The partition of compounds from water and from air into wet and dry ketones†

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Literature data on partitioning of compounds from the gas phase to ketones and from water to ketones has been collected and analyzed through the Abraham solvation equations. It is shown that for partition into both dry and wet ketones the main solvent factors that aid partitioning into the ketones are the polarizability/dipolarity, hydrogen-bond basicity and hydrophobicity (size) of the ketones. Reliable equations have been established for partitioning from the gas phase and from water to dry acetone, dry butanone, dry cyclohexanone and to wet methyl isobutyl ketone. It is further shown that partitioning into dry butanone and dry cyclohexanone leads to different equations than partitioning into the wet solvents, and that data on partitioning into the wet and dry ketones cannot be combined.

Introduction

The partition of compounds from water and from air into solvents is an important industrial process. The solvents can be saturated with water, that is 'wet' solvents, or they can be 'dry' solvents. The solvation of a compound in a solvent that is wet will not necessarily be the same as solvation in the dry solvent, as we have demonstrated for ethers,[1,2] alcohols[3,4] and acetates[5] as solvents. In all these series, solvation into the wet and dry solvents differed considerably for the lower homologs, in which water was very soluble, but less so for the higher homologs in which water was not very soluble. Ketones are also an important class of solvents; 4-methylpent-2-one or methyl isobutyl ketone, MIBK, is a well-known extractant. There have been a number of general studies on partitioning from water to solvents,[6–11] but when ketones were considered as extractants, the number of compounds in the data sets was too small for any significant conclusions to be drawn. Marcus[6] included partitioning from water to wet 4-methylhexan-2-one (this is probably a misprint for 4-methylpentan-2-one) but only for 15 compounds, and Meyer and Maurer[11] gave results for six compounds in wet 4-methylpentan-2-one, MIBK. No studies of dry ketones as solvents appear to have been published.

The aim of the present work is to collect data on the partition of solutes from water and from air to wet and dry ketones, to set out equations for the correlation and then prediction of the partition coefficients, and to examine, where possible, differences in solvation of solutes in wet and dry ketones.

Methodology

The prime experimental data for partitioning into wet (that is water-saturated) ketones are observed partition coefficients, P_s, from water to the water-saturated ketones, as listed in the Medicinal Chemistry Project data base.[12] These partition coefficients can be converted into air to water-saturated ketone partition coefficients, K_s, through eqn (1), where K_w is the air to water partition coefficient. All these partition coefficients refer to 298 K.

$$\log P_s = \log K_s - \log K_w \quad (1)$$

The air to water partition coefficient has no units when defined through eqn (2); air to solvent partition coefficients are similarly defined.

$$K_w = (\text{conc. of solute in water, mol L}^{-1})/(\text{conc. of solute in gas phase, mol L}^{-1}) \quad (2)$$

For partitioning into dry ketones, different sets of experimental data are used. Air to dry ketone partition coefficients can be obtained from the experimentally determined Henry's Law constants and the experimentally known solute vapour pressure. They can also be obtained from the solute activity coefficient at infinite dilution in the ketone, together with the solute vapour pressure. Water to dry ketone partition coefficients can be obtained from the ratio of the solute solubility in water and in the dry ketone, with a number of provisos: there should be no hydrate or solvate formation, and the secondary medium activity coefficient of the solute in water and in the dry ketone should not deviate substantially from unity. The air to dry ketone and the water to dry ketone partition coefficients are related through eqn (1).

In order to correlate the partition coefficients, we use two linear free-energy equations, eqn (3) and eqn (4), one for air to ketone partition coefficients, and one for water to ketone partition coefficients.

$$\log K_s = c + eE + sS + aA + bB + lL \quad (3)$$

$$\log P_s = c + eE + sS + aA + bB + vV \quad (4)$$

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The independent variables in eqn (3) and eqn. (4) are solute descriptors as follows.[13,14] E is the solute excess molar refraction in units of (cm^3 mol^{-1})/10, S is the solute dipolarity/polarizability, A and B are the overall or summation solute hydrogen bond acidity and basicity, V is the McGowan characteristic volume[15] in units of (cm^3 mol^{-1})/100, and L is the logarithm of the gas to hexadecane partition coefficient at 298 K. For a few solutes (alkyl anilines, alkyl pyridines, sulfoxides and a few heterocyclic compounds) partitioning from water to solvents that take up substantial quantities of water, an amended B-descriptor is used, denoted[13,14] as B^{o}.

