Supplementary Information

Crystal Nucleation of Salicylamide and a comparison with Salicylic acid

*Shubhangi Kakkar[1], K. Renuka Devi.[1], Michael Svärd[2], Åke Rasmuson[*1,2]*

[1]Synthesis and Solid State Pharmaceutical Centre, Bernal Institute, Department of Chemical Sciences, University of Limerick, Limerick, Ireland.

[2]Department of Chemical Engineering and Technology, KTH Royal Institute of Technology, Stockholm, Sweden.

** Email: Ake.Rasmuson@ul.ie*

Salicylamide Structure

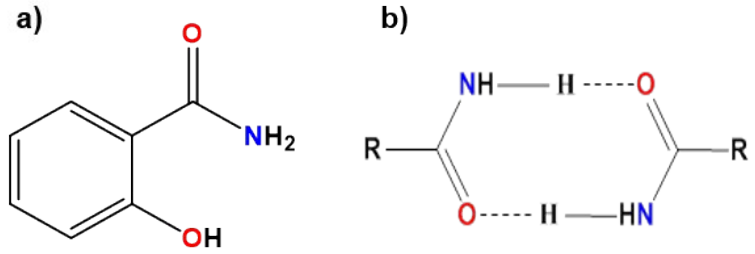

Figure S1. The chemical structure salicylamide a) and the dimer formed between the amides of two molecules in the crystal structure b).

Activity coefficient

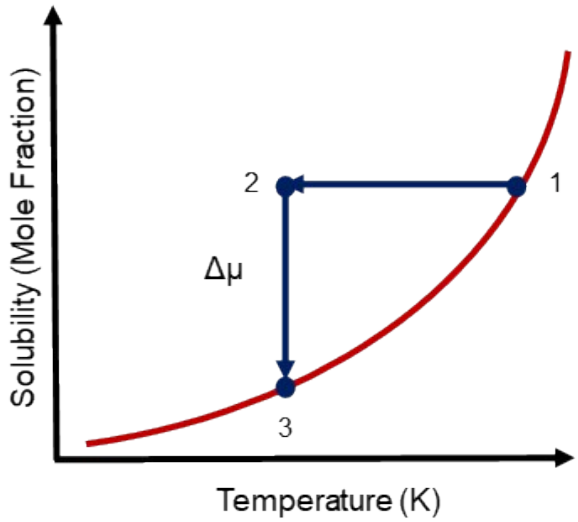

Figure S2. Schematic of driving force (Δμ) in cooling crystallization represented on the solubility diagram. Red line is the solubility curve.

Table S1. Values of activity and gamma for salicylamide and salicylic acid at 15°C in different organic solvents:

Solute	***Salicylamide***	***Salicylic acid***	***Salicylamide***	***Salicylic acid***
Solute activity (a)	0.0493	0.0821	***Mole Fraction Solubility*** $\left(x = \frac{a}{\gamma_a}\right)$	
Solvent	***Solute activity coefficient in solution*** (γ_a)			
Ethyl acetate	0.812	0.704	0.0607	0.1164
Acetonitrile	2.0792	3.719	0.0237	0.0221
Acetone	0.457	0.524	0.1079	0.1566
Methanol	1.616	0.761	0.0305	0.1078

