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On the entropy cost of making solvates / Cruz-Cabeza, Aurora J.; Wright, Sarah E.; Bacchi, Alessia. - In: CHEMICAL COMMUNICATIONS. - ISSN 1359-7345. - 56:38(2020), pp. 5127-5130. [10.1039/D0CC01050B]

Availability:

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Publisher:

Royal Society of Chemistry

Published

DOI:10.1039/D0CC01050B

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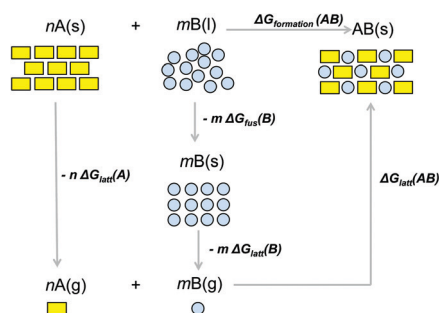
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On the entropy cost of making solvates

Aurora J. Cruz-Cabeza,* Sarah E. Wright and Alessia Bacchi*

We present a simple way of estimating the entropy cost of solvate formation in crystals.

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On the entropy cost of making solvates†

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 Cite this: DOI: 10.1039/d0cc01050b Aurora J. Cruz-Cabeza, *^a Sarah E. Wright ^a and Alessia Bacchi *^{bc}

 Received 4th March 2020,
Accepted 2nd April 2020

DOI: 10.1039/d0cc01050b

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We present a simple way of estimating the entropy cost of solvate formation in crystals. The entropy penalty of making solvates can be as low as $<1 \text{ kJ mol}^{-1}$ or as high as $>9 \text{ kJ mol}^{-1}$ and is entirely dependent on the nature of the liquid component and the temperature of solvate formation. A link is found between a low entropy cost and a higher likelihood for a solvent to make solvates.

The majority of molecular compounds that improve our lives are crystalline solids (*i.e.* medicines, pigments, agrochemicals...).¹ Beyond their pure crystal forms (neat forms), molecules often crystallise with other components in a plethora of forms including salts,² cocrystals³ and ionic cocrystals,⁴ and solvates of any of those.⁵ Whilst delivering molecular compounds as crystalline salts and cocrystals may bring advantages over neat forms (*i.e.* solubility,⁶ stability⁷...), solvates are usually less soluble than unsolvated forms^{8,9} and may have stability issues since a change in environmental conditions can lead to their decomposition. In fact, solvates are often regarded as a nuisance and are mostly discovered as unwanted by-products of crystallisation. For certain compounds (*i.e.* axitinib,¹⁰ olanzapine¹¹ or sulfathiazole¹²), solvate formation is the rule rather than the exception. For example, at least 66 different solvates are known for Pfizer's drug Axitinib.¹⁰ Producing neat forms of axitinib was found to be a challenge because most solvents of crystallisation produced a solvate.¹⁰ Under these circumstances, neat forms may need to be produced by desolvation rather than crystallisation, a process which may lead to metastable polymorphs and further problems during process development.¹⁰

Predicting whether or not a solvate will form is no easy task. Recent developments in computational crystal structure prediction (CSP) are allowing the use of these techniques for predicting solvate crystal structures.^{13,14} Whether such solvates form,^{13,14} and which are the likely stoichiometries,^{15,16} are questions which have been addressed computationally in the past making use of significant approximations. Mostly temperature and entropy contributions to solvate formation have been largely ignored. Solvate formation has been treated as an identical problem to cocrystal formation^{17,18} thus simply assuming that the stabilization energy of the solvent involved could be approximated to its lattice energy at 0 K. The lattice energies of the reactant and product crystals involved are calculated and the difference is used as a guide to predict whether or not the solvate is energetically viable. In this contribution we question whether or not this approach is valid for solvates, derive some new formulation for the problem and propose a way for correcting for entropy effects in solvate formation.

