Electronic Supplementary Information (ESI)

Evaluating the importance of fractional *Z'* polymorphs in a trifluoromethylated *N, N'*-diphenyloxalamide derivative

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**Synthesis of N^1,N^2-bis(3-(trifluoromethyl)phenyl)oxalamide (TFO) and Crystallization**

One equivalent of 3-trifluoromethyl substituted aniline was taken in a round bottomed flask containing dry dichloromethane (DCM) and put on a magnetic stirrer. The mixture was then cooled to 0 °C followed by addition of one and half equivalents of 4-Dimethylaminopyridine (DMAP). Then, two equivalents of oxalyl chloride was added drop wise (very slowly) to the reaction mixture with constant stirring under inert N_2 atmosphere (Scheme S1). The completion of the reaction was monitored with thin layer chromatography. At the end, reaction mixture was extracted by DCM solvent and product was purified by column chromatography.

The purified compound was directly used for crystallization by slow evaporation of in various organic solvents at different conditions. The slow evaporation of DCM-hexane mixture (4:1) at low temperature (4-5°C), methanol (22-25°C) and toluene (22-25°C) results in Form I phase individually.
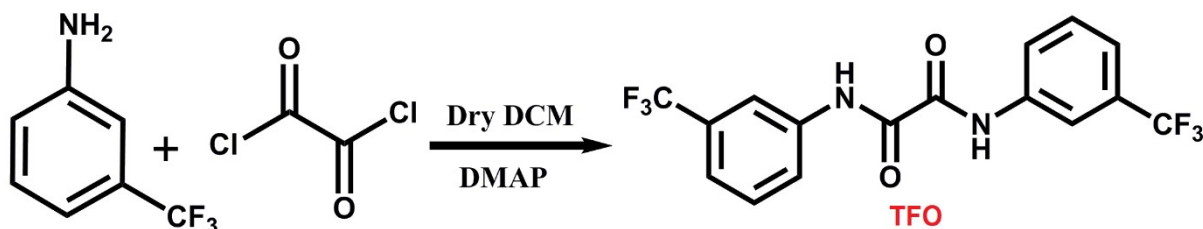
Scheme S1. General routes for synthesis of compound **TFO**.
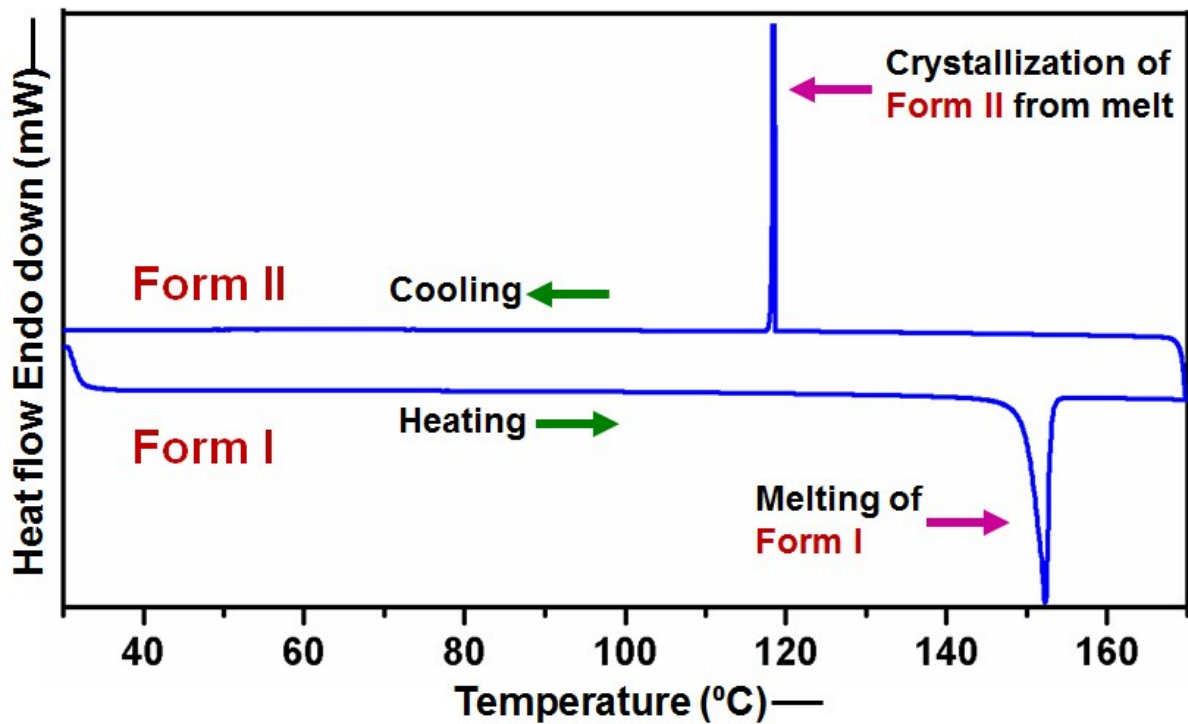
Fig. S1 Crystallization of Form II via melting of Form I phase in DSC experiment at 2°C/min scan rate.
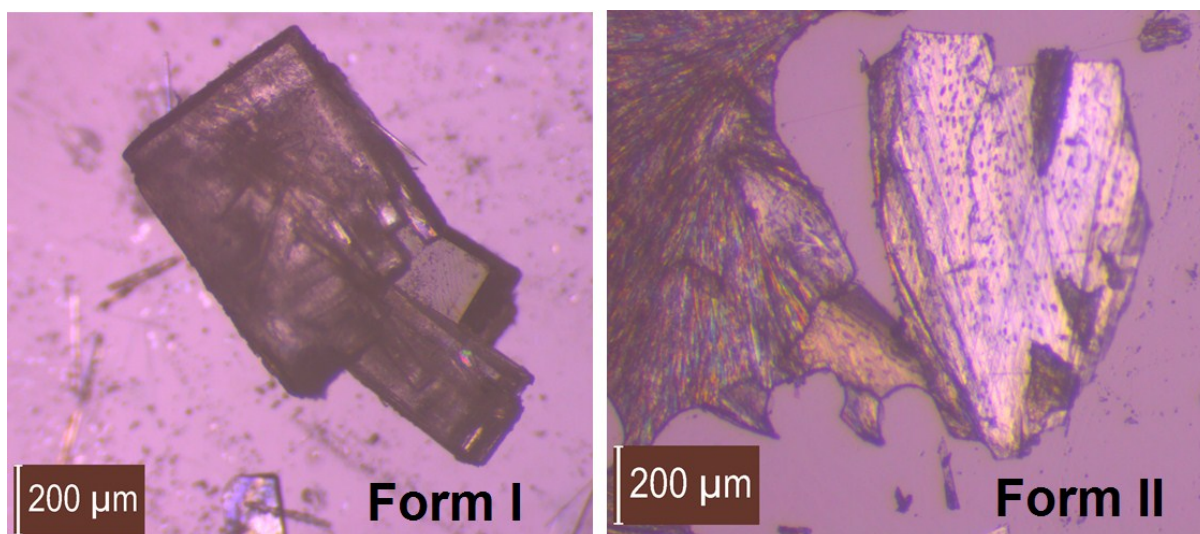
Fig. S2 Morphologies of Form I (block; left) and Form II (thin plate; right) crystals obtained after solution mediated and melt crystallizations (extracted from the DSC pan), respectively.

