Crystal Growth of Salicylic Acid in Organic Solvents

Lijun Jia [1], Michael Svärd [1,2], Åke C. Rasmuson [1,2]*

[1]Synthesis and Solid State Pharmaceutical Centre, Materials and Surface Science Institute, Department of Chemical and Environmental Science, University of Limerick, Limerick (Ireland)
[2]Department of Chemical Engineering and Technology, KTH Royal Institute of Technology, SE-100 44 Stockholm (Sweden)
**email: Ake.Rasmuson@ul.ie*

Solubility and activity coefficients of salicylic acid

The mole fraction solubility of a compound in a given solvent at a given temperature (x_{eq}) is equal to the activity of the solute in the saturated solution (a_{eq}) divided by the activity coefficient of the solute in the solution at that temperature and concentration (γ_{eq}.) The reference state for the activity (and the activity coefficient) is chosen to be the state of a pure, supercooled melt at the same temperature (the common Raoult's law definition). Then, the activity of the solute at saturation is equal to the activity of the pure solid phase (a^s), and:

$$\ln x_{eq} = \ln a^s - \ln \gamma_{eq}$$

The activity of the solid is directly related to the Gibbs energy of fusion:

$$\ln a^s = \frac{\Delta_{fus} H(T_m)}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) + \frac{1}{R}\int_{T_m}^{T} \frac{\Delta C_p}{T} \mathrm{d}T - \frac{1}{RT}\int_{T_m}^{T} \Delta C_p \mathrm{d}T$$

The heat capacity is modelled with a linear function of temperature:

$$\Delta C_p = q + r(T_m - T)$$

In Table S1, the relevant calorimetric properties of salicylic acid are listed. Values are taken from work by Nordström and Rasmuson.[1, 2]

Table S1. Melting temperature, enthalpy of fusion, and heat capacity difference regression coefficients of salicylic acid.

T_m, K	$\Delta_{fus}H(T_m)$, kJ/mol	q, J/mol/K	r, J/mol/K^2
431.35	27.09	143.3	-0.62

In Table S2, the temperature regression equation used to correlate mole fraction solubility is shown, together with coefficient values taken from Nordström and Rasmuson.[1]

Table S2. Mole fraction solubility regression model and coefficients for salicylic acid in four solvents.

Solvent	**Regression model:** $\ln x = \frac{A}{T^2} + \frac{B}{T} + C$		
	$10^{-5}A$	$10^{-3}B$	C
MeOH	2.8005	-3.3598	6.0623
MeCN	6.1837	-6.6941	11.975
AC	-0.16214	-1.0345	1.9335
EA	2.9967	-3.2949	5.6791

Figure S1 shows the saturated solution properties of salicylic acid in methanol, acetone, ethyl acetate and acetonitrile. The mass ratio solubility shown in Figure S1a is calculated from the mole fraction solubility. In mass ratio terms, the solubility of salicylic acid is relatively high in methanol and acetone and lower in ethyl acetate and acetonitrile. Solubility regression curves are also plotted in the figures over a temperature range from 10°C to 25°C, which is used in this study. Activity coefficients of salicylic acid in these four solvents are plotted in Figure S1b. The activity coefficient of salicylic acid in acetonitrile (3.9-3.3) is greater than in methanol (0.75-0.78), acetone (0.51-0.56) and ethyl acetone (0.68-0.74). A value of the activity coefficient higher than 1 implies that solute-solute (salicylic acid) interactions are stronger than interactions between salicylic acid and acetonitrile; in contrast, relatively strong interactions between salicylic acid and solvent (methanol, acetone and ethyl acetate) result in values of the activity coefficient below 1. With increasing temperature, the solution behavior approaches ideality, and the value of the activity coefficient in all solvents tend towards unity.