The solvation reaction is formulated in Fig. 1 where A(s) is the principal component, B(l) is the solvent and AB(s) is the solvate, n and m being the stoichiometries of A and B required to make one mol of solvate A_nB_m , referred to as AB hereafter for simplicity. In order to calculate the free energy of the solvation reaction, we formulate a thermodynamic cycle in which B(l) is first solidified to B(s), and then A(s) and B(s) are sublimed. The free energy of such reaction can be written in terms of such cycle as in eqn (1) at temperature T .

$$\Delta G_{\text{formation}}^{\text{AB}} = (\Delta G_{\text{latt}}^{\text{AB}} - n\Delta G_{\text{latt}}^{\text{A}} - m\Delta G_{\text{latt}}^{\text{B}}) - m\Delta G_{\text{fus}}^{\text{B}} \quad (1)$$

The first term, enclosed by the parentheses, in eqn (1) is the free energy gain in forming a mol of the crystalline AB solvate from crystalline solids A and B (with the appropriate stoichiometric ratios n and m). This term can be furthered as $\Delta G_{\text{latt-gain}}^{\text{AB}} = \Delta H_{\text{latt-gain}}^{\text{AB}} - T\Delta S_{\text{latt-gain}}^{\text{AB}}$. It is a common approximation to assume that the entropy difference between crystalline AB and crystalline A and B is small, thus $\Delta S_{\text{latt-gain}}^{\text{AB}} \sim 0$. The lattice

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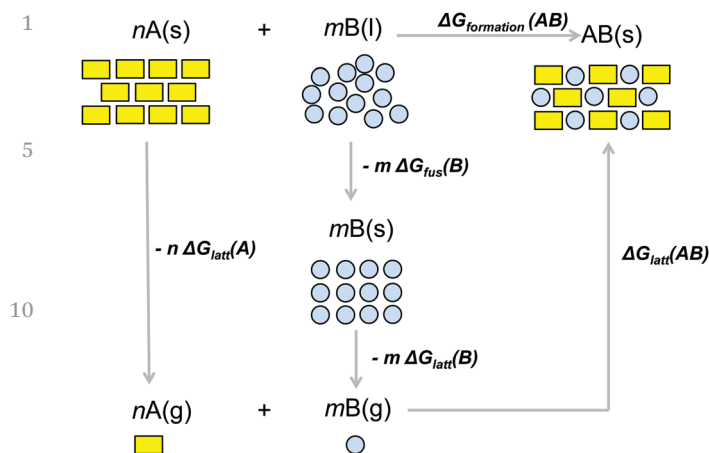


Fig. 1 Thermodynamic cycle allowing decomposition of the energy terms involved in the formation of the solvate AB(s) from a solid A(s) and a liquid B(l). n and m is the stoichiometry of A and B respectively.

enthalpy difference can also be approximated to the lattice energy difference of the solids involved since the contribution of lattice vibrations is small and their calculations can be computationally expensive.¹⁹ Thus $\Delta G_{\text{latt-gain}}^{\text{AB}} \approx \Delta H_{\text{latt-gain}}^{\text{AB}} \approx \Delta E_{\text{latt-gain}}^{\text{AB}}$. The lattice energies of crystalline solids can be accurately computed with DFT-d methods^{20,21} and thus the first term directing solvate formation can be computed readily. In fact, most computational estimations of whether or not a solvate will form,^{13,14} and its stoichiometry,^{15,16} have been performed by computing only this lattice energy term.

The last term in eqn (1) is the free energy change involved in going from liquid B to solid B times the appropriate stoichiometry (m). This term can be approximated to $-m\Delta G_{\text{fus}}^{\text{B}} \approx m\Delta S_{\text{fus}}^{\text{B}}(T - T_{\text{fus}}^{\text{B}}) \approx m\left(\frac{\Delta H_{\text{fus}}^{\text{B}}}{T_{\text{fus}}^{\text{B}}}\right)(T - T_{\text{fus}}^{\text{B}})$, a term which we refer to as the entropy penalty for solvate formation (see ESI† for detailed derivations). This term depends entirely on the solvent, B, and is dominated by the entropy loss required to solidify B times the temperature difference between the experimental temperature and the temperature of fusion ($T - T_{\text{fus}}^{\text{B}}$). We note that this term is always positive since we are considering the case of solvate formation where the experimental temperature is always higher than the melting temperature of the solvent.