Single crystal X-ray diffraction data collection, structure solution and refinement

Single crystal data of two polymorphs were collected at low temperature on the Bruker D8 VENTURE diffractometer equipped with CMOS type PHOTON 100 detector using monochromated Mo Kα radiation (λ = 0.71073 Å). Unit cell measurement, data collection, integration, scaling and absorption corrections for the crystal were performed using Bruker Apex II software.[1] Data reduction was completed by Bruker SAINT Suite.[2] Multi-scan absorption correction was applied using *SADABS* [3]. Both crystal structures were solved by direct methods using either by *SHELXS-97* [4] and refined by the full matrix least squares method using *SHELXL 2018* [5] present in the program suite *WinGX* (version 2018.1)[6]. All non-hydrogen atoms were refined anisotropically and all hydrogen atoms were positioned geometrically (HFIX 43 for C/ N) and refined using a riding model. *ORTEP*s were generated using *Mercury 3.8 (CCDC)* program.[7] Geometrical calculations were done using *PARST* [8] and *PLATON* [9].

Table S1. Crystallographic data and refinement parameters.

Identification code	Form I	Form II
CCDC	1886184	1886185
Empirical formula	C16 H10 F6 N2 O2	C16 H10 F6 N2 O2
Formula weight	376.26	376.26
Temperature	110(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	$P\,2_1/c$	P -1
Unit cell dimensions	a = 5.0637(4) Å	a = 4.9806(4) Å
	b = 4.9677(4) Å	b = 11.5051(8) Å
	c = 29.092(2) Å	c = 14.8528(12) Å
	α = 90°.	α= 68.367(5)°.
	β = 94.332(2)°.	β= 80.383(4)°.
	γ= 90°.	γ = 78.374(4)°.
Volume	729.71(10) Å^3	770.89(11) Å^3
Z′	1/2	1/2+1/2
Z	2	2
Density (calculated)	1.712 Mg/m^3	1.621 Mg/m^3

