

Supporting Information

Influence of Crystallisation Solution Environment on the Structural Pathway from Solute Solvation to the Polymorphic Forms of Tolfenamic Acid

Yu Liu,^{1,2,3} Cai Y. Ma,² Junbo Gong,³ and Kevin J. Roberts^{2,*}

¹ School of Chemical Engineering, Shenyang University of Chemical Technology, Shenyang,
China

² Centre for the Digital Design of Drug Products, School of Chemical and Process
Engineering, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, UK

³ State Key Laboratory of Chemical Engineering, Tianjin University, Tianjin, China

* Corresponding author

The supplementary material supports the main manuscript by providing further details of the following: **Figure S1** presents FTIR spectrum for form I, form II and the mixture. **Table S1** gives the MOPAC AM1 calculated electronic charges for form I and form II and their differences. **Table S2** gives the slurry experiment results. **Figure S2** presents the contributions of the different molecular fragments to the lattice energies of the two forms. **Figure S3** shows the energy minimisation of faceted molecular clusters for form I and form II of TFA. **Figure S4** presents the crystallisation outcomes of TFA as a function of initial concentration and cooling rate in different solvents. **Figure S5** shows the selection of the four representative cluster sizes.

S1. FTIR Results

FTIR are used to determine the forms of the product. Form I shows typical peaks at 741 cm^{-1} and 768 cm^{-1} , while form II at 748 cm^{-1} and 777 cm^{-1} . These regions are mainly assigned to aromatic out-of-plane CH deformation and ring deformations of the two benzene rings. Due to the different conformations and packing modes of the benzene rings, form I and form II exhibit different peak positions in these regions, which make it easy to determine the polymorphs of the product using FTIR.

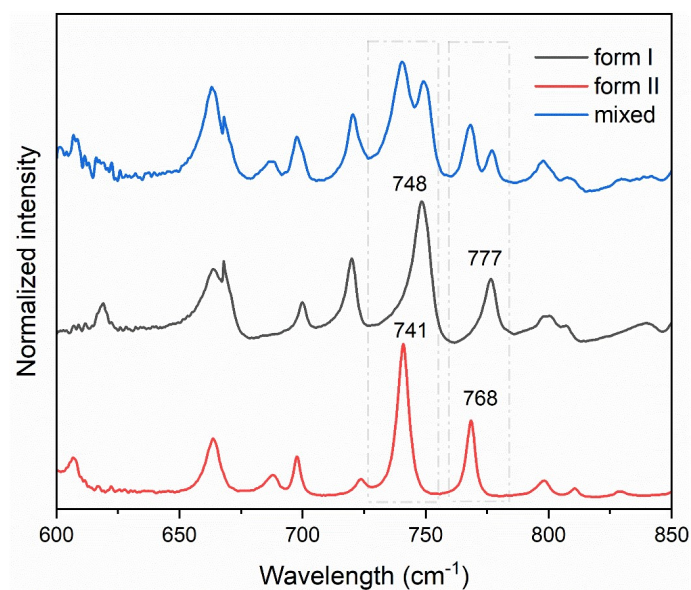


Figure S1. A standard FTIR spectrum for form I, form II and mixture (form I: form II = 1:1) of TFA.

S2. Calculated Charges of TFA Forms I and II

Table S1 The MOPAC AM1 calculated charges of different forms of TFA and their differences. Note that the highlighted columns indicate the charges which show obvious difference in form I and form II.

