Supporting Information

Mutarotation kinetic of lactulose in DMSO

In this paper, the tautomeric compositions of amorphous lactulose produced by different processes have been determined by NMR. The measurements were systemically performed 3 minutes after dissolution of lactulose in DMSO, which is the minimum preparation time required to perform the first measurement. We thus determine here the time evolution of the tautomeric composition of lactulose after dissolution in DMSO to estimate the change of tautomeric composition during this initial time laps.

The time evolution of the tautomeric composition of lactulose after dissolution is reported in Figure 6. We can note a strong decrease of the fraction of tautomer A, a strong increase of the fraction of tautomer B, and a moderate increase of the fraction of tautomer C. It thus appears that the mutarotation is slow but not totally blocked by the DMSO. The solid lines in Figure 6 represent the best fits of exponential relaxation laws to the data. Their extrapolation to t = 0 min thus gives the fraction of each tautomer just after dissolution. The corresponding values are reported in Table 4 and compared to the first measurements performed 3 minutes after dissolution. It appears that the evolution during the first 3 minutes after dissolution is very weak: 0.6% for tautomer A, 0.8% for tautomer B and 0.2% for tautomer C.

As a result, the measurement performed 3 minutes after dissolution give a good estimation of the tautomeric fraction just after dissolution and thus in the different amorphous solid states which are investigated in this paper.

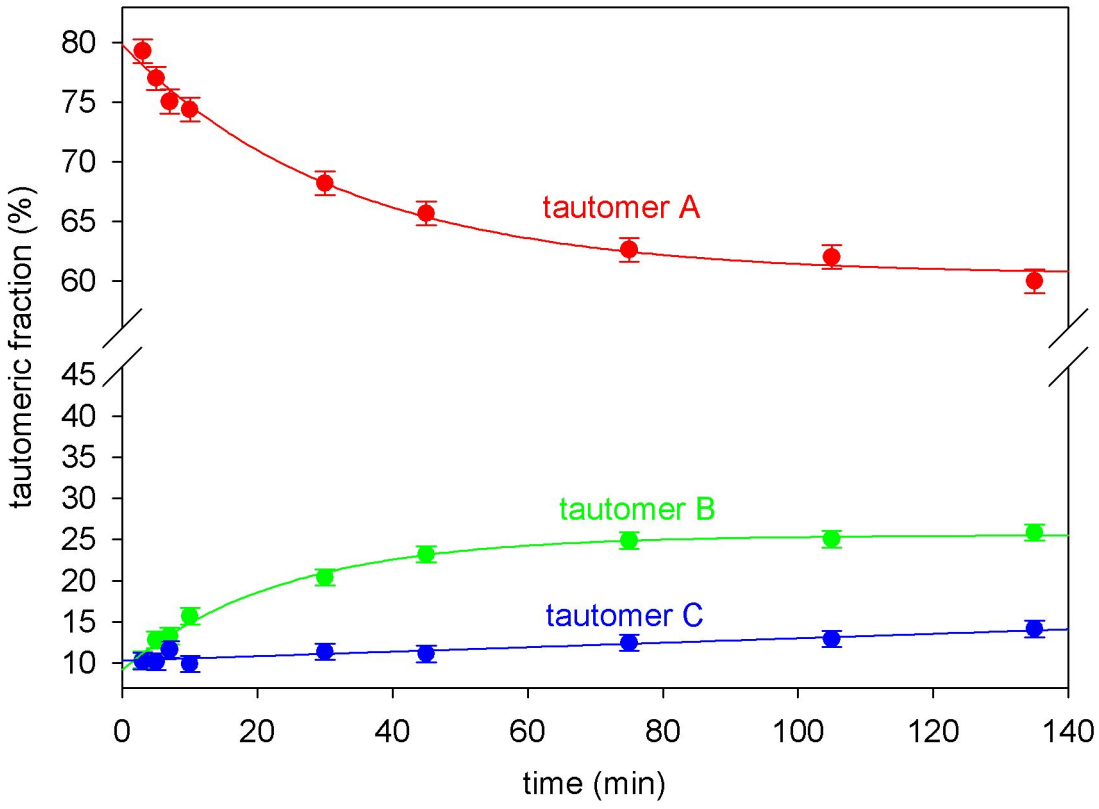

Figure 6: Time evolution of the fraction of tautomers A (red points), B (green points) and C (blue points) after dissolving the crystalline lactulose in DMSO. The solid lines represent the best fit of the data using an exponential relaxation law.

Table 4: Time evolution of the fraction of tautomers A, B and C in DMSO. The values highlighted in grey correspond to the extrapolation of the experimental values (*i.e.* from t=3 min to t=135 min) to t=0 min using an exponential relaxation law.

Time (min)	% of tautomer A (±2)	% of tautomer B (±2)	% of tautomer C (±2)
0	79.9	9.6	10.5
3	79.3	10.4	10.3
5	77.0	12.8	10.2
7	75.1	13.3	11.6
10	74.4	15.7	09.9
30	68.2	20.4	11.4
45	65.7	23.2	11.1
75	62.6	24.9	12.5
105	62.0	25.1	12.9
135	60.0	25.8	14.2

Number of intramolecular and intermolecular HBs developed by tautomers A and C

Table 5: Number of intramolecular and intermolecular HBs developed by tautomers A and C at different temperatures using different geometric criteria to determine the HBs. At all temperatures, and for all geometric criteria, tautomer A always develops slightly more intermolecular HBs than tautomer C.

a) d(O…O) < 3.4 Å and (O-H…O) > 120°

	Intramolecular HB		Intermolecular HBs	
Temperature (K)	tautomer A	tautomer C	tautomer A	tautomer C
650	1.23	1.54	9.03	8.31
600	1.20	1.52	9.94	9.25
550	1.19	1.48	10.97	10.22
500	1.13	1.42	12.03	11.18

b) d(O…O) < 3.4 Å and (O-H…O) > 150°

	Intramolecular HB		Intermolecular HBs	
Temperature (K)	tautomer A	tautomer C	tautomer A	tautomer C
650	0.18	0.31	4.21	3.80
600	0.17	0.33	4.83	4.40
550	0.18	0.34	5.56	5.08
500	0.17	0.35	6.43	5.86

c) d(O…O) < 4.0 Å and (O-H…O) > 120°

	Intramolecular HB		Intermolecular HBs	
Temperature (K)	tautomer A	tautomer C	tautomer A	tautomer C
650	1.49	1.84	13.81	12.87
600	1.45	1.81	14.72	13.91
550	1.42	1.75	15.78	14.87
500	1.33	1.66	16.67	15.75

d) d(O…O) < 4.0 Å and (O-H…O) > 150°

	Intramolecular HB		Intermolecular HBs	
Temperature (K)	tautomer A	tautomer C	tautomer A	tautomer C
650	0.23	0.39	5.38	4.91
600	0.22	0.41	5.97	5.48
550	0.22	0.42	6.62	6.09
500	0.20	0.41	7.38	6.81