Results

Propanone

Only data for dry propanone were available. We were able to assemble values of logK_s for 108 solutes, as given in Table S1, ESI†. Values were derived from Henry's Law constants or activity coefficients[16–52] or from solubilities[53–66] as detailed in Table S2, ESI†. Application of eqn (3) yielded the LFER, eqn (5); the term in bB was not significant and was omitted.

$$\log K_s\ (\text{propanone, dry}) = 0.127 - 0.387E + 1.733S + 3.060A + 0.866L \qquad (5)$$

$N = 108$, $R^2 = 0.998$, SD $= 0.168$, $F = 10417$, $Q^2 = 0.992$, PRESS $= 3.339$, PSD $= 0.180$.

In eqn (5), N is the number of data points (the number of compounds), R is the correlation coefficient, SD is the regression standard deviation, and F is the F-statistic. The leave-one-out statistics are Q^2, PRESS, and PSD (the 'predictive' standard deviation). In the leave-one-out procedure, the model is fitted without the ith observation, and this fitted model is then used to predict the response, $\hat{y}_{(i)}$ at x_i. The PRESS residuals are defined as $e_{(i)} = y_i - \hat{y}_{(i)}$, and PRESS is then given as PRESS $= \sum e^2_{(i)}$. The statistic $Q^2 = 1 - (\text{PRESS/SST})$ where SST is the total sum of squares. Although Q^2, PRESS, and PSD are calculated from the entire data set and hence cannot be truly predictive, Hawkins[67] has suggested that for data sets that are too small to divide into substantial training sets and test sets, PSD is very useful in assessment of predictive capability. PSD is defined similarly to SD; the latter is given by SD $= \sqrt{[\text{SSE}/(N - 1 - v)]}$ where SSE is the sum of squares of errors and v is the number of independent variables, and PSD $= \sqrt{[\text{PRESS}/(N - 1 - v)]}$.

To assess the predictive capability of eqn (5) by the method of training and test sets, we listed the compounds in order of logK_s and chose every other compound as a training set (54 compounds). The resulting equation, eqn (6), was then used to predict the remaining 54 values in the external test set, not used to set up eqn (6), with an average error AE $= -0.047$, an average absolute error AAE $= 0.123$, a root mean square error RMSE $= 0.188$ and a standard deviation SD $= 0.189$ log units. There is almost no bias in the predictions as shown by the very small value of AE, and the SD value of 0.189 suggests that the full eqn (5) can be used to predict further values to about 0.19 log units. Interestingly, this is almost the same as the PSD for the full eqn (5).

$$\log K_s\ (\text{propanone, dry}) = 0.136 - 0.498E + 1.882S + 3.012A + 0.864L \qquad (6)$$

$N = 54$, $R^2 = 0.998$, SD $= 0.159$, $F = 6999$.

The logK_s values can be transformed into logP_s through eqn (1), using known values[68–72] of logK_w. The resulting equation is eqn (7). Once again, we can assess the predictive capability of the equation by dividing the 108 values into a training set and an external test set, each of 54 values. The equation for the training set is eqn (8)

$$\log P_s\ (\text{propanone, dry}) = 0.313 + 0.312E - 0.121S - 0.608A - 4.753B + 3.942V \quad (7)$$

$N = 108$, $R^2 = 0.993$, SD $= 0.181$, $F = 3044$, $Q^2 = 0.992$, PRESS $= 3.826$, PSD $= 0.193$.

$$\log P_s\ (\text{propanone, dry}) = 0.322 + 0.171E + 0.100S - 0.731A - 4.966B + 3.960V \qquad (8)$$

$N = 54$, $R^2 = 0.995$, SD $= 0.160$, $F = 1761$.

Eqn (8) was then used to predict logP_s in the external test set of 54 compounds, with AE $= -0.024$, AAE $= 0.157$, RMSE $= 0.212$ and SD $= 0.214$ log units. We conclude that the full eqn (7) can be used to predict further values to about 0.21 log units.

Butanone

For butanone, log K_s and log P_s values were available for 69 solutes in dry butanol[18,19,21,34,35,40,73–93] see Table S3, ESI†, and another set of 14 values could be obtained from solubilities in dry butanone and water,[94–99] see Table S4, ESI†, making a total of 83 compounds. However, data were available for only 16 solutes in wet butanone.[12] The 83 values for partition between the gas phase and dry butanone led to eqn (9); the term in bB was not significant.

$$\log K_s\ (\text{butanone, dry}) = 0.112 - 0.474E + 1.671S + 2.878A + 0.916L \qquad (9)$$

$N = 83$, $R^2 = 0.997$, SD $= 0.162$, $F = 5937$, $Q^2 = 0.996$, PRESS $= 2.624$, PSD $= 0.183$.

