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Solution Chemistry and Structure

Roger Davey

Content: Studying and defining solute- solute interactions in the liquid phase.
Techniques available.
Speciation in solution.
Do these (thermodynamic features have) an impact on nucleation rate or outcome?
Examples – glycine/saccharin/benzoic acid/tetrolic acid/mandelic acid/paminobenzoic acid/co-crystals.

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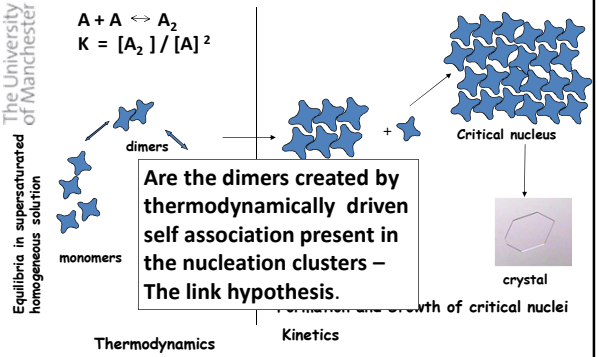
The context – making clusters

$A + A \leftrightarrow A_2$

$K = [A_2] / [A]^2$



Are these equilibria and quasi equilibria in anyway related?

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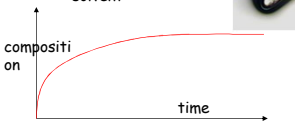
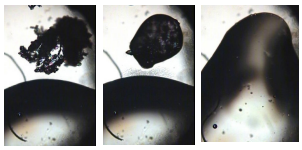
First a note about ideal solutions

The usual way: dissolve solid in solvent



The ideal way: melt solid and mix with solvent.



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A macroscopic view – 'ideal solubility' and why I use it.

Enthalpy changes: $\Delta H_{solution} = \Delta H_{sublimation} + \Delta H_{solvation}$

$\Delta H_{solution} = \Delta H_{fusion} + \Delta H_{mixing}$

In an ideal solution $\Delta H_{mixing} = 0$.
This means that $(E_{s\text{-}s} + E_{solv\text{-}solv})/2 = E_{s\text{-}solv}$
Real solutions don't have this exact balance and in a non-ideal solution ΔH_{mixing} is thus non zero.

And the ideal solubility is given by a very familiar equation:

$$\ln(x_{ideal}) = \{\Delta H_f(1/T_m - 1/T) + \Delta C_p[T_m/T - \ln(T_m/T) - 1]\}/R$$

If $x > x_{ideal}$ then negative deviation .....solvation
If $x < x_{ideal}$ then positive deviation.....aggregation.

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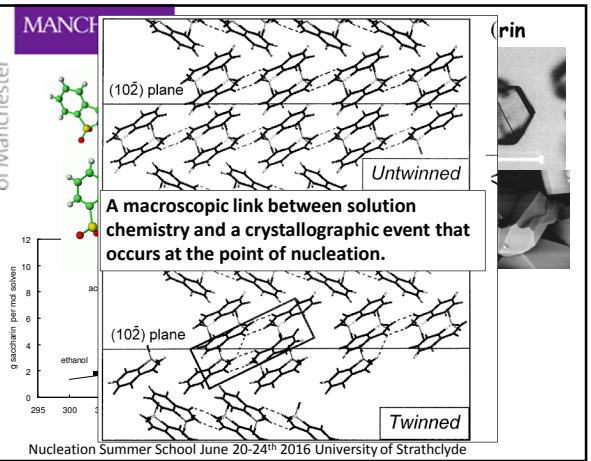

A macroscopic link between solution chemistry and a crystallographic event that occurs at the point of nucleation.

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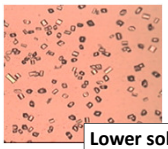
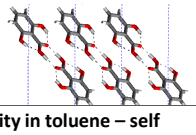
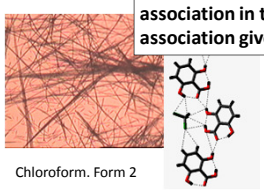
Macroscopic picture: polymorphism of dihydroxybenzoic acid.



