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Stabilizing volatile liquid chemicals using co-crystallization

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Supplementary Information

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1. General experimental details

A1-A6 were prepared using a previously reported methods.[1] **D1** was purchased from Alfa Aesar, **D2** from Sigma-Aldrich and **D3** from Matrix Scientific and used without further purification. The determinations of melting points were carried out on Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Unity plus 400 MHz spectrometer in $CDCl_3$. Infrared spectroscopy was carried out on a Nicolet 380 FT-IR. Powder diffraction patterns were recorded on a Bruker AXS D8 advance X-ray diffractometer.

2. Synthesis of Acceptors

Synthesis of A1

A solution of 30% hydrogen peroxide (2.84g, 0.084 mol) in 20 mL of acetic acid was added dropwise using a drop funnel over a period of 2.5 hours to a solution of pyrazine (3.36g, 0.042 mol) in 25 mL of acetic acid at 70-80^{o}C. Refluxing was continued for about 24 hours and confirmed the product formation with TLC. Acetic acid was removed on a rotary evaporator, and then 10 mL of water was added followed by evaporation. The residue was dissolved in 50 mL of hot chloroform and dried with a mixture of sodium sulfate and sodium carbonate and the solvent was removed on a rotary evaporator. The residue was chromatographed on silica with variant ratio mixtures of chloroform-methanol as the eluant. **A1** was isolated as an off white solid. **A1** - (3.13g, 77%); m.p.: 110-113^{0}C; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 8.09 (d, 2H), 8.45 (d, 2H).

Synthesis of A2

A solution of 30% hydrogen peroxide (2.84g, 0.084 mol) in 20 mL of acetic acid was added dropwise using a drop funnel over a period of 2.5 hours to a solution of tetramethylpyrazine (2.85g, 0.021 mol) in 25 mL of acetic acid at 70-80^{o}C. Refluxing was continued for about 24 hours and confirmed the product formation with TLC. Acetic acid was removed using a rotary evaporator, 10 mL of water was added followed by evaporation. The residue was dissolved in 50 mL of hot chloroform and dried with a mixture of sodium sulfate and sodium carbonate and the solvent removed on a rotary evaporator. The residue was chromatographed on silica with variant ratio mixtures of chloroform-methanol as the eluant. **A2** was isolated as a pure white solid. **A2** - (1.87g, 53%), m.p.: 220 -222^{0}C; ^{1}H NMR (δH; 400 MHz, $CDCl_3$): 2.56 (s, 12H).

Synthesis of A3

To a flask containing 3-cyanopyridine (2.00 g, 0.019 mol) and MeOH (20 mL) a 30% solution of NaOMe in MeOH (0.36 mL, 1.90 mmol) was added. The reaction mixture was stirred for one hour at room temperature. Aminoacetaldehyde dimethyl acetal (2.07 ml, 1 eq) followed by AcOH (2.09 mL, 37 mmol) was added dropwise. The reaction mixture was heated to reflux for

30 min. After cooling the reaction mixture to room temperature, MeOH (15 mL) and 6 N HCl in H_2O (10 ml) were added, and the mixture was heated to reflux for 8 hours. Once the cyclization was complete, the solution was evaporated to dryness on a rotary evaporator. A freshly prepared warm solution of K_2CO_3 (50% w/w in water) was added carefully, bringing pH to 10. The resulting suspension was allowed to cool to room temperature and recrystallized from boiling water to obtain 3-(imidazol-2-yl)pyridine, **A3** as an off-white solid (2.33 g, 85%): mp 197–201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (br s, 1H), 9.14 (d, 1H), 8.53 (dd, 1H), 8.26 (dt, 1H), 7.47 (dd, 1H), 7.21 (br s, 2H).

Synthesis of A4

A 100-mL flask was charged with pyrazine-2-carbonitrile (1.05 g, 10 mmol), MeOH (10 mL), and a 30% solution of NaOMe in MeOH (0.38 mL, 1 mmol). The reaction mixture was stirred for 40 minutes at room temperature. Aminoacetaldehyde dimethyl acetal (1.09 ml, 1 eq) was added to the reaction mixture followed by AcOH (1.2 mL, 20 mmol). The reaction mixture was heated to 50 °C for 1 h and then cooled to room temperature. MeOH (20 mL) and 6 N HCl in H_2O (5 mL) were added, and the reaction mixture was heated to reflux for 5 hours. Once the cyclization was complete, the solution was removed on a rotary evaporator, and the residue was taken up in a 1:1 mixture of H_2O and Et_2O. The layers were separated and the pH of the aqueous layer was adjusted to pH 9 with 2 N aqueous NaOH. Then the aqueous mixture was stirred for 30 min to allow complete precipitation of the product. The solid was collected by filtration and dried under vacuum to obtain pure 2-(1H-imidazol-2-yl)pyrazine, **A4** (0.83 g, 57%) as a white solid. mp 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (br s, 1H), 9.44 (d, 1H), 8.53 (d, 1H), 8.49 (m, 1H), 7.31 (br s, 1H), 7.23 (br s, 1H).

Synthesis of A5

2,2'-Biimidazole (0.27g, 2 mmol) and NaOH (0.32 g, 8 mmol) were placed in a 100mL round bottomed flask with 20 mL of acetonitrile. The mixture was stirred at room temperature for two hours. 4-Picolyl chloride hydrochloride (0.65 g, 4 mmol) in acetonitrile (20 mL) was added to the mixture and refluxed for 24 hours at 50^0C – 60^0C. The reaction was monitored with TLC and after completion the solvent was removed by rotary evaporation. The residue was dissolved in water (50 mL) and extracted with methylene chloride (30 mL x 3). Organic layers were combined, dried over anhydrous $MgSO_4$ and rotary evaporated to obtain **A5** as a dark brown powder. Yield: 0.35 g (56%); mp 157-160^{0}C; ^{1}H NMR (δ_H; $CDCl_3$, 400MHz):8.49 (d, 4H), 7.11 (d, 2H), 6.94 (d, 2H), 6.91 (d, 4H), 5.84 (s, 4H).

Synthesis of A6

2,2'-Biimidazole (0.27g, 2 mmol) and NaOH (0.32 g, 8 mmol) were placed in a 100mL round bottomed flask with 20 mL of acetonitrile. The mixture was stirred at room temperature for two hours. 3-Picolyl chloride hydrochloride (0.65 g, 4 mmol) in acetonitrile (20 mL) was added to the mixture and refluxed for 24 hours at 50^0C – 60^0C. The reaction was monitored with TLC and upon completion the solvent was removed by rotary evaporation. The residue was dissolved in water (50 mL) and extracted with methylene chloride (30 mL x 3). Organic layers were combined, dried over anhydrous $MgSO_4$ and rotary evaporated to obtain **A6** as a brownish orange powder. Yield: 0.45 g (71%); mp 112-115^{0}C; ^{1}H NMR (δ_H; $CDCl_3$, 400MHz):8.46 (d, 2H), 8.45 (s, 2H), 7.39 (d, 2H), 7.17 (m, 2H), 7.11 (d, 2H), 6.95 (d, 2H), 5.78 (s, 4H).

3. Synthesis of co-crystals

Grinding experiments

D1-**D3** were subjected to grinding experiments with the six acceptors (**A1**-**A6**). For grinding, 1:1 (iodoperfluoroalkane: **A1**-**A4**) or 2:1 (iodoperfluoroalkane: **A5**-**A6**) stoichiometric amounts were mixed together and was grinded using a drop of methanol for several minutes. After the solvent was completely evaporated the IR spectra were recorded. Successful interactions between the acceptor and donor were identified using the specific shifts of the peaks of halogen bond donors, Table S1.

Table S1: IR analysis of grinding experiments

Mixture	IR bands (cm^{-1})		Shifts Δcm^{-1}	Result
	Halogen bond donors	Grounded Mixture		
D1A1	1153 1099	1168 1075	+15 -24	Co-crystal
D1A2	1153 1099	1184 1117	+31 +18	Co-crystal
D1A3	1153 1099	1181 1108	+28 +9	Co-crystal
D1A4	1153 1099	1140 1082	-13 -17	Co-crystal
D1A5	1153 1099	1118 1083	-35 -16	Co-crystal
D1A6	1153 1099	1131 1083	-22 -16	Co-crystal
D2A1	1192 1133	1184 1117	-8 -16	Co-crystal
D2A2	1192	1182	-10	Co-crystal

	1133	1103	-30	
D2A3	1192 1133	1189 1130	-3 -3	Co-crystal
D2A4	1192 1133	1166 1117	-26 -16	Co-crystal
D2A5	1192 1133	1157 1099	-35 -34	Co-crystal
D2A6	1192 1133	1162 1137	-30 +4	Co-crystal
D3A1	1199 1141	1211 1168	+12 +27	Co-crystal
D3A2	1199 1141	1202 1137	+3 -4	Co-crystal
D3A3	1199 1141	1196 1137	-3 -4	Co-crystal
D3A4	1199 1141	1209 1137	+10 -4	Co-crystal
D3A5	1199 1141	1211 1134	+12 -7	Co-crystal
D3A6	1199 1141	1213 1138	+14 -3	Co-crystal

Solvent experiments

The solid ground mixtures were dissolved in a minimum amount of methanol and kept in a slightly open vial for the single crystal formation. Once the crystals are formed they were analyzed using IR spectroscopy and melting point analysis was done. Table S2 and Figures S1, S2, S3 includes the melting point results. Subsequently suitable crystals were analyzed using single crystal X-ray diffraction.

