SAMPL4, a blind challenge for computational solvation free energies: the compounds considered

J. Peter Guthrie

Abstract For the fifth time I have provided a set of solvation energies (1 M gas to 1 M aqueous) for a SAMPL challenge. In this set there are 23 blind compounds and 30 supplementary compounds of related structure to one of the blind sets, but for which the solvation energy is readily available. The best current values of each compound are presented along with complete documentation of the experimental origins of the solvation energies. The calculations needed to go from reported data to solvation energies are presented, with particular attention to aspects which are new to this set. For some compounds the vapor pressures (VP) were reported for the liquid compound, which is solid at room temperature. To correct from $VP_{subcooled\ liquid}$ to $VP_{sublimation}$ requires ΔS_{fusion}, which is only known for mannitol. Estimated values were used for the others, all but one of which were benzene derivatives and expected to have very similar values. The final compound for which ΔS_{fusion} was estimated was menthol, which melts at 42 °C so that modest errors in ΔS_{fusion} will have little effect. It was also necessary to look into the effects of including estimated values of ΔCp on this correction. The approximate sizes of the effects of inclusion of ΔCp in the correction from $VP_{subcooled\ liquid}$ to $VP_{sublimation}$ were estimated and it was noted that inclusion of ΔCp invariably makes ΔG_S more positive. To extend the set of compounds for which the solvation energy could be calculated we explored the use of boiling point (b.p.) data from Reaxys/Beilstein as a substitute for studies of the VP as a function of temperature. B.p. data are not always reliable so it was necessary to develop a criterion for rejecting outliers. For two compounds (chlorinated guaiacols) it became clear that inclusion represented overreach; for each there were only two independent pressure, temperature points, which is too little for a trustworthy extrapolation. For a number of compounds the extrapolation from lowest temperature at which the VP was reported to 25 °C was long (sometimes over 100°) so that it was necessary to consider whether ΔCp might have significant effects. The problem is that there are no experimental values and possible intramolecular hydrogen bonds make estimation uncertain in some cases. The approximate sizes of the effects of ΔCp were estimated, and it was noted that inclusion of ΔCp in the extrapolation of VP down to room temperature invariably makes ΔGs more negative.

Keywords Solvation energies · Solubility · Vapor pressure · Henry's Law Constant
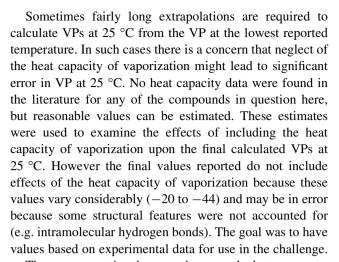
Introduction

SAMPL is a series [1–4] of blind challenges, in which the computational chemistry community is offered a chance to predict some property of a system which is known but not readily available. Blind challenges have been used for over 10 years in the protein folding community [5–7]. One of the SAMPL challenges has been to predict the solvation energies (i.e. the free energy change upon transfer of a molecule from the gas phase at a concentration of 1 M to aqueous solution at a concentration of 1 M). This problem is a subset of the problem of calculating binding constants for organic molecules and proteins, a topic of wide current interest [8, 9]. I am engaged in preparing a database of solvation energies, which already holds over 3,000 compounds, many more than the collections customarily used

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to validate computational methods. Some of the compounds newly added to the database are suitable for use in a challenge. These are not truly blind, but are at least obscure, else they would be included in standard data sets.

In this year's set are 14 compounds for which experimental determination of solubility has been reported but for which no experimental study of vapor pressure (VP) has been reported (or at least none was found on searching the literature). However there have been reports of the boiling points at various pressures, which can lead to VPs at 25 °C by use of the Clausius–Clapeyron Equation. These reported values were measured to characterize a compound or document a procedure and were not intended as part of a study of VP as a function of temperature, so careful vetting for logical consistency was needed; not all were found to be reliable. This kind of search for boiling points at various pressures is made possible by Reaxys [www.reaxys.com] ("Reaxys is a combination of three chemistry databases [Beilstein (organic), Gmelin (inorganic), and Patent Chemistry] with experimentally validated data, including structures, reactions (including multistep reactions), and physical properties." [libguides.lib.uci.edu/reaxys]); access is by way of an annual license, in my case by the university library. Because the Reaxys database is constantly changing and expanding, a citation to Reaxys would not lead to the set of data used in this work but to a modified set probably expanded by more information but possibly missing some. Accordingly I have given references to the original papers for the boiling points that I used. A possible objective criterion for excluding some b.p. data from the Clausius–Clapeyron fit was proposed and used.

For some solid compounds the VP of the subcooled liquid rather than of the solid at room temperature is all that is available directly from the literature. In this case a correction is necessary, using the entropy of fusion. Here too it was necessary to look into the effects of including estimated values of ΔCp on this correction. The approximate sizes of the effects of inclusion of ΔCp in the correction from $VP_{sub\text{-}cooled\ liquid}$ to $VP_{sublimation}$ were estimated and it was noted that inclusion of ΔCp invariably makes ΔG_S more positive. The heat capacity of sublimation was taken as -12 for all compounds as recommended [10, 11], although this may not be correct for the smaller molecules. The heat capacity of sublimation for benzene has been determined as -6.5 cal/K/mol [12].

For very soluble or water miscible compounds the "solubility" for saturated solutions may be too high for any assumption of ideality, or if miscible, it may be undefined. Here we search for activity coefficients, or osmotic coefficients (which can be converted into activity coefficients). From solubility and activity coefficient we can derive the ideal solubility or the free energy of transfer from pure compound to ideal 1 M aqueous solution, which is what we need, along with the VP in order to calculate the solvation energy.

Sometimes fairly long extrapolations are required to calculate VPs at 25 °C from the VP at the lowest reported temperature. In such cases there is a concern that neglect of the heat capacity of vaporization might lead to significant error in VP at 25 °C. No heat capacity data were found in the literature for any of the compounds in question here, but reasonable values can be estimated. These estimates were used to examine the effects of including the heat capacity of vaporization upon the final calculated VPs at 25 °C. However the final values reported do not include effects of the heat capacity of vaporization because these values vary considerably (-20 to -44) and may be in error because some structural features were not accounted for (e.g. intramolecular hydrogen bonds). The goal was to have values based on experimental data for use in the challenge.

The one exceptional case where we had to use non-experimental values is that of compounds which are solids at 25 °C but liquid at the temperatures where VP was studied. For these compounds we used estimated values of ΔS_{fus} to calculate the VP of the solid at 25 °C from the extrapolated value for the sub-cooled liquid. This can perhaps be excused because for small rigid molecules ΔS_{fus} is to a good approximation 13.5 cal/mol/K; the average estimate for aromatic compounds treated here was 13.9. Menthol and mannitol do not fit the rigid molecule pattern so well but menthol melts at 42 °C so the extrapolation to 25 °C, for which the value of ΔS_{fus} is needed, is small enough that errors in ΔS_{fus} will have little effect; for mannitol there is an experimental value of ΔS_{fus} which can be used with some confidence to calculate the VP at 25 °C. Although experimental, the value of $\ln(VP_{sub\text{-}cooled\ lliquid})$ are based on gas chromatographic retention times and a correlation between retention time and VP. This is an empirical correlation and thus its reliability depends on how closely the new compounds resemble the original parameterization set. These values of $\ln(VP_{sub\text{-}cooled\ liquid})$ are necessarily less reliable than values from more direct measurement.

Test calculations involving estimated ΔCp values were used to estimate the possible systematic error for compounds where there was a long extrapolation from experimental measurements of VP and 25 °C. This possible systematic error using estimated ΔCp values is given for the final ΔGs values as well as the error calculated by propagation of error methods [13] with the assumption that ΔCp can be neglected in all cases. Derivations of equations for the effects of including heat capacity effects both on long extrapolations and on correction from $VP_{sub\text{-}cooled\ liquid}$ to $VP_{sublimation}$ are found in the "Appendix".

Results and discussion

As mentioned in the introduction, I am preparing a database of aqueous solvation energies and quantities leading

to them. This database is structured with one line per (x,t) point (i.e. value of a quantity and temperature at which it was measured). As far as possible the data are entered exactly as recorded in the source paper. This database, as a text file, is the input for a program which does the calculations, including units conversions, needed to extract solvation energies. Depending on what has been reported, for each compound weighted values of VP, aqueous solubility, and directly measured ΔGs (or equivalent Henry's Law Constants or partition constants which are all easily converted to ΔGs) are calculated and written to an output file. If both VP and aqueous solubility (AQSOL) are available, then an indirect ΔGs can be calculated for the compound, with an uncertainty calculated by standard propagation of error methods [13]. When both indirect and direct values of ΔGs are available a weighted average of the two values is calculated; if only one value is available then that is reported as the average.

