹, including a temperature correction of +15 K to account for friction under MAS, compared to 16.7 kJ mol⁻¹, obtained from ²H T_1 relaxation times. Given the different timescales being probed by the ²H T_1 relaxation times compared to the linewidth measurements along with the likelihood that the sulphonamide motion is not simple, it is reasonable to suppose that the underlying process is the same for both datasets. The estimate from the linewidths is considerably more suspect: firstly, since it assumes that any other contributions to linewidth are independent of temperature, and secondly values obtained from fitting the full T_1 minimum are intrinsically more robust that values derived from a limited section of the "rate" vs. inverse temperature curve.

¹H-¹H Correlation

The ¹H DQ/SQ experiment shown in Fig. S10 probed dipolar interactions between closely packed hydrogen atoms to see if the ¹H-¹H intermolecular distances proved to be sensitive to the local structure of the furan ring. The two hydrogen atoms in HBs, H12 and H11, have significantly higher chemical shifts than the other protons and are easy to distinguish in the spectrum. A weak correlation (**D**) is observed to H11 in Figure S9, assigned as H11–H2' ($r_{H11-H2'}$ = 2.53 Å). Correlation **A** is assigned as the correlation between H12 and H1' on the INA molecule ($r_{H12-H1'}$ = 2.53 Å). Two other correlations **B** and **C** are also observed to H12, corresponding to either H4' on the INA molecule ($r_{H12-H4'}$ = 2.69 Å) or H72 associated with the disordered furan ring ($r_{H12-H72}$ = 2.66 Å (**R1**), > 4 Å (**R2**)). **B** was assigned as the H12–H72 correlation because the heteronuclear C102/C112–H72/H82 correlation was observed in the HETCOR spectrum at a lower ¹H chemical shift than the C2'/C4'–H3'/H4' correlation. **C** was therefore assigned as the H12–H4' correlation.



Figure S10 ¹H-¹H DQSQ spectrum of FS-INA at 50 kHz MAS showing correlations from H12 and H11. The correlation D is overlaid as an inset magnified by 2. Hydrogen atom labelling is also shown.

The ¹H-¹H double-quantum single-quantum (DQ/SQ) spectrum given in Fig. S10 was recorded at a ¹H frequency of 499.7 MHz using a 1.3 mm rotor (r.o.d.) at 50 kHz MAS using 4 rotor cycles in the back-to-back (BABA)¹ recoupling sequence. The recycle delay was 10 seconds and a 16-step phase cycle was applied with a rotor synchronisation

period of 16.67 μ s. For each of the 32 t_1 increments 1024 transients were co-added using the States-TPPI method. Increasing the MAS rate to 62 kHz did not give a significant enhancement in resolution.

Rapid dynamic disorder of a 180° rotation of the **FS2** the furan ring would reduce the dipolar coupling between H12 and H72 by close to a factor of two: averaging the dipolar tensors corresponding to r_{H-H} distances of 2.66 Å and 5.43 Å, taking into account the difference of 50° in the tensor orientations, gives a mean dipolar coupling of 3.26 kHz corresponding to an effective internuclear distance of 3.3 Å. This compares to a coupling of 6.38 kHz for the 2.66 Å distance in **R1** conformation. This reduction is relatively small and, since it is difficult to measure ¹H-¹H dipolar couplings very accurately due to spin diffusion, it is hard to be sure whether correlation **B** was affected by dynamic disorder of the furan ring or not. This would be even more difficult if **FS2** was undergoing small angle motion. More definitive results might be obtained in a system where the major occupied position resulted in a weak dipolar coupling while the minor position resulted in a strong coupling, the opposite case to FS-INA. Better still would be a system that contained an isolated spin pair, for example if H12 was substituted for a fluorine, in which case the ¹⁹F-¹³C dipolar coupling strength could be accurately measured.

¹³C T₁ Relaxation Data

Tomporaturo / K	Noise ^b / 10 ⁷	T_1 / seconds						
		C101	C102/C112	C122	C121	C111ª		
353	1.6	2.3(5)	1.8(2)	1.5(1)	1.2(1)	-		
343	1.6	2.4(4)	1.5(1)	1.06(7)	1.02(8)	2(1)		
333	1.7	1.3(2)	1.1(1)	0.75(7)	0.93(9)	1.9(6)		
323	1.7	1.2(1)	0.97(7)	0.67(6)	0.81(8)	1.8(7)		
313	1.5	1.0(1)	0.81(4)	0.61(4)	0.75(5)	1.6(5)		
303	1.3	0.84(5)	0.7(3)	0.45(2)	0.67(4)	1.1(2)		
293	1.6	0.67(5)	0.69(3)	0.39(2)	0.69(5)	1.4(2)		
283	1.6	0.71(5)	0.62(3)	0.38(2)	0.65(5)	2.3(7)		
273	1.5	0.70(5)	0.66(3)	0.35(2)	0.65(5)	2.3(7)		
263	1.7	0.56(4)	0.61(4)	0.32(2)	0.72(6)	2.0(7)		
248	1.7	0.59(4)	0.65(4)	0.40(2)	1.2(1)	1.5(5)		
233	1.9	0.70(6)	0.90(9)	0.43(3)	0.8(2)	-		

Table S5 Variable temperature ${}^{13}CT_1$ parameters for the carbon sites of the two furan rings.^a

^a C111 was too noisy to be fit satisfactorily.

^b Standard deviation of the noise level calculated in Topspin and used as the noise level in the fitting procedure.

Alternate modelling of 2FS-INA XRD data

Figure S11 shows the result of fitting the 2FS-INA XRD data using single atomic sites and anisotropic ADPs for all non-hydrogen atoms. Note that the elongated ADPs of the **FS1** furan ring (left), which was originally modelled with split sites and isotropic ADPs, i.e. two orientations of the ring, are not significantly larger than those of **FS2**, with was originally modelled with single sites and anisotropic ADPs. The R-factors for this fitting and the original model are very similar (9.8% and 10.5%, respectively, noting the former has 19 free parameters more) i.e. in this case it was not possible to distinguish between small-angle and large-angle reorientations of the furan ring on the basis of a single-temperature XRD experiment. This was part of the rationale for the present solid state NMR study.



Figure S11 The asymmetric unit of 2FS-INA with the disordered groups modelled as elongated ADPs.

1. M. Feike, D. E. Demco, R. Graf, J. Gottwald, S. Hafner and H. W. Spiess, *J. Magn. Reson.*, 1996, 122, 214-221.