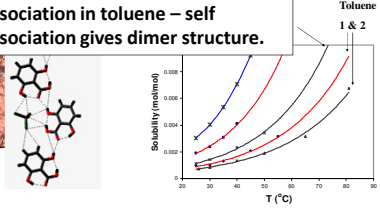
Form 1. Toluene



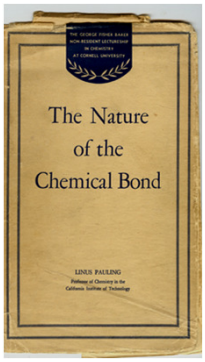
Lower solubility in toluene – self association in toluene – self association gives dimer structure.



Chloroform. Form 2



Solution chemistry – the path to more direct insights.

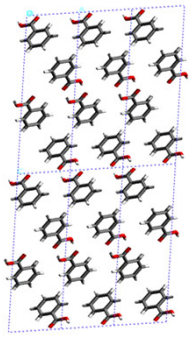


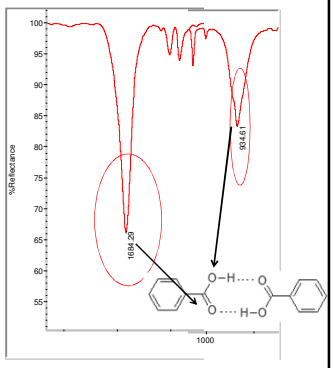
Year 1945 : page 307

'Benzoic acid and other carboxylic acids have been shown to associate to double molecules in solution in certain solvents such as benzene, chloroform, carbon tet and carbon disulphide. Benzoic acid exists in monomeric form in solution in acetone, acetic acid, ethyl ether, ethyl acetate and phenol; in these solutions single molecules are stabilised by hydrogen bond formation with the solvent.'

These data came from freezing point depression but could we now observe it directly using spectroscopy?

FTIR Spectroscopy – crystalline benzoic acid.





Saturated benzoic acid in toluene

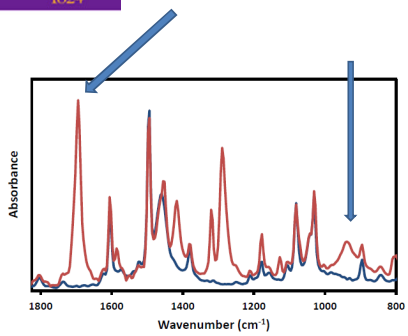
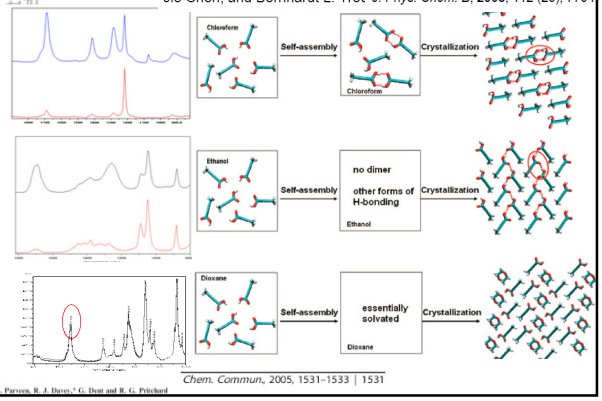


Figure 5.15: C=O region of the solution state FTIR spectra for toluene (dark blue) and saturated benzoic acid in toluene (red) (0.67M) at 25°C.

Tetrolic acid and the link.