Atom Number	Form I	Form II	Differences
C11	-0.0423	-0.0385	-0.0038
O1	-0.3201	-0.3052	-0.0149
H1	0.2577	0.259	-0.0013
O2	-0.4085	-0.4141	0.0056
N1	-0.3024	-0.2839	-0.0185
H6	0.2684	0.2645	0.0039
C1	0.3882	0.3822	0.006
C2	-0.2184	-0.2116	-0.0068
C3	-0.0146	-0.02	0.0054
C4	-0.2077	-0.2017	-0.006
C5	-0.0417	-0.0452	0.0035
C6	-0.2229	-0.2147	-0.0082
C7	0.1934	0.1886	0.0048
C8	0.0564	0.0844	-0.0280
C9	-0.1224	-0.1517	0.0293
C10	-0.1135	-0.1015	-0.0120

C11	-0.1115	-0.1324	0.0209
C12	-0.0479	-0.0295	-0.0184
C13	-0.0502	-0.087	0.0368
C14	-0.1752	-0.1755	0.0003
H2	0.138	0.1393	-0.0013
H3	0.1326	0.1334	-0.0008
H4	0.1255	0.1262	-0.0007
H5	0.1367	0.1393	-0.0026
H7	0.1382	0.1386	-0.0004
H8	0.1355	0.1327	0.0028
H9	0.143	0.143	0
H10	0.0969	0.0959	0.001
H11	0.0954	0.0941	0.0013
H12	0.0935	0.0914	0.0021

S3. Slurry Experiment Results of TFA

Table S2 The final forms and transformation time for slurry experiments of TFA in different solvents

Solvent	5°C		20°C		40°C	
	Polymorph	Time	Polymorph	Time	Polymorph	Time
Methanol	Form I	5h	Form I	30min	Form I	10min
Ethanol	Form I	4h	Form I	30min	Form I	10min
Acetonitrile	Form I	15h	Form I	1h	Form I	10min
Toluene	Form I	20h	Form I	1h	Form I	10min

S4. Contributions of Molecular Fragments to Lattice Energy

Examination of the contributions of the different molecular fragments to the lattice energies of the two forms is shown in **Figure S2**, revealing no significant differences between the molecular contributions between forms I and II for any fragment. In both form I and form II, carboxyl group contributes about 28% to lattice energy with the two phenyl rings also contributing about 28%, indicating that both hydrogen bonds and aromatic interactions play vital roles in stabilising the crystal structures of TFA. Notably, the contributions of two

phenyl rings of form II were found to be slightly higher than form I, which could be associated with the stronger aromatic interactions in form II.

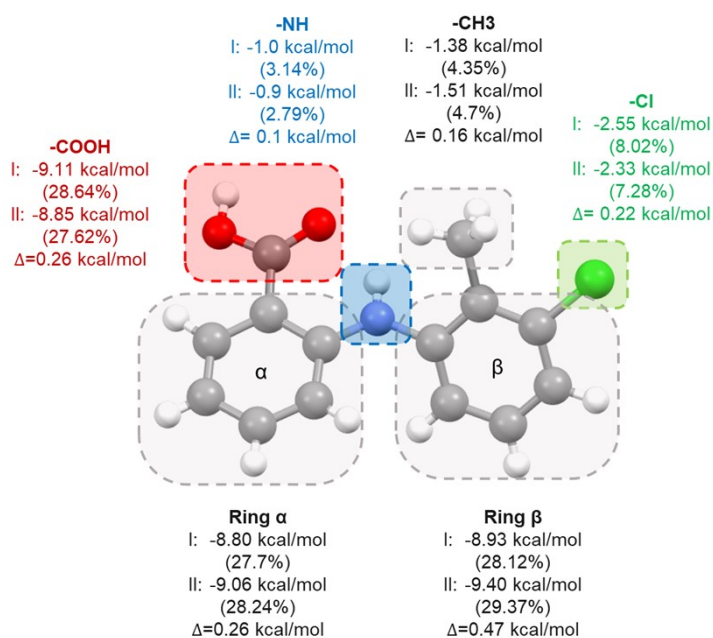


Figure S2. Absolute energies and relative contributions of the different molecular fragments to the total lattice energy of TFA form I and form II.