Induction time Experiments

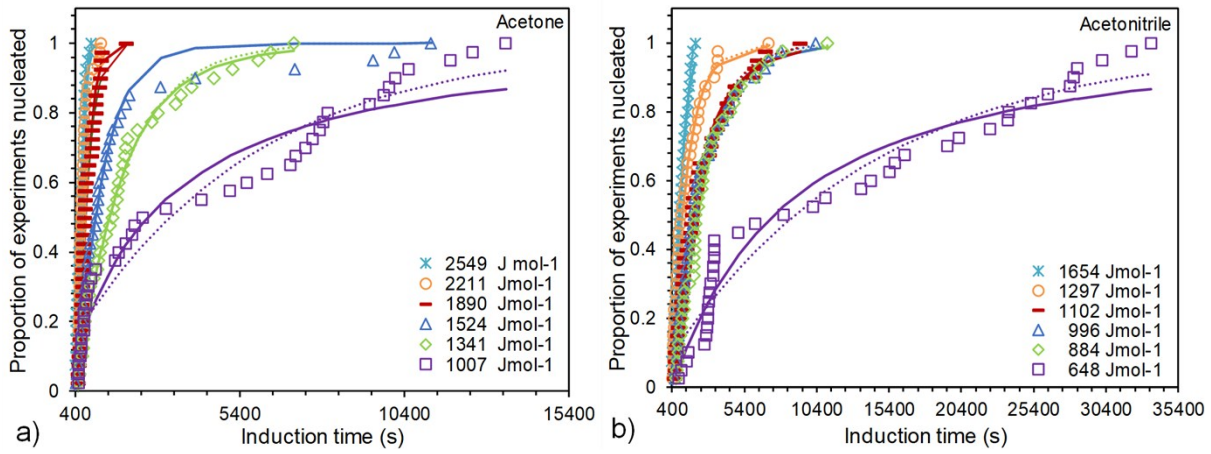

Figure S3. Nucleation distribution for salicylamide in a) acetone b) acetonitrile at different thermodynamic driving forces (Δμ). Each data point represents the induction time obtained for a particular experiment while the lines represent the lognormal cumulative distribution function (solid line) and poisson distribution function (PDF) (dashed line) curve fit.