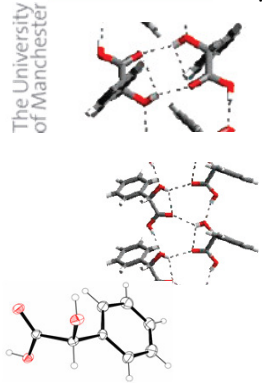
Jie Chen, and Bernhardt L. Trout *J. Phys. Chem. B*, **2008**, 112 (26), 7794

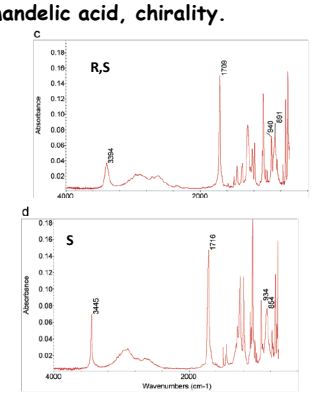


Chem. Commun., 2005, 1531–1533 | 1531

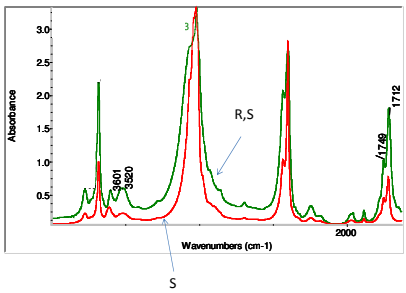
S. Parveen, R. J. Davey,* G. Dent and R. G. Pritchard

Some times there is no link – mandelic acid, chirality.





Saturated solutions in $CHCl_3$ identical vc=o .



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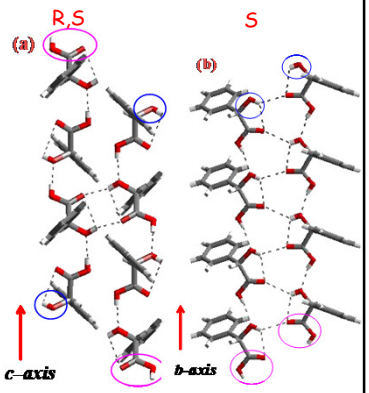
Solutions the same - But Structures are so different - no link.



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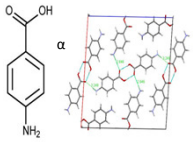
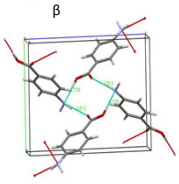
Some times there is no link -pABA

para-aminobenzoic acid



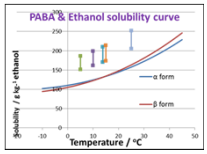
α

β



CSD: AMBNAC01and AMBNAC04.

water		Temp / °C			
		10	13.8	15	25
Supersaturation (S)	1.3	β	β	β	β
	1.6	α	α	α	α



Ethanol and any other organic solvent – α under all conditions.

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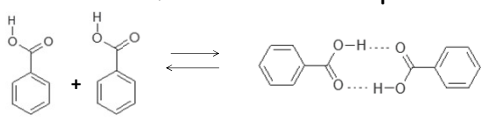
Self assembly : carboxylic acid dimers –concentration dependence.



$A + A = A_2$ and $K = [A_2]/[A]^2$ with $[A] + 2[A_2] = [A]_o$

$[A]$ and $[A_2]$ are the equilibrium concentrations of monomer, A, and that of dimer, A_2, respectively; $[A]_o$ is the initial concentration species, A.

Leads to $[A_2]/[A] \alpha K[A_o]^{½}$

So in the IR the relative intensity of the peaks increases with solution concentration.

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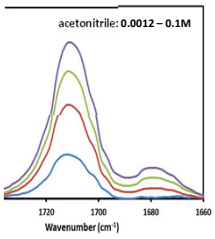
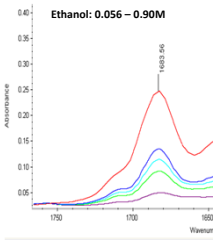
pABA: Solution Chemistry – FTIR concentration dependence





Δν = 30cm-1

I 1710/1680 = 15 (0.0012M) --- 1.41 (0.38M)

Mixture of solvated monomers and dimers.

Δν = 20cm-1

I 1710/1685 = 5.5 (0.056M) --- 5.6 (0.9M)

Only solvated monomers.