S5. Energy Minimisation of Faceted Molecular Clusters

The results reveals that the clusters of metastable form II are always more energetically favourable compared to the clusters of form I with same sizes for both non-minimised (**Figure S3(a)**) and minimised (**Figure S3(b)**) structures. This is consistent with the findings of α - and β -form L-glutamic acid (Hammond et al., 2005, Hammond et al., 2012). However, the stability orders as a function of size were found to change following relaxation of the molecular conformations (**Figure S3(c)**), indicating that the conformational adjustment plays an important role during the formation of the early assembly of the crystal structure post-nucleation. With the increase of cluster size, the data reveals two crossover points in cluster

energy distributions for the optimised clusters at sizes at 20 and 290 molecules, respectively, as shown in **Figure S3(c)**.

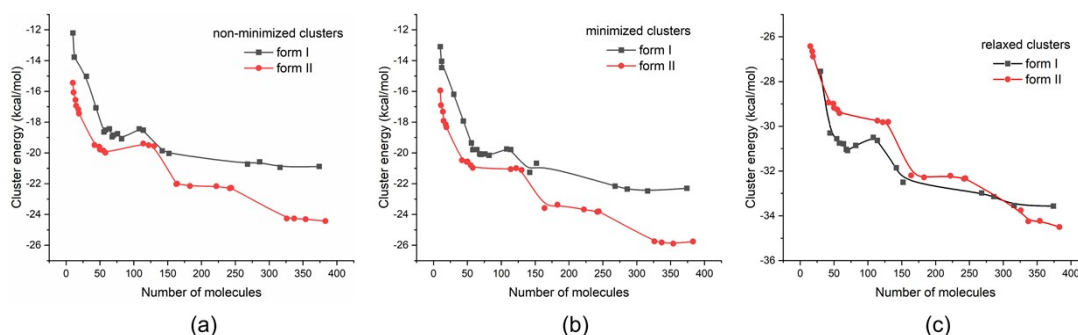


Figure S3. Energy minimisation of faceted molecular clusters for form I and form II of TFA: (a) non-optimised structures; (b) minimised structures; (c) optimised structures.

S6. Crystallisation outcomes of TFA Forms I and II

To assess the effect of cooling rates and initial solute concentrations on polymorphic selection, crystallisation results were re-summarised as a function of the following two factors:

- (1) For example, in **Figure S4(e)**, we summarised all experiment results in terms of cooling rates including all the initial solute concentrations. At the point where cooling rate is 0.3, the probability is calculated basing the results of the initial solute concentrations of 4.0×10^{-3} , 5.0×10^{-3} , 6.0×10^{-3} and 6.6×10^{-3} mol/mol.
- (2) The concentrations in **Figure S4(e)-(h)** represent the initial solute concentrations of the crystallisation experiments.

