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The Conformation-dependent Lipophilicity of Morphine Glucuronides as Calculated from their Molecular Lipophilicity Potential

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Abstract: *A whole range of conformers of morphine-6-O-glucuronide and morphine 3-O-glucuronide were examined for their theoretical log P values using the molecular lipophilicity potential method. The results substantiate the "chameleonic" behavior of morphine glucuronides to exist in water as hydrophilic, extended conformers, and in lipidic media as folded, more lipophilic conformers.*

Despite the large variety of approaches developed to predict lipophilicity, many authors have noted the lack of a highly reliable, fully computerized method for log P prediction capable of accounting for variations in lipophilicity due to topological or conformational changes in a molecule. The conclusions of a very recent paper[1] in this area prompt us to report an application of our molecular lipophilicity potential (MLP) method[2], a new tool to quantitate lipophilicity variations in the conformational space of drug molecules.

Morphine in animals and humans undergoes a variety of metabolic pathways, in particular glucuronidation of the 3-OH phenolic group and of the 6-OH alcoholic group to yield morphine-3-O-β-D-glucuronide (M3G) and morphine-6-O-β-D-glucuronide (M6G), respectively. Following oral administration of morphine to humans, the M6G and M3G plasma AUC (area-under-the-curve) exceeds that of the parent drug by large factors.[3] Interestingly, μ-opiate receptor affinities and efficacies have been reported for M6G that are comparable to that of morphine, while M3G appears to be a weak antagonist.[4-10]

When injected to rats, M6G was found to be considerably more potent as an analgesic than morphine.[11,12] More important, M6G in rats was more active as an analgesic than morphine when the two compounds were administered subcutaneously.[11] That M6G and M3G can penetrate into the brain despite their "high polarity" has been proven unambiguously.[13,14] Within current knowledge, the far from negligible brain penetration and relatively slow renal excretion of M3G and M6G are difficult to reconcile with the expected pharmacokinetic behavior of highly polar, hydrophilic conjugates. This discrepancy was resolved when we showed experimentally that the two glucuronides are far less hydrophilic than predicted.[15] To explain this unexpected behavior, conformational calculations were conducted which revealed that the two conjugates each exist as two conformers of equal energy, an extended and a folded form. The extended conformers, because they efficiently expose their polar groups, were postulated to be highly hydrophilic forms predominating in polar media such as water. In contrast, the folded conformers mask part of their polar groups, suggesting that they must have an enhanced lipophilicity and be predominant in media of low polarity such as biological membranes.[15]

The above interpretation of conformational results was limited by its purely qualitative character, and could not be supported by a comparison of polar and nonpolar surface areas due to their arbitrary definition. In the present study, we make use of the MLP method[2] to calculate the theoretical lipophilicity of different conformers of M3G and M6G and demonstrate that these compounds indeed behave as "molecular chameleons" able to adapt their lipophilicity to the solvent.[15]

Calculating logP values from the MLP

On each point of the molecular surface, the MLP technique yields a value (positive or negative) quantifying at this point the sum of the various intermolecular interactions encoded by lipophilicity. The separate sums of all non-polar and polar values on the molecular surface (ΣMLP^+ and ΣMLP^-, respectively) can be used as independent variables in a regression equation with $logP_{octanol}$ as dependent variable. This was done in the original publication with a limited set of compounds.[2] Here, we first extend this approach to 115 unionized solutes (Eq. 1):

$$\log P = 2.95 \bullet 10^{-3} (\pm 0.38 \bullet 10^{-3}) \Sigma MLP^+ + 2.12 \bullet 10^{-3} (\pm 0.28 \bullet 10^{-3}) \Sigma MLP^- - 0.21(\pm 0.35)$$

$$n = 115; \quad Q^2 = 0.92; \quad r^2 = 0.93; \quad s = 0.43; \quad F = 688 \qquad \text{(Eq. 1)}$$

where 95% confidence limits are given in parentheses, Q^2 is the cross-validated correlation coefficient,[16] and r^2 is the squared correlation coefficient. The solutes used were chemically diverse (mono- and disubstituted benzenes, protected amino acids and dipeptides) and of well-distributed lipophilicity (Figure 1). The model thus obtained is of very good statistical quality and allows a reliable back-calculation of partition coefficients from the MLP, within the explored range.