Table S2: Melting point analysis for the co-crystals obtained

Co-crystal	**Melting point of the iodoperfluoroalkane (^{0}C)**	**Melting point of the acceptor (^{0}C)**	**Melting point/decomposition point of the co-crystal (^{0}C)**
D1A2	-21	220-222	120-122
D1A3	-21	197-201	95-98
D1A5	-21	157-160	57-59
D2A1	-9	110-113	85-89
D2A2	-9	220-222	165-157
D2A3	-9	197-201	132-135
D2A4	-9	196-198	150-154
D2A5	-9	157-160	118-121

D2A6	-9	112-115	75-77
D3A2	25	220-222	119-122
D3A4	25	196-198	125-127
D3A5	25	157-160	94-98
D3A6	25	112-115	95-98

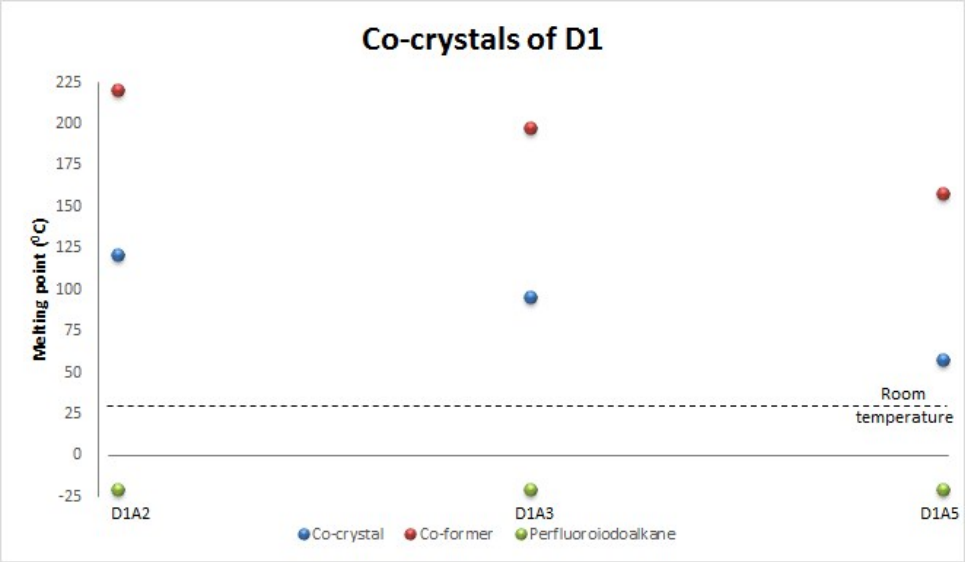

Figure S1: Melting point analysis for the co-crystals of **D1**

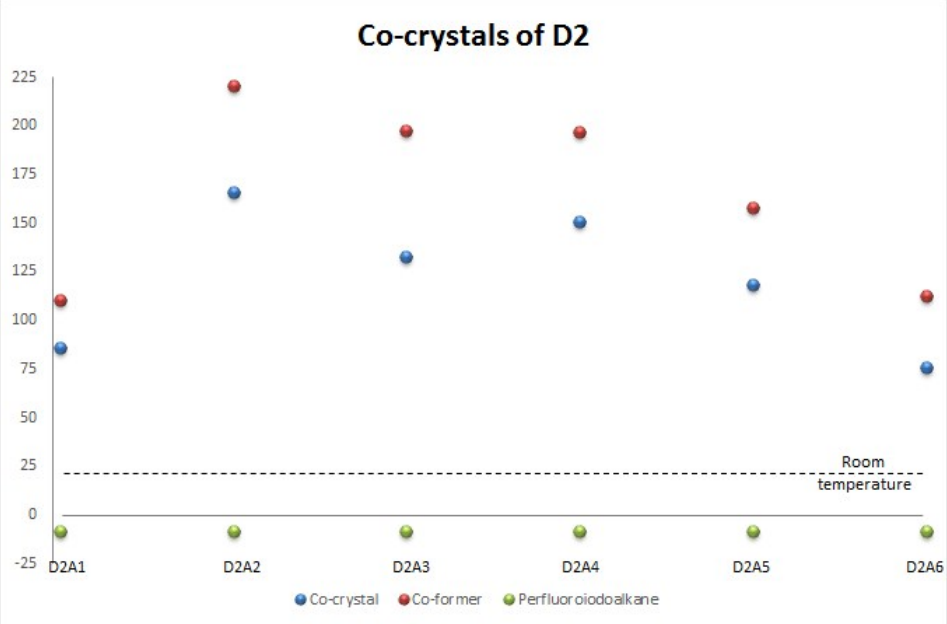

Figure S2: Melting point analysis for the co-crystals of **D2**

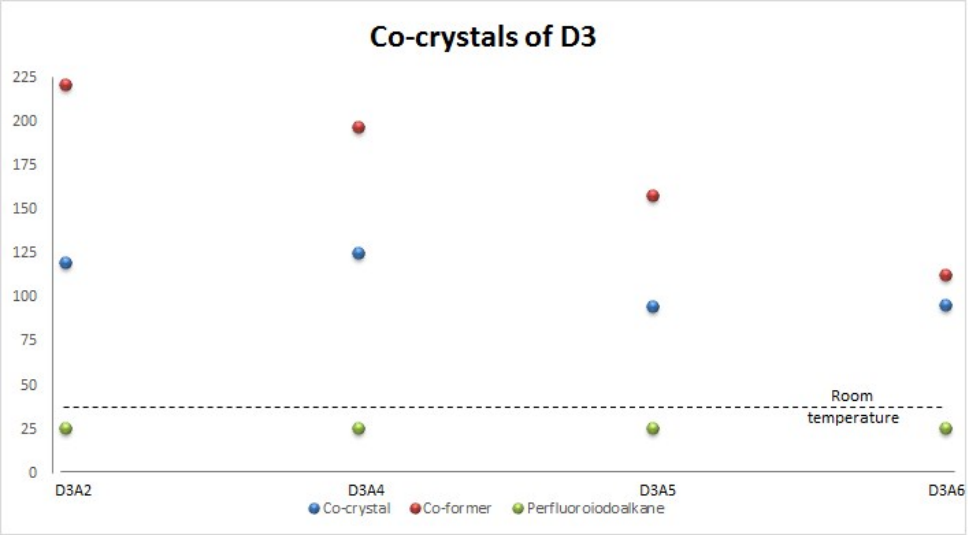

Figure S3: Melting point analysis for the co-crystals of **D3**

4. X-Ray crystallography

Out of eighteen experiments thirteen employed crystals suitable for single crystal X-ray diffraction. The thirteen co-crystal structures obtained are **D1A2, D1A3, D1A5, D2A1, D2A2, D2A3, D2A4, D2A5, D2A6, D3A2, D3A4, D3A5** and **D3A6**. The crystal structure details and interaction explanations for structures **D1A3, D1A5, D2A3, D2A4, D2A5, D2A6, D3A4, D3A5** and **D3A6** are reported elsewhere.[2] Crystallographic data and halogen bond geometries obtained for the **D1A2**, **D2A1**, **D2A2** and **D3A2** are reported in table S3 and S4. Table S3 also contains the crystallographic data for the two co-formers **A2** and **A5** (CCDC 1037236-1037241).

Datasets were collected on a Bruker APEX II system using MoKα radiation using APEX2 software.[3] Initial cell constants were found by small widely separated "matrix" runs. Data collection strategies were determined using COSMO.[4] Scan speed and scan widths were chosen based on scattering power and peak rocking curves. All datasets were collected at -153 °C using an Oxford Croystream low-temperature device.

Unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT,[5] using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Multi-scan absorption corrections were performed with SADABS.[6] Data were reduced with SHELXTL.[7] The structures were solved in all cases by direct methods without incident. Except for **D3A2**, all molecules were fully ordered. In **D3A2** the unit cell contains two halo compounds and two half-pyrazines. The contents were divided into two SHELXL RESIdues for refinement. One of the four $–CF_2I$ termini was slightly disordered, in an ~ 85%:15% ratio. Thermal parameter constraints and distance restraints were used to refine the minor species to convergence.