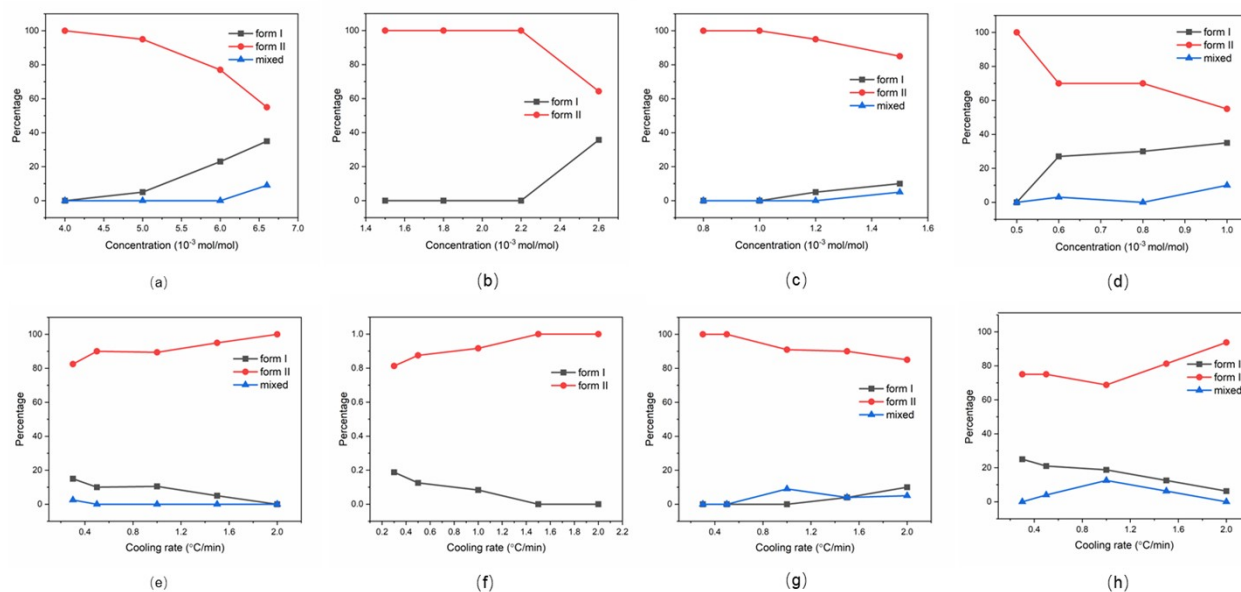


Figure S4. Crystallisation outcomes of TFA as a function of initial concentration and cooling rate in (a, e) ethanol, (b, f) methanol, (c, g) toluene and (d, h) acetonitrile.

S7. Representative Cluster Sizes for Cluster Energies

Four representative cluster sizes for the two polymorphic forms, notably 12, 54, 108 and 374 molecules for form I; 11, 50, 114 and 354 molecules for form II, were used to compare the conformational differences at four different stages during the cluster evolution. These cluster sizes represent the four stages in the cluster energies as shown in **Figure S5**:

- (1) 11~12 molecules: the initial clusters where form II cluster is slightly stable than form I.
- (2) 50~54 molecules: the stability of cluster I and cluster II changed where form I is more stable than form II.
- (3) About 110 molecules: The first platform of the cluster energy for both form I and form II where form I is more stable than form II.
- (4) 350~370: the final clusters and also another platform of the cluster energy for both form I and form II. In this period, form II is more stable than form I.

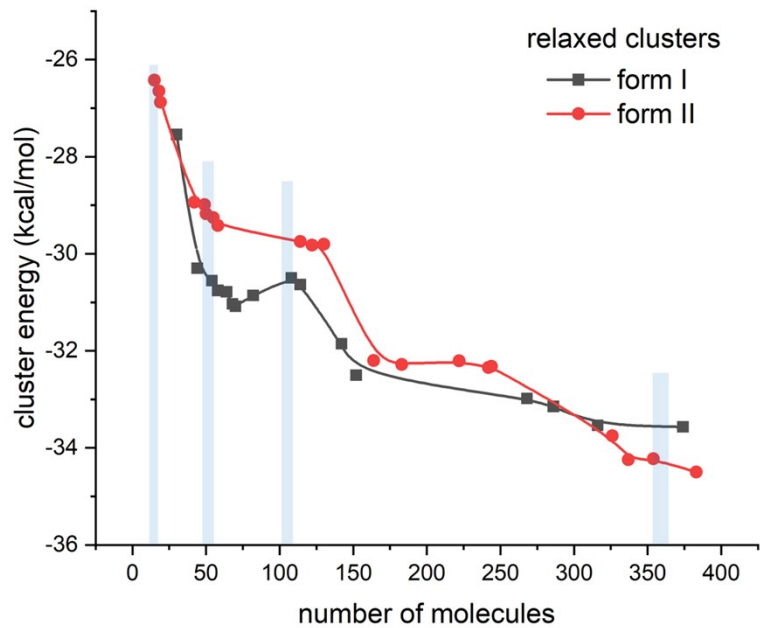


Figure S5. Energy of faceted molecular clusters for form I and form II of TFA after structure optimisation. The four positions which are used for conformation analysis are highlighted in blue.