When data are reported at different temperatures the data are fitted, using weighted least squares [10], to a modified version of the Clausius–Clapeyron equation, with the value of $\ln(p_\theta)$ at 25 °C as one of the parameters, so that the value and its uncertainty are immediately available from the fit. Equation 1 is the standard Clausius–Clapeyron equation for $\ln(p_T)$ at any temperature T; Eq. 2 is the same equation for $\ln(p_\theta)$ at room temperature, $\theta = 25\ °C = 298.15\ °K$. Solving Eq. 2 for a and substituting in Eq. 1 gives the desired equation with intercept = $\ln(p_\theta)$

$$\ln(p_T) = a + \frac{b}{T} \tag{1}$$

$$\ln(p_\theta) = a + \frac{b}{\theta} \tag{2}$$

$$\ln(p_T) = \ln(p_\theta) + b\left(\frac{1}{T} - \frac{1}{\theta}\right) \tag{3a}$$

This equation is more convenient if it is rewritten as:

$$p_T = p_\theta e^{\left(b\left(\frac{1}{T} - \frac{1}{\theta}\right)\right)} \tag{3b}$$

Mannitol is one of a limited number (4) of compounds in this challenge set in being very soluble in water and is unique among the four in being a solid at room temperature: a saturated solution is 1.186 m, meaning that it contains 183 g of mannitol per 1,000 g of water [14]. This can hardly be assumed to be ideal. Robinson and Stokes [15] measured the osmotic coefficient, from which they derived γ_c, the activity coefficient defined with infinitely dilute solution as reference state, as a function of concentration.

From the results just listed one can derive the ideal saturated molarity as 1.05 ± 0.30, and that for this compound in water the difference between molal and molar on

the final result is trivial. The derivation is found in the "Appendix".

In a number of cases (2,6-dichlorosyringaldehyde, 2-chlorosyringaldehyde, 3,5-dichlorosyringol, 3-chlorosyringol 4,5-dichloroguaiacol, 5-dichloroguaiacol, mannitol, and menthol) the reported VP was for the sub-cooled liquid, yet the compound was a solid at room temperature. To correct the VP to the equilibrium sublimation pressure requires the entropy of fusion, which is frequently not available. Only for mannitol was an experimental entropy of fusion reported. For the others it was necessary to estimate a value using a published set of parameters [16]; the uncertainty in estimated values of ΔS_{fus} was taken as 4.45 cal/K/mol [16]. Fortunately all the compounds were aromatic with only small substituents, and thus expected to have similar values. Yalkowsky [17] has suggested a useful average value of 13.5 cal/mol/K for rigid molecules. The average of the ΔS_{fus} values estimated by additivity is 12.2 cal/mol/K. A derivation of the equation for the conversion of $\ln(p_{\text{sub-cooled liquid}})$ to $\ln(p_{\text{sublimation}})$ is given in the "Appendix" as is one for the next approximation including ΔCp effects.

$$c = (\Delta S_{fus}/(R\ \theta))(T - \theta) \tag{4}$$

where c is the amount which must be added to $\ln(VP_{\text{sublimation}})$ to get $\ln(VP_{\text{subcooled liquid}})$.

For the compounds where ΔS_{fus} was calculated following Chickos [16], these calculations are shown in Table 4. The calculation of $VP_{\text{sublimation}}$ is shown in Table 3. The calculation is carried out to give $VP_{\text{sublimation}}$ which is assumed to be more readily interpreted by the reader than $\ln(VP_{\text{sublimation}})$. Error propagation throughout the calculation was carried out following the standard rules [13]. Sometimes the error is larger than the value, warning the reader that this value is ill-defined by the experiments reported to date. Provided we follow the rules of error propagation this value can be carried forward and used in the calculation of ΔGs.

In principle one should also be concerned about the effect of ΔCp (sublimation) but examination of the literature [18] suggests that it will be much smaller than ΔCp (vaporization). Any such corrections have been neglected in this work.

Before the final fit to determine VP at 25 °C, the dataset for each compound was tested for outliers, which were deleted from the set. The boiling points in the literature were determined in order to characterize the compounds and thus may be less reliable than (p,t) points from experiments aimed at determining VP. Quite often boiling points reported at pressures below 1 Torr are unreliable presumably because there was a significant pressure drop between distillation vessel and manometer, and there are sometimes serious disagreements at higher pressures. I
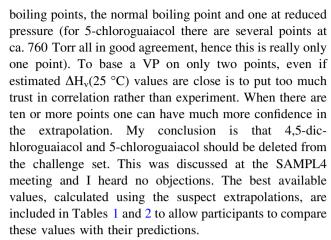
sought an objective way to decide which points were suspect and should be deleted from the set. Initially the data sets for boiling point at various pressures were pruned by a rather ad hoc procedure of discarding points which diverged too far from a least squares line. When data are not very good the least squares line will be strongly influenced by divergent points, precisely the ones which should probably be discarded. In the hope of a more objective approach, a different procedure was used for pruning data sets for boiling point at various pressures.

The procedure adopted to pick outliers used the empirical relation between $\Delta H_v(25\,°C)$ and boiling temperature and pressure [19] to estimate $\Delta H_v(25\,°C)$ for each (p,t) point. Then the average and standard deviation (σ) were calculated for $\Delta H_v(25\,°C)$ for all points as were the difference between each $\Delta H_v(25\,°C)$ value and the average. Any points where the difference was greater than two σ were discarded. If any point was deleted, the process was repeated till all remaining $\Delta H_v(25\,°C)$ values differ from the final average by less than two σ. This is a stricter test than looking for departures from linearity, because even with only two points, the corresponding heat of vaporization values can indicate if the data are consistent or not. This procedure was followed exactly where data were abundant (more than ten points). With fewer points, a value which differed by less than two σ might still be discarded if it differed from the average by more than twice the usual σ for such data (0.5 kcal/mol).

Some caveats are in order. The values of ΔH_v from the empirical relationship to p and t are often logically inconsistent with values from the Clausius–Clapeyron fit to experiment (ΔH_v at a higher temperature). The implied value of ΔCp was sometimes unreasonably negative and sometimes positive, contrary to all expectation. ΔCp is invariably negative, since ΔH_v grows continuously smaller as temperature increases, reaching zero at the critical point. A likely source for most of the problems is that the correlation of ΔH_v with p,t was for non-associating liquids and some of the compounds considered here are definitely capable of hydrogen bonding, thus falling outside the range of the correlation for ΔH_v. Benson type additivity schemes [20, 21] have been shown to predict ΔH_v [22], so it is not unreasonable to argue that ΔH_v from p and t will be in error by the additive contribution of the interacting group yet remain useful for the task in hand even though the absolute value is in error. There are of course dangers that a valid point will be rejected, because in the nature of a Gaussian distribution 5 % of the points will deviate from the mean by 2σ. In some cases the criterion led to rejecting five out of twenty boiling points, far too many for these to be the tail of a Gaussian distribution.

For the two chlorinated guaiacols the data turned out to be very sparse. For these two the VP is based on only two boiling points, the normal boiling point and one at reduced pressure (for 5-chloroguaiacol there are several points at ca. 760 Torr all in good agreement, hence this is really only one point). To base a VP on only two points, even if estimated $\Delta H_v(25\,°C)$ values are close is to put too much trust in correlation rather than experiment. When there are ten or more points one can have much more confidence in the extrapolation. My conclusion is that 4,5-dichloroguaiacol and 5-chloroguaiacol should be deleted from the challenge set. This was discussed at the SAMPL4 meeting and I heard no objections. The best available values, calculated using the suspect extrapolations, are included in Tables 1 and 2 to allow participants to compare these values with their predictions.

Another concern, when long extrapolations are involved, is that the assumption implicit in the use of the two parameter Clausius–Clapeyron equation, namely that ΔCp (Table 3) for vaporization can be ignored, may be inadequate. For the compounds in question no experimental values are available; to use estimated values would introduce uncertainty and mean that computed solvation energies were not really being tested against experiment. What I have done here is to use estimated values of ΔCp to approximate the magnitude of the error. In the equations which follow, ΔH_v is represented by by ΔH_v (value evaluated at some temperature, not yet specified), ΔH_v^T (value evaluated at temperature = T) or ΔH_v^θ (value evaluated at temperature = θ; the reference temperature, here 298.15 K). ΔC_p is symbolized analogously. If ΔH_v is independent of temperature:

$$\ln(p) = A - \Delta H_v / RT \tag{5}$$

If ΔC_p is independent of temperature:

$$\Delta H_v^T = \Delta H_v^\theta + \Delta C_p^\theta(\theta - T) \tag{6}$$

and

$$\ln(p) = A - \frac{\Delta H_v^\theta}{RT} + \frac{\Delta C_p^\theta \theta}{RT} - \frac{\Delta C_p^\theta}{R}\ln(T) \tag{7}$$

An often useful form relates $\ln(p_\theta)$ to $\ln(p_T)$, some known VP at higher temperature:

$$\ln(p_\theta) = -\left(\frac{\Delta C_p^\theta}{R}\right)\ln\left(\frac{T}{\theta}\right) + \left(\frac{\Delta C_p^\theta}{R}\right)\left(1 - \frac{\theta}{T}\right)$$
$$+ \left(\frac{\Delta H_v^\theta}{R}\right)\left(\frac{1}{T} - \frac{1}{\theta}\right) + \ln(p_T) \tag{8}$$

where θ is the reference temperature, 25 °C, at which thermodynamic quantities are evaluated or estimated.