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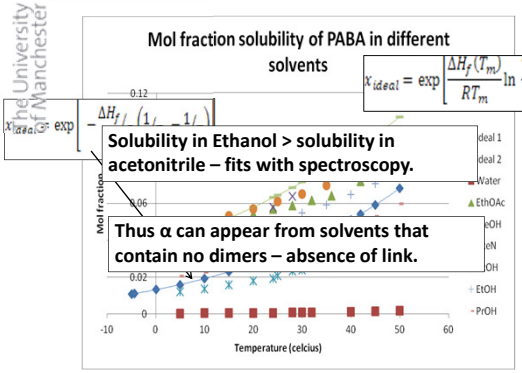
Compare to solubility data

Mol fraction solubility of PABA in different solvents

$$x_{ideal} = \exp\left[\frac{\Delta H_f(T_m)}{RT_m}\ln\frac{T_m}{T}\right]$$



Solubility in Ethanol > solubility in acetonitrile – fits with spectroscopy.

Thus α can appear from solvents that contain no dimers – absence of link.

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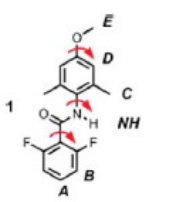
Self assembly: nmr, concentration dependant chemical shifts – more links.

A ^{1}H NMR study of crystal nucleation in solution†

Andrea Spitaleri,[a] Christopher A. Hunter,*[a] James F. McCabe,[b] Martin J. Packer[c] and Scott L. Cockroft[a]

CrystEngComm, 2004, 6(80), 489–493



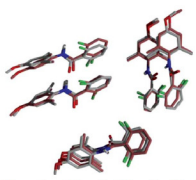


Fig. 3 Three orthogonal views of the **1** dimer. The solution NMR structure is shown in grey and the X-ray crystal structure is shown in brown. The rmsd between the two structures is 0.44 Å.[14] Click here to access a 3D image of Fig. 3.

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Data analysis – *C.A* Hunter and M. J. Packer,

Chem Eur. J., 1999, **5**, 1891- 1897

NMRDil_Dimer which use a Simplex procedure to fit the experimental data and determine the optimum solutions for the association constant, and the limiting bound and free chemical shifts. Thus, for example, *NMRDil_Dimer* fits the data to a dimerisation isotherm by solving the following equations.

$$[AA] = \frac{1 + 4K_d[A]_0 - \sqrt{1 + 8K_d[A]_0}}{8K_d}$$

$$[A] = [A]_0 - 2[AA]$$

$$d_{obs} = 2[AA]/[A]_o\, d_d + [A]/[A]_o\, d_f$$

In which $[A]_0$ is the total concentration, $[A]$ is the concentration of unbound free species, $[AA]$ is the concentration of dimer, K_d is the dimerisation constant and d_f and d_d are the chemical shifts of the free and limiting bound dimer respectively.

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NMR – visualisation using SHIFTY.

The method used to determine and visualise three-dimensional structures from the measured complexation-induced changes in the chemical shifts (CIS), *SHIFTY,*

CIS values are calculated by building the molecules in XED 2.8 using standard bond lengths and angles.

The anisotropy parameters used for the base were taken from *ab-inito* calculations.

The representation used treats the five-membered ring as aromatic with a ring current factor of 1.03, and the six-membered ring as non-aromatic.

A genetic algorithm was used to optimise the structure of the dimeric complex, so that the calculated CIS values matched the experimental values as closely as possible. The conformational search was divided into five steps, each with population size of 750 and 2000 generations. In the first step, the intermolecular distance was set to 10 Å, the range of allowed rotations of one molecule relative to the other was set to 360°. Intramolecular torsions were allowed to change within the full range of 360° for both molecules. In subsequent steps, each search space parameter was reduced to half of its previous value.

The self-association constant (K*f*) was varied by a factor of 10, to scale the experimental values to allow for errors in the isotherm curve fitting.

All the solutions showed a root mean square difference between the experimental and calculated chemical shifts of less than 0.002 ppm.

The scaling factor applied to the self association constant was close to one in all cases with an average value of 1.2, suggesting that the experimental value is reasonably accurate. The final structure predicted using *SHIFTY* may be compared with the actual crystal structures of the associated polymorph.