Eqn (1) thus becomes eqn (2) where the first term, the enthalpy gain, $\Delta E_{\text{latt-gain}}^{\text{AB}}$ can be computed readily and the second term, the entropy penalty, can be calculated at the required temperature from experimental temperatures and enthalpies of fusions.

$$\Delta G_{\text{formation}}^{\text{AB}} \approx \Delta E_{\text{latt-gain}}^{\text{AB}} + m\left(\frac{\Delta H_{\text{fus}}^{\text{B}}}{T_{\text{fus}}^{\text{B}}}\right)(T - T_{\text{fus}}^{\text{B}}) \quad (2)$$

In order to quantify the importance of the entropy term in the free energy of the solvation reaction, we have compiled enthalpies and temperatures of fusion for 78 solvents retrieved from either the NIST webbook or the CRC and calculated the entropy term at 300 K for all of them. A plot of T_{fus} against the entropy

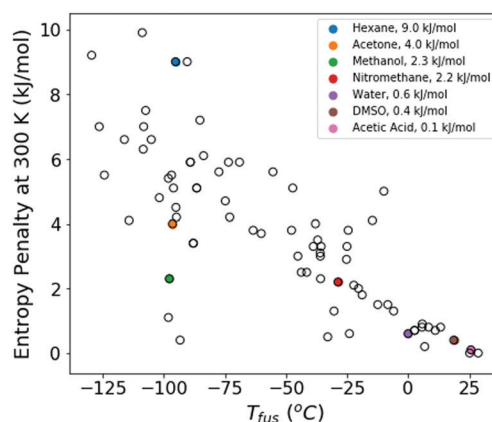


Fig. 2 Melting temperature versus entropy penalty at 300 K for 78 solvents.

penalty at 300 K is given in Fig. 2 with a few important solvents highlighted in the plot and a selection of them in Table 1 (full list of solvents is given in the ESI†). As expected, the lower the melting point of the solvent considered, the higher the entropy cost would be for solvate formation. This entropy correction can be as high as $>9 \text{ kJ mol}^{-1}$ for some solvents such as 2-methylpentane, pentane, hexane and heptane or as low as $<1 \text{ kJ mol}^{-1}$ for solvents such as 1,4-dioxane, water, DMSO or acetic acid. We also note that lowering or raising the experimental temperature can decrease or increase the entropy penalty. For example, whilst the entropy penalty of making solvates of hexane, acetone and water is 9.0, 4.0 and 0.6 kJ mol^{-1} respectively at room temperature, it increases to 11.4, 5.1 and 1.3 kJ mol^{-1} at $60 \text{ }^\circ\text{C}$ and it decreases to 7.0, 3.1 and 0.0 kJ mol^{-1} at $0 \text{ }^\circ\text{C}$. This is consistent with the fact that some solvates can only be made at low temperatures.

Given our derivation, we may wonder whether this entropy penalty affects the likelihood of solvate formation. In order to explore this, we calculated Cambridge Structural Database (CSD) solvate occurrences (O_{solvate}), corrected by the likelihood

Table 1 Solvents and entropy penalty (EP, in kJ mol^{-1}) at 300 K for 48 selected solvents (full list of 78 in the ESI)

Solvent	EP	Solvent	EP	Solvent	EP
Acetic acid	0.1	Nitromethane	2.2	Ethanol	4.1
Cyclohexane	0.2	Methanol	2.3	2-Pentanol	4.2
DMSO	0.4	1,2-DCE ^a	2.3	DCM ^a	4.2
Cyclopentane	0.4	Acetonitrile	2.5	Toluene	4.5
Water	0.6	Pyridine	2.5	Dodecane	5.0
Carbon tetrachloride	0.6	<i>o</i> -Xylene	2.9	2-Butanone	5.1
1,4-Dioxane	0.7	Trichloroethene	3.0	Cumene	5.1
Formamide	0.7	Chlorobenzene	3.0	1-Pentanol	5.6
Formic acid	0.8	3-Pentanone	3.3	1-Butanol	5.9
Benzene	0.8	2-Propanol	3.4	Ethyl acetate	6.1
<i>p</i> -Xylene	0.8	DMF	3.7	Diethylether	6.6
Nitrobenzene	0.9	<i>m</i> -Xylene	3.8	THF	7.0
Aniline	1.3	Chloroform	3.8	Isooctane	7.5
Butanoic acid	1.5	Furfural	4.0	Hexane	9.0
<i>N,N</i> -Dimethylacetamide	1.8	Acetone	4.0	Heptane	9.0
Propanoic acid	2.0	1-Octanol	4.1	Pentane	9.2

^a 1,2-DCE = 1,2-dichloroethane; DCM = dichloromethane.