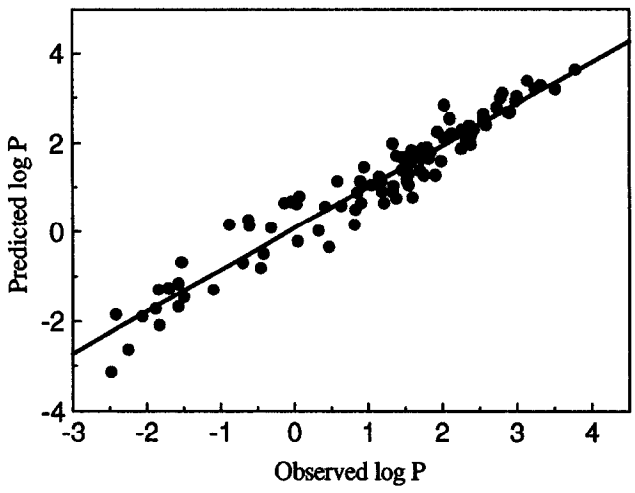

Figure 1:
Prediction of experimental log P values using Equation 1.

Conformational behavior and MLP of morphine glucuronides

The conformational hypersurface of the neutral forms of morphine, glucuronic acid, M3G and M6G was explored by high-temperature molecular dynamics.[17] The choice of neutral rather than ionized forms was dictated by the fact that the MLP technique is not optimally parametrized for ionic compounds. We thus identified 33 conformers for glucuronic acid, 24 for morphine, 45 for M3G and 49 for M6G. The MLP and theoretical logP was calculated for each conformer. For each compound, Table 1 reports the relevant values of three conformers, i.e. the minimum-energy conformer, and the two conformers (within the 10 kcal/mol range) with lowest and highest logP values.

Table 1 Conformation-dependent lipophilicity of morphine glucuronides[18]

	Relative energy a)	ΣMLP^-	ΣMLP^+	calculated logP b)
Glucuronic acid				
conformer A c)	0.0	-1877	1	-4.2
conformer B c)	9.3	-1789	2	-4.0
conformer C c)	7.1	-2010	1	-4.5
Morphine				
conformer A	0.0	-539	846	1.1
conformer B	8.4	-411	833	1.4
conformer C	3.2	-581	839	1.0
M3G				
conformer A	0.0	-1816	773	-1.8
conformer B	6.0	-1676	807	-1.4
conformer C	3.1	-1919	713	-2.2
M6G				
conformer A	0.0	-1667	821	-1.3
conformer B	2.6	-1517	800	-1.0
conformer C	7.2	-1553	652	-1.6

a) in kcal/mol (only conformers of relative energy lower than 10 kcal/mol appear in this table)

b) calculated from Eq. 1

c) Conformers A, B and C are those of minimal energy, of highest logP value, and of lowest logP value, respectively.

It appears from Table 1 that the variation in the logP values of glucuronic acid (0.5) are due exclusively to the polar part. These variations result from differences in the pattern of internal hydrogen bonds and in the accessibility of the polar groups. Similarly, the variations in the logP values of morphine (0.4) result almost exclusively from changes in polar interactions (orientation of the hydroxyl groups).

The variations in the logP values of M3G and M6G are somewhat larger (0.8 and 0.6, respectively), and interestingly result from significant changes in both polar and hydrophobic interactions. In fact, these changes may even partly cancel each other, as seen with M6G. Various intramolecular effects are believed to account for these changes, e.g. variations in the internal hydrogen bonds of the glucuronyl moiety, and mainly folding of the molecule governed by an H-bond between the carboxyl group of the glucuronyl moiety and the free hydroxyl group of the morphine moiety.

That folding of morphine glucuronides influences their lipophilicity is best seen in Figure 2, where the calculated logP values of M3G are plotted against the distance between the 6-hydroxy group of morphine and the carboxyl group of the glucuronic moiety. Three clusters of conformers (energy < 10 kcal/mol) emerge, namely a) folded, internally bonded conformers of higher logP values, b) extended conformers of lower logP values, and c) intermediates cases. Variations within each cluster are due to the flexibility of the glucuronyl moiety.

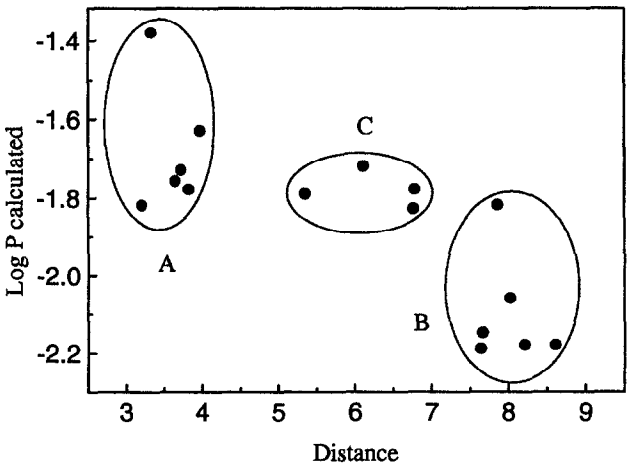

Figure 2:
Variation of log P as a function of folding in M3G, as quantified by the distance between the 6-OH group of morphine and the COOH group of glucuronic acid.

