On the Solubility of Quercetin

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ABSTRACT

There is considerable disagreement over the solubility of quercetin in water. Experimental values of $\log C_w$ with C_w in mol/L range from -2.52 to -5.89, a difference of over three log units. We have applied a methodology based on linear free energy equations for water-solvent and gas-solvent partitions to study solubilities. These are related to partition coefficients through $Ps = C_s/C_w$ where C_s and C_w are solubilities of a given solute in a solvent and in water. We find that known solubilities of quercetin in methanol and ethanol at 298 K and a known water-solvent partition coefficient can be accommodated in the same model if the water solubility at 298 K, as $\log C_w$, is taken as -3.90, that is near to the middle of the range of experimental values. Our model successfully predicts solubilities of quercetin in water-ethanol mixtures near to the ethanol rich mixtures.

Keywords:

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1. Introduction

It is known that quercetin (3,5,7,3',4'-pentahydroxyflavone) is very sparingly soluble in water, but determinations of the actual solubility yield very varied results. Althans et al. [1] have recently summarized the various measurements that have been made, and in Table 2 we list recorded solubilities in water at 298 K, as $\log C_w$ in units of mol/L. Although these determinations vary by more than three log units, it seems almost impossible to make a selection, especially given the very low solubility and the consequent experimental difficulty of the measurements. On numerous occasions, we have studied the solubility of a given compound in nonaqueous solvents, and have shown that it is possible to obtain an indirect estimate of the solubility in water. It seemed of interest to apply this indirect method to the solubility of quercetin and so provide another route altogether for the estimation of the solubility in water.

Table 1

Recorded solubilities of quercetin in water at 298 K, as $\log C_w$

Log C_w (mol/L)	Ref
-2.52	[2]
-3.70	[3]
-4.30	[4]
-4.52 (323 K)	[5]
-4.59	[6]
-5.89	[1]

2. Methodology

Our method is based on two linear free energy equations, Eq. (1) and Eq. (2). The dependent variable, SP , consists of a series of values of some physicochemical property of a series of solutes in a given solvent system. In the present work, SP in Eq. (1) can be a water-solvent partition, as $\log P$, of a series of solutes in a given water-solvent, and SP in Eq.(2) can be a gas-solvent partition, as $\log K$, of a series of solutes in a given gas-solvent system.

$$SP = c + e \mathbf{E} + s \mathbf{S} + a \mathbf{A} + b \mathbf{B} + v \mathbf{V} \quad (1)$$

$$SP = c + e \mathbf{E} + s \mathbf{S} + a \mathbf{A} + b \mathbf{B} + l \mathbf{L} \quad (2)$$

The independent variables, or descriptors, in Eq. (1) and Eq. (2) are properties of solutes as follows [7-9] : **E** is an excess molar refraction in $\text{cm}^3 \text{mol}^{-1}/10$, **S** is a combined dipolarity/polarizability descriptor, **A** is the overall solute hydrogen bond acidity, **B** is the overall solute hydrogen bond basicity, **V** is McGowan's characteristic molecular volume in $\text{cm}^3 \text{mol}^{-1}/100$ and **L** is the logarithm of the gas to hexadecane partition coefficient at 298 K. The set of coefficients, *c*, *e*, *s*, *a*, *b*, *v* and *l* characterise the system and are determined by multiple linear regression analysis. The descriptors in Eq. (1) and Eq. (2) are obtained from known equations for water-solvent partition coefficients, and known values of the corresponding partition coefficients for a given solute. The method has been described in considerable detail [8-11], especially by Clarke and Mallon [11] who give a number of specific examples.

