Nucleation, crystal growth, nuclei stability, and polymorph selection in supercooled Tolbutamide melt

Ruslan A. Andrianov, Tatiana A. Morozova, Daniil S. Snetkov, Ilyas I. Nizamov, Christoph Schick and Timur A. Mukhametzyanov.

Supplementary materials

1. Nucleation and crystallization of tolbutamide, additional figures.

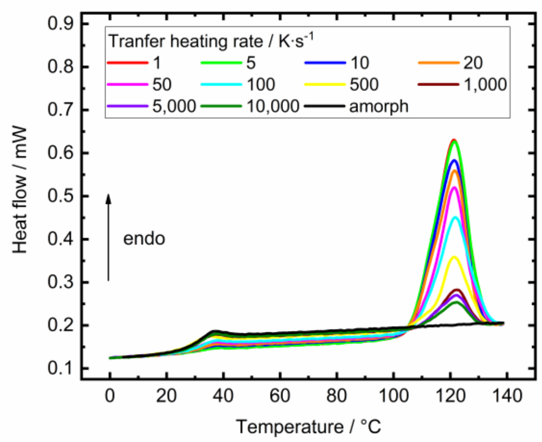

Fig. S1. Heat flow curves obtained using the temperature program from Fig. 5. Nucleation at 20 °C for 30 s and development at 75 °C for 25 s with vaying transfer heating rates. The magnitude of the melting effect with onset at .ca 100 °C corresponds to the crystallinity of the sample.

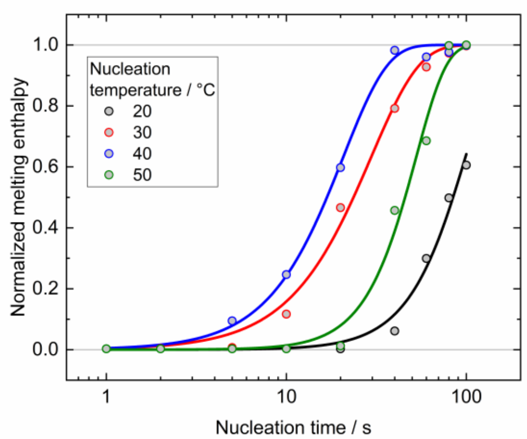

Fig. S2. Nucleation time and temperature dependence of the normalized melting enthalpy based on measurements according to the temperature-time profile from Fig. 7. The curves approximate the experimental points using Eq. (1).

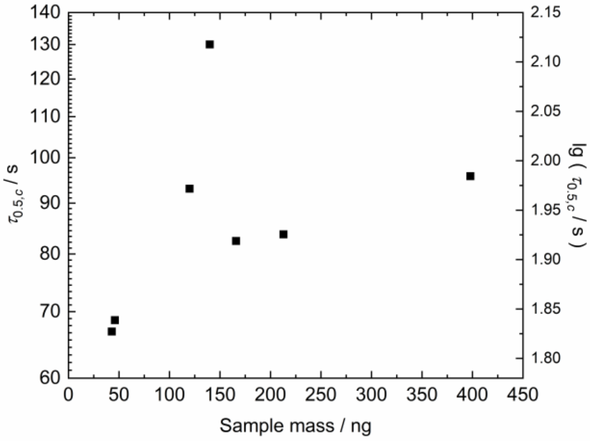

Fig. S3. Half-time of crystallization of tolbutamide vs. sample mass after isothermal crystallization at 50 °C.

2. Scan rate dependence of the glass transition of tolbutamide

The scan rate dependence of tolbutamide was analysed using the approach described in literature.[1] The ISO midpoint and fictive temperatures of glass transition was determined using STARe software. The scan rate range where reliable determination of glass transition is limited by cooling performance of UFS1 sensor in the temperature range of the glass transition (from the top) and crystallization of tolbutamide (from the bottom). Because of this, the glass transition temperature of tolbutamide was studied in the scan rate range from 30 to 1000 $K \cdot s^{-1}$. The glass transition temperature was determined by averaging the values determined on cooling and heating at the same absolute scan rate. Due to a limited available scan rate range VFTH fit was unsuccessful; the regular Arrhenius fit of data produces the apparent activation energy value of 295 ± 30 $kJ \cdot mol^{-1}$ using both the ISO midpoint and fictive temperatures. The scan rate variation of the glass transition temperature of tolbutamide is ca. 5K per decade, which is greater than 4K per decade typical for polymers,[2] inicating that tolbutamide glass is less fragile than the typical polymer glass.