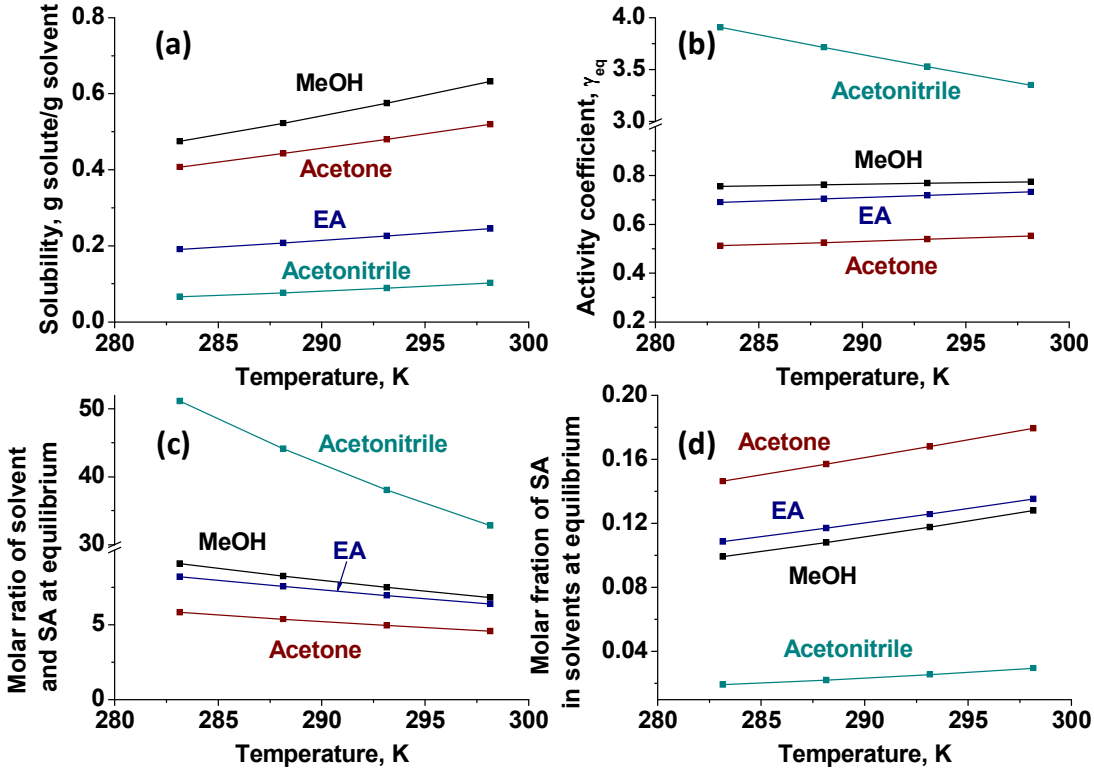

Figure S1 Solubility, scatter plot obtained from experimental data and solid line obtained from regression curves (a); activity coefficients (b); molar ratio of solvent to solute (c) and molar fraction of solute (d).

The molar ratio of solvent to solute (salicylic acid) in saturated solution and mole fraction solubility are compared at different temperatures in Figures S1c,d. Unsurprisingly, the molar ratio of acetonitrile to salicylic acid is much higher compared with the values in other solvents due to the lower solubility of salicylic acid in acetonitrile. The solvation of salicylic acid in these solvents has been investigated by Khamar et al.[3]; in their paper, the binding

energy of solvation clusters have been calculated theoretically. It is interesting to notice that the molar ratio of solvent to solute in a solvation cluster reported in this paper is much greater than that in a saturated solution (methanol, acetone and ethyl acetate) except the one with acetonitrile as solvent; we can therefore infer that the salicylic acid molecule was not fully solvated during desupersaturation experiments in the solvent with high solubility. It is notable that salicylic acid molecules exist mainly as dimers in both the solid crystalline and the pure liquid phase; however, no sign of dimers existing in the salicylic acid solutions of these four solvents could be detected through Raman measurements.[3]