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Carbamazepine – solvent dependence

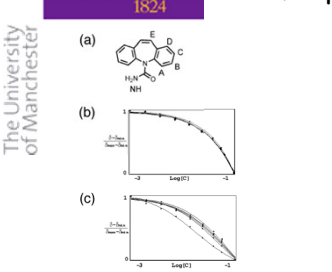

Figure 2. (a) Structure of carbamazepine, showing the proton labeling scheme. (b) Normalised changes in chemical shift observed for all protons of carbamazepine as a function of concentration in CD_3OH solution at 295 K. The lines represent the best fit to a dimerization isotherm. (c) Normalised changes in chemical shift observed for all protons of carbamazepine as a function of concentration in $CDCl_3$ solution at 295 K. The lines represent the best fit to a dimerization isotherm.

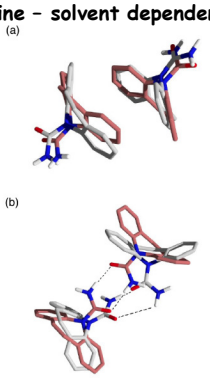

Figure 4. Comparison of carbamazepine dimer motifs found in the X-ray crystal structure (grey) with solution phase NMR structures of carbamazepine dimers (red) determined in CD_3OH (a) and in $CDCl_3$ (b). The rmsd between the solution and solid state structures is 1.0 Å in CD_3OH and 1.8 Å in $CDCl_3$.

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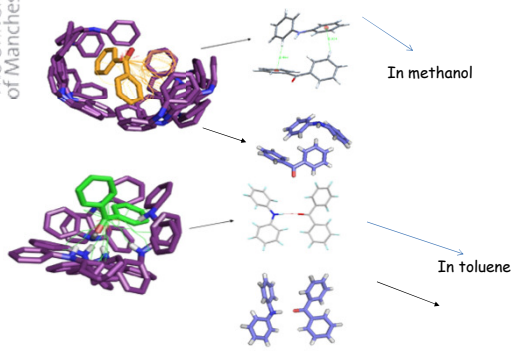
The co-crystal BZP-DPA – solvent dependence .of dimer



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Using UV/vis – conc dependence of ε.

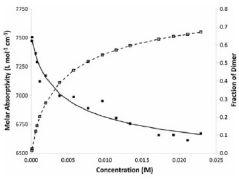

Fig. 11 Concentration dependence of the apparent molar absorptivity of TFA at λ_{max} = 346 nm. The solid line is a fit of the data according to Eq. 1; the dimer fraction is also shown as dash line versus the total TFA concentration.

species. By measuring UV absorbance at different concentrations, the molar absorptivity was calculated and plotted as a function of concentration (Fig. 11). Hypochromic deviation from the Beer-Lambert law is evident, suggesting self-association of solute molecules (43,60). The total absorbance may be regarded as a sum of individual species in the solution:

$$\varepsilon\, C_T = \varepsilon_m\, C_m + \varepsilon_n\, n\, K_{1,n} (C_m)^n \qquad (1)$$

where ε is the apparent molar absorptivity determined from the experimental absorbance; ε_m and ε_n are the molar absorption coefficients of monomers and *n*-mer aggregates of solute molecules, respectively. In addition, *n* is the size of

Alessandra Mattei • Tonglei Li

Pharm Res (2012) 29:460–470

Polymorph Formation and Nucleation Mechanism of Tolfenamic Acid in Solution: An Investigation of Pre-nucleation Solute Association

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Probing the radial distribution function – Neutron Scattering