There is no easy answer to the question of how permissible it is to report a solvation energy based on extrapolations using inadequate equations. Raising this question leaves open the question of how inadequate must

Table 1 Summary of solvation energies for the compounds in the 2013 challenge set

Smiles	Name	MW	ΔGs av latest values		ΔGs values sent to participants		Change latest–Sent out[a]	Systematic error[b]
C(CC=CCC)OC(=O)C	(e)-3-Hexenyl acetate	141.192	−2.61	0.1 kcal/mol	−2.61	0.10	0	
O=C1c2c(cccc2 NCCO)C(=O)c2c1 cccc2	1-(2-Hydroxyethylamino)-9,10-anthraquinone	267.28	−14.21	1.10 kcal/mol	−14.21	1.10	0	
C=C(c1 cccc1)c2ccccc2	1,1-Diphenylethene	180.245	−2.78	0.10 kcal/mol	−2.78	0.10	0	
O(C)c1 cccc1OC	1,2-Dimethoxybenzene	138.17	−5.33	0.10 kcal/mol	−5.33	0.10	0	
Oc1c2c(cc1)C(=O)c3c(cccc3)C2=O)O	1,2-Dihydroxy-9,10-anthraquinone	240.218	−10.60	0.10 kcal/mol	−10.60	0.10	0	
O(N(=O)=O)C(CCON(=O)=O)C	1,3-bis-(nitrooxy)butane	180.12	−4.29	0.39 kcal/mol	−4.29	0.39	0	
O(N(=O)=O)C(CCON(=O)=O)C	1,3-bis-(nitrooxy)propane	166.09	−4.80	0.39 kcal/mol	−4.80	0.39	0	
O=C1c2c(C(=O)c3c1 cccc3)c(N)ccc2 N	1,4-Diamino-9,10-anthraquinone	238.25	−11.85	0.35 kcal/mol	−11.85	0.35	0	
O1CCOCC1	1,4-dioxane	88.11	−5.08	0.10 kcal/mol	−5.08	0.10	0	
Nc1c2c(cc1)OC(=O)c3c(cccc3)C2=O	1-Amino-4-hydroxy-9,10-anthraquinone	239.23	−9.53	0.28 kcal/mol	−9.53	0.28	0	
Nc1c2c(ccc1)C(=O)c3c(cccc3)C2=O	1-Amino-9,10-anthraquinone	223.23	−9.44	0.74 kcal/mol	−9.44	0.74	0	
c1(ccccc1)Cn2cncc2	1-benzylimidazole	159.214	−7.63	0.12 kcal/mol	−7.63	0.12	0	
O(CC(O)C)CCC	1-Butoxy-2-propanol	132.2	−5.73	0.15 kcal/mol	−5.73	0.15	0	
c1 cccc(C)c1CC	1-Ethyl-2-methylbenzene	120.2	−0.85	0.10 kcal/mol	−0.85	0.10	0	
Clc1c(C=O)c(Cl)c(OC)c(O)c1OC	2,6-Dichlorosyringaldehyde	251.06	−8.68	0.76 kcal/mol	−8.24	0.76	−0.44	0.93
O(C)c1 cccc(OC)c1O	2,6-Dimethoxyphenol	154.16	−6.96	0.10 kcal/mol	−6.96	0.10	0	
O=C1c2c(ccc(N)c2)C(=O)c2c1 cccc2	2-Amino-9,10-anthraquinone	223.23	−11.53	0.29 kcal/mol	−11.53	0.29	0	
Clc1c(OC)c(O)c(OC)cc1C=O	2-Chlorosyringaldehyde	216.62	−7.78	0.77 kcal/mol	−7.78	0.77	0	0.87
C(C)OCCOC(=O)C	2-Ethoxyethyl acetate	132.16	−5.31	0.10 kcal/mol	−5.31	0.10	0	
Oc1 ccccc1CC	2-Ethylphenol	122.17	−5.66	0.10 kcal/mol	−5.66	0.10	0	
Oc1 cccc1C=O	2-Hydroxybenzaldehyde	122.12	4.68	0.10 kcal/mol	4.68	0.10	0	
COc1c(cccc1)O	2-Methoxyphenol	124.14	−5.94	0.10 kcal/mol	−5.94	0.10	0	
O=Cc1 cccc1C	2-Methylbenzaldehyde	120.15	−3.93	0.10 kcal/mol	−3.93	0.10	0	
Clc1cc(O)ccc1Cl	3,4-Dichlorophenol	163	−7.29	0.10 kcal/mol	−7.29	0.10	0	
Clc1cc(Cl)c(OC)c(O)c1OC	3,5-Dichlorosyringol,	223.05	−6.44	0.38 kcal/mol	−6.24	0.38	−0.2	
Clc1cc(OC)c(O)c1OC	3-Chlorosyringol	188.61	−6.86	0.13 kcal/mol	−6.86	0.13	0	
Clc1cc(OC)c(O)cc1Cl	4,5-Dichloroguaiacol	193.03	−3.58	0.21 kcal/mol	−3.58	0.62	0.79	0.04
Cc1cc(cc1)O)OC	4-Methyl-2-methoxyphenol	138.17	−5.80	0.10 kcal/mol	−5.80	0.10	0	
Oc1ccc(cc1OC)CCC	4-propylguaiacol	166.217	−5.26	0.18 kcal/mol	−5.26	0.18	1.18	−0.64
Clc1cc(O)c(OC)cc1	5-Chloroguaiacol	158.58	−5.26	0.12 kcal/mol	−5.26	0.37	2.95	0.71
C1c2c(Cc3c1cccc3)cccc2	9,10-Dihydroanthracene	180.25	−3.76	0.10 kcal/mol	−3.78	0.10	0.02	
CN(C)CCC=C1c2ccccc2CCc3c1cccc3	Amitriptyline	277.41	−7.43	1.35 kcal/mol	−7.43	0.60	−0.51	−0.79
c12c(cc3c(c1)cccc3)cccc2	Anthracene	178.23	−4.14	0.10 kcal/mol	−4.14	0.10	0	

Table 1 continued

Smiles	Name	MW	ΔGs av latest values		ΔGs values sent to particpants		Change latest–Sent out[a]	System-atic error[b]
O1c2c(Oc3c1cccc3)cccc2	Dibenzo-p-dioxin	184.19	−3.16	0.10 kcal/mol	−3.16	0.10	0	
OC1CC(CC=C1C(C)=C	Carveol	152.24	−4.44	0.30 kcal/mol	−4.44	0.43	0.59	−0.63
C1CCC=CC1	Cyclohexene	82.15	0.14	0.10 kcal/mol	0.14	0.10	0	
CC1C(=O)CC(CC1)C(=C)C	Dihydrocarvone	152.238	−3.75	0.29 kcal/mol	−3.75	0.21	0.71	−0.16
c1ccccc1C(c2ccccc2)OCCN(C)C	Diphenhydramine	255.363	−9.34	0.62 kcal/mol	−9.34	0.62	0	−0.75
O(c1ccccc1)c1ccccc1	Diphenyl ether	170.21	−2.32	0.10 kcal/mol	−2.87	0.69	0	−0.87
OC\C=C(\CCC=C(C)C)/C	Geraniol	154.25	−4.97	0.59 kcal/mol	−4.45	0.24	−0.52	−0.63
O(C(=O)C)CCCCCC	Hexyl acetate	144.21	−2.29	0.12 kcal/mol	−2.29	0.12	0	
O([N+](=O)[O−])CCCCCC	Hexyl nitrate	147.17	−1.66	0.10 kcal/mol	−1.66	0.10	0	
CC(=CCCC(C)(C=C)OC(=O)C)C	linalyl acetate	196.292	−2.49	0.85 kcal/mol	−2.49	0.85	0	−1.70
C(C(C(C(CO)O)O)O)O	Mannitol	182.178	−23.62	−0.31 kcal/mol	−24.38	0.32	−0.760	0.82
Cc1c(cccc1Nc2ccccc2C(=O)O)C	Mefenamic acid	241.29	−6.78	0.10 kcal/mol	−6.78	0.10	0	−0.11
OC1CC(CCC1C(C)C	Menthol	156.27	−3.20	0.27 kcal/mol	−3.20	0.25	0.32	0.43
CC1CC(C(=O)C1C(C)C	Menthone	154.25	−2.53	0.25 kcal/mol	−2.53	0.25	−0.02	−0.34
CC(=CCCC=CCO)C	Nerol	154.254	−3.96	0.20 kcal/mol	−4.78	0.25	0.82	−0.32
O=C\C1=C\CC(\C(=C)C)CC1	1-Perillaldehyde	150.22	−4.09	0.17 kcal/mol	−4.09	0.17	0	
N1CCCCC1	Piperidine	85.15	−5.05	0.10 kcal/mol	−5.05	0.10	0	
CC1=CC(=O)C(CC1)C(C)C	Piperitone	152.238	−4.51	0.065 kcal/mol	−4.51	0.10	−0.03	−0.46
O1CCCCC1	Tetrahydropyran	86.13	−3.13	0.10 kcal/mol	−3.13	0.10	0	

[a] For a few compounds the DGs values changed during late examination of the calculations; for these the change is shown

[b] Estimated for compounds where there was a long extrapolation to 25 °C, using estimated heat capacity terms; see text. The change in ΔGs was invariably to become more negative for all compounds examined. Also estimated for corrections from VP$_{\text{subcooled liquid}}$ to sublimation pressure; the change in DGs was invariably to become more positive.

