

# Estimation of Aqueous Solubility for Some Guanine Derivatives Using Partition Coefficient and Melting Temperature

ALBIN KRISTL

Contribution from Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

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**Abstract** □ Aqueous solubilities for some guanine derivatives were estimated by semiempirical equations developed by Yalkowsky and Valvani<sup>1</sup> using the data for partition coefficient and melting temperature. It was shown that in the case of guanine derivatives examined in this study, the solubility values could not be estimated adequately by these equations.

## Introduction

There exist several different methods of aqueous solubility estimation for organic compounds:<sup>1</sup> methods based directly on group contributions to measured aqueous activity coefficients; techniques based on experimental physicochemical properties such as partition coefficient, chromatographic retention, boiling point, and molecular volume; methods based on properties that cannot be experimentally determined but can be calculated from molecular structure (molecular surface area, molecular connectivity, and parachor); and techniques based on combinations of two or more parameters that can be experimentally measured, calculated, or generated empirically (solubility parameter, linear solvation energy relationship and others).

The first who recognized the relationship between aqueous solubility and *n*-octanol water partition coefficient (*P*) were Hansch et al.<sup>2</sup> One of the most well-known and popular equations for predicting the solubility of liquid and solid organic solutes using the *n*-octanol water partition coefficient was derived by Yalkowsky and Valvani:<sup>1,3</sup>

$$\log S_w \approx -1.00 \log P - 1.11 \frac{\Delta S_f(\text{mp} - 25)}{1364} + 0.54 \quad (1)$$

where  $S_w$  is aqueous solubility in mol/L, mp is the solute melting point temperature in °C, and  $\Delta S_f$  is the entropy of fusion. The parameter *P* is given as the concentration ratio in octanol and aqueous phases ( $C_o/C_w$ ).

For rigid molecules, where  $\Delta S_f$  was taken as 56.7 J/molK, one obtains

$$\log S_w \approx -1.05 \log P - 0.012 \text{mp} + 0.87 \quad (2)$$

These semiempirical equations showed excellent correlation between the values for aqueous solubility and *P* for many nonelectrolytes, weak electrolytes, and even for acidic and basic substances.<sup>1,3,4</sup> They were used by many different researchers for aqueous solubility estimation of various substances, and good correlation between experimentally determined and calculated solubility values was shown.<sup>5,6</sup>

In this work we wanted to evaluate eqs 1 and 2 for predicting the aqueous solubility for some antiviral guanine derivatives, acyclovir (ACV) and deoxyacyclovir (DCV), and their acetyl derivatives.

## Materials and Methods

The substances examined in this study, ACV (9-(2-hydroxyethoxymethyl)guanine) and DCV (2-amino-9-(2-hydroxyethoxymethyl)-9-*H*-purine) with their *O*-acetyl (OAcACV and OAcDCV), *N*-acetyl (NACACV and NACDCV), and *N,O*-diacetyl (diAcACV and diAcDCV) congeners were synthesized at the National Institute of Chemistry, Ljubljana, Slovenia.<sup>7</sup>

The melting temperatures (mp), entropies of fusion ( $\Delta S_f$ ) and corresponding activity coefficients ( $\gamma$ ) as well as the values for aqueous solubility ( $S_w$ ), partition coefficients, and different octanol/water solubility ratios at  $22 \pm 0.1$  °C were determined previously<sup>8</sup> and are given in Table 1. Additionally, the thermal analysis measurements for all tested substances showed no enthalpy changes that would correspond to desolvation, except for ACV, which existed in hydrated form but after drying ( $T = 150$  °C, air atmosphere), a stable anhydrous form was obtained.<sup>9</sup>

Experimentally determined values for partition coefficients<sup>8</sup> were used in eqs 1 and 2. The values for partition coefficients of tested guanine derivatives calculated by Rekker's fragmental approach differed significantly from those obtained by the experiment.<sup>10</sup>

## Results and Discussion

Calculated values for aqueous solubility of tested substances, using eqs 1 and 2 are presented in Table 1. Equation 2, where the entropy value for the rigid molecules (56.5 J/mol K) is used, gives completely different results from the measured values, although tested substances are rigid and mostly do not have more than five nonhydrogen atoms in a flexible chain (the molecules with more than five units in the side chain are assumed to be partially flexible molecules).<sup>1,3</sup> These results were expected because all the experimentally determined values of  $\Delta S_f$  for tested substances (Table 1) differ a lot from 56.5 J/mol K (except for ACV for which the  $\Delta S_f$  value is close to 56.5 J/mol K).

Comparing the logarithmic values for aqueous solubility calculated by eq 1 (where the experimentally determined values for  $\Delta S_f$  were used) with the measured ones reveals a rather large disagreement. The log *P* values determined for the same compound are acceptable if they do not differ by  $>0.2$  log units<sup>11</sup> or even 0.3 log units,<sup>12</sup> which represent about two times higher/lower values in the nonlogarithmic scale. Using these estimations, one can say that calculated (by eq 1) and experimentally determined log  $S_w$  values are in good accordance for diAcACV and diAcDCV, are rather good for OAcACV and OAcDCV, and differ by large amounts in the case of the other tested substances.