Table S3: Crystallographic data

Systematic name	**D1A2** I-$(CF_2)_2$-I, 2,3,5,6-Me_4-pyrazine-1,4-dioxide	**D2A1** I-$(CF_2)_4$-I, pyrazine 1-oxide	**D2A2** I-$(CF_2)_4$-I, 2,3,5,6-Me_4-pyrazine-1,4-dioxide	**D3A2** $[I-(CF_2)_6-I]_2$, 2,3,5,6-Me_4-pyrazine-1,4-dioxide	**A2** 2,3,5,6-Me4-pyrazine-1,4-dioxide	**A5** 1,1'-di[(4-pyridyl)methyl]-2,2'-biimidazole
Formula moiety	$(C_8H_{12}N_2O_2)$ $(C_2F_4I_2)$	$(C_4H_4N_2O)($ $C_4F_8I_2)$	$(C_8H_{12}N_2O_2)$ $(C_4F_8I_2)$	$(C_8H_{12}N_2O_2)$ $(C_6F_{12}I_2)_2$	$C_8H_{12}N_2O_2$	$C_{18}H_{16}N_6$
Empirical formula	$C_{10}H_{12}F_4I_2N_2$ O_2	$C_8H_4F_8I_2N_2O$	$C_{12}H_{12}F_8I_2N_2$ O_2	$C_{20}H_{12}F_{24}I_4N$ $_2O_2$	$C_8H_{12}N_2O_2$	$C_{18}H_{16}N_6$
Molecular weight	522.02	549.93	622.04	1275.92	168.20	316.37
Color, Habit	colourless plate	yellow prism	colourless plate	colourless prism	colourless rod	bronze prism
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group, Z	P2(1)/c, 2	P-1, 2	P2(1)/c, 2	P-1, 2	P2(1)/c, 2	P2(1)/c, 2
a, Å	8.6275(16)	5.3515(5)	9.3817(10)	12.3893(14)	3.8328(9)	5.1637(9)
b, Å	12.005(2)	11.1482(11)	12.8620(14)	12.6332(14)	10.291(3)	16.705(3)
c, Å	8.3466(15)	12.0159(12)	8.1127(9)	13.1553(14)	10.396(3)	9.1021(16)
α, °	90.00	85.076(2)	90.00	67.319(4)	90.00	90.00
β, °	118.080(5)	80.408(3)	110.521(3)	75.273(4)	98.770(9)	98.398(6)
γ, °	90.00	84.424(2)	90.00	67.884(4)	90.00	90.00
Volume, $Å^3$	762.7(2)	701.72(12)	916.82(17)	1745.6(3)	405.26(17)	776.7(2)
Density, g/cm^3	2.273	2.603	2.253	2.427	1.378	1.353
Temperature, °K	120(2)	120(2)	120(2)	120(2)	120(2)	120(2)
Crystal size, min x mid x max	0.10 x 0.22 x 0.28	0.14 x 0.28 x 0.34	0.08 x 0.26 x 0.40	0.18 x 0.24 x 0.32	0.42 x 0.16 x 0.12	0.22 x 0.26 x 0.40
X-ray wavelength, Å	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
μ, mm^{-1}	4.167	4.571	3.517	3.723	0.101	0.086
Absorption corr	multi-scan	multi-scan	multi-scan	multi-scan	multi-scan	multi-scan
Trans min / max	0.3883 / 0.6807	0.3056 / 0.5670	0.3336 / 0.7662	0.3821 / 0.5538	0.9590/ 0.9880	0.9664 / 0.9813
θ_{min}, °	2.68	2.61	2.32	1.69	2.80	2.44
θ_{max}, °	32.03	33.72	32.95	32.11	31.55	31.61
Reflections						
collected	11427	18809	11185	38902	4747	7122
independent	2488	5086	3188	11420	1245	2402
observed	2326	4597	2911	9437	987	2092
Threshold expression	>2σ(I)	>2σ(I)	>2σ(I)	>2σ(I)	>2σ(I)	>2σ(I)
R1 (observed)	0.0227	0.0258	0.0230	0.0421	0.0456	0.0482
wR_2 (all)	0.0527	0.0723	0.0615	0.1218	0.1333	0.1653
Goodness of fit (all)	1.039	1.128	1.082	0.994	1.103	1.319
Δρ max / min	2.752 / -1.138	0.639 / -0.969	0.776 / -1.122	1.496 / -1.733	0.364/ -0.214	0.470 / -0.397
2θ limit	31.00	30.00	30.00	30.00	30.00	27.50
Completeness to 2θ limit	0.981	0.988	0.997	0.980	0.967	0.954

Table S4: Halogen bonding geometries

Co-crystal	C-I---N/O	I---N/O (Å)	C-I---N/O (^{0})
D1A2	C(31)-I(1)-O(11)	2.7767(16)	171.75(7)
D2A1	C(21)-I(1)-O(11) C(24)-I(2)-N(14)#1	2.8543(18) 2.902(2)	163.78(8) 177.95(10)
D2A2	C(31)-I(1)-O(11)	2.7617(16)	174.62(7)
D3A2	C311-I11-O111 C361-I21-O112 C312-I32-O112	2.812(3) 2.770(3) 2.810(3)	174.45(13) 175.87(14) 175.72(17)

5. Stability studies of co-crystals for an extended time period

Three co-crystals, representing one for each iodoperflouoroalkane **D1A3**, **D2A5** and **D3A2** were selected and kept open to the environment. Initially co-crystal IR spectra were compared with their respective co-former IR spectra to confirm the formation of co-crystals. Confirmation was done by looking for specific peak shifts of the co-crystals IR spectrum compared to co-former IR spectra (Figure S4, S6 and S8). Then the single crystals obtained from co-crystal experiments were analyzed using IR spectroscopy and for their melting points up to six months. Figure S4-S9 shows the IR analysis for the three co-crystals up to six months. Table S5 summarizes the melting point data for the three co-crystals.

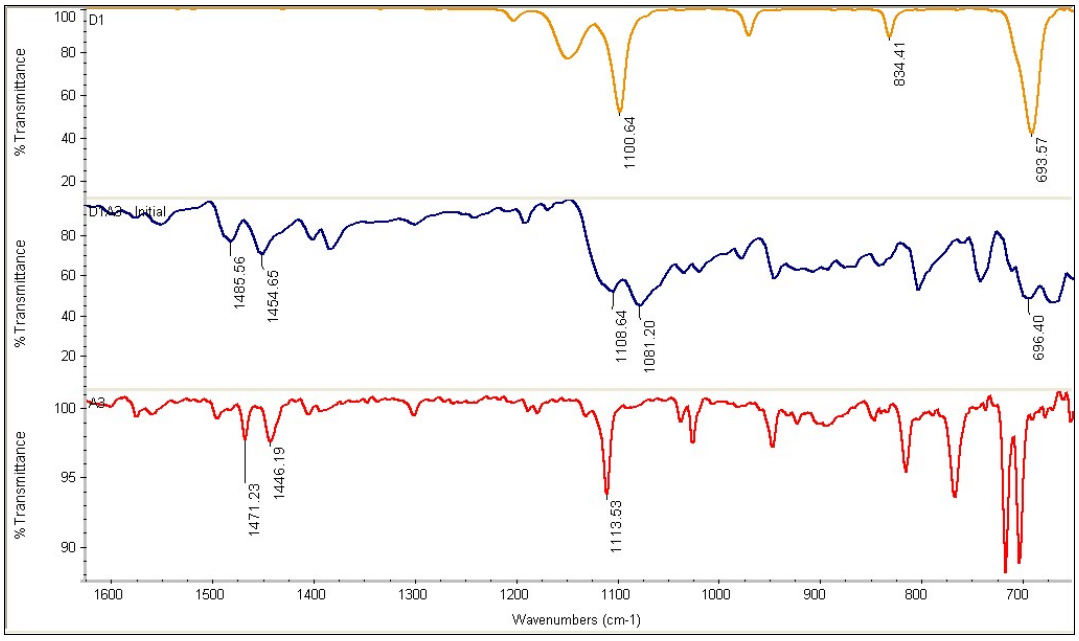

Figure S4: Comparison of IR peaks of **D1** and **A3** with the co-crystal **D1A3**