Absorption coefficient	0.165 mm^{-1}	0.157 mm^{-1}
F(000)	380	380
Crystal size	0.420 x 0.280 x 0.120 mm^3	0.500 x 0.290 x 0.130 mm^3
Theta range for data collection	2.809 to 30.497°.	2.810 to 30.146°.
Index ranges	-7<=h<=7, -7<=k<=6, -40<=l<=41	-7<=h<=7, -16<=k<=16, -20<=l<=20
Reflections collected	11752	25315
Independent reflections	2200 [R(int) = 0.0275]	4468 [R(int) = 0.0658]
Completeness to theta = 25.242°	99.8 %	99.9 %
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	2200 / 0 / 118	4468 / 0 / 235
Goodness-of-fit on F^2	1.068	1.018
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0984	R1 = 0.0501, wR2 = 0.1074
R indices (all data)	R1 = 0.0413, wR2 = 0.1021	R1 = 0.0843, wR2 = 0.1221
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.7461 and 0.7001	0.7460 and 0.6829
Largest diff. peak and hole	0.406 and -0.365 e.Å^{-3}	0.580 and -0.290 e.Å^{-3}
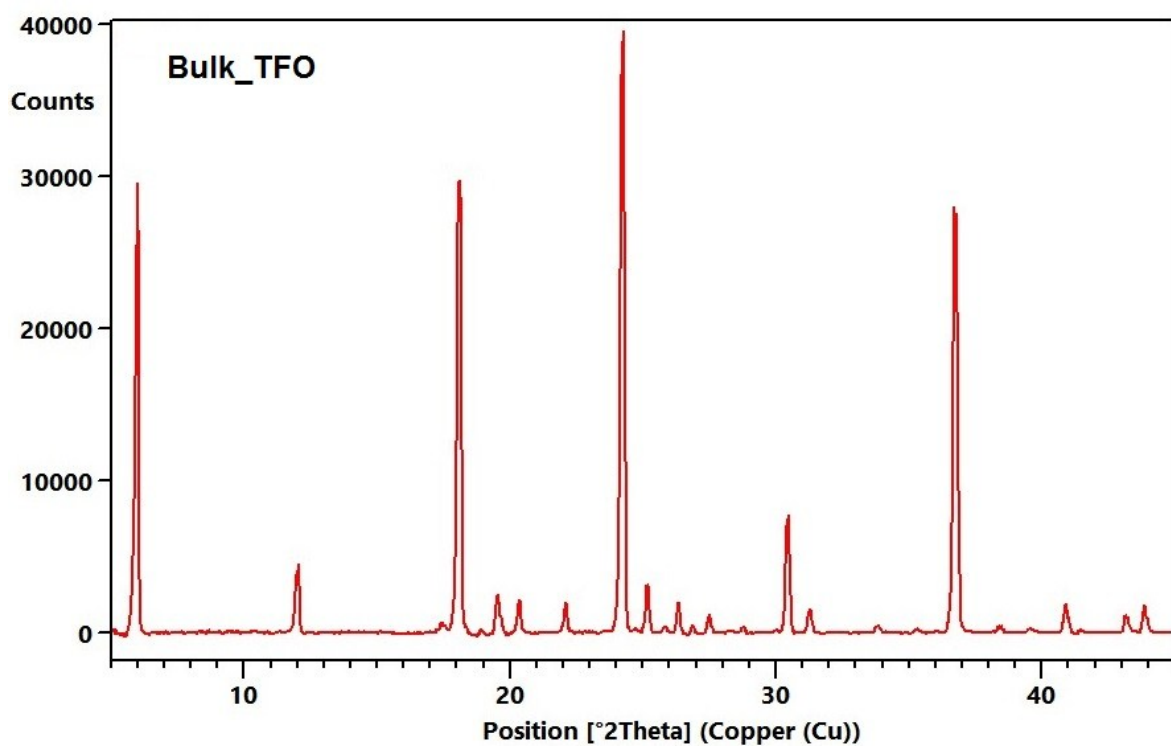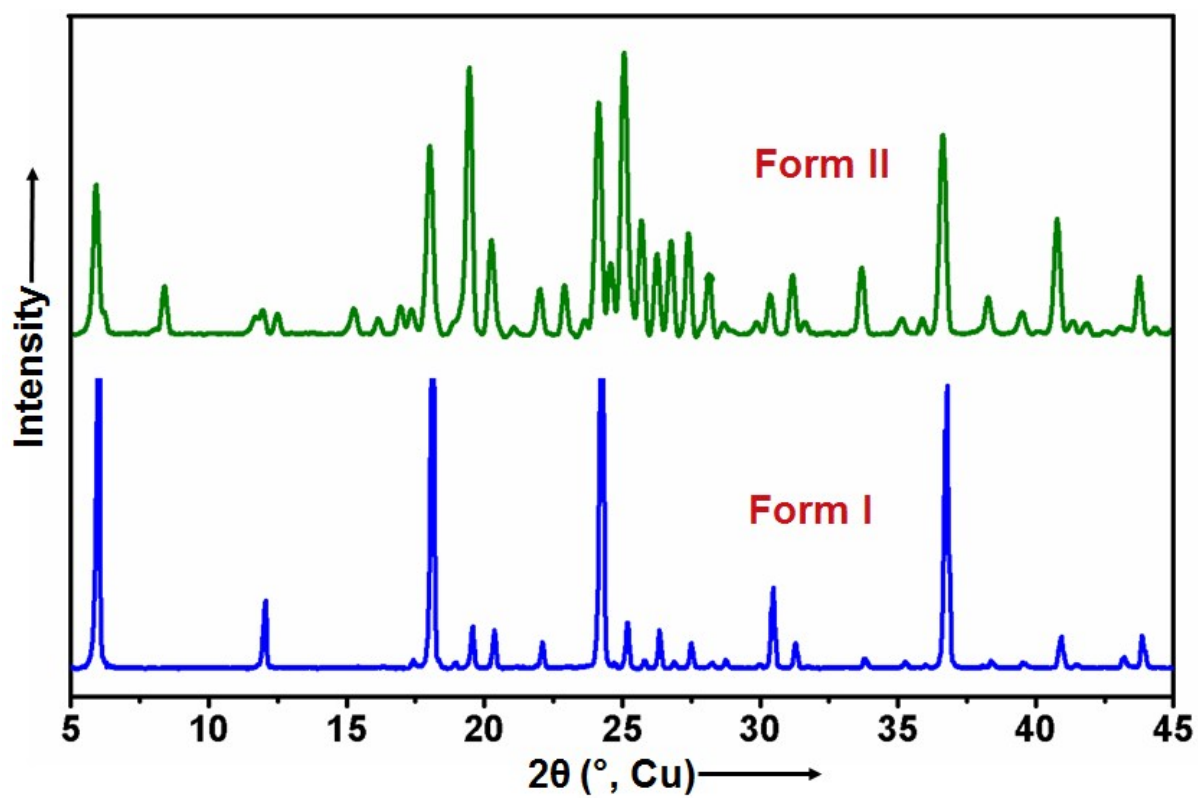