In order to apply the method to solubilities, *C*, the latter are converted into water-solvent partition coefficients through Eq. (3), where *P_s* is a water to solvent partition coefficient, *C_s* is the molar solubility in the solvent and *C_w* is the molar solubility in water. Usually, solubilities are measured with dry solvents and so *P_s* in Eq. (3) will then refer to the (hypothetical) partition between water and a dry solvent.

$$P_s = C_s/C_w \quad (3)$$

It is useful to introduce another descriptor, *K_w*, the gas to water partition coefficient (no units) so that all values of *P_s* can be converted into the corresponding values of *K_s*, the gas to solvent partition coefficient, Eq. (4).

$$K_s = C_s/C_g \quad K_s = P_s \cdot K_w \quad (4)$$

In the special case for which *C_w* in Eq. (3) is unknown, this can be used as another descriptor to be determined, and is obtained by trial and error together with the other unknown descriptors. Then we start with no less than eight descriptors that have to be determined from a set of equations, viz: **E**, **S**, **A**, **B**, **V**, **L**, *K_w* and *C_s*. However, **E** can be obtained either from a calculated refractive index at 293 K [12], or even better as a calculated value using the ACD software[13] and **V** can be calculated from structure [7]. In the present case, we are fortunate that Whaley et al. [14] have determined **A**-values for hydroxyflavones using an NMR method [15],

and we can use this data to assign $A = 1.92$ for quercetin. Then the outstanding descriptors of quercetin to calculate are reduced to S , B , L , $\log K_w$ and $\log C_w$.

3. Results

A value for the water-octanol partition coefficient of quercetin, $\log P(\text{oct}) = 2.06$, is available [16], Althans et al. [1] have determined the solubility in ethanol and Razmara et al.[2] the solubility in methanol at 298 K. Then use of C_w allows $\log P(\text{ethanol})$ and $\log P(\text{methanol})$ to be deduced, and use of K_w allows $\log K$ values for gas to ethanol partition and gas to methanol partition to be deduced. In addition, we have equations on the lines of Eq. (1) and Eq. (2) for gas to water partitions, thus leading to eight equations from which to calculate the five required descriptors. The equations and their coefficients are in Table 2. We include also equations and coefficients for partition from water to various water-ethanol mixtures, with compositions expressed as vol %.

Table 2

Equations and coefficients for water-solvent and gas-solvent partitions, as $\log P$ and $\log K$

Solvent	c	e	s	a	b	v	l
Log P , Eq. (1).							
Water - octanol, wet	0.088	0.562	-1.054	0.034	-3.460	3.814	0.000
Water-methanol	0.276	0.334	-0.714	0.243	-3.320	3.549	0.000
Water-ethanol	0.222	0.471	-1.035	0.326	-3.596	3.857	0.000
Water- 96% ethanol	0.238	0.353	-0.833	0.297	-3.533	3.724	0.000
Water- 95% ethanol	0.239	0.328	-0.795	0.294	-3.514	3.697	0.000
Water- 90% ethanol	0.243	0.213	-0.575	0.262	-3.450	3.545	0.000
Water- 80% ethanol	0.172	0.175	-0.465	0.260	-3.212	3.323	0.000
Water- 70% ethanol	0.063	0.085	-0.368	0.311	-2.936	3.102	0.000
Water- 60% ethanol	-0.040	0.138	-0.335	0.293	-2.675	2.812	0.000
Water- 50% ethanol	-0.142	0.124	-0.252	0.251	-2.275	2.415	0.000
Water- 40% ethanol	-0.221	0.131	-0.159	0.171	-1.809	1.918	0.000
Water- 30% ethanol	-0.269	0.107	-0.098	0.133	-1.316	1.414	0.000
Water- 20% ethanol	-0.252	0.042	-0.040	0.096	-0.823	0.916	0.000
Water- 10% ethanol	-0.173	-0.023	-0.001	0.065	-0.372	0.454	0.000
Gas – water	-0.994	0.577	2.549	3.813	4.841	-0.869	0.000
Log K , Eq. (2)							
Gas - octanol, wet	-0.198	0.002	0.709	3.519	1.429	0.000	0.858