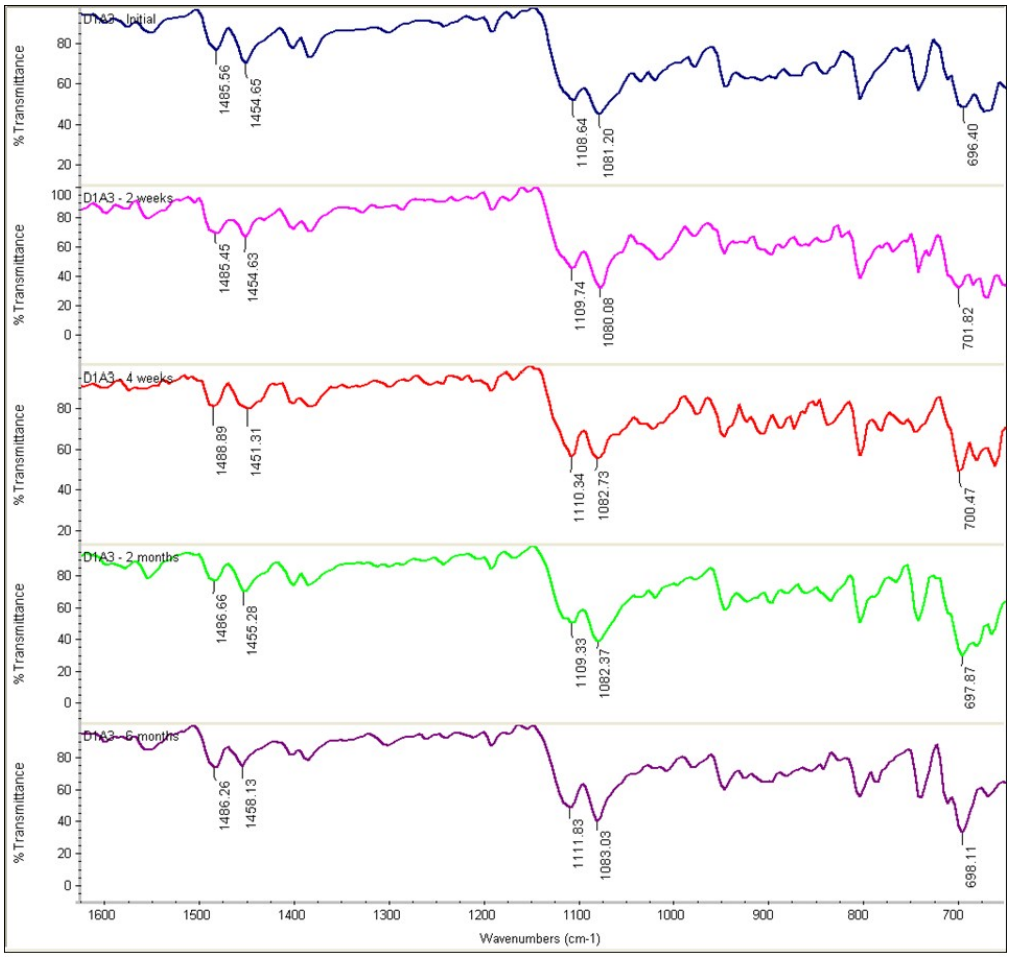

Figure S5: IR analysis of co-crystal **D1A3** for the stability

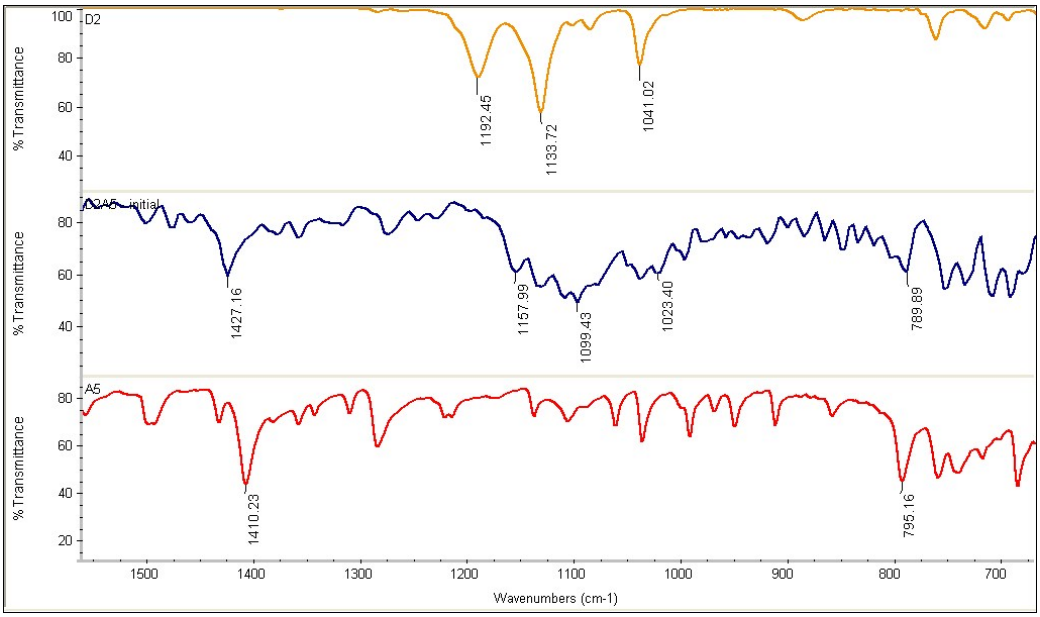

Figure S6: Comparison of IR peaks of **D2** and **A5** with the co-crystal **D2A5**

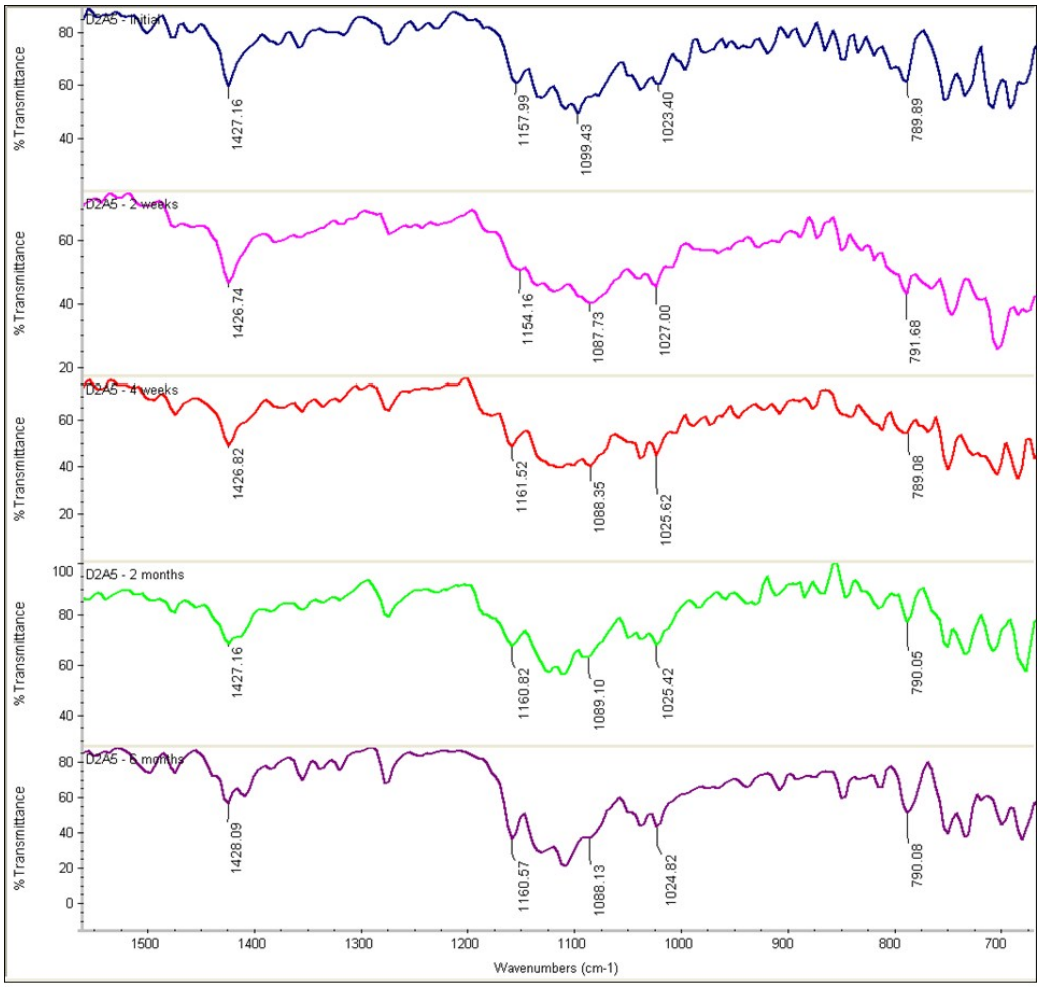

Figure S7: IR analysis of co-crystal **D2A5** for the stability

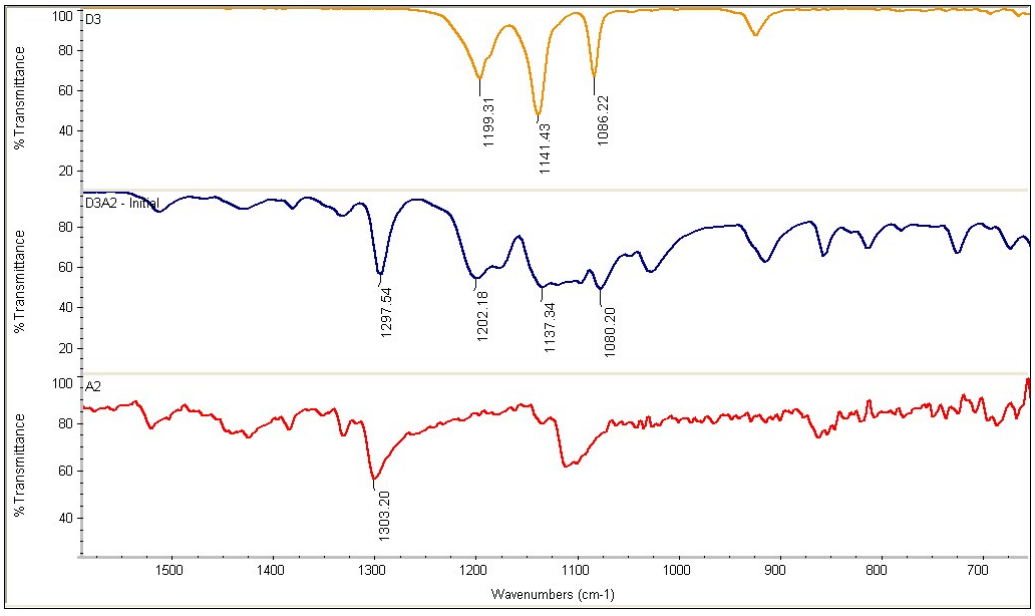

Figure S8: Comparison of IR peaks of **D3** and **A2** with the co-crystal **D3A2**