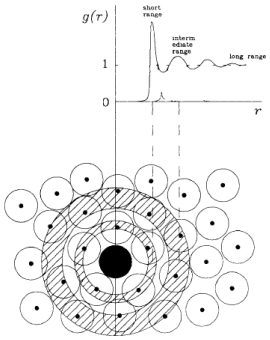
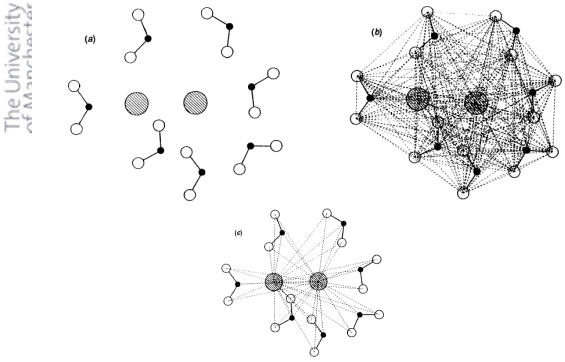
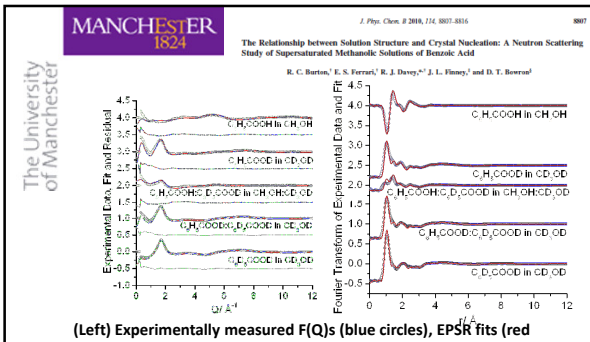


Figure 1 A two-dimensional liquid and its corresponding pair correlation function, showing the relation between the liquid structure and its pair correlation function description

Neutron scattering is isotope specific.

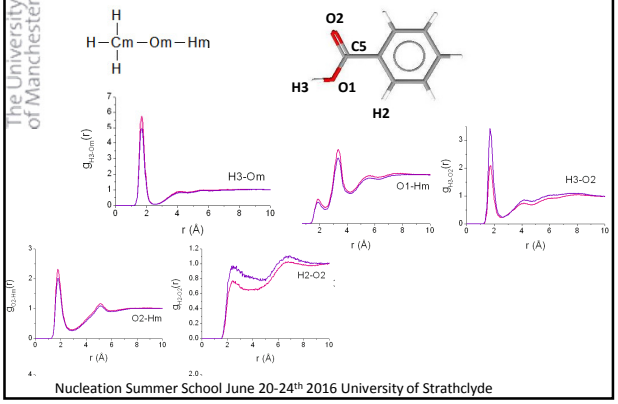
oxygen For a simpler two-component liquid system AB, we can describe the liquid mixture in terms of three *partial* pair correlations, $g_{AA}(r)$, $g_{AB}(r)$, $g_{BB}(r)$ where $g_{AA}(r)$ describes the probability of finding an A atom at a distance r from another A atom and so on Now, if we can change the neutron scattering power of, for example, component A by isotope substitution, we can make neutron scattering measurements on both (chemically similar) liquids Although the structures of the two liquid samples are essentially the same, the neutron scattering pattern is different, and this difference is caused by the different neutron scattering powers in the two cases of the atom which has been isotope substituted Taking the difference of these scattering patterns and then performing a Fourier transform results in a pair correlation function, *but one which is centred on the A atom In essence, by using isotope substitution on a given atom, we can in effect 'sit on the substituted atom and survey our environment from the vantage point of that atom* By performing a further substitution of the B atom, we can discriminate also the identity of the neighbouring atoms



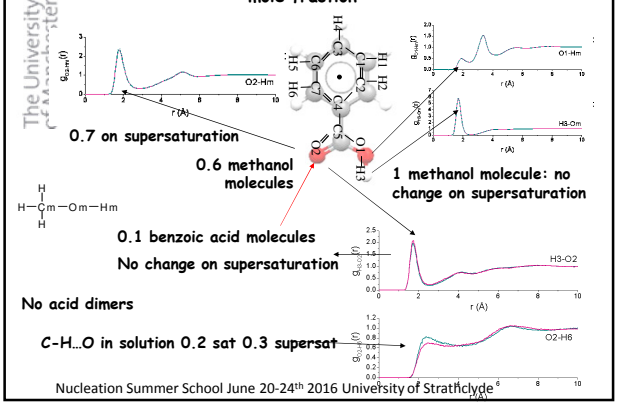


(Left) Experimentally measured F(Q)s (blue circles), EPSR fits (red lines) and fit residuals (green dotted lines) for 0.60 mole fraction of benzoic acid in methanol at 25°C. (Right) Composite g(r)s determined by Fourier Transform of the experimental F(Q)s (blue circles) and EPSR fits (red lines).