Fig. S3 Overlay of experimental powder X-ray diffraction patterns of dimorphs (up) and bulk (below) synthesised compound **TFO**. The bulk is a representative of Form I phase.
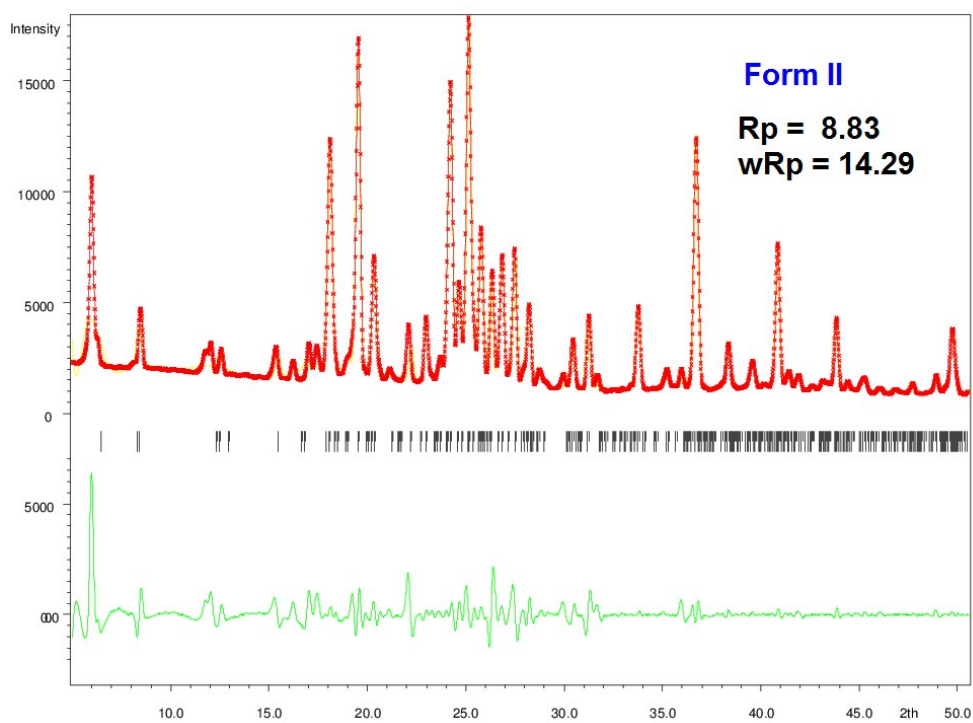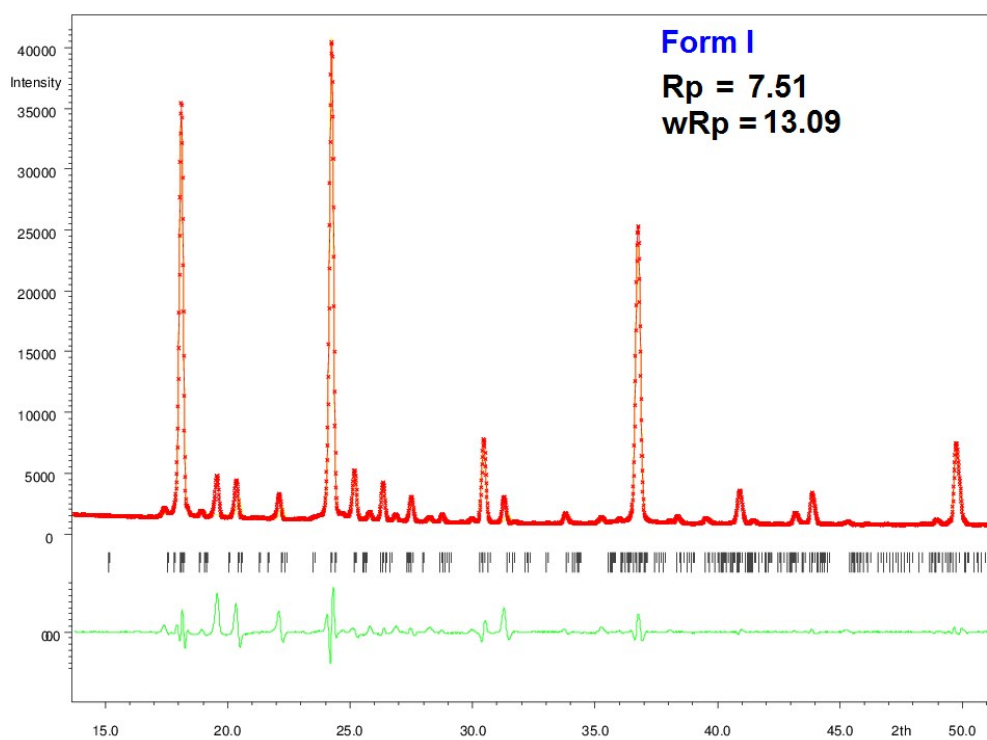
Fig. S4 Results of the profile fitting refinements (using Jana 2006[11]), performed for Form I (up) with its recorded powder pattern and Form II (below) with its recorded powder pattern.
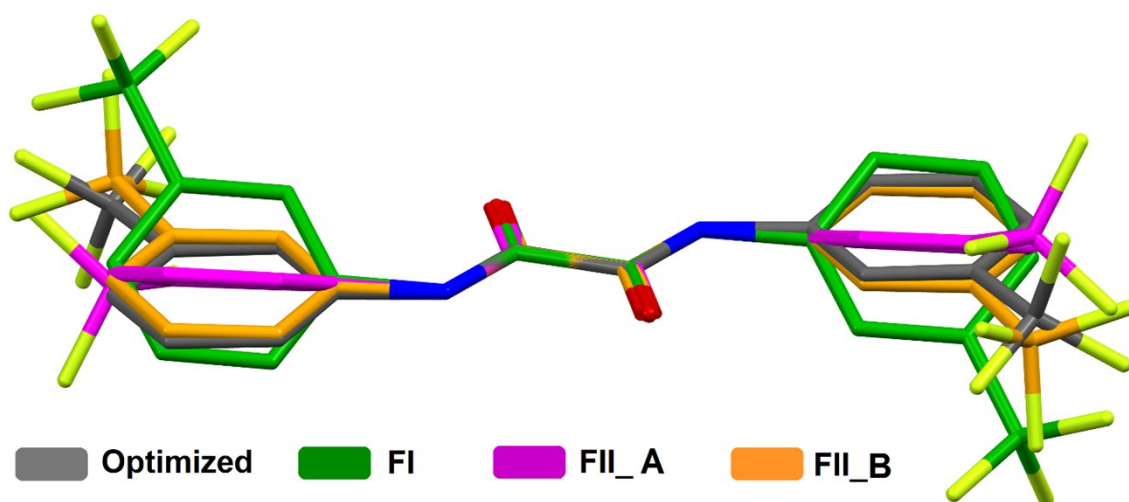
Fig. S5 Overlay of **TFO** molecules in gas phase and crystal conformations of two polymorphs.