We can again assess the predictive capability by constructing a training set and an independent test set. The training set of 42 compounds yielded eqn (10)

$$\log K_s\ (\text{butanone, dry}) = 0.116 - 0.460E + 1.740S + 2.734A + 0.912L \qquad (10)$$

$N = 42$, $R^2 = 0.995$, SD $= 0.192$, $F = 1962$.

Eqn (10) was then used to predict values for the 41 compound external test set with AE $= -0.016$, AAE $= 0.089$, RMSE $= 0.141$, SD $= 0.143$ log units. We suggest that the full eqn (9) could be used to predict new values of logK_s with an error of about 0.16 log units.

The corresponding equation for $\log P_s$ is given as eqn (11), and the equation for the training set of 42 compounds is eqn (12)

$$\log P_s \text{ (butanone, dry)} = 0.246 + 0.256E - 0.080S - 0.767A - 4.855B + 4.184V \quad (11)$$

$N = 83$, $R^2 = 0.998$, SD $= 0.182$, $F = 6272$, $Q^2 = 0.997$, PRESS $= 3.127$, PSD $= 0.200$.

$$\log P_s \text{ (butanone, dry)} = 0.255 + 0.244E + 0.068S - 0.984A - 4.883B + 4.126V \quad (12)$$

$N = 42$, $R^2 = 0.996$, SD $= 0.209$, $F = 2027$.

When the training equation was used to predict the 42 compounds in the external test set, the result was AE $= -0.032$, AAE $= 0.141$, RMSE $= 0.178$ and SD $= 0.181$, so that eqn (11) can be used to predict further values with an error of about 0.18 log units.

We only have 16 compounds for partition from air or water to wet butanone—too few to construct reliable equations with four or five descriptors. However, it seemed useful to set out these equations in order to see if the coefficients were the same, or nearly the same as those for equations for partition to dry butanone. Equations for partition into wet butanone are:

$$\log K_s \text{ (butanone, wet)} = -0.724 + 1.591E + 1.780S + 4.088A + 1.645B + 0.438L \quad (13)$$

$N = 16$, $R^2 = 0.997$, SD $= 0.177$, $F = 633$, $Q^2 = 0.976$, PRESS $= 2.410$, PSD $= 0.491$.

$$\log P_s \text{ (butanone, wet)} = 0.020 + 1.338E - 0.439S + 0.260A - 2.754B + 2.173V \quad (14)$$

$N = 16$, $R^2 = 0.891$, SD $= 0.240$, $F = 16$, $Q^2 = 0.290$, PRESS $= 3.749$, PSD $= 0.612$.

The predictive power of eqn (13) and (14) as judged from the large values of PSD is very poor, as expected. However, the equations are important in that they show conclusively that solubility in wet butanone cannot be taken to be the same as solubility in dry butanone. Hence data for wet and dry butanone cannot be combined.

Cyclohexanone

As for butanone, there is a reasonable amount of data for solubility in dry cyclohexanone; $\log K_s$ and $\log P_s$ values were available[21,40,78,100,101] for 50 compounds, see Table S6, ESI†, and solubility data were available for another 12 compounds,[57,97–99,102–107] see Table S7, ESI†, making 62 in all. For wet cyclohexanone, $\log P_s$ values were listed for 25 compounds.[12] The equations in $\log K_s$ and in $\log P_s$ for dry cyclohexanone are eqn (15) and eqn (16)

$$\log K_s \text{ (cyclohexanone, dry)} = -0.086 - 0.441E + 1.725S + 2.786A + 0.957L \quad (15)$$

$N = 62$, $R^2 = 0.999$, SD $= 0.140$, $F = 9533$, $Q^2 = 0.998$, PRESS $= 1.513$, PSD $= 0.163$.

$$\log P_s \text{ (cyclohexanone, dry)} = 0.038 + 0.225E + 0.058S - 0.976A - 4.842B + 4.315V \quad (16)$$

$N = 62$, $R^2 = 994$, SD $= 0.157$, $F = 1956$, $Q^2 = 0.992$, PRESS $= 1.997$, PSD $= 0.189$.

With a total of 62 compounds, any external test set would be rather small, and so we follow Hawkins and take the PSD values as an estimate of the predictive capability of the equations.