The manner by which folding affects lipophilicity can also be seen in figure 3, which compares the 3D MLP of a folded and an extended conformer of M6G. A comparison of the regions of equipotential demonstrate how folding decreases the polar (red) intermolecular interactions and increases the non-polar (blue) interactions, resulting in a global increase in calculated logP. The masking of polar groups by internal H-bonds is the main factor accounting for these changes.

We noted above that the calculations reported here were performed for the compounds in their neutral form. Conformational calculations of the glucuronides in their ionized form (particularly the carboxylate form, results not shown) indicate an internal -COO^-•••HO- bond stronger than a -COOH•••HO- bond. Preliminary MLP calculations of these anions indicate a larger difference in the calculated log P values of the more polar and the more lipophilic conformers of M3G (1.9) and M6G (1.4). Work is in progress to validate the application of our MLP approach to ionized species.

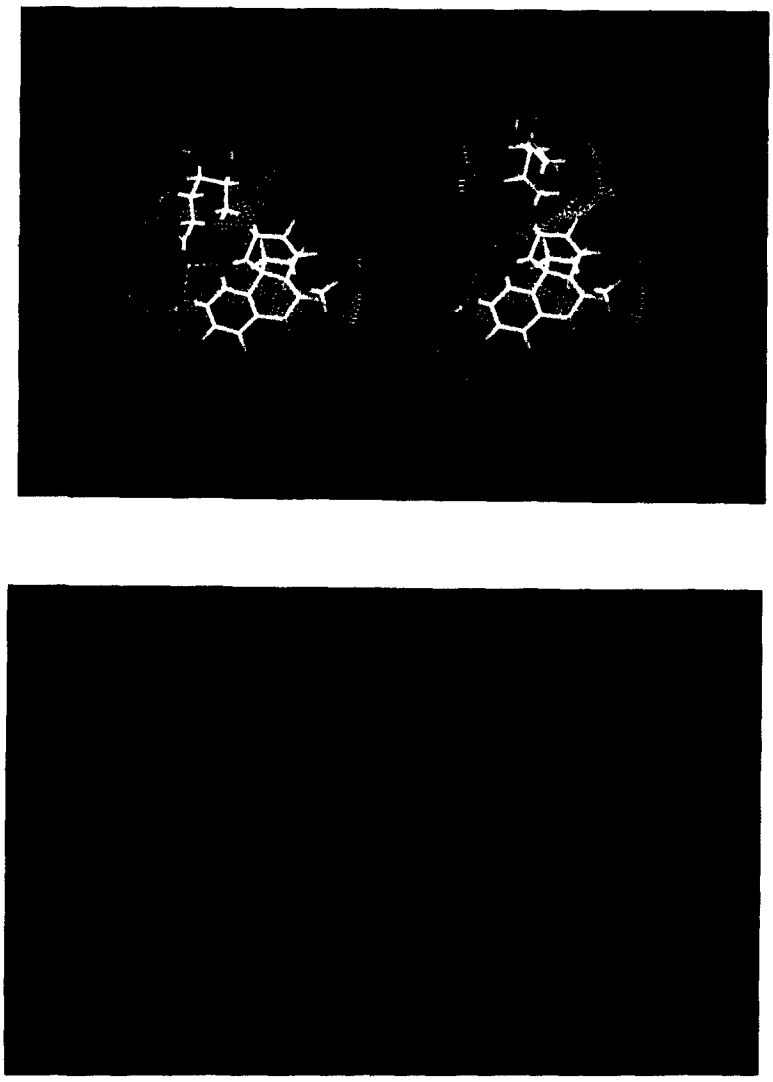

Figure 3:

Top: MLP representation on the accessible surface area in a folded (left) and an extended (right) conformer of M6G. The blue dots represent the non-polar part and the red the polar part.

Bottom: MLP isopotential surface for the non-polar part (blue) and the polar part (red) of a folded (left) and an extended (right) conformer of M6G.

Conclusion

The calculations reported here document that the glucuronides of morphine exist as folded and extended conformers differing in their partition properties. Indeed, the folded conformers, when compared to the extended conformers, have a reduced propensity to hydration but offer more surface for hydrophobic interactions with apolar media. This substanciates the "chameleonic" behavior[15] of morphine glucuronides to be hydrophilic in water and less polar in lipidic media such as membranes.

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18. The molecular dynamics calculations described here were performed with the SYBYL software (Tripos Associates Inc., Saint Louis, Missouri) version 6.0 or 6.0.1 running on Silicon Graphics workstations (Iris 4D 35, Power Series 4D 320 or Indigo R4000). The MLP calculations were done with a Fortran program fully interfaced with the SYBYL package.

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