Table S2. List of intra-and intermolecular interactions present in both polymorphic forms.

motif	Symmetry	D···A(Å)	H···A(Å)	<D−H···A(^{0})
Form I				
C2-H2···O1	x, y, z (intra)	2.937(1)	2.40	109
N1-H1···O1	x+1, y, z	2.905(1)	2.01	144
F1···C4(π)		3.242(1)		
π···π stacking		5.064(1)		
C4-H3···F2	x, y+1, z	3.709(1)	2.79	143
C5-H4···F1	x+1, y+1, z	3.458(1)	2.60	136
C6-H5···O1		3.483(1)	2.73	127
C4-H3···F2	-x+2, y+1/2, -z+3/2	3.458(1)	2.56	140
π···π ring stacking (Cg-Cg)	x, y-1, z	4.968(2)	-	-
F3···F2	-x+1, y+1/2, -z+3/2	3.122(1)	-	-
F3···F1		3.112(1)	-	-
Form II				
C2-H2···O1	x, y, z (intra)	2.937(2)	2.40	109
C10-H13···O2		2.891(2)	2.20	120
F4···C4(π)	x, y, z	3.162(3)	-	-
F4···F3		3.308(2)	-	-
C10-H13···F3		4.172(2)	3.44	126
N1-H1···O1	x-1, y, z	2.881(2)	2.03	138
F3···C4(π)		3.211(2)	-	-
π···π stacking		4.981(3)	-	-

C4-H4···O2	x-1, y, z	3.401(3)	2.34	168
C5-H5···F4		3.539(2)	2.55	151
C6-H6···F5	-x, -y+2, -z	3.755(3)	2.69	168
C6-H6···F6		3.535(3)	2.67	136
C12-H11···O1		3.602(2)	2.56	161
C12-H11···F1		3.375(2)	2.34	160
N2-H2A···F3	-x+1, -y+2, -z+1	3.205(2)	2.22	160
C14-H9···F3		3.461(2)	2.55	142
Molecular stacking	-x+1, -y+2, -z+1	3.356(2)	-	-
F5···C8(π)	-x+1, -y+2, -z	2.926(2)	-	-
C13(π)···C2(π)		3.353(2)	-	-

Computational Details

Geometry optimization and MESP plot

The crystal geometry of the molecule TFO (full molecule) was optimized at M06-2X/ 6-311g(d, p) level of theory using *Gaussian 09* software [10] and gas phase geometry was used for mapping the MESP plot.

Coordinates of gas optimized geometry for molecule TFO:

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Molecule Name

F   -6.496400 -1.132400 -1.244600

F   -5.489900 -2.018400   0.441500

F   -7.145300 -0.667500   0.753500

O   -1.165400 -1.296900   0.015200

N   -1.479000   0.985100 -0.001300

H   -0.912700   1.826700 -0.011100

C   -6.059500 -0.892000   0.000500

C   -5.112700   0.274500   0.032100

C	-3.744600	0.036500	0.023400
H	-3.358600	-0.971400	0.039300
C	-2.876800	1.129600	0.003100
C	-0.757400	-0.154500	0.004500
C	-5.636100	1.561200	0.020400
H	-6.707900	1.712400	0.035400
C	-4.761100	2.639600	-0.000200
H	-5.145700	3.651600	-0.006500
C	-3.391100	2.428000	-0.009300
H	-2.710200	3.272100	-0.023200
F	6.496500	1.132400	1.244500
F	5.489900	2.018400	-0.441500
F	7.145300	0.667600	-0.753500
O	1.165400	1.296900	-0.015000
N	1.479000	-0.985100	0.001300
H	0.912700	-1.826700	0.011100
C	6.059500	0.892000	-0.000600
C	5.112700	-0.274500	-0.032200
C	3.744600	-0.036500	-0.023400
H	3.358600	0.971400	-0.039200
C	2.876800	-1.129600	-0.003100
C	0.757500	0.154500	-0.004400
C	5.636100	-1.561200	-0.020500
H	6.707900	-1.712400	-0.035600
C	4.761100	-2.639600	0.000200
H	5.145700	-3.651600	0.006400
C	3.391100	-2.428000	0.009300
H	2.710200	-3.272100	0.023100

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Energy Framework and energy decomposition calculation

The pairwise intermolecular interaction energies in crystal were computed from CE-B3LYP/ 6-31g(d,p) molecular wave functions calculations by *CrystalExplorer17.5*. The total interaction energy in each molecular pair in crystal was estimated by summing up the electrostatic, polarization, dispersion and exchange-repulsion terms. Absolute values of decomposed energy can be obtained from the scaling scheme [Reference number 23a in the main manuscript]. The energy cut-off and tube size were 5 kJ/mol and 80 respectively, for generating the energy framework of two polymorphs.