3. Crystal morphology of tolbutamide

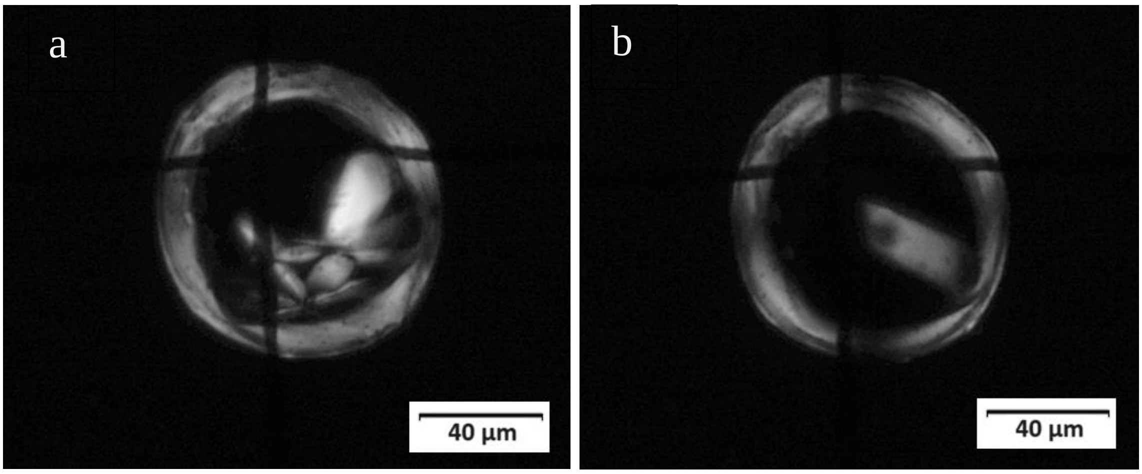

Fig. S4. Microphotographs of growing tolbutamide crystals in polarized light: a) isothermal growth at 60 °C; b) growth at 90 °C after nucleation at 50 °C for 60 s.

4. Nuclei stability of tolbutamide, additional figure

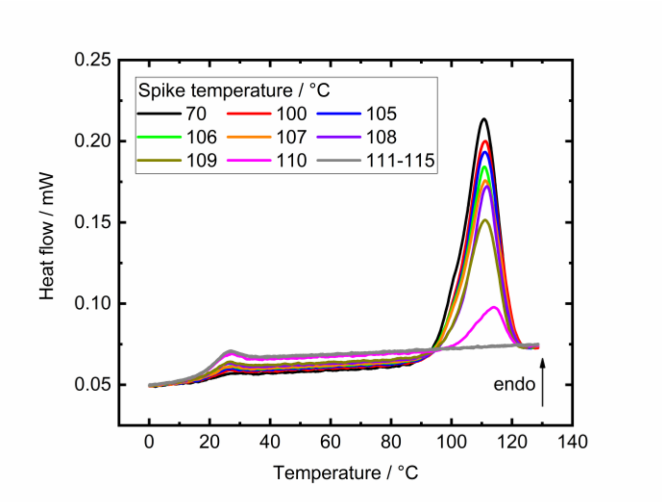

Fig. S5. Heat flow curves obtained using the temperature program from Fig. 9. Nucleation conditions: 40 °C, 20 s, development conditions: 70 °C, 10 s.

Evaluation of the growth rate of tolbutamide crystals was performed by analyzing frame by frame the videos of crystallization of samples at different conditions. Example of the growth of disc-like crystals of polymorph V can be viewed at https://youtu.be/MN0N1Dlkckk and in Supplementary video file.

Example of the growth of rod- or needle-like crystals of polymorph II can be found at https://youtu.be/X75PSSQisXQ and in Supplementary video file.