Table 2 Experimental solvation energies and citations to the literature sources of the data used to calculate them

Name	AQSOL Meas. Refs	AQSOL Ave./M	AQSOL Err	VP Meas Refs	VP Ave./atm	VP Err	ΔGs ave. kcal/mol	ΔGs ave. Err	ΔGs Direct Meas. Refs	ΔGs Direct Ave. kcal/mol	ΔGs Direct Err	Final ΔGs ΔG_s	Final ΔGs Err	Note [a]
(e)-3-Hexenyl acetate									[33]	−2.61	0.07	−2.61	0.10	
1-(2-Hydroxyethylamino)-9,10-anthraquinone	[34]	1.65E−05	1.50E−06	[35, 36]	1.59E−14	2.94E−14	−14.21	1.10				−14.21	1.10	
1,1-Diphenylethene	[37]	3.66E−05	3.66E−06	[38]	8.36E−06	1.42E−07	−2.78	0.06				−2.78	0.10	
1,2-Dimethoxybenzene	[39]	4.84E−02	4.27E−04	[40]	1.48E−04	5.19E−07	−5.33	0.01				−5.33	0.10	
1,3-bis-(nitrooxy)butane				[41]	4.51E−05	1.75E−06			[42]	−4.29	0.39	−4.29	0.39	
1,3-bis-(nitrooxy)propane				[41]	3.51E−05	8.60E−07			[42]	−4.80	0.39	−4.80	0.39	
1,4-Diamino-9,10-anthraquinone	[34, 43–48]	4.96E−07	5.67E−08	[49, 50]	2.58E−14	1.51E−14	−11.85	0.35				−11.85	0.35	
1,4-Dioxane	[51, 52]	9.85E+00	1.55E−01	[53]	4.59E−02	1.38E−04	−5.08	0.01	[51, 52]	−5.06	0.02	−5.08	0.10	A
1-Amino-4-hydroxy-9,10-anthraquinone	[34, 44, 46–48, 56]	9.86E−07	1.54E−07	[48, 50, 57]	2.53E−12	1.12E−12	−9.53	0.28				−9.53	0.28	
1-Amino-9,10-anthraquinone	[34, 44, 46, 48]	1.12E−06	8.90E−08	[48, 49, 57]	3.37E−12	4.19E−12	−9.44	0.74				−9.44	0.74	
1-Benzylimidazole	[26]	5.50E−03	1.10E−03	[27]	3.51E−07	3.19E−09	−7.63	0.12				−7.63	0.12	
1-Butoxy-2-propanol	[58]	1.09E+00	1.21E−01						[58]	−5.73	0.15	−5.73	0.15	A
1-Ethyl-2-methylbenzene	[59]	6.21E−04	6.21E−06	[60]	4.18E−03	1.20E−04	−0.77	0.02	[61]	−0.88	0.01	−0.85	0.10	
2,6-Dichlorosyringaldehyde	[62]	1.43E−04	4.78E−06	[29]	1.55E−09	1.99E−09	−8.68	0.76				−8.68	0.76	C, GC, S
2,6-Dimethoxyphenol									[63]	−6.96	0.01	−6.96	0.10	
2-Amino-9,10-anthraquinone	[44, 46]	4.67E−07	8.11E−08	[48, 50]	4.11E−14	1.88E−14	−11.53	0.29				−11.53	0.29	
2-Chlorosyringaldehyde	[62]	1.52E−04	3.32E−06	[29]	7.46E−09	9.71E−09	−7.78	0.77				−7.78	0.77	C, GC, S
2-Ethoxyethyl acetate	[64]	1.17E+00	1.98E−01	[65]	3.73E−03	1.12E−04	−5.31	0.10	[64, 66]	−5.34	0.11	−5.31	0.10	A
2-Ethylphenol	[67]	1.15E−01	1.74E−03	[68, 69]	2.03E−04	7.55E−06	−5.66	0.02				−5.66	0.10	
2-Hydroxybenzaldehyde				[40, 68]	2.50E−04	2.42E−06			[70]	−4.68	0.02	−4.68	0.10	
2-Methoxyphenol	[71, 72]	1.32E−01	2.44E−02				−5.62	0.11	[63]	−5.95	0.01	−5.94	0.10	
2-Methylbenzaldehyde									[70]	−3.93	0.02	−3.93	0.10	
3,4-Dichlorophenol	[73]	5.68E−02	1.60E−03	[74]	6.40E−06	6.47E−08	−7.29	0.02				−7.29	0.10	C, GC, S
3,5-Dichlorosyringol	[62]	1.09E−03	2.69E−05	[29]	5.12E−07	3.25E−07	−6.44	0.38				−6.44	0.38	C, GC, S
3-Chlorosyringol	[62]	2.74E−02	6.52E−04	[29]	6.38E−06	1.39E−06	−6.86	0.13				−6.86	0.13	C, GC, S
4,5-Dichloroguaiacol	[71]	2.35E−03	2.65E−04	b.p. refs: [75, 76]	8.92E−05	3.02E−05	−3.84	0.21				−3.84	0.21	C, GC, S
4-Methyl-2-methoxyphenol									[63]	−5.80	0.02	−5.80	0.10	
4-Propylguaiacol	[72]	4.57E−03	9.02E−04	b.p. refs: [77–95]	1.58E−05	3.80E−06	−5.26	0.18				−5.26	0.18	
5-Chloroguaiacol	[71]	2.55E−02	3.69E−03	b.p. refs: [76, 96–99]	8.82E−05	1.3E−05	−5.26	0.12				−5.26	0.12	C, S
9,10-dihydroanthracene	[100]	7.32E−06	3.75E−08	[101, 102]	3.15E−07	7.93E−09	−3.76	0.02				−3.76	0.10	
Amitriptyline	[26, 103]	2.54E−05	7.25E−06	b.p. refs: [104–112]	2.25E−09	5.08E−09	−7.43	1.35				−7.43	1.35	

Table 2 continued

Name	ΔGs indirect — AQSOL			ΔGs indirect — VP			ΔGs ave.		ΔGs Direct			Final ΔGs		Note
	Meas. Refs	Ave./M	Err	Meas Refs	Ave./atm	Err	kcal/mol	Err	Meas. Refs	Ave kcal/mol	Err	ΔGs	Err	[a]
Anthracene	[113–117]	2.50E−07	1.50E−09	[118–128]	5.65E−09	3.30E−10	−4.15	0.03	[129–133]	−3.88	0.20	−4.14	0.10	
Dibenzo-p-dioxin	[134, 135]	4.91E−06	1.96E−07	[123]	5.86E−07	1.87E−08	−3.16	0.03				−3.16	0.10	
Carveol	[136, 137]	1.00E−02	4.93E−03	b.p. refs: [138–145]	1.37E−04	1.33E−05	−4.44	0.30				−4.44	0.30	
Cyclohexene	[146–148]	3.35E−03	3.59E−04	[149–151]	9.31E−02	6.34E−03	0.07	0.08	[152]	0.16	0.03	0.14	0.10	
Dihydrocarvone	[137]	3.03E−03	4.54E−04	b.p. refs: [138, 139, 153–167]	1.33E−04	6.20E−05	−3.75	0.29				−3.75	0.29	
Diphenhydramine	[26]	1.13E−03	2.80E−05	b.p. refs: [168–178]	4.03E−09	4.19E−09	−9.34	0.62				−9.34	0.62	
Diphenyl ether	[179, 180]	1.10E−04	2.61E−06	[68]	5.39E−05	6.75E−06	−2.32	0.08				−2.32	0.1	
Geraniol	[137, 181]	3.53E−03	1.16E−03	b.p. refs: [182–198]	1.97E−05	1.84E−05	−4.97	0.59				−4.97	0.59	
Hexyl acetate	[199]	3.54E−03	3.54E−04	[200]	1.55E−03	8.45E−06	−2.39	0.06	[33]	−2.14	0.07	−2.29	0.12	
Hexyl nitrate	[201]						−1.66		[201]	−1.66	0.03	−1.66	0.1	
Linalyl acetate	[202, 203]	3.54E−04	5.07E−04	[204]	1.31E−04	2.91E−06	−2.49	0.85				−2.49	0.85	
Mannitol	[14]	1.06E+00	0.075	[205]	1.31E−16	6.93E−17	−23.62	0.32				−23.62	−0.31	
Mefenamic acid	[26, 206]	1.82E−07	4.51E−09	[207]	4.83E−11	7.31E−12	−6.78	0.09				−6.78	0.10	A
Menthol	[137, 208]	1.63E−03	6.99E−04	b.p. refs: [209–222]	1.81E−04	2.68E−05	−3.20	0.27				−3.2	0.27	
Menthone	[137, 181, 208]	1.57E−03	6.43E−04	b.p. refs: [217, 222–237]	5.43E−04	4.67E−05	−2.53	0.25				−2.53	0.25	C,S
Nerol	[137, 181, 238]	3.22E−03	1.02E−03	b.p. refs: [187, 196, 239–247]	9.96E−05	1.22E−05	−3.96	0.20				−3.96	0.20	
l-perillaldehyde	[181]	4.20E−03	4.20E−04	b.p. refs: [248–253]	1.05E−04	2.86E−05	−4.09	0.17				−4.09	0.17	A
Piperidine	[254]	8.95E+00	1.44E−01				−5.05		[54, 254]	−5.05	0.01	−5.05	0.10	
Piperitone	[255]	1.62E−02	1.62E−04	b.p. refs: [256–269]	1.97E−04	2.15E−05	−4.51	0.06				−4.51	0.10	
Tetrahydropyran	[51, 52]	7.69E−01	1.91E−02				−3.13		[51, 270]	−3.13	0.01	−3.13	0.10	