There are 25 compounds for which data are available for wet cyclohexanone, the relevant equations being eqn (17) and eqn (18).

$$\log K_s \text{ (cyclohexanone, wet)} = -0.052 + 0.614E + 1.437S + 4.179A + 0.399L \quad (17)$$

$N = 25$, $R^2 = 0.999$, SD $= 0.469$, $F = 2968$, $Q^2 = 0.998$, PRESS $= 14.985$, PSD $= 0.888$.

$$\log P_s \text{ (cyclohexanone, wet)} = 0.282 + 1.109E - 0.518S + 0.566A - 4.245B + 3.346V \quad (18)$$

$N = 25$, $R^2 = 0.864$, SD $= 0.492$, $F = 24$, $Q^2 = 0.828$, PRESS $= 15.633$, PSD $= 0.907$.

The very large values of PSD in eqn (17) and eqn (18) show that these equations cannot possibly be used to estimate further values. The equations are of use only in that they show solubility in wet cyclohexanone to be markedly different to solubility in dry cyclohexanone, and hence that data in wet and dry cyclohexanone cannot be combined.

Methyl isobutyl ketone, MIBK

There are a large number of compounds for which water to wet MIBK partition coefficients are recorded.[12] We were not able to obtain descriptors for erythromycin and berythromycin, probably because these two compounds have properties well outside the range of those we used to set up the defining equations. We also left out a few compounds where there was doubt about the experimental values of $\log P_s$. For example, 2,4,6-trinitrophenol had recorded values from -0.15 to $+3.75$ log units, possibly because some of these values refer to the ionized species and not the neutral compound. We were left with 86 compounds for which we had descriptors, see Table S8, ESI†, where the corresponding values of $\log K_s$ are given as well as the values of $\log P_s$. We could find data on only four compounds for dry MIBK, and so we ignore these altogether. The equation for partition from the gas phase to wet MIBK is given as eqn (19).

$$\log K_s \text{ (MIBK, wet)} = 0.244 + 0.183E + 0.987S + 3.418A + 0.323B + 0.854L \quad (19)$$

$N = 86$, $R^2 = 0.994$, SD $= 0.257$, $F = 2523$, $Q^2 = 0.993$, PRESS $= 6.030$, PSD $= 0.274$.

There are enough data points to test the predictive capability of eqn (19) by the method of training and external test sets, and so we divided the 86 points into a training set and an external test set, each of 43 points.

$$\log K_s \text{ (MIBK, wet)} = 0.009 + 0.267E + 1.249S + 3.321A + 0.716B + 0.796L \quad (20)$$

$N = 43$, $R^2 = 0.995$, SD $= 0.234$, $F = 2523$.

When eqn (20) was used to predict the 43 values in the external test set we found AE = −0.100, AAE = 0.280, RMSE = 0.352, SD = 0.356 log units. In this case, there are significant differences in the coefficients for the full set and for the training set, and so it is possible that the training set is not a very representative sample. The SD value of 0.356 for the external test set is much larger than that for the full set, 0.234, and much larger than PSD = 0.274 for the full set. We think that the latter is a more reasonable value and suggest that eqn (19) can be used to predict further values with an error of about 0.27/0.28 log units.

The equation for the water to MIBK partition coefficients is given as eqn (21), and the corresponding equation for a training set of 43 compounds is eqn (22).

$$\log P_s\,(\text{MIBK, wet}) = 0.383 + 0.801E - 0.831S - 0.121A - 4.441B + 3.876\,V \qquad (21)$$

$N = 86$, $R^2 = 0.977$, SD = 0.272, $F = 676$, $Q^2 = 0.974$, PRESS = 6.727, PSD = 0.290.

$$\log P_s\,(\text{MIBK, wet}) = 0.265 + 0.837E - 0.679S - 0.205A - 4.132B + 3.685V \qquad (22)$$

$N = 43$, $R^2 = 0.979$, SD = 0.265, $F = 344$.

Eqn (21) was used to predict the values of the 43 compound external test set, with AE = −0.090, AAE = 0.262, RMSE = 0.328 and SD = 0.332 log units. As for eqn (19) and eqn (20), the SD value for the test set predictions is quite a bit larger than PDS in eqn (21), and we think that a reasonable prediction error is 0.30 log units.

Discussion

The PSD statistic seems to be very useful in assessing the predictive capability of a given equation, even, as we pointed out above, it is obtained from an analysis of all the data. In Table 1 we collect the SD and PSD values for the full equations, and the SD values for the external test set where available. In our view, it is reasonable to take the PSD value for the full equation as a measure of its predictive capability. Of course, in cases where there is not enough data to construct training sets and test sets, any assessment has to be made on the full equation only, and PSD then seems very valuable indeed. For example eqn (13) might superficially seem a quite reliable equation, with SD = 0.177, but the PSD of 0.491 indicates that eqn (13) is not soundly based—because of the restricted number of data points in a five parameter equation.