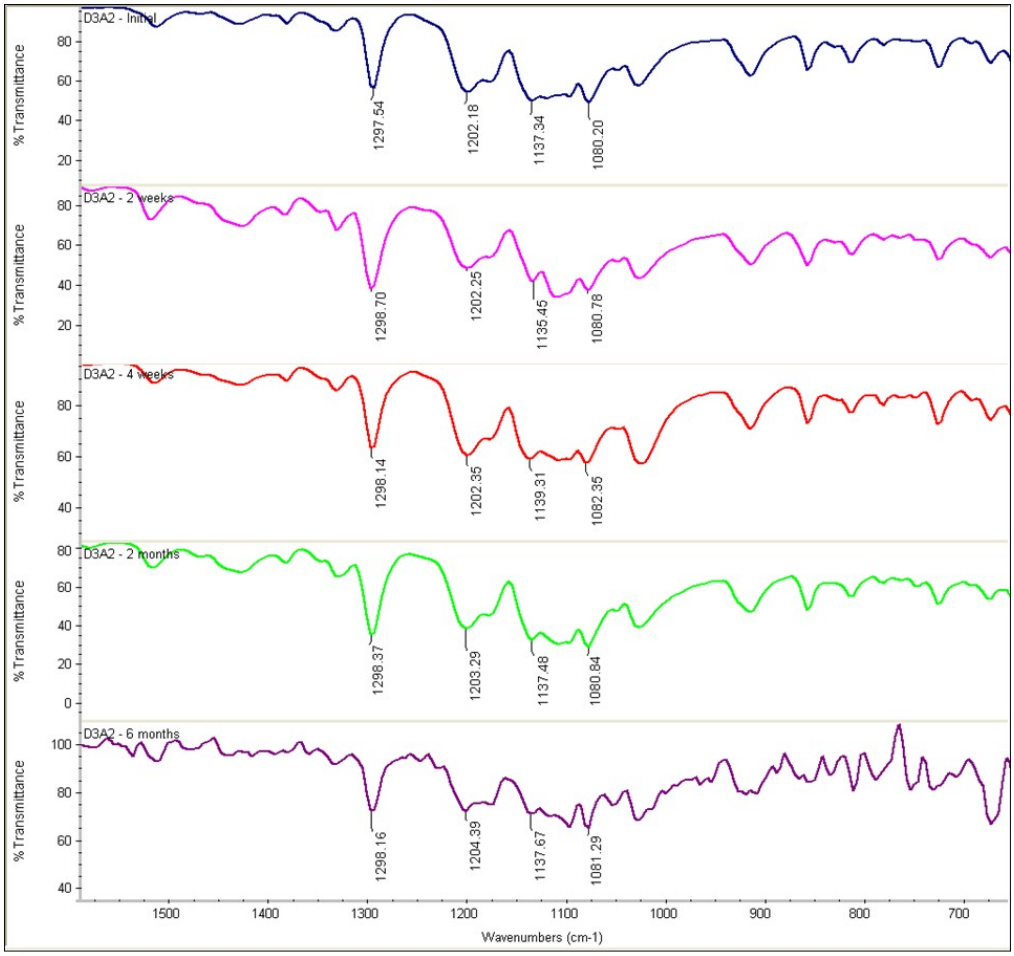

Figure S9: IR analysis of co-crystal **D3A2** for the stability

Table S5: melting point analysis of the selected co-crystals up to six months

	D1A3	**D2A5**	**D3A2**
Initial	95-98	118-121	119-122
2 weeks	90-93	115-118	119-122
4 weeks	95-99	114-116	115-118
2 months	96-101	117-120	117-121
6 months	97-100	115-119	120-122

6. Stability studies of co-crystals under different conditions

Co-crystals of **D1A3**, **D2A5** and **D3A2** were synthesized in bulk quantities (~1 g) using seed crystallization. After recording the initial PXRD patterns for three co-crystals the co-crystals were divided into three portions and kept under three different environmental conditions (open environment, 43.2% humidity and 83.2% humidity). The PXRD patterns for all nine experiments (three co-crystals x 3 environmental condition) were recorded in 3 weeks, 6 weeks and 12 weeks of time intervals. Finally the PXRD patterns were compared with initial PXRD pattern of co-crystals, simulated pattern as well as the simulated and experimental powder patterns of the respective co-former. Comparisons of PXRD patterns for the nine experiments were shown in Fig S10-S18.