All at 25 °C; free energies are in kcal/mole, standard states are the ideal gas at 1 atm for VP and 1 M gas for ΔGs, and 1 M ideal aqueous solution with an infinitely dilute reference state. Where bp data were used to calculate the VP at 25 °C the corresponding references are marked off by the message: "b.p. refs;" Abbreviations used are: "Meas. refs." Measurement references; "Ave." average; "AQSOL" aqueous solubility; "VP" vapor pressure; "err." Experimental error = standard deviation; "ΔGs indirect" free energy of solvation (1 M gas to 1 M aqueous) calculated from VP and solubility; "ΔGs direct" free energy of solvation (1 M gas to 1 M aqueous) calculated from measurement of equilibrium concentrations in gas and aqueous phases

[a] A—limiting aqueous activity coefficient used, converted to ideal solubility, C—heat capacity of vaporization of sublimation estimated (see text), GC—sub-cooled VP determined from GC retention times, using a calibration equation based on compounds with directly measured VP, S—entropy of fusion estimated (see text)

an equation be for its use to be rejected. Clarke and Glew [23] give equations for temperature effects on thermodynamic quantities extending to the third derivative with regard to temperature of head capacity. For most experimental work this is way beyond the quality of the data, though they gave an example where the final term could be evaluated by fitting. Is the use of any less elaborate equation not at example of using an equation known to be wrong? In fact if one looks at the Statistical Mechanics definitions of ΔCp and $\partial\Delta Cp/\partial T$ there is no limit to the number of derivatives which could be included. On must content oneself with "enough" terms. There can be differences of opinion over what is "enough".

There are additivity methods at the atom, bond and group levels for estimating the heat capacity of vaporization [24]. For many of the compounds of interest here there are one or two missing group level parameters, so the closest available group had to be used for a few groups in each compound or else atom level parameters were used. The use of atom level parameters gave an RMS error of 1.50 (comparing observed and calculated values for the defining dataset of 193 compounds [24]) while the use of group level parameters gave an RMS error of 1.05 [24] (for the defining dataset of 177 compounds [24]). There is a particular problem for mannitol for which there are six hydroxyls on the six carbon atoms of the molecule and a high likelihood that the standard alcohol parameters will be inadequate because four of them will be engaged in intramolecular hydrogen bonding. For what it is worth the best conformation for gas phase mannitol as reported by the GMXX model in PCMODEL [25] has four hydroxyl groups engaged in intramolecular hydrogen bonds and only the two primary hydroxyls not so engaged. Intermolecular attractions will be less than expected for a hexol, and there will be less flexibility to the molecule; these effects may well affect ΔCp.

Mannitol seems likely to have multiple normal hydrogen bonds, while the o-methoxy phenols (guaiacol or syringol derivatives) are likely to have weak intramolecular hydrogen bonds The true values of ΔCp are likely to be smaller in absolute magnitude; the group contribution for an ether $[O(C)_2] = -4.6$ is smaller than that for an alcohol $[OH(C)] = -6.68$. A crucial point to make is that whatever the true value of ΔCp the result of using the second approximation (ΔCp is temperature independent but ΔH_v is not) is to make ΔGs more negative.

There are serious problems in trying to assess the reliability of using the simple Clausius–Clapeyron equation for four of the anthraquinone dyes (1,4-diamino, 1-amino-4-hydroxy, 1-amino, 2-amino). These compounds are all reported by Shimizu et al. who gave the parameters for the Clausius–Clapeyron equation for all four compounds (as well as others), but the paper contains no solid information

about the temperature range for which VP was measured for any of them. This makes it essentially impossible to say how much effect inclusion of ΔCp would have. The situation is better for the paper by Nishida et al. who states that the his apparatus had temperature control ± 0.5 °C from 100 to 180 °C, so presumably all the compounds he studied were run at the whole temperature range. Once again he gave only the parameters for the Clausius–Clapeyron equation. Neither of these papers gave any uncertainties in the parameters. With reasonable assumptions about the average temperature of measurements for these compounds, the systematic error due to ΔCp^{sub} was found to be no larger than the uncertainties already reported for ΔG_s for these compounds.

For 1-benzylimidazole, there was one paper giving experimental solubility [26] and one giving VP results [27]. However it became clear that something was wrong with the VP results, because the numbers in the table were inconsistent with the words in the body of the paper. Communication with the authors elicited the correct data which were indeed consistent with the text. I thank Juan Davalos [28] for communicating these results.

For several compounds (3-chlorosyringol, 3,5-dichlorosyringol, 2-chlorosyringaldehyde, 2,6-dichlorosyringaldehyde, and 4,5-dichloroguaiacol) the only paper giving experimental VPs was Ref. [29] which determined VP indirectly by a GC correlation: the retention time was converted to VP using a relationship based on four chlorinated phenols. This sort of correlation method is much used but it depends utterly on the quality of the reference data and whether they were good models for the compounds of interest.

Four compounds (1,4-dioxane, 2-ethoxyethyl acetate, mannitol and piperidine) were very soluble in water and some were miscible. For these compounds the limiting aqueous activity coefficient, γ^∞, was used; from it an ideal solubility can be calculated and this is what is reported in Table 2.

The final values for the free energy of solvation (ΔG_s) are found in Table 1, a summary which includes the values submitted to the organizers and the latest values after reexamination and revision, some inspired by questions and challenges from participants. It includes estimates of possible systematic errors found in trial calculations including heat capacity terms. For compounds which are solids but for which the VP of the sub-cooled liquid at 25 °C was available there are in some cases two possible systematic errors: the error from extrapolating the VP to 25 °C without taking account of the heat capacity of vaporization, and the error from heat capacity effects on the correction from $VP_{sub-cooled\ liquid}$ to $VP_{sublimation}$. The effect of including heat capacity in the original extrapolation upon the free energy of solvation is always negative.

Table 3 Correction of VP$_{subcooled\ liqud}$ to VP$_{solid}$ using the entropy of fusion, experimental or estimated

Name	VP/atm		mp	ΔS_{fus}	VP$_{sub}$/VP$_{scl}$		VP$_{sub}$	
	Value	Error			Value	Error	Value	Error
2,6-Dichlorosyringaldehyde	2.47E−07	4.93E−08	195.6	17.64	6.27E−03	7.94E−03	1.55E−09	1.99E−09
2-Chlorosyringaldehyde	7.80E−07	1.56E−07	197	16.04	9.56E−03	1.23E−02	7.46E−09	9.71E−09
3,5-Dichlorosyringol	4.59E−06	9.18E−07	106	16.07	1.11E−01	6.72E−02	5.12E−07	3.25E−07
3-Chlorosyringol	8.14E−06	1.63E−06	35	14.46	7.84E−01	6.63E−02	6.38E−06	1.39E−06
4,5-Dichloroguaiacol	3.39E−04	8.98E−08	70	17.6	2.63E−01	8.92E−02	8.92E−05	3.02E−05
5-Chloroguaiacol	1.14E−04	1.26E−05	37	12.69	7.74E−01	7.59E−02	8.82E−05	1.30E−05
Mannitol	5.1E−14	2.64E−14	140.95	30.54	2.56E−03	2.85E−04	1.31E−16	6.93E−17
Menthol	2.36E−04	1.51E−05	42	9.20	7.68E−01	1.02E−01	1.81E−04	2.68E−05

ΔS_{fus} was evaluated at the melting point, and is assumed to be temperature independent; units are cal/mol/K. The error in estimated values (all except mannitol for which the error was reported as) was taken as 4.4 cal/mol/K. The error in m.p. was taken as 2 °C. VPsub/VPscl was calculated using Eq. 4; VP$_{sub}$ is the sublimation pressure at 25 °C; VP$_{scl}$ is the VP of the sub-cooled liquid at 25 °C

The effect of including heat capacity effects on correction from VP$_{sub-cooled\ liquid}$ to VP$_{sublimation}$ on the the free energy of solvation is always positive.