Growth kinetics – fits of power law equation

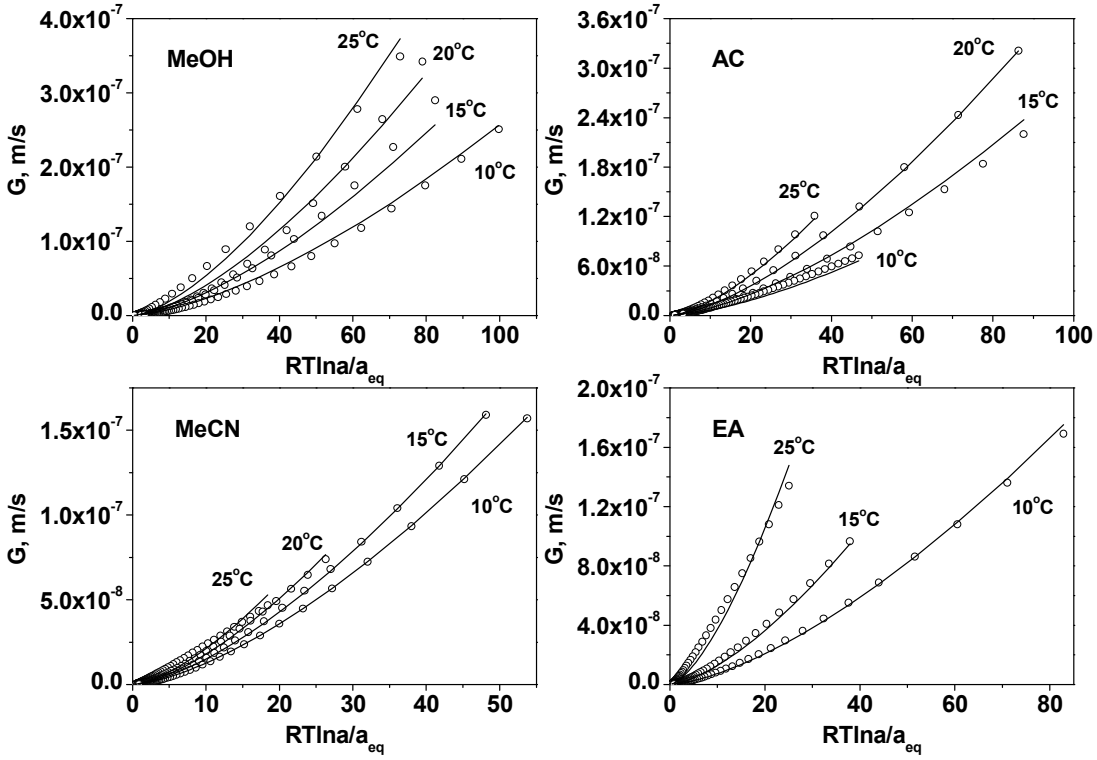

Figure S2 Power law equation fitting plotted with true driving force (scatter plot) modified power law fitting based on true driving force with g=1.5 (solid line)

Table S3. Fitted kinetic parameters in modified power law equation with g=1.5

Solvent	MeOH	AC	MeCN	EA
k_{g0}, m/s/(J/mol)^g	5.3e-3±2.8e-3*	5.1e-2±3.4e-2*	1.1e-5±0.4e-5*	2.3e4±1.1e4*
Ea, kJ/mol	39.7±1.3*	45.5±1.6*	24.2±0.8*	75.9±1.2*

*) 95% confidence interval.

References:

(1) Nordström, F. L.; Rasmuson, Å. C. Solubility and Melting Properties of Salicylic Acid. *J. Chem. Eng. Data* **2006,** 51, 1668.

(2) Nordström, F. L.; Rasmuson, Å. C. Determination of the activity of a molecular solute in saturated solution. *J. Chem. Thermodyn.* **2008,** 40, 1684.

(3) Khamar, D.; Zeglinski, J.; Mealey, D.; Rasmuson, Å. C. Investigating the Role of Solvent–Solute Interaction in Crystal Nucleation of Salicylic Acid from Organic Solvents. *J. Am. Chem. Soc.* **2014,** 136, 11664.