5. Data from the study

Data from **Fig. 6**

Nucleation time at 25 °C / s									
200		100		50		30		10	
Transfer heating rate	Normalized melting enthalpy	Transfer heating rate	Normalized melting enthalpy	Transfer heating rate	Normalized melting enthalpy	Transfer heating rate	Normalized melting enthalpy	Transfer heating rate	Normalized melting enthalpy
K/s		K/s		K/s		K/s		K/s	
0.5	0.98990	0.5	1.00288	0.5	1.01999	0.5	1.01143	0.5	1.01143
1	0.99226	2	1.00701	1	1.00937	1	1.00288	1	1.00495
2	0.99639	3	0.99639	2	0.99639	2	1.00288	5	0.96012
3	0.98371	5	0.98784	3	0.99226	3	1.00701	7	0.87429
4	0.98784	6	0.99226	4	0.99639	4	1.00495	8	0.95156
5	0.97280	7	0.97486	6	0.98577	5	0.97280	10	0.85718
6	0.97722	8	0.97722	8	0.97280	7	0.87842	50	0.48851
7	0.98990	9	0.96867	9	0.93003	10	0.95569	100	0.37702
7.5	0.99433	10	0.96218	10	0.89346	20	0.69201	200	0.19475
8	1.00082	20	0.86131	50	0.61710	50	0.63214	300	0.21628
9	1.01143	50	0.77135	100	0.63863	100	0.57197	400	0.00185
10	0.99226	100	0.65131	200	0.29562	200	0.20772	500	0.05760
20	1.00288	200	0.58702	300	0.27615	400	0.32776	1000	0.00021
50	1.00937	300	0.71355	400	0.14136	500	0.10685	2000	0.00421
100	1.04152	400	0.52272	500	0.18413	1000	0.22070	5000	0.02545
200	0.85512	500	0.55929	1000	0.24636	2000	0.25491	10000	0.08768
300	1.02648	1000	0.59999	2000	0.26996	5000	0.16702		
400	0.93003	2000	0.55280	5000	0.05996	10000	0.17764		
500	0.88726	5000	0.61504	10000	0.13487				
1000	0.85512	10000	0.66635						
2000	0.99433								
5000	0.86986								
10000	0.87222								

Data from **Fig. 9**

Annealing time	Normalized melting enthalpy							
	Annealing temperature / °C							
s	20	30	40	50	60	70	80	90
1	0	0	0	--	0	0	0	0
2	0	0	0	--	0	0	0	0
5	0	0	0	--	0	0	0	0
10	0	0	0	0	0	0	0.01	0
20	0	0	0	0	0	--	--	0
50	0	0	0	0.01	0.12	0.57	0.47	0
100	0	0	0.03	0.22	0.67	0.95	0.97	0
150	0	--	--	0.66	--	--	--	--
200	0	--	0.29	0.96	0.94	0.98	0.98	0

300	0	--	--	0.98	--	--	--	--
400	0	--	--	1	--	--	--	--
500	0	0.39	0.98	1	0.95	0.98	--	0
1000	0	0.91	--	--	--	--	--	0

Data from **Fig. 10**

Sample	Nucleation temperature / °C							
	20		30		40		50	
	$\tau_{0.5,n}$	n_n	$\tau_{0.5,n}$	n_n	$\tau_{0.5,n}$	n_n	$\tau_{0.5,n}$	n_n
1	84	2.30	24.1	1.71	21.3	1.57	24.3	2.20
2			29.7	1.47	10.4	1.83	46	3
3			19.2	2.3	17	2.10		
4			16.5	2.19				
5			14.2	2.21				
6			24	1.64				
Average	84	2.30	21 ± 6	1.9 ± 0.4	16 ± 6	1.8 ± 0.3	35 ± 15	2.6 ± 0.4

Sample	Annealing temperature / °C													
	20		30		40		50		60		70		80	
	$\tau_{0.5,c}$	n_c	$\tau_{0.5,c}$	n_c	$\tau_{0.5,c}$	n_c	$\tau_{0.5,c}$	n_c	$\tau_{0.5,c}$	n_c	$\tau_{0.5,c}$	n_c	$\tau_{0.5,c}$	n_c
1	6365	3	463.3	3	114.6	3	72.98	2.89	93.06	2.95	14.93	3	47.81	0.87
2			573.3	1.16	135.1	3	121.59	2.26	133.9	3	11.38	1.64	125.2	2.91
3			774.6	2.54	261.3	0.86	110.3	3	95.79	3	45.53	1.33		
4			724.5	2.57	255.5	1.95	132.78	2.69	83.71	2.19	19.73	3		
5					110.8	2.37	197.83	3	82.45	1.45	172.15	3		
6					161.9	2.17	163.8	3	36.33	1.63				
7							170.82	3	68.62	1.31				
8							118.9	3	66.83	1.7				
9							146.39	3						
10							78.44	3						
11							69.29	3						
12							78.57	2.96						
13							58.9	3						
Average	6365	3	634 ± 142	2.1 ± 0.9	173 ± 69	2.2 ± 0.8	117 ± 44	2.9 ± 0.2	83 ± 28	2.2 ± 0.7	68 ± 53	2.2 ± 0.9	87 ± 55	1.9 ± 1.5

Data from **Fig. 11**

Temperature	Thermodynamic driving force of crystallization / J*m^{-3}		
°C	Form I	Form II	Form V
125	857344.15579		
120	2.2594E6		
115	3.62788E6	610022.67716	
110	4.9628E6	2.11505E6	