The table includes the difference between the latest values of ΔG_s and the values sent out to participants, on which analysis was based. The most serious change is for 4-propylguaiacol, which changed by 1.18 kcal/mol when I discarded (p,t) points corresponding to ΔH_v(25 °C) values which were too different from the average. Three points were discarded, all of which fell below the Clausius–Clapeyron line in the plot using all data, and thus had pulled the line and the VP at 25 °C lower, making ΔG_s more negative.

In the tables the final errors for free energy of solvation are adjusted so that any estimated error less than 0.1 kcal/mol is adjusted to 0.1. This treatment is based on an awareness from working with the database that obtaining a precise value is quite difficult and thus unlikely unless very great care were taken. This adjustment has been made in the previous SAMPL reports.

More detail is provided in Table 2 which gives references to all the sources of data used to derive the final ΔG_s values. The list of references under AQSOL in the column headed measurement references ("Meas. refs.") contains references to all of the solubility values averaged to give the numerical values in the column headed "Ave. M". The same convention applies to the references under "Meas. refs." under VP or "ΔG_s direct". The list of references for b.p. values obtained from Reaxys are indicated by "b.p. refs.:" to distinguish them from any list of papers more directly intended to measure thermodynamic properties.

Thus upon reading a new paper by an author unknown to you, reporting a previously unknown VP, at best it is likely to be is ±0.1 in ln(p), and at worst it could be wrong by several orders of magnitude. I am less convinced that it is really very informative to talk about real world errors, as opposed to best statistical estimate based on the currently available data. Every working scientist should know that experimenters are human, that long extrapolations entail sizeable uncertainty, and that mistakes happen, and thus that a published value may be wildly in error. One of the great values of procedures to calculate solubility or VP by some computationally affordable method is that one can check for gross errors of this kind. (Bearing in mind that some estimation methods may also occasionally be severely wrong.)

Calculations

There are differences of opinion about how to average discordant data; there is less problem for data which are in agreement within experimental error because the effect of choice of averaging method is less significant. When the data are discordant, i.e. varying by one or more orders of magnitude, then the method chosen has significant effects on the value obtained. However the most important thing to note is that in such a case there must be significant systematic errors in at least some of the data. If examination of the primary literature source for the data does not reveal which one(s) are wrong then the best that can be done is to report a weighed average and weighted standard deviation based on external consistency, i.e. on the differences between observed and average values. The large standard deviation shows that the quantity is ill defined by the experiments. If one or several reported values appear to be more reliable then they could be given larger weights (or the others given smaller weights) which would lessen both the effect of the outliers on the average or the estimated standard deviation of the average.

Weighted arithmetic means were calculated for data at a single temperature: the calculations followed Bevington

[10] and Deming [30]. Weights are taken as $1/\sigma^2$ [10, 30] the average as

$$\bar{X} = \frac{\sum \frac{x_i}{\sigma_i^2}}{\sum \frac{1}{\sigma_i^2}}$$

and the uncertainty in the weighted mean as:

$$\sqrt{\frac{\sum \frac{1}{\sigma_i^2} \sum \frac{x_i^2}{\sigma_i^2} - \left(\sum \frac{x_i}{\sigma_i^2}\right)^2}{(m-1) \sum \frac{1}{\sigma_i^2} \sum \frac{1}{\sigma_i^2}}}$$

(the latter based on the unbiased estimate of the standard error by external consistency, Deming p. 29).

When data are reported at different temperatures the data are fitted to a modified version of the Clausius–Clapeyron (if VP, otherwise van t'Hoff) equation, with the value of p^θ at 25 °C as one of the parameters, so that the value and its uncertainty are immediately available from the fit. Equation 3b derived earlier was used for these fits.

Experimental errors were taken from the original reference if supplied. Otherwise a standard assumption of 10 % error in the reported VP or solubility was made: for a few very experienced laboratories an assumption of 1 % error might be made.

Some authors report only the equation and its parameters a and b. Sometimes they also report the statistical uncertainties in a and b from the least squares fit. Unfortunately this leads to incorrectly large uncertainties in p^θ calculated from these parameters because they have not given the covariance, which is necessary to get correct results [31, 32]. I use the calculation assuming zero covariance, even though this leads to excessively large uncertainties/standard deviations. Even worse are the papers which do not include even the statistical uncertainties in a and b. Here we estimate a possible error from the extreme lines fitting: (a) ln(p) at highest reported temperature plus assumed error in ln(p) and ln(p) at lowest reported temperature minus assumed error in ln(p); and (b) ln(p) at highest reported temperature minus assumed error in ln(p) and ln(p) at lowest reported temperature plus assumed error in ln(p). Extrapolation to 298.15 K gives an estimate of the desired error in p^θ. If the error in each p value is taken as ±10 %, then the error in ln(p) is ±0.10 by the rules for error propagation.

It is not unheard of for the error in a quantity (VP or solubility) extrapolated using in effect an equation of the form ln(y) = a + b/T, to be larger than the quantity itself, because different laboratories sometimes report values for the same conditions which vary over orders of magnitude. In such a case the true value is only very approximately known, but the free energy of solvation which uses the logarithm of the quantity will still be known with useful

precision in free energy, even if the uncertainty is larger than desired. The large uncertainty serves as a warning that further experimental determinations are needed.

Appendix

No claim is made for originality of the derivations given here; they are included to help the reader understand where the final equations used in the calculations actually came from.

Derivation of ideal solubility for mannitol

Robinson and Stokes [15] have reported the osmotic, ϕ. and activity, γ, coefficients for mannitol (species C in what follows) as functions of concentration (molal)

$$\phi^\circ = 1 + .0034 m_c + 0.0042 m_c^2$$

$$\mathrm{Log}_{10}\gamma_C = 0.00295 m_c + 0.00274 m_c^2$$

The solubility of mannitol is 1.186 m [14]. ΔG for mannitol going from saturated solution to 0.01 m (assumed ideal; $\gamma_c = 1.000$) can be calculated from:

$$M = 1.186, \gamma_c = 10^{(0.00295 \times 1.186 + 0.00274 \times 1.186^2)} = 1.017$$

$$M = 0.01, \gamma_c = 10^{(0.00295 \times 0.01 + 0.00274 \times 0.01^2)} = 1.000$$

$$\Delta G = RT \ln((0.01 \times 1.000)/(1.184 \times 1.017)) = -2.84$$

ΔG for mannitol going from 0.01 m solution to 1.00 m solution, assuming ideality

$$\Delta G = RT \ln(1.000/0.01) = +2.73$$

No literature values of the densities for mannitol solutions were found. A sucrose solution with the same g/100 g concentration had density = 1.08 [271] while a glycerol solution with the same g/100 g concentration had density = 1.05 [271].

Definitions for molal and molar concentrations were taken from Alberty et al. [272]

$$m = 1000 n_2/n_1 M_1 = 1000 n_2/1000 \text{ for water}$$

$$M = 1000 \rho n_2/(n_1 M_1 + n_2 M_2)$$
$$= 1000 \rho n_2/(1000 + 215.7) = \rho m/(1 + 215.7/1000)$$

If $\rho = 1.08$, $M = 1.08 * 1.186/(1 + .2157) = 1.05$

If $\rho = 1.05$, $M = 1.05 * 1.186/(1 + .2157) = 1.02$

For conversion of a 0.01 M to saturated solution (M scale), if $\rho = 1.05$, $\Delta G = .593*\ln(1.05/.01) = +2.76$ kcal. If instead $\rho = 1.02$, $\Delta G = .593*\ln(1.02/.01) = +2.74$.

The average = 2.75. Thus ΔG for solid to 1 M aqueous is $-2.84 + 2.75 = -0.09$ kcal/mol. A simple conclusion

is that in the case of mannitol, using m or M makes very little difference to the value of ΔG for solid to 1 M aqueous.