Gas-methanol	-0.039	-0.338	1.317	3.826	1.396	0.000	0.773
Gas-ethanol	0.017	-0.232	0.867	3.894	1.192	0.000	0.846
Gas – water	-1.271	0.822	2.743	3.904	4.814	0.000	-0.213

Razmara et al. [2] also determined solubilities in a number of water-ethanol mixtures. In view of the large disparity in the solubility in water determined by Razmara et al. [2] and by Althans et al. [1] we chose not to use these solubilities in our analysis but to predict the water-ethanol solubilities and then to compare the predictions with the experimental values. The required coefficients for partition between water and water-ethanol mixtures are in Table 2 [31]. Chebil et al. [5] have also determined solubilities in a few nonaqueous solvents, but only at 323 K, and so we did not use these results, especially as Althans et al. [1] have shown that quercetin in water decomposes at temperatures higher than 316 K.

Our analysis of the quercetin data is shown in Table 3. For the eight values of $\log P_s$ observed and calculated, the average deviation $AE = 0.009$, the absolute average deviation $AAE = 0.051$ and the standard deviation $SD = 0.071$ log units, so that the fit is excellent. The obtained descriptors for quercetin are in Table 4. The deduced value of the solubility in water, as $\log C_w$ at 298 K is -3.90 and the corresponding solubilities in methanol and ethanol are in Table 3. As shown by the example of partition into wet octanol, it is now possible to predict values of $\log P_s$ for partition of quercetin into any solvent for which the coefficients in Eq. (1) are known, and then to obtain the corresponding solubilities at 298 K. Currently equation coefficients have been reported for more than 55 different organic solvents [9].

Table 3
Analysis of the data for quercetin at 298 K

System	Log P_s		Log C_s	
	Obs	Calc		Calc
Water-wet octanol	2.06	1.98		-1.92
Water-methanol	2.26	2.39	-1.64	-1.51
Water-ethanol	2.37	2.37	-1.53	-1.53
Gas-water	18.56	18.55		
Gas-wet octanol	20.62	20.71		
Gas-methanol	20.82	20.79		
Gas-ethanol	20.93	20.88		
Gas-water	18.56	18.58		

Table 4

The obtained descriptors for quercetin

E	S	A	B	V	L	Log K_w
2.68	2.20	1.92	1.40	1.9632	12.33	18.53

Our deduced solubility for quercetin in water, obtained from a ‘best-fit’ analysis of the data in Table 3, is $\log C_w = -3.90$ at 298 K, with units of C_w in mol/L. This is in the middle of the various experimental determinations, as shown in Table 1. Although solubilities in water are notoriously difficult to predict, it is useful to compare the values in Table 1, and also our suggested value, with predicted values. The EPI Suite [17] gives a predicted value of $\log C_w$ from a fragmentation scheme as -3.02 and the SPARC method [18] yields a prediction of -4.81 so that our estimated value is again somewhere in the middle.

From the descriptors in Table 4, and the coefficients listed in Table 2, it is possible to predict values of $\log P_s$ in the various water-ethanol mixtures, and then from $\log C_w = -3.90$ to predict the corresponding solubilities as $\log C_s$. In Fig. 1 we compare predicted and observed [2] solubilities in water-ethanol mixtures, and also our fitted value of $\log C_w$ with the experimental values in Table 1. As might be expected, our predicted solubilities in the water-ethanol system are in good agreement with the experimental solubilities [2] at large vol % ethanol, but diverge considerably as the proportion of water increases. Our suggested value for $\log C_w$ is about in the mid-range of the various recorded solubilities in water.

Our conclusion is that an indirect method for estimation of aqueous solubilities leads to a solubility for quercetin in water at 298 K of $\log C_w = -3.90$ with units of mol/L. This estimated solubility is in the middle of the range of solubilities that have been experimentally determined.

Fig. 1. Solubilities of quercetin. ● Experimental values in water-ethanol solvents [2], ▲ experimental values in water from Table 1, □ predicted values in water-ethanol solvents and a fitted value in water itself.

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