Benzoic acid partial radial distributions.



Hydrogen bonded interactions in solution: saturated pink, supersaturated blue. 0.16 mole fraction



0.7 on supersaturation

0.6 methanol molecules

1 methanol molecule: no change on supersaturation

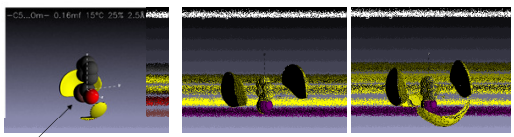
0.1 benzoic acid molecules

No change on supersaturation

No acid dimers

C-H…O in solution 0.2 sat 0.3 supersat

Spatial density functions

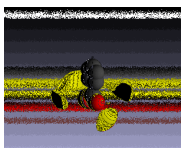


solvation

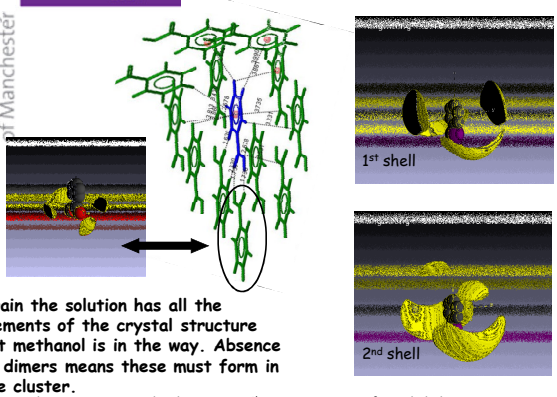
Ring-ring self assembly, saturated and supersaturated solutions.

OH

C5-C5 no dimers

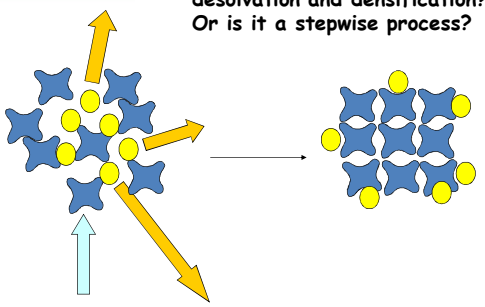


Solution vs crystal structure



Again the solution has all the elements of the crystal structure but methanol is in the way. Absence of dimers means these must form in the cluster.

A general picture – concerted desolvation and densification? Or is it a stepwise process?



Solute densified

Solvent rejected

Nucleation of Organic Crystals—A Molecular Perspective

Roger J. Davey, Sven L. M. Schroeder, and Joop H. ter Horst*

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Self association – link hypothesis summary.

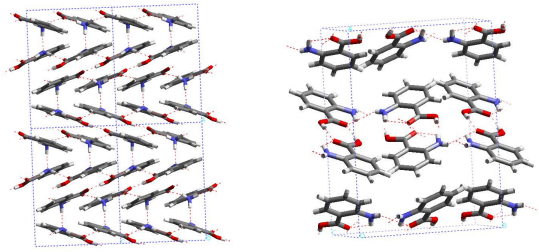
There are cases which show a clear correspondence between solution and crystal synthon but also cases that do not.

Table 2: Comparison of experimentally and computationally derived solution associates with synthons found in the respective crystal structures.