A full error analysis was carried out for the calculation of the ideal saturated molarity for Mannitol.

$$M = \rho * \phi * n_2/(1 + n_2 M_2/1000)$$

$$\begin{aligned}\sigma_M = \text{sqrt}(&(\sigma_\rho * \phi * n_2/(1 + n_2 M_2/1000))^2 \\ &+ (\sigma_\phi * \rho * n_2/(1 + n_2 M_2/1000))^2 \\ &+ (\sigma_{n2} * \rho * \phi/(M_2 n_2/1000 + 1)^2)^2)\end{aligned}$$

With $\rho = 1.015$, $\sigma_\rho* = 0.02$, $\phi = 1.017$, $\sigma_\phi = 0.02$, $n_2 = 1.184$, and $\sigma_{n2} = 0.01$ this formula leads to $\sigma_M = 0.029$

Derivation of effect of finite ΔC_p on extrapolated vapor pressure

Constant ΔH_v

The data are centered on $T = T_x$. By fitting to the Clausius–Clapeyron equation we get $\Delta H_v^{T_x}$. On this assumption, the VP at $T = \theta$ is given by

$$\ln(p^\theta) = \ln(p^{T_x}) - \left(\frac{\Delta H_v^{T_x}}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right)$$

Constant ΔC_p, variable ΔH_v

If we know or have estimated ΔC_p at $T = \theta$, ΔC_p^θ, then we can calculate ΔH_v^θ from $\Delta H_v^{T_x}$:

$$\Delta H_v^{T_x} = \Delta H_v^\theta + \Delta C_p^\theta(T_x - \theta)$$

On this assumption, the VP at $T = \theta$ is given by

$$\ln(p^\theta) = \ln(p^{T_x}) - \left(\frac{\Delta H_v^\theta}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) + \frac{\Delta C_p^\theta}{R}\ln\left(\frac{\theta}{T_x}\right) + \frac{\Delta C_p^\theta \theta}{R}\left(\frac{1}{\theta} - \frac{1}{T_x}\right)$$

which can be simplified to

$$\ln(p^\theta) = \ln(p^{T_x}) - \left(\frac{\Delta H_v^\theta}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) + \frac{\Delta C_p^\theta}{R}\ln\left(\frac{\theta}{T_x}\right) + \frac{\Delta C_p^\theta}{R}\left(1 - \frac{\theta}{T_x}\right)$$

The free energy of vaporization (pure compound to vapor at 1 M, $p = p_{1M}$ atm) is given by

$$\Delta G_v = -RT\ln(p_{1M}/VP)$$

$$p_{1M} = \left(\frac{n}{V}\right)R'T = R'T$$

where R is the gas constant in kcal mol^{-1} K^{-1} and R′ is the gas constant in L atm mol^{-1} K^{-1}.

Thus

$$\Delta G_v = -RT\ln(R'T) + RT\ln(p^\theta)$$

The effect on the free energy of solvation of changing from the constant ΔH_v assumption to the constant ΔC_p assumption is then

$$\Delta\Delta G_v = R\theta\ln(p_C^\theta) - R\theta\ln(p_H^\theta)$$

where p_C^θ is the VP at temperature θ calculated assuming constant ΔC_p and temperature dependent ΔH_v and p_H^θ is the VP at temperature θ calculated assuming constant ΔH_v.

$$\begin{aligned}\Delta\Delta G_v = R\theta\Bigg(&\ln(p^{T_x}) - \left(\frac{\Delta H_v^\theta}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) + \frac{\Delta C_p^\theta}{R}\ln\left(\frac{\theta}{T_x}\right) \\ &+ \frac{\Delta C_p^\theta}{R}\left(1 - \frac{\theta}{T_x}\right)\Bigg) - R\theta\Bigg(\ln(p^{T_x}) \\ &- \left(\frac{\Delta H_v^{T_x}}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right)\Bigg)\end{aligned}$$

which simplifies to:

$$\begin{aligned}\Delta\Delta G_v = R\theta\Bigg(&\left(\frac{\Delta H_v^{T_x}}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) - \left(\frac{\Delta H_v^\theta}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) \\ &+ \frac{\Delta C_p^\theta}{R}\ln\left(\frac{\theta}{T_x}\right) + \frac{\Delta C_p^\theta}{R}\left(1 - \frac{\theta}{T_x}\right)\Bigg)\end{aligned}$$

Substituting for $\Delta H_v^{T_x}$:

$$\begin{aligned}\Delta\Delta G_v = R\theta\Bigg(&\left(\frac{\Delta H_v^\theta}{R} + \frac{\Delta C_p^\theta}{R}(T_x - \theta)\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) \\ &- \left(\frac{\Delta H_v^\theta}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_x}\right) + \frac{\Delta C_p^\theta}{R}\ln\left(\frac{\theta}{T_x}\right) \\ &+ \frac{\Delta C_p^\theta}{R}\left(1 - \frac{\theta}{T_x}\right)\Bigg)\end{aligned}$$

which simplifies to:

$$\Delta\Delta G_v = \Delta C_p^\theta(T_x - \theta) + \Delta C_p^\theta \theta \ln\left(\frac{\theta}{T_x}\right)$$

The solvation free energy is given by

$$\Delta\Delta G_s = -R\theta\ln\left(\frac{c}{p}\right) - R\theta\ln(R'\theta)$$

where c is the concentration of the compound in water. The effect of changing from a VP p_H^θ based on an assumed constant ΔH_v to a VP p_C^θ based on an assumed constant ΔC_p is given by

$$\Delta\Delta G_s = -R\theta \ln\left(\frac{c}{p_C^\theta}\right) + R\theta \ln\left(\frac{c}{p_H^\theta}\right)$$

$$\Delta\Delta G_s = R\theta \ln\left(p_C^\theta\right) - R\theta \ln\left(p_H^\theta\right) = \Delta\Delta G_v$$
$$= \Delta\Delta C_p^\theta\left((T_x - \theta) + \theta\ln\left(\frac{\theta}{T_x}\right)\right)$$

The function $(T_x - \theta) + \theta\ln\left(\frac{\theta}{T_x}\right)$ is invariably positive, and ΔC_p^θ is always negative so $\Delta\Delta G_s$ is always negative. It seems that ΔC_p^θ must always be negative for normal liquids because ΔH_v^θ has a finite value at room temperature but is zero at the critical point.

Derivation of the correction from VP$_{sub\text{-}cooled\ liquid}$ to VP$_{solid}$

At the outset, for most of the compounds which are solid at room temperature but for which the VP refers to the liquid or sub-cooled liquid, all that is known are: the VP at θ; the melting point, T_{fus}; that the $\ln(p)$ versus $1/T$ lines meet at $1/T_{fus}$ and the entropy of fusion (measured or estimated). In the first treatment we are implicitly assuming that ΔCp can be ignored for both liquid and solid; this is a reasonable assumption for sublimation, where it is common to use a general value of $\Delta Cp = -12$ cal/K/mol, but less so for evaporation of a liquid where for the sizes of molecules considered here ΔCp is in the range -30 to -40. Next we will examine the effects of going to the next approximation, namely that ΔH varies with temperature but ΔCp is constant

(a) First assumption (ΔH terms are temperature independent)

Let $\ln(p) = a + b/T$ for the liquid at any temperature and $\ln(p) = a' + b'/T$ for the solid at temperatures at or below the m.p., T_{fus}.

$b = -\Delta H_v/R$

$b' = -(\Delta H_v + \Delta H_{fus})/R$

At $T = T_{fus}$

$a + b/T_{fus} = a' + b'/T_{fus}, b'$

At $T = \theta$

$a + b/\theta = a' + b'/\theta + c_H$ where c_H is the amount which must be added to $\ln(vp_{\text{sublimation}})$ to get $\ln(vp_{\text{subcooled liquid}})$. The subscript c_H denotes the assumption of temperature independent ΔH values.

Take the difference between the equations for $T = T_{fus}$ and, substitute for b' and simplify

$(b/T - b/\theta) = (b'/T_{fus} - b'/\theta) - c_H$

$c_H = (\Delta S_{fus}/(R\,\theta))(T_{fus} - \theta)$

(b) Second assumption (The ΔCp terms are temperature independent):

Assume that we know $\Delta H_v^{T_{fus}}$ (It will cancel out in the end.), ΔC_p^{vap}, ΔC_p^{sub} and $\ln(p_{sub\text{-}cooled})$. We will derive an expression for c_C the correction to be added to $\ln(p_{sublimation})$ to obtain $\ln(p_{sub\text{-}cooled})$. The subscript c_C denotes the assumption of temperature independent ΔC_p values.