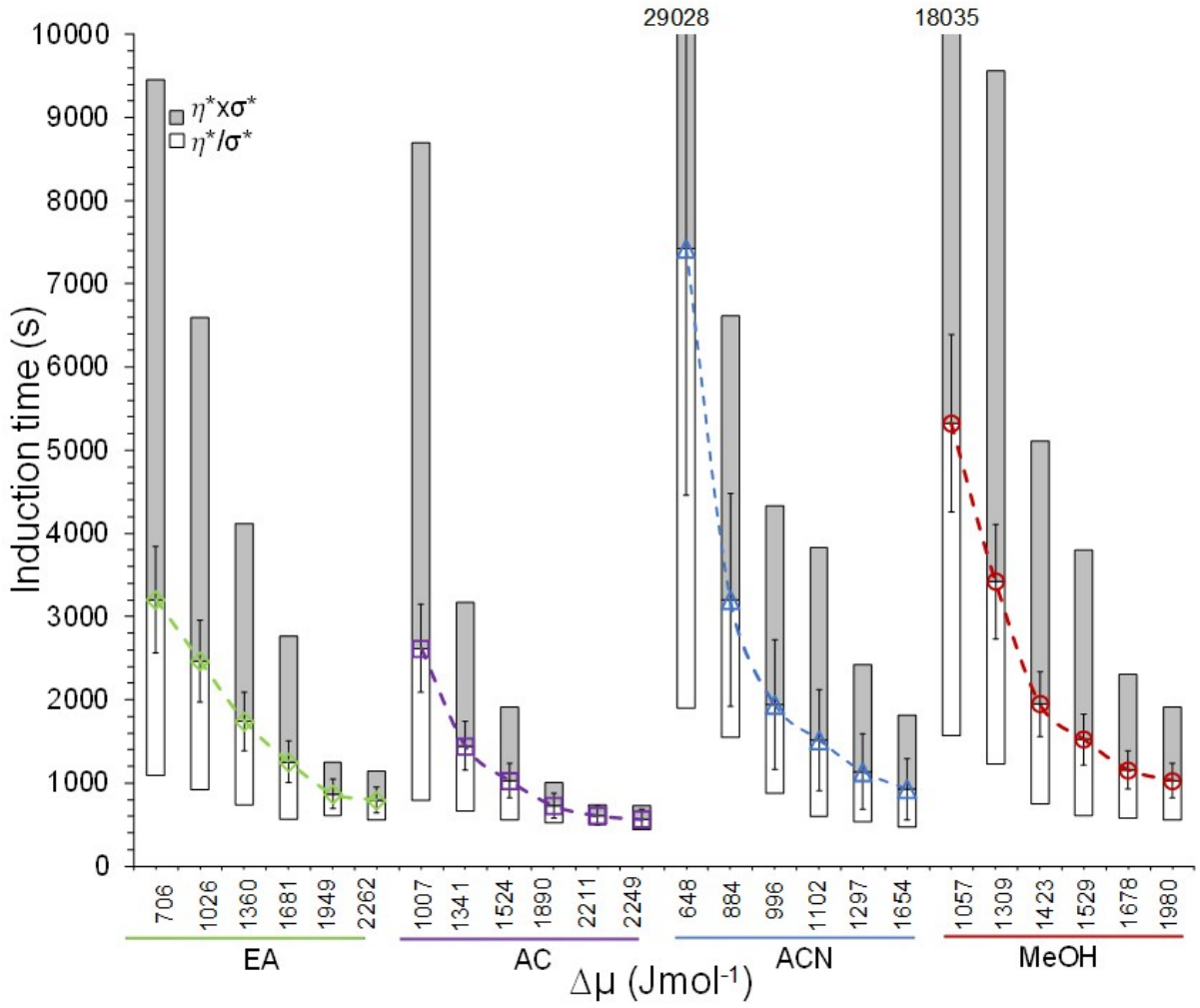

Figure S4. The effect of the thermodynamic driving force (Δμ) on the induction time distributions in; ethyl acetate (♦), acetone (■), acetonitrile (▲), and methanol (—). Symbols represent the geometric mean (n*) position. For the necessity of the scale, the numbers above a data set represent the highest value for that data set.

Table S2. Induction time experiment results: calculated nucleation rate (J), critical energy, size (R*) using equation S1 and number (N*) of the critical nucleus, the geometric mean induction time (n*) and geometric standard deviation (σ*) are shown:

Solvent	$\Delta\mu$ *(J mol^{-1})*	τ_{50} *(s)*	*J (m^{-3} s^{-1})*	Δg^* *(J mol^{-1})*	R^* *(Å)*	N^*	*n*(s) x/ σ**	R^2_L	R^2_P	*tg (s)*
Ethyl Acetate	706	3042	13.58	7156	9.35	20.23	3202 x/ 2.95	0.99	0.98	708
	1026	2514	27.97	3384	6.43	6.58	2462 x/ 2.18	0.99	0.99	686
	1360	1649	36.99	1927	4.85	2.83	1740 x/ 2.77	0.99	0.98	503
	1681	1520	42.01	1263	3.93	1.50	1454 x/ 2.20	0.98	0.98	491
	1959	837	44.78	929	3.37	0.95	870 x/ 1.43	0.97	0.97	476
	2262	787	46.82	697	2.92	0.61	795 x/ 1.44	0.98	0.98	451
Acetone	1007	2470	18.13	4378	7.05	8.68	2620 x/ 4.32	0.95	0.95	524
	1341	1547	40.21	2469	5.30	3.68	1445 x/ 2.19	0.99	0.99	519
	1524	1051	50.71	1913	4.66	2.51	1030 x/ 1.86	0.99	0.99	484
	1890	692	67.05	1244	3.76	1.31	727 x/ 1.37	0.96	0.98	479
	2211	598	77.11	908	3.21	0.82	609 x/ 1.20	0.99	0.98	474
	2549	581	84.70	683	2.79	0.54	565 x/ 1.29	0.98	0.95	385
Acetonitrile	648	8104	7.31	5595	8.87	17.27	7431 x/ 3.91	0.94	0.94	850
	884	2067	21.54	3007	6.50	6.80	2198 x/ 2.07	0.99	0.99	707
	996	1906	28.16	2365	5.77	4.74	1944 x/ 2.23	0.99	0.99	632
	1102	1787	33.74	1932	5.21	3.50	1816 x/ 2.32	0.99	0.99	545
	1297	1062	42.21	1395	4.43	2.15	1133 x/ 2.14	0.99	0.99	478
	1654	916	52.82	858	3.47	1.04	925 x/ 1.66	0.99	0.97	393
Methanol	1057	4934	9.14	5818	7.63	11.00	5327 x/ 3.39	0.99	0.99	615
	1309	3714	21.26	3793	6.16	5.79	3420 x/ 2.79	0.99	0.99	578
	1423	1546	27.09	3211	5.67	4.51	1950 x/ 3.62	0.95	0.91	532
	1529	1314	32.43	2779	5.27	3.63	1522 x/ 2.50	0.99	0.98	458
	1678	1147	39.45	2309	4.81	2.75	1157 x/ 1.99	0.97	0.98	450
	1980	1064	51.73	1659	4.07	1.68	1030 x/ 1.86	0.99	0.99	445

R^2_L: r-squared value of fit from the lognormal cumulative distribution function

R^2_P : r-squared value of fit from the poisson probability distribution function

Interfacial Energy and Pre-Exponential Factor

Table S3. Interfacial energy (γ) and pre-exponential factor (A) of salicylamide in different solvents calculated from fitting the different probability distribution functions:

Solvent		***Median***	***PDF***	***Lognormal*** $\frac{1}{2} erfc(-\frac{\ln(t)-n}{\sigma\sqrt{2}})$	***Log-Log*** $\frac{1}{1+(\lambda/t)^{\beta}}$	***Weibull*** $1-e^{-(t/\lambda)^{\beta}}$	***Diao*** $e^{-(\frac{t}{\tau})^{\beta}}$
Ethyl acetate	γ (mJ m-^{2})	3.24	3.37	3.22	3.22	3.40	3.06
	A (m^{-3} s^{-1})	74.57	50.45	72.95	73.22	65.18	85.40
Acetonitrile	γ (mJ m-^{2})	2.90	2.94	2.85	2.85	2.98	2.70
	A (m^{-3} s^{-1})	80.65	55.72	74.83	75.06	63.29	87.71
Acetone	γ (mJ m-^{2})	3.49	3.90	3.52	3.52	3.86	3.00
	A (m^{-3} s^{-1})	112.68	122.01	114.61	114.93	118.80	104.11
Methanol	γ (mJ m-^{2})	3.96	4.03	3.99	4.00	4.17	3.80
	A (m^{-3} s^{-1})	103.26	59.31	100.90	101.77	84.13	119.95

Even though there are some differences in the actual numerical values obtained from all the fits represented in Table S3, the order with respect to the solvent with few exceptions is the same.

Viscosity of Solutions and Intrinsic nucleation rate constant

Table S4. Viscosity of solutions (η) for salicylamide (SLA) and salicylic acid (SA) experimentally determined at 15°C and 30°C, respectively, using the method explained in section 2 and intrinsic nucleation rate constant (A_0) of salicylamide at 15°C:

Solvent	*η of SLA at 15°C (mPas)*	*A_0 at 15°C (mPa m^{-3} K^{-1})*	*η of SA at 30°C (mPas)*
Ethyl acetate	0.64	0.167	0.64
Acetonitrile	0.51	0.143	0.51
Acetone	0.71	0.278	0.67
Methanol	0.89	0.318	1.07

Radius of Critical Nuclei

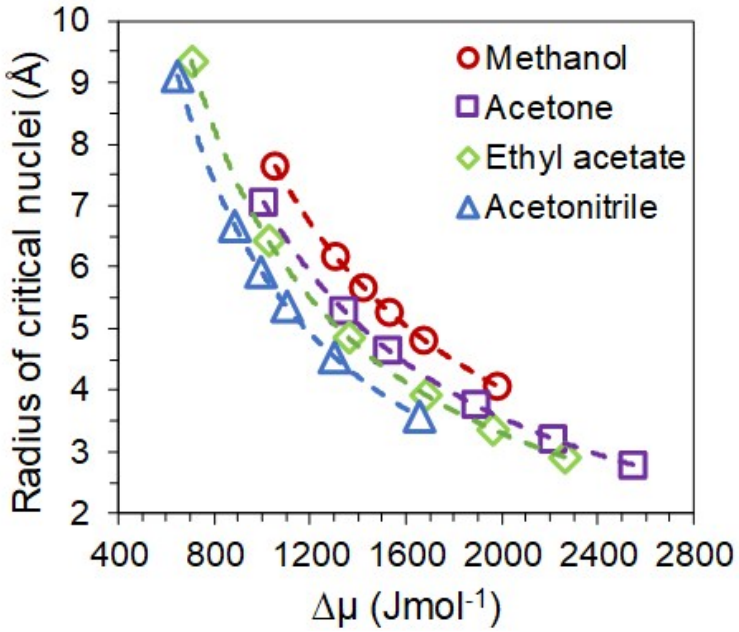

Figure S5. Trend of the radius of critical nuclei with respect to the driving force.