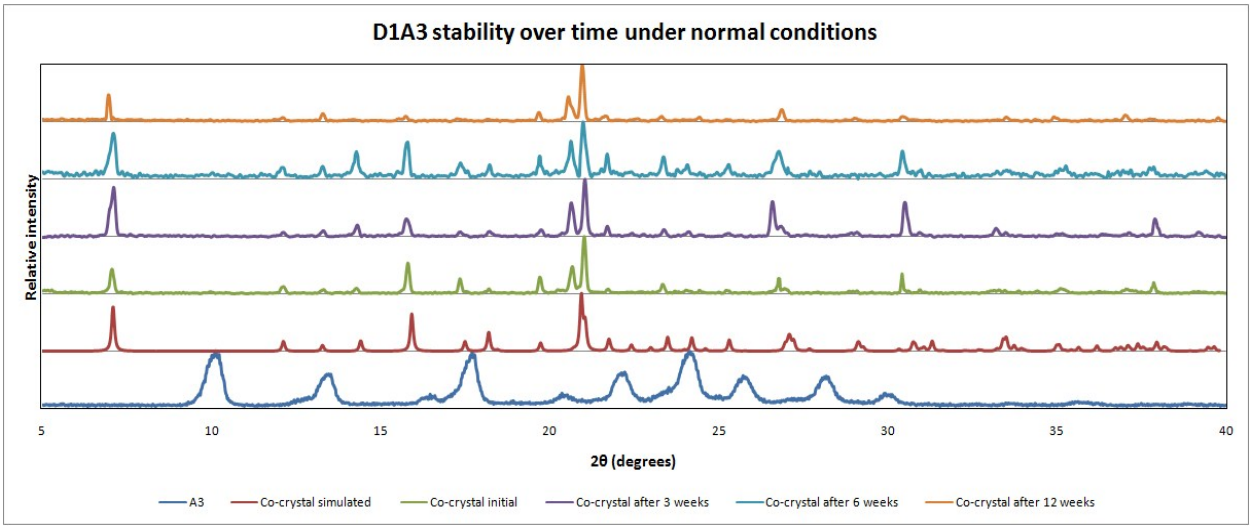

Figure S10: Powder pattern comparisons for **D1A3** kept under normal conditions

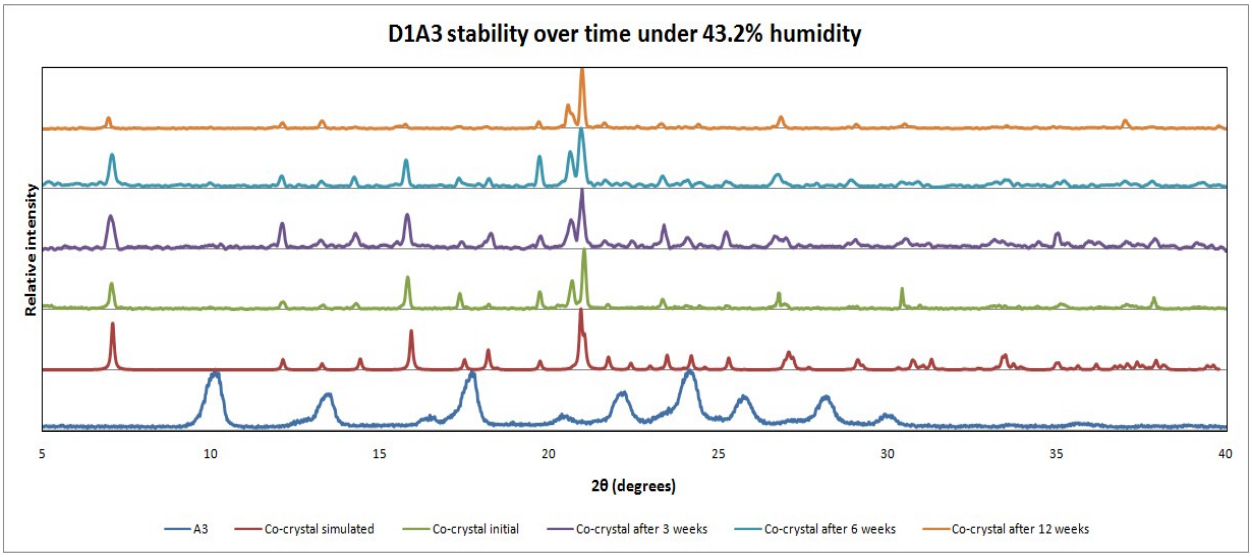

Figure S11: Powder pattern comparisons for **D1A3** kept under 42.3% humidity

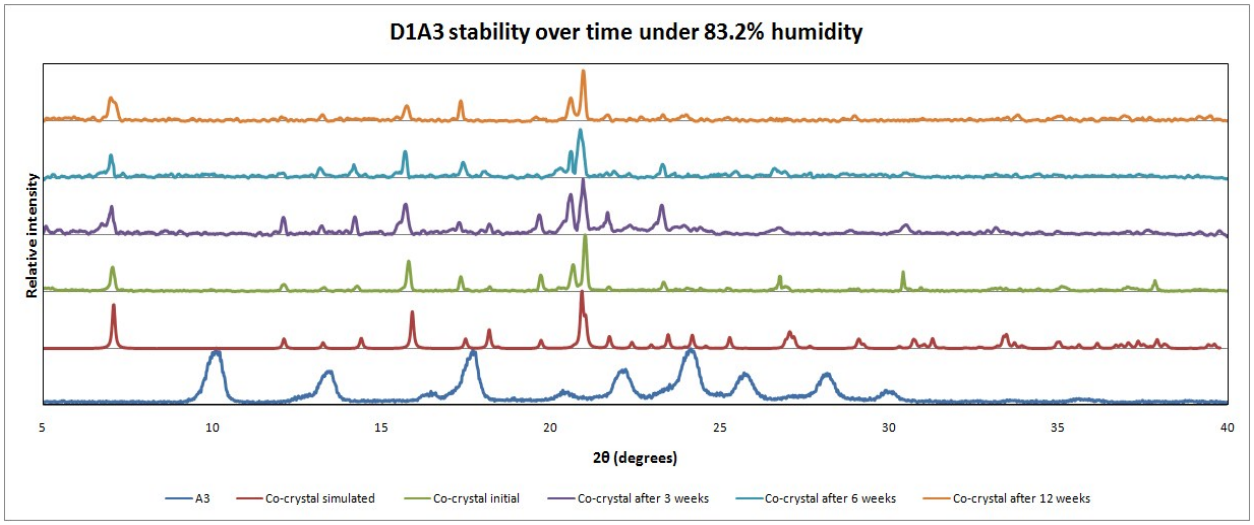

Figure S12: Powder pattern comparisons for **D1A3** kept under 82.3% humidity

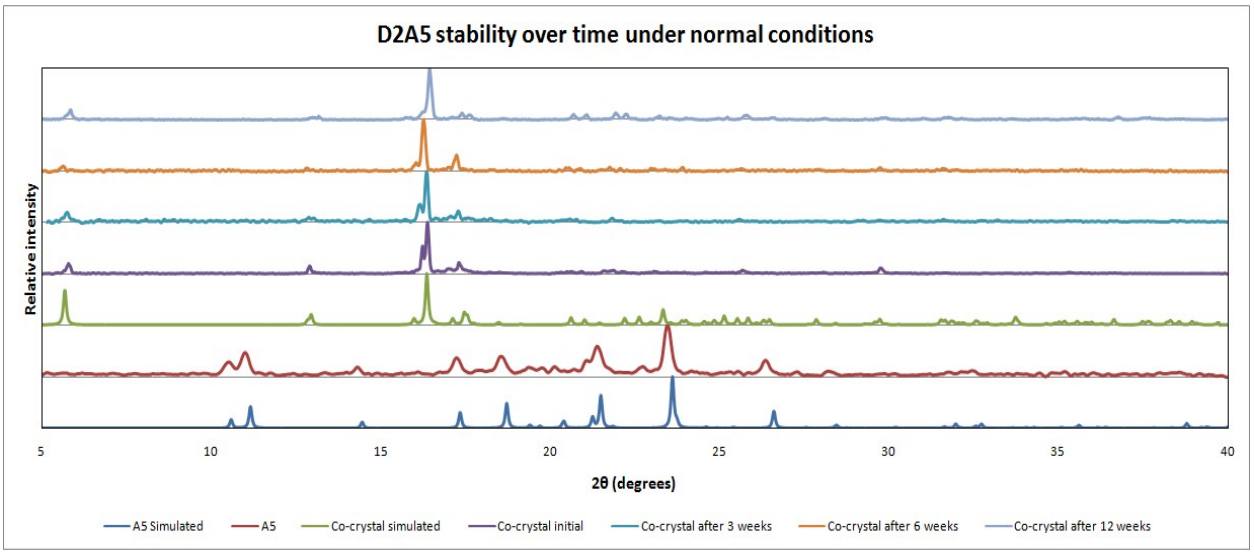

Figure S13: Powder pattern comparisons for **D2A5** kept under normal conditions

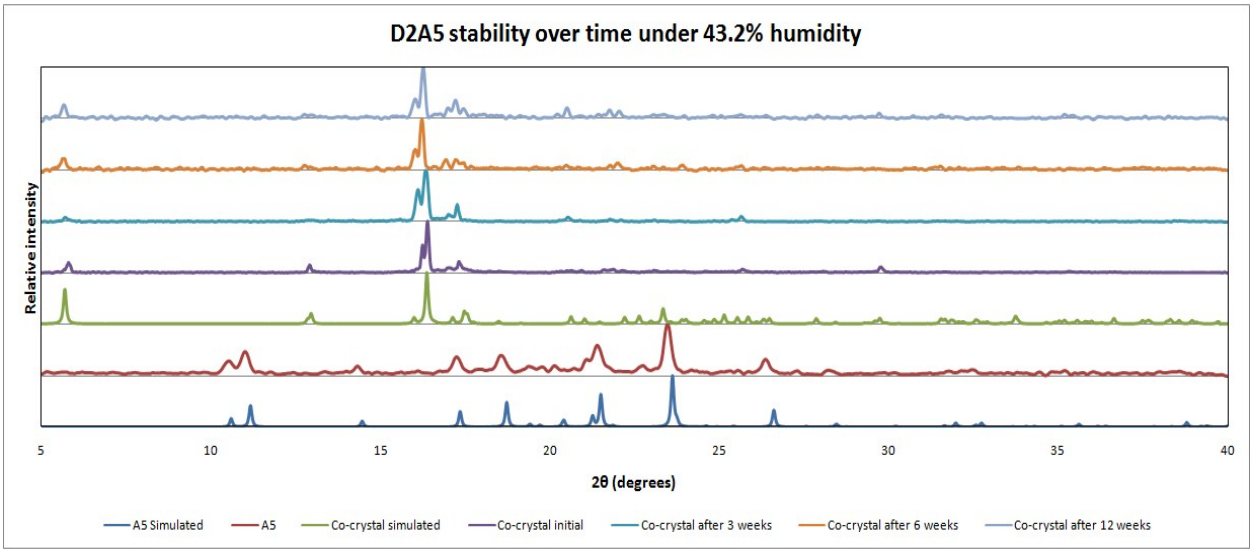

Figure S14: Powder pattern comparisons for **D2A5** kept under 42.3% humidity

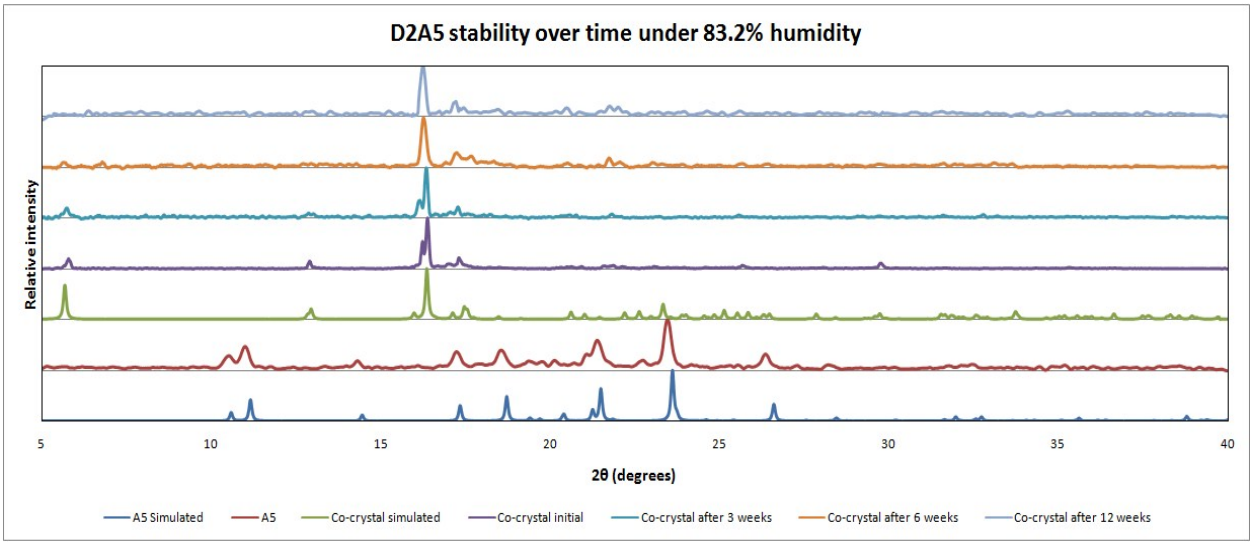

Figure S15: Powder pattern comparisons for **D2A5** kept under 82.3% humidity