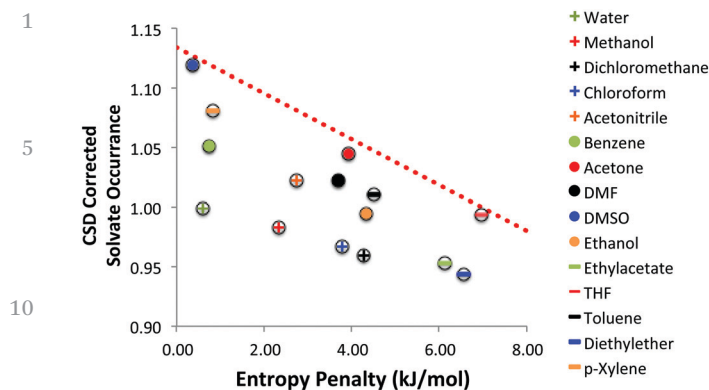


Fig. 3 Corrected CSD solvate occurrences versus entropy penalty at 300 K for the top 15 solvates in the CSD. The dashed line is plotted as a guidance to aid the eye for the solvate occurrence maxima as a function of entropy penalty.

of solvent to be used in crystallisation, for the top fifteen solvate types in the CSD. For this, the CSD occurrence for each solvate type ($P_{\text{solvate-CSD}}$) was corrected for the probability of that particular solvent to be used in a crystallization experiment ($P_{\text{solvent-cryst}}$) as in $O_{\text{solvate}} = P_{\text{solvate-CSD}}/P_{\text{solvent-cryst}}$. Since a significant dataset is required to derive these occurrences, only solvates with 200 crystal structures or more were considered. This resulted in fifteen solvent types considered including: water, methanol, dichloromethane, chloroform, acetonitrile, benzene, acetone, DMF, DMSO, ethanol, ethylacetate, THF, toluene, diethylether and *p*-xylene. The derivation of the probability of a solvent to be used in crystallisation is given in the ESI.† We note that our derived probabilities correlate well with other approaches used in the past (ESI†).²² When plotting the corrected occurrences versus the entropy penalty for such solvates (Fig. 3), we can see that as the entropy penalty increases, the maximum attainable solvate occurrence (maximum value of occurrence reached at a given entropy penalty value) decreases. This again, supports the importance of the entropy term in solvate formation. Whilst each individual solvate case is different and would result in a different $\Delta E_{\text{latt-gain}}^{\text{AB}}$ value, the higher the entropy penalty for a given solvent the less likely it would be that the lattice energy gain beats the entropy penalty.

Next, we computed lattice energy gains involved in solvate formation ($\Delta E_{\text{latt-gain}}^{\text{AB}}$) for a number of pairs of solvate:unsolvated forms in solvates of DMSO, water, toluene and ethylacetate (Table S5, ESI†). The average lattice energy gains per solvate type and stoichiometry are presented in Table 2. We observe that the average energy gain per solvent type and stoichiometry is always larger in absolute value than the corresponding entropy term with the exception of water. As a consequence, the free energy term for solvate formation is usually negative (this is the case for the vast majority of our systems: Table 2 and ESI†) and thus solvate formation is spontaneous. Solvates with smaller entropy penalties like DMSO (0.4 kJ mol^{-1} 1:1) require a less stabilising lattice energy gain (on average we computed -4.0 kJ mol^{-1}) whilst solvates with larger entropy penalties such as ethylacetate (6.1 kJ mol^{-1})

Table 2 Average computed lattice energy gains, entropy penalty (EP) term and average solvate formation free energies (in kJ mol^{-1}) at 300 K for a number of solvate types and stoichiometries (Stoi. $n:m$). N is the number of solvate:unsolvated pairs computed (see Table S5, ESI)

Solvent	N	A : B Stoi. $n:m$	EP term	Average $\Delta E_{\text{latt-gain}}^{\text{AB}}$	Average $\Delta E_{\text{formation}}^{\text{AB}}$	N with $\Delta E_{\text{formation}}^{\text{AB}}$
DMSO	5	1:1	0.4	-3.9	-3.5	4
Water	16	1:1	0.6	3.1	3.7	2
Water ^a	16	1:1	0.6	-5.6 ^a	-5.0 ^a	16 ^a
DMSO	3	1:2	0.8	-5.9	-5.1	2
Toluene	9	1:1	4.5	-7.4	-2.9	7
EA ^b	4	1:1	6.1	-11.8	-5.7	4

^a Using a more realistic computed lattice energy for ice as calculated by Brandenburg *et al.*²³ ^b EA = ethylacetate.

mol^{-1}) require a more stabilising lattice energy gain (on average $-11.8 \text{ kJ mol}^{-1}$). Since the entropy penalty is per mol of solvent incorporated in the lattice, disolvates (1:2) require larger energy gains than monosolvates (1:1).