Output of interaction energy calculations and energy decompositions for dimorphs-
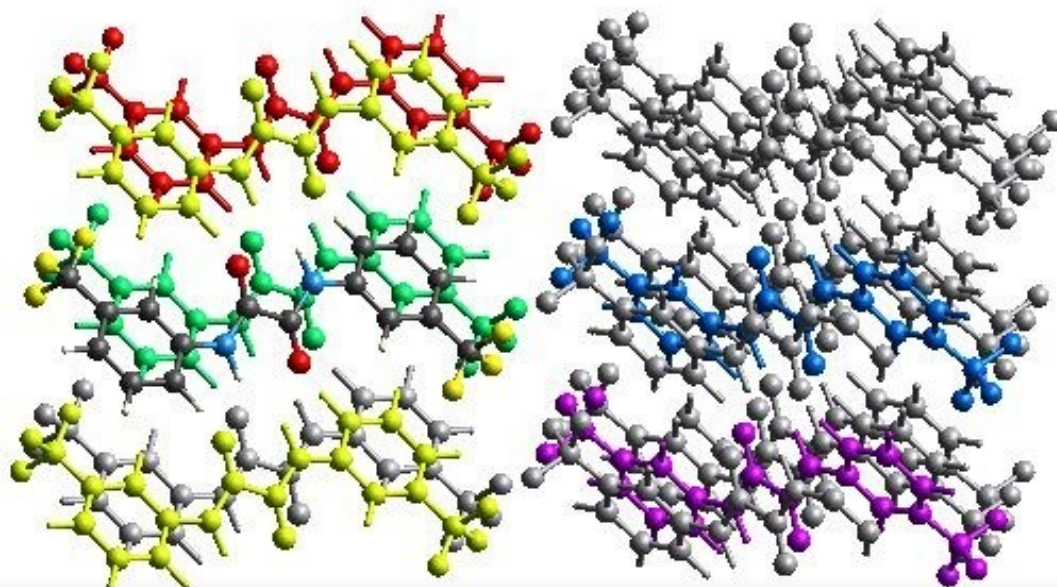
Form I

🔳 Information

| Crystal | Atoms | Surface | Energies |

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the
four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
🟥	1	x, y, z	7.09	B3LYP/6-31G(d,p)	-3.5	-4.0	-31.0	19.3	-21.7
🟨	2	x, y, z	5.06	B3LYP/6-31G(d,p)	-46.6	-9.6	-59.2	63.6	-68.6
🟩	1	x, y, z	4.97	B3LYP/6-31G(d,p)	-9.1	-2.4	-68.7	36.5	-48.7
🟦	1	-x, y+1/2, -z+1/2	14.76	B3LYP/6-31G(d,p)	-1.7	-0.4	-7.9	3.2	-7.1
🟪	1	-x, y+1/2, -z+1/2	15.24	B3LYP/6-31G(d,p)	1.2	-0.2	-5.3	0.8	-3.1