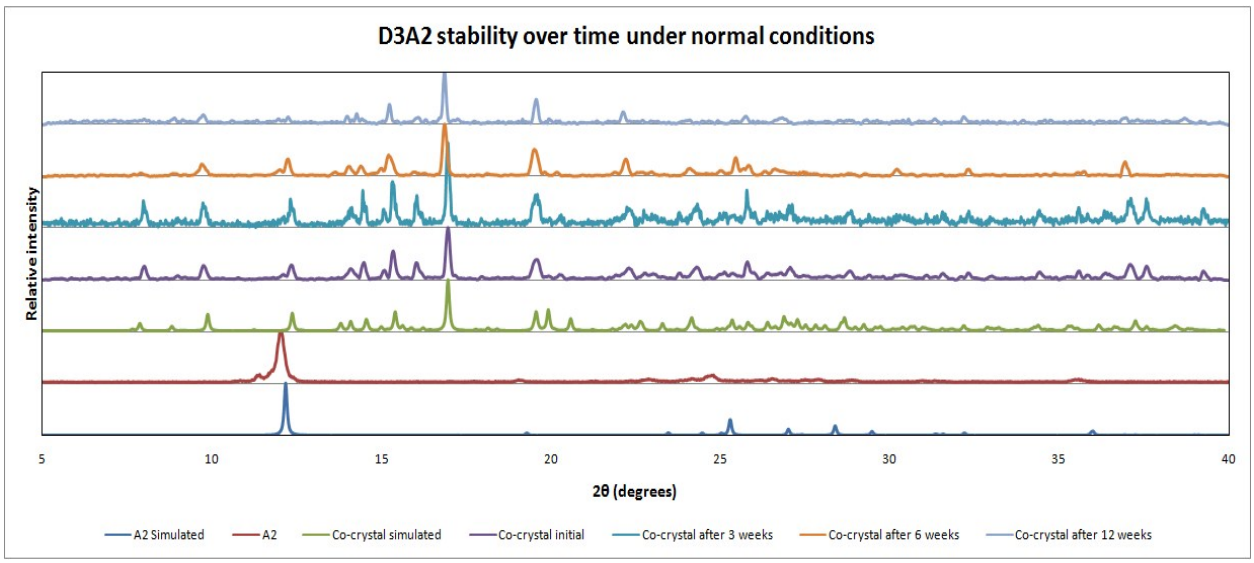

Figure S16: Powder pattern comparisons for **D3A2** kept under normal conditions

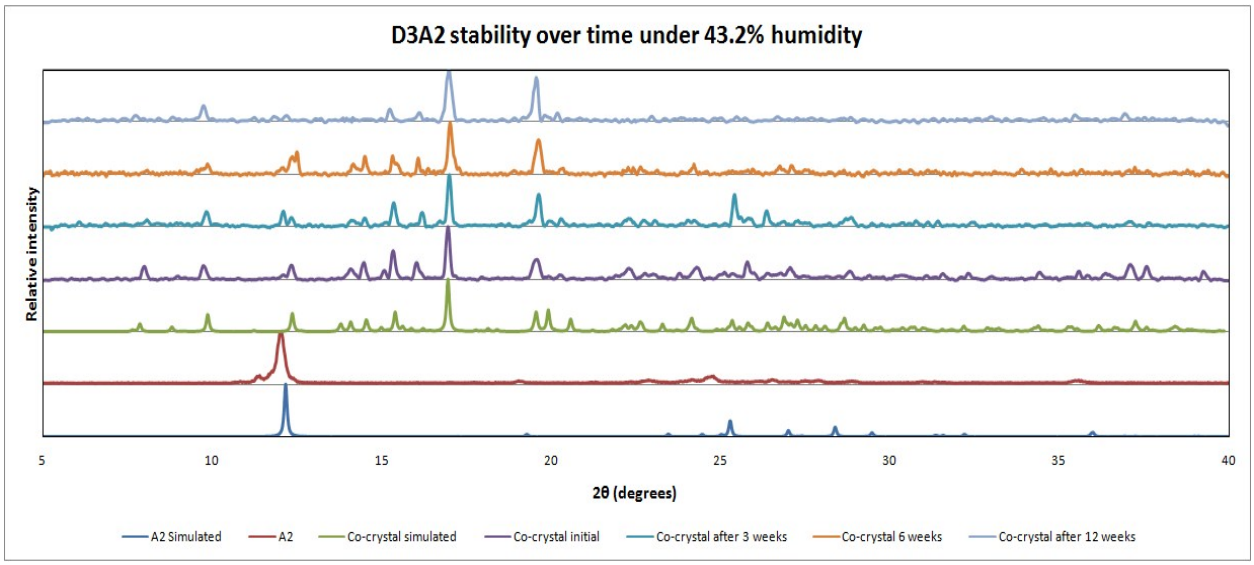

Figure S17: Powder pattern comparisons for **D3A2** kept under 42.3% humidity

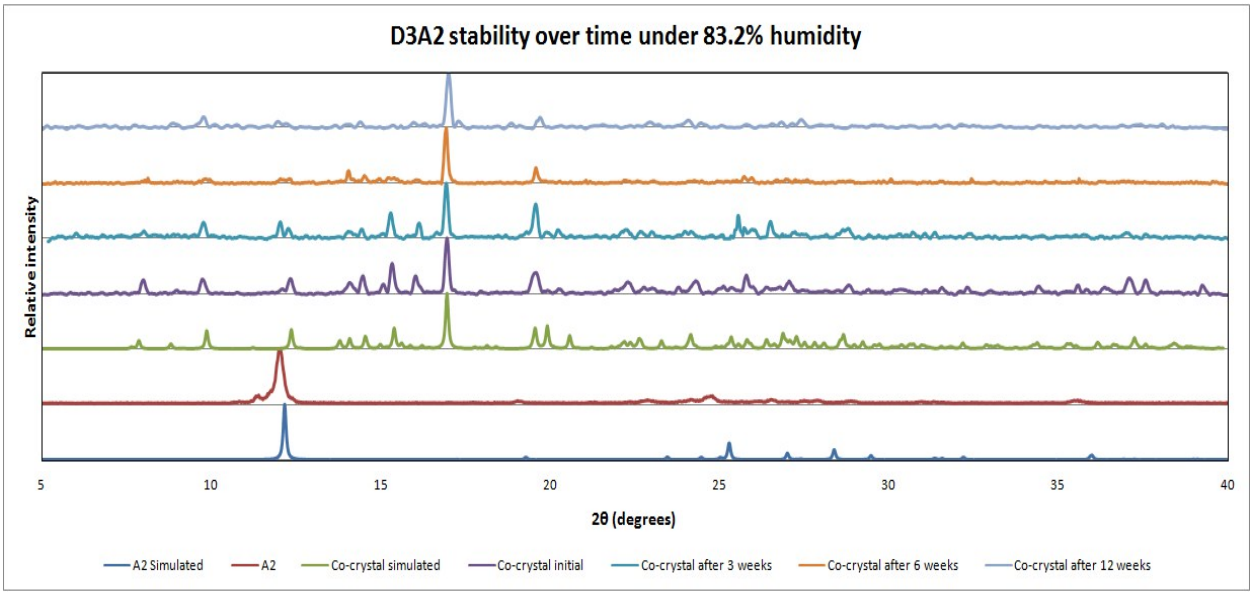

Figure S18: Powder pattern comparisons for **D3A2** kept under 82.3% humidity

7. Separation of individual components from co-crystals

200 mg of co-crystal **D3A2** was taken into hexane (20ml) and extracted with water (10 ml x 4). Water was removed under vacuum to obtain pure **A2** from aqueous layer. The organic layer was kept inside the fridge for hexane to evaporate and pure **D3** was obtained. NMR spectra of the separated products are shown in Figure S19- S22.