Equations 1 and 2 were derived on the basis of the following rationales:<sup>13</sup>

(1) The solubility of nonpolar and semipolar solutes in octanol is approximately equal to the ideal solubility,  $\gamma_o = 1$ . Because  $P = \gamma_w/\gamma_o$ , it follows that  $\log \gamma_w \approx \log P$ .

(2) The ideal solubility can be estimated from mp and  $\Delta S_f$  of the solute.

(3) The  $\Delta S_f$  of the solute is constant for rigid molecules.

Table 1. Melting Temperatures (mp, in °C), Entropies of Fusion ( $\Delta S_f$ , in J/Mol K), Activity Coefficients in Neat Water ( $\gamma_w$ ) and in Neat Octanol ( $\gamma_o$ ), and Logarithmic Values of Aqueous Solubilities

parameter	ACV	NACACV	OACACV	diACACV	DCV	NACDCV	OACDCV	diACDCV
$T_m$	255.0	217.0	242.0	204.0	189.0	181.0	135.0	134.0
$\Delta S_f$	57.7	109.9	96.9	99.3	91.4	121.0	104.6	104.0
$\gamma_w^a$	33.9	0.81	5.93	5.22	1.40	0.17	4.41	2.73
$\gamma_o^a$	252.1	11.8	96.0	26.9	14.7	4.75	12.7	23.1
$\log S_w^b$	-053	-2.37	-2.58	-2.16	-1.38	-1.91	-1.17	-0.70
$\log S_w^c$	-0.54	-0.37	-0.91	-0.69	-0.26	0.09	-0.11	0.36
$\log S_w^d$	-2.14	-1.92	-2.70	-2.14	-1.08	-0.86	-0.97	-0.73
$\log P^d$	-1.57	-1.30	-1.07	-0.85	-1.08	-1.33	-0.61	-1.05
$\log S_o/S_w^d$	-1.82	-2.10	-2.15	-1.66	-1.96	-2.40	-1.40	-1.90
$\log S_{ow}/S_{wo}^d$	-1.60	-1.45	-1.16	-0.96	-1.26	-1.54	-0.72	-1.12

<sup>a</sup> Activity coefficients ( $\gamma$ ) were calculated by the equation  $\gamma = (f_2/f_2^0)/S_2V_1$ , where  $f_2$  and  $f_2^0$  are the fugacities of the pure solid solute and of its subcooled liquid at the temperature of the solution, respectively,  $S_2$  is the molar solubility of the solute and  $V_1$  is the molar volume of the solvent.<sup>8</sup> <sup>b</sup> Calculated by eq 1 at  $T = 22$  °C. <sup>c</sup> Calculated by eq 2 at  $T = 22$  °C. <sup>d</sup> The logarithms of aqueous solubilities ( $\log S_w$ ), partition coefficients ( $\log P$ ), octanol/water solubility ratios ( $\log S_o/S_w$ ) and mutually saturated octanol/water solubility ratios ( $\log S_{ow}/S_{wo}$ ) for examined substances are also given ( $T = 22 \pm 0.1$  °C).<sup>8</sup>

(4) The ratio  $S_o/S_w$  is equivalent to  $P$ , that is,  $S_w$  is equal to  $S_o$  divided by  $P$ . These statements were additionally supported by recently published papers<sup>14,15</sup> where the authors confirmed the negligible effect of octanol/water mutual saturation on the partition coefficient. They stated that the octanol/water solubility ratio,  $S_o/S_w$ , can be used as the estimate for the partition coefficient and that there is negligible effect of octanol/water mutual saturation on the partition coefficient, although the average absolute estimation errors (when correlating  $\log P$  with  $\log(S_o/S_w)$  for 82 solutes) were  $>0.4$  log units (which means  $>2.5$ -fold higher/lower values in the nonlogarithmic scale).<sup>14</sup> Additionally, the solubility of different organic compounds in octanol (using 124 solutes) was estimated by five methods (i.e.; ideal solubility, regular solution approach, UNIFAC approach,  $PS_w$  method, and OCTASOL), and the most reliable results were obtained by  $PS_w$  method ( $\log S_o = \log P + \log S_w$ ), where the average error of estimates is 0.29 log units (2-fold higher/lower value than the experimental one in nonlogarithmic scale).<sup>15</sup>

Regarding the observed discrepancies in calculated and experimentally determined values for aqueous solubilities of tested guanine derivatives one can assume that some of the aforementioned rationales could be invalid for predicting the aqueous solubility of these substances; although they represent semipolar solutes.<sup>16</sup> The values for  $\gamma_o$  of tested substances (Table 1) differ significantly from 1 in all cases, indicating that the solubility of these substances in *n*-octanol is not ideal. Despite these differences, the observed and calculated  $\log S_w$  values (by the eq 1) are reasonably close in four out of the eight cases. This nonideal solubility in *n*-octanol also indicates that the activity coefficients of tested substances in water ( $\gamma_w$ ) cannot be equal to  $P$ , expressed in mole fractions.