Solute (Solvent)	Technique employed	Correspondence between solution associate and crystal synthon?	Ref.
tetrolic acid (ethanol, chloroform, dioxane)	FTIR	yes (exp. and computation), polymorph and solvate	[86,88]
5-fluorouracil (nitromethane/water)	molecular modeling	yes (exp. and computation), polymorph	[104]
sulfonamides (acetone)	NMR	yes	[79]
BZP/DPA cocrystal (methanol, toluene)	NMR	yes	[91]
α-inosine (water)	NMR	yes	[80]
inosine dehydrate (water)	NMR	no	[80]
(R,S)-mandelic acid (nitromethane, acetonitrile)	FTIR	no	[81]
benzoic acid (methanol)	neutron scattering	no	[93]
3-azabicyclo-[3.3.1]nonane-2,4-dione	FTIR	yes, monomers in solution, catemer in the solid.	[94]
benzophenone (methanol, toluene)	NMR	yes	[91]
diphenylamine (methanol, toluene)	NMR	yes	[91]
p-acetanisidide (chloroform)	NMR	yes	[84]
isonicotinamide (methanol, nitromethane)	FTIR, Raman	yes	[89]
carbamazepine (methanol, chloroform)	NMR	yes	[105, 106]

Finally some words about speciation.

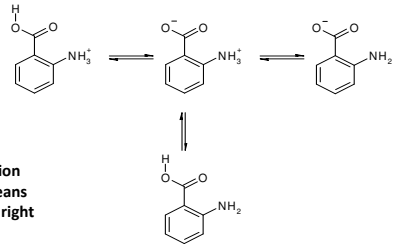
Polymorphism of anthranilic acid



Form I contains zwitterion

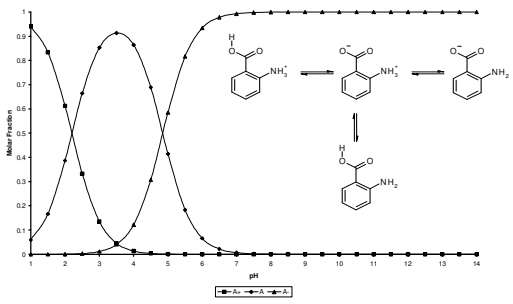
Form II – no zwitterion

Anthranilic Acid: equilibria



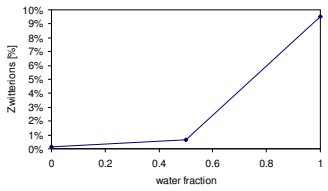
Defining a crystallisation process means having the right molecular species.

Speciation vs pH for anthranilic acid in water



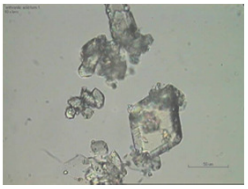
Solvent effect on zwitterion proportion.

2-ABA	pK1	pK2	% zwitterion
water	2.38	4.86	9.550%
W+E (0.5)	2.08	5.91	0.661%
EtOH	1.95	8.86	0.129%

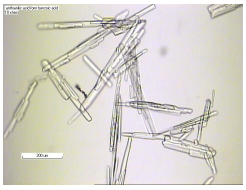


pK_As in different solvents are estimated from 4-ABA [3]

Crystallisation outcomes anthranilic acid



Form I, (zwitterions) from water

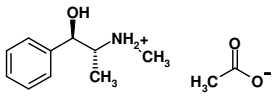


Form II, non zwitterions from benzyl alcohol

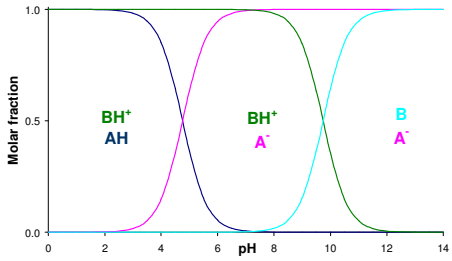
Finally – making salts - ΔpK_a rule.

You need the right species!

Ephedrine Acetate



pK_a = 9.7 pK_a = 4.8



Solution Chemistry and Structure

Roger Davey

Content: Studying and defining solute- solute interactions in the liquid phase.
Techniques available.
Speciation in solution.
Do these (thermodynamic features have) an impact on nucleation rate or outcome?
Examples – glycine/saccharin/benzoic acid/tetrolic acid/mandelic acid/paminobenzoic acid/co-crystals.