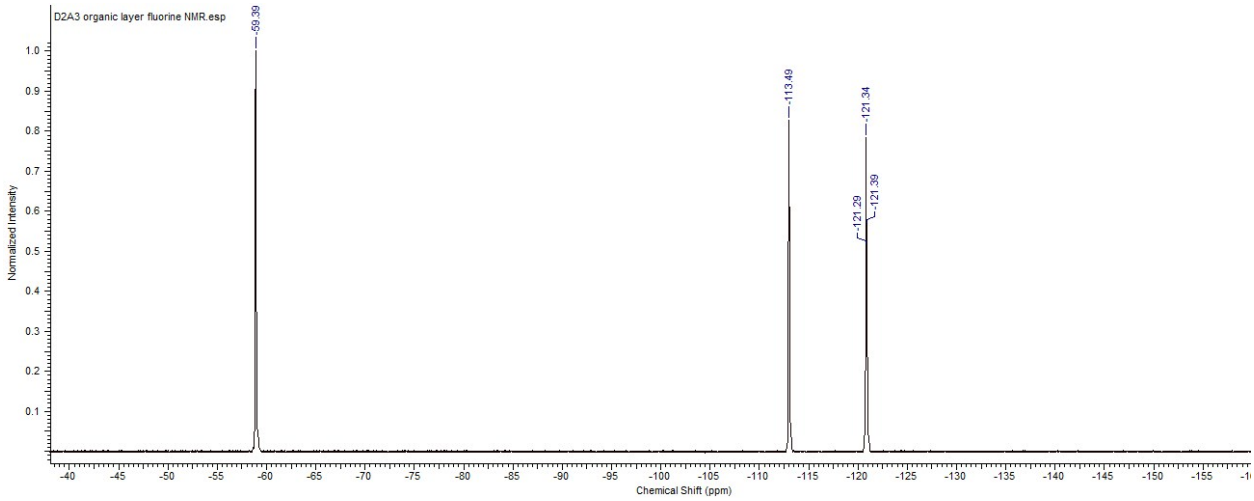

Figure S19: ^{19}F NMR spectrum of the separated organic layer

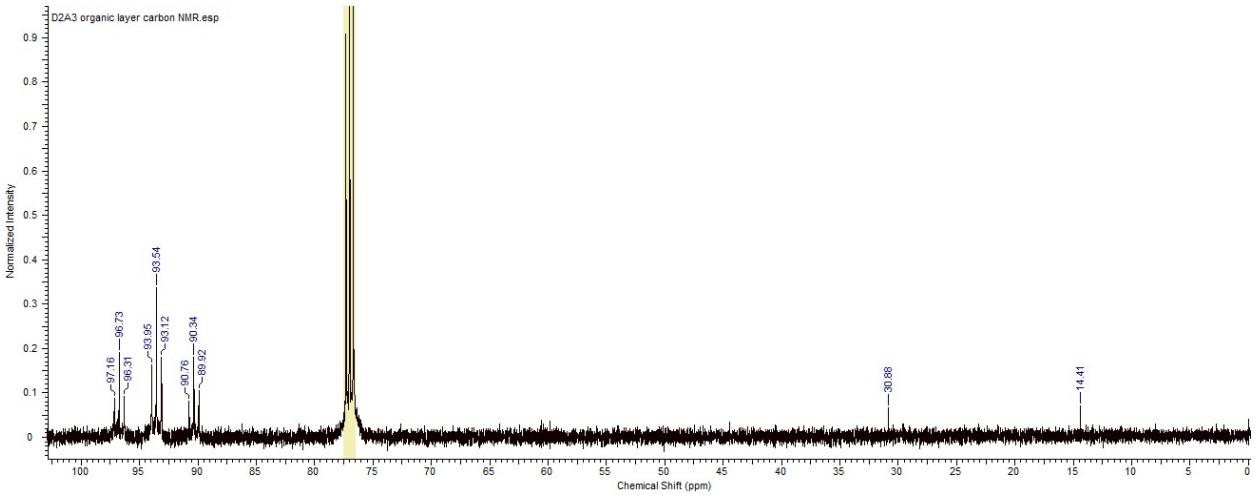

Figure S20: ^{13}C NMR spectrum of the separated organic layer (only D3 present, no A2)

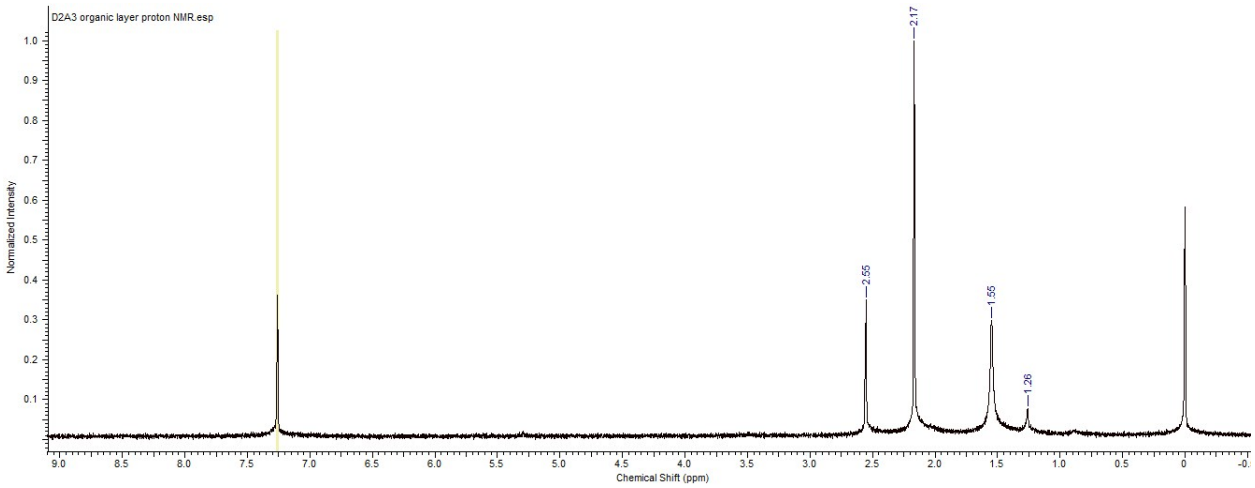

Figure S21: ^{1}H NMR spectrum of the separated organic layer (no A2 present)

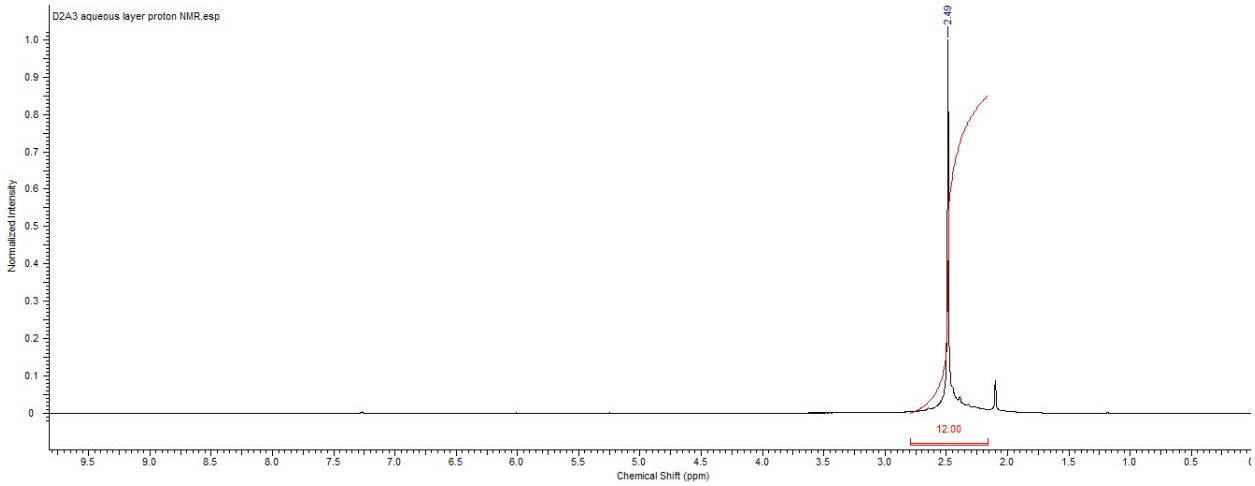

Figure S22: ^{1}H NMR spectrum of the separated aqueous layer

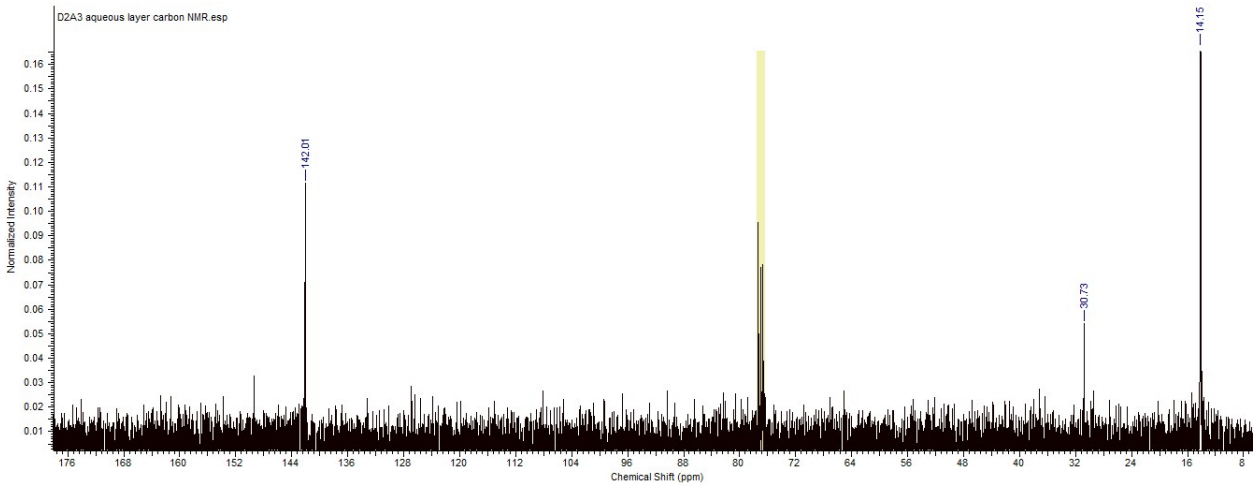

Figure S23: ^{13}C NMR spectrum of the separated aqueous layer (only A2 present, no D3)

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