The numerical value of radius of critical nuclei (R*) is calculated using the equation S1 as shown in Table S2:

$$R^* = \frac{2(\gamma\vartheta)}{kTlnS} \qquad \text{(S1)}$$

Activity Coefficient Correction

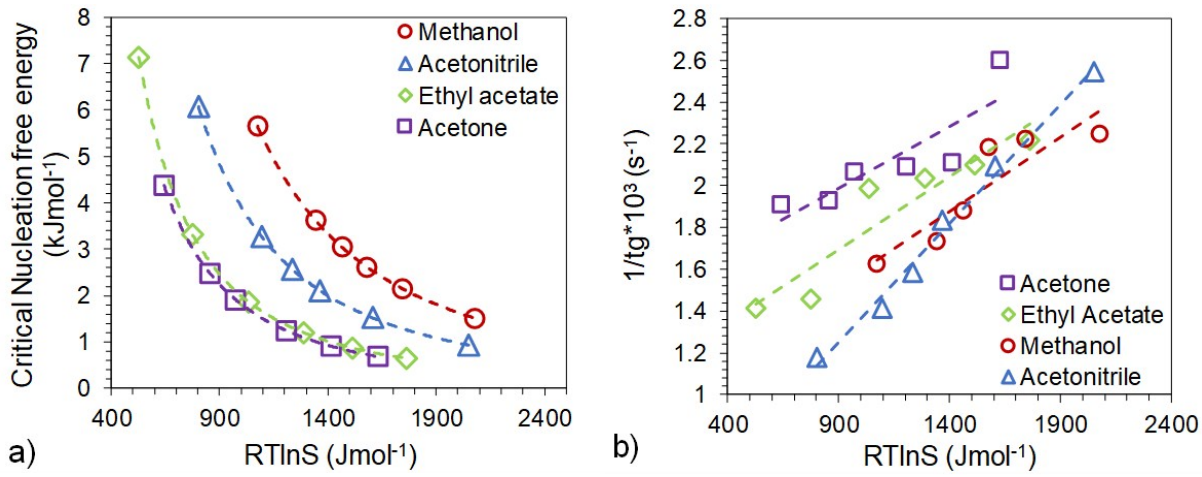

Figure S6. Trend for a) critical nucleation free energy and b) growth time at the value of driving force not corrected for activity coefficient.

On average, the increase in driving force on activity coefficient correction was found to be in the order acetone (56 %) and ethyl acetate (31%), a decrease in driving force was observed in methanol (3%) and acetonitrile (19%). The value of interfacial energies without activity coefficient corrected driving forces (where S = x/x^*) were 3.97 mJm^{-2} in methanol, 3.34 mJm^{-2} in acetonitrile, 2.67 mJm^{-2} in ethyl acetate and 2.59 mJm^{-2} in acetone. In comparison to the values obtained with activity coefficient corrected driving forces as 3.96 mJm^{-2} in methanol, 3.49 mJm^{-2} in acetone, 3.24 mJm^{-2} in ethyl acetate and 2.90 mJm^{-2} in acetonitrile. The increase in driving forces is reflected in the change in interfacial values. The critical nucleation free energy (Figure S4 a) with respect to driving force (where S = x/x^*) changed to ethyl acetate < acetone < acetonitrile < methanol. The values are found to be lower here, with a swap between acetone and acetonitrile. In addition, a change in the order of solvents growth rate (Figure S4b) is observed: acetone > ethyl acetate is the highest and methanol and acetonitrile are the lowest.

Induction time results for Salicylamide and Salicylic acid

Table S5: Induction time experiment results for salicylamide and salicylic acid at 15°C in 10 ml solution: summary of driving forces, induction time values (τ_{50}) and calculated nucleation rate (J) using Equation 3 are shown:

		Salicylamide		***Salicylic acid***	
Solvent	$\Delta\mu$ ***(Jmol^{-1})***	τ_{50} ***(s)***	***J (m^{-3}s^{-1})***	τ_{50} ***(s)***	***J (m^{-3}s^{-1})***
Ethyl Acetate	919	1503	67	1228	81
	984	1405	71	1022	98
	1049	1244	80	924	108
	1114	1079	93	727	138
	1179	937	107	547	183
	1244	751	133	347	288
Acetone	1357	778	129	694	144
	1453	618	162	458	218
	1549	503	199	358	280
	1645	417	240	289	346
	1741	355	282	248	404
	1837	228	439	218	458
Acetonitrile	958	1022	98	972	103
	1028	924	108	705	142
	1098	760	132	465	215
	1168	686	146	376	266
	1239	586	171	313	319
	1309	466	215	304	329
Methanol	929	2969	34	1798	56
	996	2554	39	1444	69
	1063	2161	46	1095	91
	1131	1760	57	719	139
	1198	1564	64	537	186
	1265	1245	80	470	213