The VP at T_{fus} can be written:

$$\ln\left(p_v^{T_{fus}}\right) - \ln\left(p_v^\theta\right) = \int_\theta^{T_{fus}} \frac{\Delta\Delta H_v^{T_{fus}} + \Delta C_p^{vap}(T - T_{fus})}{RT^2}dT$$
$$= \left(\frac{\Delta H_v^{T_{fus}}}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_{fus}}\right)$$
$$+ \left(\frac{\Delta C_p^{vap}}{R}\right)\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$

Or the VP at θ in terms of temperatures, $\Delta H_v^{T_{fus}}$, and ΔC_p^{vap} can be written as:

$$\ln\left(p_v^\theta\right) = \ln\left(p_v^{T_{fus}}\right) - \left(\frac{\Delta H_v^{T_{fus}}}{R}\right)\left(\frac{1}{\theta} - \frac{1}{T_{fus}}\right)$$
$$- \left(\frac{\Delta C_p^{vap}}{R}\right)\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$

Now we will do the same for the sublimation pressure. First we note that at any temperature T (less than or equal to T_{fus}):
$\Delta H_{sub}^T = \Delta H_v^T + \Delta H_{fus}^T$
$\Delta C_p^{sub} = \Delta C_p^{vap} + \Delta C_p^{fus}$

and

$\Delta C_p^{fus} = \Delta C_p^{sub} - \Delta C_p^{vap}$

Now writing ΔH_{sub}^T in terms of temperature independent quantities and T itself we obtain:

$$\Delta H_{sub}^T = \Delta H_v^{T_{fus}} + \Delta C_p^{vap}(T - T_{fus}) + \Delta H_{fus}^{T_{fus}}$$
$$+ \left(\Delta C_p^{sub} - \Delta C_p^{vap}\right)(T - T_{fus})$$
$$= \Delta H_v^{T_{fus}} + \Delta H_{fus}^{T_{fus}} + \Delta C_p^{sub}(T - T_{fus})$$

$$\ln\left(p_{sub}^{T_{fus}}\right) - \ln\left(p_{sub}^\theta\right) = \int_\theta^{T_{fus}} \frac{\left(\Delta H_v^{T_{fus}} + \Delta H_{fus}^{T_{fus}} + \Delta C_p^{sub}(T - T_{fus})\right)}{RT^2}dT$$
$$= \frac{\left(\Delta H_v^{T_{fus}} + \Delta H_{fus}^{T_{fus}}\right)}{R}\left(\frac{1}{\theta} - \frac{1}{T_{fus}}\right)$$
$$+ \frac{\Delta C_p^{sub}}{R}\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$

$$\ln\left(p_{sub}^\theta\right) = \ln\left(p_{sub}^{T_{fus}}\right) - \frac{\left(\Delta H_v^{T_{fus}} + \Delta H_{fus}^{T_{fus}}\right)}{R}\left(\frac{1}{\theta} - \frac{1}{T_{fus}}\right)$$
$$- \frac{\Delta C_p^{sub}}{R}\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$

Now we can write the revised definition of the correction c_C, the quantity to be added to $\ln(p_{sub}^{\theta})$ to obtain $\ln(p_v^{\theta})$, recalling that at T_{fus}, $\ln(p_{sub}^{T_{fus}}) = \ln(p_v^{T_{fus}})$

$$c_C = \left(\frac{\Delta C_p^{sub}}{R}\right)\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$
$$- \left(\frac{\Delta C_p^{vap}}{R}\right)\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$
$$+ \Delta H_{fus}^{T_{fus}}\left(\frac{1}{\theta} - \frac{1}{T_{fus}}\right)$$

Or in terms of $\Delta S_{fus}^{T_{fus}}$

$$c_C = \left(\frac{\Delta C_p^{sub}}{R}\right)\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$
$$- \left(\frac{\Delta C_p^{vap}}{R}\right)\left(1 - \frac{T_{fus}}{\theta} + \ln\left(\frac{T_{fus}}{\theta}\right)\right)$$
$$+ \left(\frac{\Delta S_{fus}^{T_{fus}}}{R\theta}\right)(T_{fus} - \theta)$$

If the heat capacity terms are set to zero, then this becomes the equation deduced above for the first hypothesis.

In the challenge dataset the worst case was 2,6-syringealdehyde, which is the highest melting compound of those where VP for the sub-cooled liquid must be reduced to VP for the solid. For this compound inclusion of the estimated ΔC_p values lowers $\ln(vp)$ by 2.99. What is of interest is the effect on ΔG_s. From the derivation of the effect of including heat capacity terms on the extrapolated VP, the effect on ΔG_s can be written as:

$$\Delta\Delta G_s = R\theta\ln(p_C^{\theta}) - R\theta\ln(p_H^{\theta})$$

where p_C^{θ} is the VP at temperature θ calculated assuming constant ΔC_p values and temperature dependent ΔH_v values and p_H^{θ} is the VP at temperature θ calculated assuming constant ΔH_v values.

$$R\theta\ln(p_C^{\theta}) = R\theta\ln(p_{sub-cooled}^{\theta}) - R\theta c_C$$

$$R\theta\ln(p_H^{\theta}) = R\theta\ln(p_{sub-cooled}^{\theta}) - R\theta c_H$$

Thus

$$\Delta\Delta G_s = -R\theta c_C + R\theta c_H = R\theta(c_H - c_C)$$

In the case of 2,6-syringealdehyde, the change in ΔG_s on inclusion of ΔC_p values relative to the value of the change in ΔG_s values assuming constant ΔH terms, is (at 25 °C) $+0.593*1.57 = +0.93$ kcal/mol, meaning that the correction from $VP_{sub-cooled\ liquid}$ to $VP_{sublimation}$ would be smaller with inclusion of ΔC_p terms. This value is based on estimated ΔC_p values, which may be in error.

The additivity scheme reported by Chickos et al. [16] has some unusual features which make it a bit tricky to

apply until one gets on to it. Accordingly this table is included to help the interested reader who wishes to apply the method (Tables 4, 5).

Table 4 Estimation of entropy of fusion

Compound	Contribution	Parameter	Parameter identification
2,6-Dichlorosyringaldehyde			
	35.20	2*A1	CH$_3$-R
	9.42	2*A32	–O–
	21.50	A34	–CHO
	20.30	A31	Phenol
	32.40	2*A22*B22	Cl
	−45.00	6*A12	C$_B$-R(sp^2)
DHfus (J/K/mol)	73.82		
DHfus (cal/K/mol)	17.64		
2-Chlorosyringaldehyde			
	35.20	2*A1	CH$_3$-R
	9.42	2*A32	–O–
	7.40	A10	C$_B$-H
	20.30	A31	Phenol
	10.80	A22	Cl
	−37.50	5*A12	C$_B$-R(sp^2)
	21.50	A34	–CHO
DHfus (J/K/mol)	67.12		
DHfus (cal/K/mol)	16.04		
3,5-Dichlorosyringol			
	35.20	2*A1	CH$_3$-R
	9.42	2*A32	–O–
	7.40	A10	C$_B$-H
	20.30	A31	Phenol
	32.40	2*A22*B22	Cl
	−37.50	5*A12	C$_B$-R(sp^2)
DHfus (J/K/mol)	67.22		
DHfus (cal/K/mol)	16.07		
3-Chlorosyringol			
	20.30	A31	Phenol
	−30.00	4*A12	C$_B$-R(sp^2)
	14.80	2*A10	C$_B$-H
	10.80	A22	Cl
	9.42	2*A32	–O–
	35.20	2*A1	CH$_3$-R
DHfus J/K/mol	60.52		
DHfus (cal/K/mol)	14.46		

Table 4 continued

Compound	Contribution	Parameter	Parameter identification
4,5-Dichloroguaiacol			
	20.30	A1	Phenol
	−30.00	4*A12	C_B-R(sp^2)
	14.80	2*A10	C_B-H
	32.40	2*A22*B22	Cl
	4.71	A32	–O–
	17.60	A1	CH$_3$-R
DHfus (J/K/mol)	59.81		
DHfus (cal/K/mol)	14.29		
5-Chloroguaiacol			
	−22.50	3*A12	C_B-R(sp^2)
	22.20	3*A10	C_B-H
	10.80	A22	Cl
	4.71	A32	–O–
	17.60	A1	CH$_3$-R
	20.30	A31	Phenol
DSfus (J/K/mol)	53.11		
DSfus (cal/K/mol)	12.69		
Menthol			
	52.80	A1*3	CH$_3$-R
	−16.40	A3	CHR$_3$
	−44.10	3*A16	–CHR– in ring
	1.70	A30	oh
	33.40	A14	ring
	11.10	A15*(6–3)	ring
DSfus (J/K/mol)	38.50		
DSfus (cal/K/mol)	9.20		

DSsub estimated using the scheme in Ref. [16]; –O– represents an ether; C_B is a benzenoid carbon; –CHO is an aldehyde

Table 5 Estimated heat capacities of vaporization

Compound	ΔC_p^{vap}	Compound	ΔC_p^{vap}
2,6-Dichlorosyringaldehyde	−38.17	Diphenhydramine	−33.12
2-Chlorosyringaldehyde	−35.95	Dihydrocarvone	−20.5
3,5-Dichlorosyringol	−32.73	Diphenyl ether	−22.81
3-Chlorosyringol	−30.51	Geraniol	−23.81
4,5 Dichloroguaiacol	−26.39	Mannitol	−44.16
4-Propylguaiacol	−26.9	Menthol	−21.76
5-Chloroguaiacol	−24.17	Menthone	−20.26
Amitriptyline	−31	Nerol	−23.81
Carveol	−27.44	Piperitone	−20.4

Estimated from an atomic additivity scheme as described in the text

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