We now turn to water and notice that water does not follow this trend and that our computed $\Delta E_{\text{latt-gain}}^{\text{AB}}$ are almost always positive. We highlight that our calculations have been performed with a standard energy model using the affordable PBE functional and a common D2 dispersion correction as implemented in VASP. Whilst this model provides very good results in molecular crystals, water and ice are known to significantly overbind with these methods.²³ Our calculated lattice energy for ice Ih is $-73.8 \text{ kJ mol}^{-1}$ compared to the experimental $-59.9 \text{ kJ mol}^{-1}$ value or to computed values with more accurate (and computationally expensive) models of around -65 kJ mol^{-1} .²³ Using the lattice energy computed with more expensive hybrid models of -65 kJ mol^{-1} , the average $\Delta E_{\text{latt-gain}}^{\text{AB}}$ becomes -5.6 kJ mol^{-1} and all hydrates have negative free energies of formation.

Finally, although we only considered ordered solvates above, we note that some of the entropy penalty arising from solvate formation may be offset by either positional or dynamic disorder in the solvate itself. A CSD analysis of disorder in solvates revealed that this can range from just $\sim 20\%$ in hydrates or methanol solvates to $\sim 30\%$ in ethanol solvates, 40% in DMSO solvates and up to 50% in hexane and toluene solvates (ESI†). This may lower the entropy penalty by $\sim 2 \text{ kJ mol}^{-1}$ (for a two orientation positional disorder, $\text{RTln}2$), 3 kJ mol^{-1} (for a three orientational positional disorder) or even more for the case of dynamic disorder.²⁴

In summary, through a thermodynamic cycle we have approximated the free energy of solvate formation to this simple equation:

$$\Delta G_{\text{formation}}^{\text{AB}} \approx \Delta E_{\text{latt-gain}}^{\text{AB}} + m \left(\frac{\Delta H_{\text{fus}}^{\text{B}}}{T_{\text{fus}}^{\text{B}}} \right) (T - T_{\text{fus}}^{\text{B}}).$$

The first term of the equation relates to the enthalpy gain linked to solvate formation whilst the second term relates to the entropy penalty that needs to be paid during this process. The first term can be computed with various models whilst the second term can be readily calculated with experimental

1 enthalpy and temperature of fusion for most solvents. We have
 2 compiled a database of 78 values of this entropy penalty in the
 3 ESI† and a selection of common solvents in this note. Our
 4 thermodynamic derivation together with the compilation of
 5 solvent data will be useful for solid-state chemists or crystal-
 6 lisation scientists either pursuing the discovery of new solvates
 7 or their avoidance and for computational chemist seeking their
 8 prediction. Solvates with a higher entropy penalty require a more
 9 negative enthalpy gain for their formation, thus they are less
 10 likely to occur. Most importantly, we have shown that prediction
 11 of solvate formation requires the calculation of lattice energy
 12 gain as well as the entropy penalty. Since the entropy penalty can
 13 be significant (up to 10 kJ mol⁻¹), it needs to be accounted for in
 14 solvate formation calculations. With our above equation and our
 15 compiled data, the free energy of formation of a given solvate can
 16 thus be estimated readily once the lattice energy gain is calcu-
 17 lated with the available computational methods. This approach
 18 would be very useful for future crystal structure prediction
 19 studies of solvates and hydrates alike,^{13,14} an important topic
 20 of research in the pharmaceutical industry. The approach could
 21 also be helpful in guiding cocrystallization of liquid APIs, a
 22 subject which has recently attracted attention.²⁵⁻²⁸

23 AJCC thanks the Royal Society for an Industry Fellowship in
 24 AstraZeneca. SEW thanks the CCDC and EPSRC for financial
 25 support. AB thanks the COMP-HUB initiative, funded by the
 26 ‘Department of Excellence’ Project of the Italian Ministry for
 27 Education, University and Research (MIUR). The authors thank
 28 Dr Alessandro Patti for helpful discussions.

30 Conflicts of interest

The authors declare no conflict of interest.

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