Critique of Recent Comparison of log *P* Calculation Methods

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Received August 16, 1994; accepted December 12, 1994

In a recent note to this journal Moriguchi *et al.*[1] compared the reliability of several methods for calculating log *P* octanol/water from structure. The structures chosen were 22 drugs which Rekker and Manhold had analyzed earlier.[2] On the basis of these values a statistical analysis indicated that the reliability of the methods decreased in the order: Moriguchi, Hansch, Rekker and Suzuki. The fact that regression equations relating measured to calculated values produced such unreasonably high deviations ($s=0.764$ to 1.240) and poor correlation coefficients (0.701 to 0.901) should have alerted the authors that some of the measured log *P* value were in error. Three major errors are apparent, and these affect the statistics to such an extent that the comparisons are not valid.

Key words octanol/water; log *P*; ionization correction; CLOGP

All the methods attempt to calculate the log *P* for the neutral solute molecule. If the solute cannot be measured at a pH where it is essentially uncharged, then, if an accurate pK_a is available, a correction can be made for the amount of neutral form present. The assumption is then made that only the neutral form partitions into the octanol phase. This may be justified if the pH is no more than 2.0 log units on the ionic side of the pK_a and the counter ion is not lipophilic. Propafenone has a pK_a of 9.62 and was partitioned at pH 5.0.[3] This means that the concentration of ion in the aqueous phase was over 40000 times that of the neutral species. A great deal of the response measured at pH 5.0 must be due to the ionic form, and when a correction of 4.62 log units was applied,[3] it greatly overstated the hydrophobicity of the neutral molecule. The Hansch–Leo method (current CLOGP ver. 3.55) estimates it at 3.42 rather than 4.63. This drug (#18) and also disopyramide (#9) should be dropped from the regression until values at or above the pK_a can be measured.

The other obvious outlier is the acidic drug, furosemide (#11), which is given a value of −0.83. This appears to be a value reported by Horstmann *et al.*[4] with no pH control mentioned. It was dropped as an outlier from Rekker's analysis.[2] Recently Mørk *et al.*[5] measured it at pH 2.0 and obtained a log *P* of 2.03. This certainly appears more reasonable in light of the CLOGP value of 1.77 (a Hansch–Leo value of 2.04 is calculated by Moriguchi[1]). A wide variety of log *P* values have been reported for propranolol. Currently we prefer a log *P* of 2.98, which is closer to that calculated by Moriguchi *et al.* (2.53) than the value they accepted from Rekker[2] (3.56).

With three or four serious data errors in a set of 22, the regression equation can lead to very misleading results. A recent report[6] compared the Hansch–Leo calculation (using the program CLOGP) against the measured values in the Pomona College Masterfile subset of recommended neutral $\log P_{octanol}$ values, called Starlist. Even the recommended Starlist values must contain some errors, but when there are 7250 structures studied, it can be assumed that the statistics are fairly reliable. These gave the following equation[6]:

$$\log P^* = 0.914(\pm 0.004)\text{CLOGP} + 0.184(\pm 0.010) \quad (1)$$
$$n=7250, \quad r=0.982, \quad s=0.300$$

When the two drugs without reliable neutral values are removed from the Moriguchi regression and the correct value for furosemide is used, their Eq. 5 becomes:

$$\log P = 0.927(\pm 0.08)\text{CLOGP} + 0.263(\pm 0.25) \quad (2)$$
$$n=20, \quad r=0.984, \quad s=0.29$$

The regression coefficient and standard deviation of the small set of drugs is almost identical to the larger set, which is what one should expect. Presumably if Moriguchi *et al.* were aware of Eq. 1 they would have been more critical of the measured log *P* values they employed, since the equation they derived has a standard deviation almost 2.5 times as high. With the same corrections to the measured values, the Moriguchi method produces the following equation:

$$\log P = 1.079(\pm 0.286)M + 0.113(\pm 0.743) \quad (3)$$
$$n=20, \quad r=0.882, \quad s=0.759$$

This equation is superior to that reported by the authors in two respects: it has a more favorable coefficient of the calculated log *P* (closer to 1.0) and it has a smaller intercept. However, the statistics are not quite as good as originally reported ($r=0.90$ and $s=0.764$) and are much poorer than those for CLOGP. Of greater importance is the disturbing fact that the calculations using the Moriguchi method for the smaller set of 22 (or 20) drugs yielded so much poorer statistics than their larger set of 1230 miscellaneous structures where $r=0.952$ and $s=0.411$.

We, and other serious users of the CLOGP program, often find that a discrepancy between measured and calculated values have led us to look for and find errors in the measurements. Other times when the measurements are valid, the discrepancy can readily be ascribed to fragment interactions not yet coded into the program. For instance, CLOGP does not allow for an acyclic internal H-bond of the type which may well form in atropine. If given the usual HB correction, it would almost eliminate the current deviation of +0.51. In chloramphenicol an-

alogs lacking a strong electronic substituent on the ring (nitro for the parent) CLOGP calculations are very close, but it does not allow for an electronic interaction of the nitro with the hydroxyl group on the benzyl carbon, and thus underpredicts chloramphenicol by +0.45. Keeping a few of these "manual" corrections in mind, the serious CLOGP user can obtain an average deviation below that given by regression analysis. But one would certainly not find a method useful which had an average derivation of nearly 0.9.

A few facts stand out clearly: There are many pitfalls to be avoided in measuring partition coefficients for the neutral form of ionizable solutes, and values taken from the literature must be scrutinized carefully. It is unwise to gauge the reliability of a calculation procedure with a small set of structures and obviously impossible to do so using un-reliable data.

References

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