105	6.26416E6	3.59147E6	
100	7.53194E6	5.03927E6	697427.48761
95	8.76616E6	6.45846E6	1.8587E6
90	9.96681E6	7.84904E6	3.01858E6
85	1.11339E7	9.211E6	4.17707E6
80	1.22674E7	1.05444E7	5.33418E6
75	1.33674E7	1.18491E7	6.4899E6
70	1.44338E7	1.31252E7	7.64424E6
65	1.54666E7	1.43727E7	8.79718E6
60	1.64658E7	1.55916E7	9.94874E6
55	1.74315E7	1.67819E7	1.10989E7
50	1.83636E7	1.79436E7	1.22477E7
45	1.92622E7	1.90767E7	1.33951E7
40	2.01272E7	2.01811E7	1.45411E7
35	2.09586E7	2.1257E7	1.56857E7
30	2.17564E7	2.23042E7	1.6829E7
25	2.25207E7	2.33228E7	1.79708E7
20	2.32514E7	2.43128E7	1.91113E7
15	2.39486E7	2.52742E7	2.02504E7
10	2.46121E7	2.6207E7	2.13881E7
5	2.52422E7	2.71112E7	2.25244E7
0	2.58386E7	2.79867E7	2.36593E7

Data from **Fig. 12**

Spike temperature	Normalized melting enthalpy		
	Nucleation time at 40 °C / s		
°C	10	20	50
70	0.12	0.652	0.984
95	0.1	0.612	0.96
100	0.1	0.58	0.976
105	0.072	0.464	0.984
106	0.06	0.424	0.996
107	0.036	0.4	0.988
108	0.028	0.364	0.98
109	0.02	0.288	0.984
110	0	0.08	0.792
111	0	0	0.644
112	0	0	0.38
113	0	0	0
114	0	0	0
115	0	0	0

Data from **Fig. 14**

Rmax / nm
Nucleation temperature / °C

20		30		40	
20	1.99328	15	2.34111	20	6.82921
50	2.4598	15	2.75098	20	7.59372
50	1.27231	15	2.27864	50	9.79408
100	2.05988	15	2.53656	50	10.56133
100	2.06977	15	1.85667	80	8.93023
100	2.89602	15	2.38032	80	7.59372
100	2.22351	15	2.3671	100	9.13146
200	3.07247	15	1.88077	200	12.48123
200	5.31871	20	3.11818		
		20	3.18943		
		20	3.14157		
		20	2.69824		
		20	2.56728		
		20	2.3157		
		20	2.69824		
		20	3.11818		
		20	2.82469		
		20	5.11965		
		20	4.31496		
		20	3.73181		
		20	3.60246		
		20	4.60391		
		20	3.31591		
		20	3.48196		
		20	3.26577		
		25	3.36943		
		25	3.63393		
		25	3.18943		
		25	3.2898		
		25	3.34245		
		25	4.60391		
		25	4.0607		
		25	4.60391		
		30	6.20586		
		30	4.40709		
		30	4.65594		
		30	5.05661		
		30	4.87662		
		30	5.1843		
		30	3.57154		
		35	3.14157		
		35	3.14157		
		35	3.09515		
		40	5.1843		
		40	4.93515		
		40	5.93544		
		40	4.50331		

		40	3.9075		
		40	4.81948		
		40	3.9826		
		40	5.46039		
		50	4.87662		
		50	5.05661		
		50	3.80011		
		50	4.0607		
		50	5.1843		
		50	4.55305		
		50	5.68788		
		60	6.40045		
		60	4.81948		
		60	6.40045		
		60	5.85053		
		80	4.22668		
		80	5.05661		
		80	3.94468		
		100	7.06616		
		100	5.76804		
		100	7.4545		
		100	8.04479		
		200	6.02289		
		200	6.71666		
		200	6.47523		

Data from **Fig. 15**

T	Rate	Error
°C	µm/s	µm/s
20	1.4E-5	4.46E-6
30	2.3E-5	3.17E-6
40	2.4E-5	8.43E-6

T	u||	u⊥
°C	µm/s	µm/s
87	10.09	2.27
82	11.75	2.21
77	7.82	1.53
72	5.24	0.79
67	5.33	0.75

References

1 J. E. K. Schawe, Measurement of the thermal glass transition of polystyrene in a cooling rate range of more than six decades, *Thermochim. Acta*, 2015, **603**, 128–134.

2 L.-P. Blanchard, J. Hesse and S. L. Malhotra, Effect of Molecular Weight on Glass Transition by Differential Scanning Calorimetry, *Can. J. Chem.*, 1974, **52**, 3170–3175.