Additionally it was shown that in the case of tested guanine derivatives,  $\Delta S_f$  of the solute is not constant for rigid molecules and cannot be taken as  $\Delta S_f = 56.7$  J/mol K.

We also found large differences in the solubility values determined in neat and mutually saturated solvents and consequently in the solubility ratios (Table 1), showing that mutual saturation plays an important role in partitioning and solubility not only of many highly lipophilic and hydrophilic solutes but also of semipolar substances such as the tested guanine derivatives.<sup>8</sup> It can be deduced that the values for partition coefficients ( $P$ ) are not equivalent to the neat octanol/water solubility ratios ( $S_o/S_w$ ) but more to the mutual saturated octanol/water solubility ratios ( $S_{ow}/S_{wo}$ ; Table 1). These findings were also confirmed with the partition experiments performed with some higher alkanols (i.e., heptanol and nonanol).<sup>17</sup>

One can thus conclude that eqs 1 and 2 in the case of tested guanine derivatives do not give reasonable estimation of aqueous solubility.

## References and Notes

1. Jalkowsky, S. H.; Banerjee, S. *Aqueous solubility (Methods of estimation for organic compounds)*; Marcel Dekker: New York, 1992.
2. Hansch, C.; Quinlan, J. E.; Lawrence, G. L. The linear free energy relationships between partition coefficients and the aqueous solubility of organic liquids. *J. Org. Chem.* **1968**, *33*, 347–350.
3. Yalkowsky, S. H.; Valvani, S. C. Solubility and partitioning I: Solubility of nonelectrolytes in water. *J. Pharm. Sci.* **1980**, *69*, 912–922.
4. Yalkowsky, S. H.; Pinal, R.; Banerjee, S. Water solubility: A critique of the solvatochromic approach. *J. Pharm. Sci.* **1988**, *77*, 74–77.
5. Mayer, J. M.; Rowland, M. Determination of aqueous solubilities of a series of 5-ethyl-5-alkylbarbituric acids and their correlation with  $\log P$  and melting points. *Drug Dev. Ind. Pharm.* **1984**, *10*, 69–83.
6. Pranker, R. J.; McKeown, R. H. Physicochemical properties of barbituric acid derivatives: IV. Solubilities of 5,5-disubstituted barbituric acids in water. *Int. J. Pharm.* **1994**, *112*, 1–15.
7. Štimac, A.; Muhić, D.; Kobe, J. A novel palladium-catalysed deoxygenation of guanine O<sup>6</sup>-arene sulfonates. A practicable synthesis of 2-amino purine nucleosides and related analogues. *Nucleosides Nucleotides* **1994**, *13*, 625–636.
8. Kristl, A.; Vesnaver, G. Thermodynamic investigation of the effect of octanol–water mutual miscibility on the partitioning and solubility of some guanine derivatives. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 995–998.
9. Kristl, A.; Srčić, S.; Vrečer, F.; Šuštar, B.; Vojnovic, D. Polymorphism and pseudopolymorphism: influencing the dissolution properties of the guanine derivative acyclovir. *Int. J. Pharm.* **1996**, *139*, 231–235.
10. Kristl, A.; Pečar, S. Hydrophilic anomalies of some guanine derivatives. *Eur. J. Med. Chem.* **1997**, *32*, 3–8.
11. Rekker, R. F.; Mannhold, R. *Calculation of drug lipophilicity (The hydrophobic fragmental constant approach)*; VCH: Weinheim, New York, 1992.
12. Dearden, J. C.; Bresnen, G. M. The measurement of partition coefficients. *Quant. Struct. Act. Relat.* **1988**, *7*, 133–144.
13. Yalkowsky, S. H.; Valvani, S. C.; Roseman, T. J. Solubility and Partitioning VI: Octanol Solubility and Octanol–Water Partition Coefficients. *J. Pharm. Sci.* **1983**, *72*, 866–870.
14. Pinsuwan, S.; Li, A.; Yalkowsky, S. H. Correlation of Octanol/Water Solubility Ratio and the Partition Coefficients. *J. Chem. Eng. Data* **1995**, *40*, 623–626.
15. Li, A.; Pinsuwan, S.; Yalkowsky, S. H. Estimation of Solubility of Organic Compounds in 1-Octanol. *Ind. Eng. Chem. Res.* **1995**, *34*, 915–920.
16. Kristl, A.; Mrhar, A.; Kozjek, F. The Ionization Properties of Acyclovir and Deoxyacyclovir. *Int. J. Pharm.* **1993**, *99*, 79–82.
17. Kristl, A. Thermodynamic Investigation of the Effect of the Mutual Miscibility of Some Higher Alkanols and Water on the Partitioning and Solubility of Some Guanine Derivatives. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 1721–1724.

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