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

Form II

Information

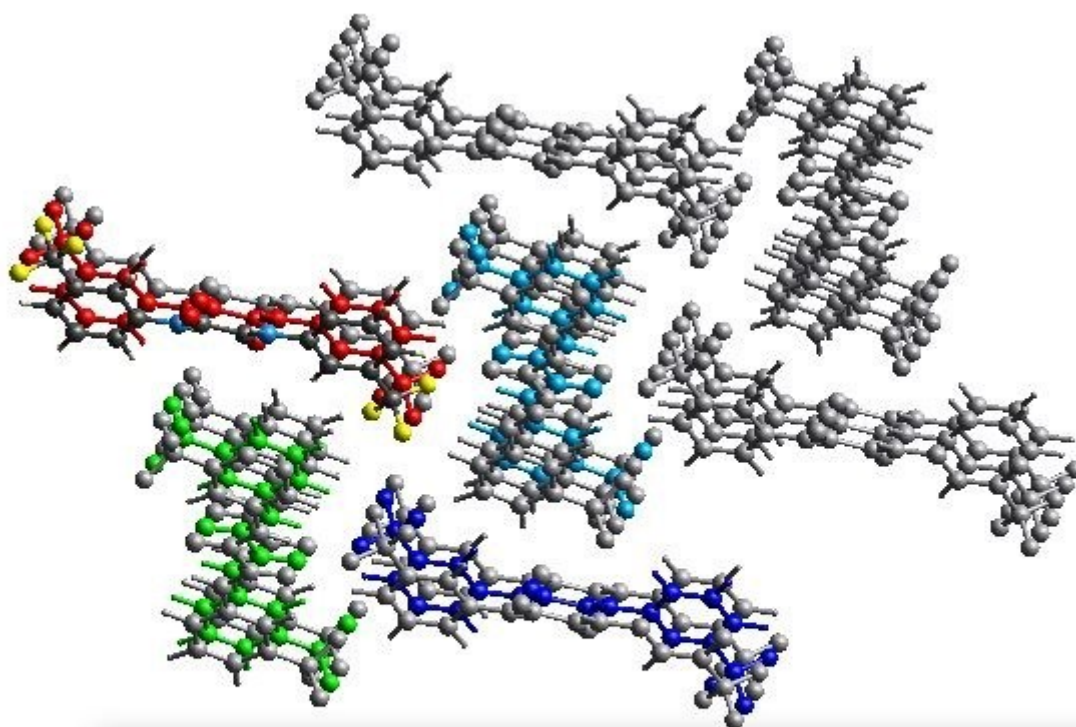| Crystal	Atoms	Surface	Energies

Interaction Energies (kJ/mol)
R is the distance between molecular centroids (mean atomic position) in Å.

Total energies, only reported for two benchmarked energy models, are the sum of the
four energy components, scaled appropriately (see the scale factor table below)

	N	Symop	R	Electron Density	E_ele	E_pol	E_dis	E_rep	E_tot
	1	x, y, z	4.98	B3LYP/6-31G(d,p)	-42.9	-9.0	-58.6	60.0	-66.1
	0	-	10.68	B3LYP/6-31G(d,p)	-17.7	-3.1	-21.7	21.5	-26.7
	0	x, y, z	4.98	B3LYP/6-31G(d,p)	-7.4	-2.3	-88.3	44.4	-59.0
	1	-	7.96	B3LYP/6-31G(d,p)	-4.1	-1.2	-33.7	16.1	-24.6
	0	x, y, z	14.86	B3LYP/6-31G(d,p)	0.3	-0.1	-2.3	0.0	-1.7
	1	-	11.74	B3LYP/6-31G(d,p)	-0.4	-0.5	-9.5	3.0	-7.2
	1	x, y, z	14.85	B3LYP/6-31G(d,p)	1.8	-0.2	-4.7	0.4	-2.1
	0	-	10.67	B3LYP/6-31G(d,p)	-11.7	-1.8	-19.9	14.0	-22.4
	0	-	11.82	B3LYP/6-31G(d,p)	-1.9	-0.5	-6.7	1.4	-7.4

Scale factors for benchmarked energy models
See Mackenzie et al. IUCrJ (2017)

Energy Model	k_ele	k_pol	k_disp	k_rep
CE-HF ... HF/3-21G electron densities	1.019	0.651	0.901	0.811
CE-B3LYP ... B3LYP/6-31G(d,p) electron densities	1.057	0.740	0.871	0.618

References

1. Apex2, Version 2 User Manual, M86-E01078, Bruker Analytical X-ray Systems Madison, WI, 2006.

2. Siemens, SMART System, Siemens Analytical X-ray Instruments Inc. Madison, MI, 1995.

3. G. M. Sheldrick, SADABS, Bruker AXS, Inc.: Madison, WI, 2007.

4. G. M. Sheldrick, *Acta Crystallogr.,* 2008*,* **A64**, 112.

5. G. M. Sheldrick, *Acta Crystallogr.,* 2015, **C71**, 3.

6. L. J. Farrugia, *J. Appl. Crystallogr.,* 1999, **32**, 837.

7. C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, *J. Appl. Crystallogr*., 2008, **41**, 466. www.ccdc.cam.ac.uk/mercury

8. M. Nardelli, *J. Appl. Crystallogr.,* 1995, **28**, 659.

9. A. L. Spek, *ActaCrystallogr.,* 2009, **D65**, 148.

10. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. M. HasegawaIshida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S, Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09*, Revision D.01, Gaussian, Inc., Wallingford, CT, 2009.

11. V. Petricek, M. Dusek, and L. Palatinus, *Z. Kristallogr*. 2014, **229**, 345.