Table 1 Values of SD and PSD for full equations, and SD for the external test set

Equations	SD (full)	PSD (full)	SD (test)
Eqn (5) and eqn (6)	0.168	0.180	0.189
Eqn (7) and eqn (8)	0.181	0.193	0.214
Eqn (9) and eqn (10)	0.162	0.183	0.145
Eqn (11) and eqn (12)	0.182	0.200	0.181
Eqn (13)	0.177	0.491	—
Eqn (14)	0.240	0.612	—
Eqn (15)	0.140	0.163	—
Eqn (16)	0.157	0.189	—
Eqn (17)	0.469	0.888	—
Eqn (18)	0.492	0.902	—
Eqn (19) and eqn (20)	0.257	0.274	0.356
Eqn (21) and eqn (22)	0.272	0.290	0.332

The coefficients in eqn (3) and eqn (4), as we have pointed out several times, are not just fitting coefficients, but encode information about the chemical nature of the solvent phase. The coefficients in eqn (3) are easier to interpret than those in eqn (4); the former include contributions only from the ketone solvent, whereas the latter include contributions from both the ketone solvent and water. For all the ketones, both wet and dry, the main terms in eqn (3) are those in *sS*, *aA* and *lL*. The ketones are all polarizable/dipolar (large *s*-coefficient), are all hydrogen-bond bases (very large *a*-coefficient) and all are to some extent hydrophobic (medium to large *l*-coefficient). The *bB* term is zero for the dry ketones, because they do not possess any hydrogen-bond acidity, but the presence of water in the ketones leads to hydrogen-bond acidity and hence the wet ketones give rise to positive *b*-coefficients.

We have already shown that for a series of acetates,[5] and even more rigorously, for a series of alkan-1-ols,[3,4] that as the homologous series of alcohols is ascended, solubility in the wet alcohol becomes closer to the solubility in the dry alcohol, as indicated by value of the coefficients in eqn (3) and eqn (4). Eqn (3) is the easier to interpret. The *a*-coefficient and the *b*-coefficient are larger for solubility in the wet ketones than in the dry ketones, because the presence of water will increase the solvent hydrogen-bond basicity and increase the solvent hydrogen-bond acidity; both of these will aid the solubility of compounds with polar functional groups. On the other hand, the presence of water decreases the solvent hydrophobicity and leads to a decrease in the *l*-coefficient; this leads to a decrease in the solubility of non-polar solutes in the wet ketones. As we have shown for the alkan-1-ols, these differences between wet and dry solvents become smaller as the number of carbon atoms in the solvent, Nc, becomes larger and the solvent takes up less water at saturation. The effect of water on the solvent hydrophobicity is quite dramatic, as shown in Fig. 1.

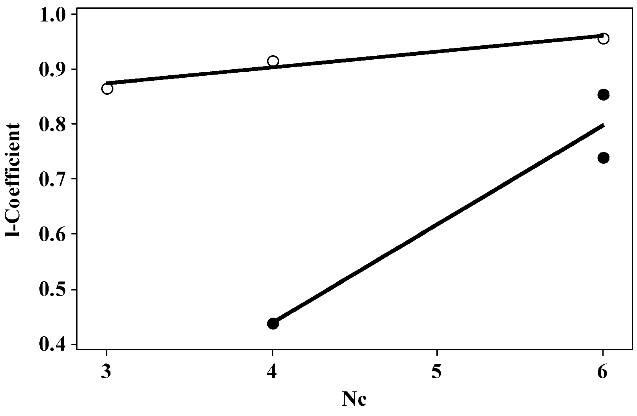

Fig. 1 Variation of the *l*-coefficient with the number of carbon atoms in the ketone; ○ dry ketones, ● wet ketones.

Conclusion

We have set out equations for the solubility of gases and vapors in dry propanone, dry butanone and dry cyclohexanone that can be used to predict further values of $\log K_s$ with an estimated prediction error of about 0.18 log units. For the hypothetical partitions from water to dry propanone, dry butanone and dry cyclohexanone, the prediction error is about 0.20 log units. The only reliable equations for wet solvents are those for solubility in wet MIBK. For solubility of gases and vapors in wet MIBK, the estimated prediction error is about 0.27 log units, and for distribution from water to wet MIBK our estimated prediction error is about 0.29 log units. The only previous studies on ketone solvents are those of Marcus[6] and of Meyer and Maurer[11] but since these involved only fifteen and six solutes, respectively, there are no studies with which to compare our results. The coefficients in the fitting equations for $\log K_s$ and $\log P_s$ can be used to deduce the chemical factors that influence solubility and partitioning in the air to ketone and water to ketone systems that we have studied.

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