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Lipophilicity of morphine microspecies and their contribution to the lipophilicity profile

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ABSTRACT

The complete set of experimental microscopic partition coefficients of morphine was determined for the first time for any compound. The acid–base microequilibria were characterized by combining pH-potentiometry and deductive methods using auxiliary compounds of reduced complexity. The results show around three times as many non-charged than zwitterionic microspecies in aqueous solution. Partition of the individual microspecies was mimicked by model compounds of the closest possible similarity, then correction factors were determined and introduced. Thus the intrinsic partition coefficients of all the microspecies could be quantitated, including the non-charged and the zwitterionic ones. The non-charged microspecies is 1070 times as lipophilic as its zwitterionic protonation isomer. Their contribution ratio to the overall lipophilicity is 3090. The lipophilicity profile of morphine was expressed, calculated and depicted in terms of species-specific lipophilicities over the entire pH range.

1. Introduction

Morphine, the best known opiate alkaloid, has been used to treat severe acute and chronic pain for centuries. Morphine binds to specific opioid receptors in the central nervous system and in other body compartments, like the gastrointestinal tract. The three principal classes of opioid receptors, μ, κ, δ (mu, kappa, delta), are all G-protein coupled receptors acting on GABAergic neurotransmission. Morphine interacts predominantly with the μ-opioid receptor. Activation of the μ-opioid receptors is associated with analgesia, sedation, euphoria, physical dependence and respiratory depression (Willette, 1998).

Morphine is modestly absorbed from the gastrointestinal tract, and its significant first-pass metabolism in the liver further diminishes its bioavailability. It is usually administered intravenously, though if adjustment is made for variability of first-pass metabolism and clearance, adequate relief of pain can be achieved with oral administration as well. Compared with more lipid-soluble opiods, morphine crosses the blood–brain barrier at a considerably lower rate (Yaksh and Wallace, 2010).

The fate of morphine and most other drugs in the body is significantly influenced by two physico-chemical parameters: acid–base properties and lipophilicity.

Morphine contains one acidic and one basic site, thus it exists in solutions in four microscopic protonation forms (microspecies), including the cationic, zwitterionic, non-charged, and anionic ones (Bjerrum, 1923; Noszál, 1990). Determination of the concentration of such species, and the concomitant acid–base microscopic equilibrium constants in aqueous solutions became a well-established principle in terms of methodology and interpretation for the characterization of small bio- and drug molecules (Noszál, 1990).

Lipophilicity is a molecular property of immense importance in pharmacy, bio- and medicinal chemistry. The ability of drugs to diffuse passively through biological membranes is influenced to a large extent by their lipophilicity (Fujita, 1990). The pH-partition hypothesis postulates that absorption of ionizable drugs mainly takes place in compartment(s) where the local pH ensures the maximum concentration of the non-charged form relative to the ionized form(s) (Avdeef, 2002). In addition, lipophilicity is a tool to unravel biologically relevant intramolecular interactions and intermolecular forces of recognition (Testa et al., 1996; Liu et al., 2011).

log$P$ is the logarithm of the partition coefficient, the concentration ratio of a solute present in a single electrical state and in equilibrium between two immiscible solvents. The organic solvent of choice is usually octanol. When more than one electrical species are present in solution, the observed ratio of concentrations is the distribution coefficient (D), which takes into account the intrinsic lipophilicity of the various electrical species present (p_i), and their mole fractions in the aqueous phase (x_i)

$$D = \sum x_i p_i. \quad (1)$$

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The lipophilicity profile (the variation of log$D$ as a function of the aqueous pH) of a drug is a *sine qua non* condition to understand its pharmacokinetic, toxicokinetic and even pharmacodynamic properties (Pagliara et al., 1997).

For a long time the lipophilicity of ionizable drugs and solutes has been underrepresented in the literature, due mainly to the lack of reliable methods to determine the partition coefficients of the ionic forms. This is especially true for ionization/protonation isomers, such as the zwitterionic and non-charged forms of amphoteric compounds.

The necessity of microspecies-specific partition coefficient, by analogy with the microscopic acid–base constants, has long been evident (Taylor and Cruickshank, 1985; Takács-Novák et al., 1992). Considerations, however, were usually restricted to some of the partitioning microspecies, due to the apparently unsurmountable difficulties in determining all the microscopic partition coefficients. Abraham et al. (1997) developed an equation to predict the blood–brain distribution coefficient of a drug based on the microscopic partition coefficient of the non-charged species, its hydrogen-bond acidity and its hydrogen-bond basicity. These models assumed, however, that only the non-charged species partitions into the organic phase, although the contribution of charged species to the distribution coefficient may not be insignificant in a number of cases (Irwin et al., 1988; Pagliara et al., 1997; Takács-Novák and Szász, 1999; Mandić and Gabelica, 2006).

In order to gain species-specific insight into the partition microequilibria of amphoteric drugs, we recently elaborated a method in which the partition properties of the parent compound and its synthetic derivatives, closely mimicking each microspecies, were studied and exemplified on niflumic acid, a highly lipophilic non-steroidal anti-inflammatory drug. We reported, for the first time for any compound, experimental microscopic partition coefficients for the two protonation isomers (Mazák et al., 2011).

Concerning the lipophilicity character of morphine and niflumic acid, two fundamental differences had been foreseen:

(1) The predominant neutral species in aqueous niflumic acid solutions is the zwitterionic one, contributing thus significantly to the overall partition, even though its inherent lipophilicity is less than that of its non-charged counterpart. For morphine, the zwitterionic species is doubly disadvantageous in the process of partition into the organic phase: it is the minor neutral species, and its species-specific lipophilicity is expected to fall way below that of the non-charged one. Determination of the lipophilicity of the zwitterionic morphine microspecies – to the best of our knowledge – has not therefore been experimentally attempted before. But our method can be used to characterize the lipophilicity of the zwitterion, which is inferior both in concentration and partitioning propensity.
(2) Concerning methodology, morphine is much less lipophilic than niflumic acid, which needs extreme experimental conditions in most partitioning investigations.

Here we report the acid–base and partition microequilibrium analyses of morphine, visualizing – for the first time for any compound – the contribution of all the four microspecies to the lipophilicity profile of the molecule.

2. Materials and methods

2.1. Materials

Morphine and codeine was of pharmacopoeial grade. Morphine methylchloride (*N*-methylmorphine chloride) was provided by ICN Alkaloida Hungary Co. Ltd. (Tiszavasvári, Hungary). All other reagents were of analytical grade (Reanal). All solutions were prepared from freshly boiled distilled water.

2.2. Determination of protonation constants by pH-potentiometric titrations

A 716 DMS Titrino automatic titrator (Metrohm) with a Metrohm 6.0204.100 combined pH glass electrode was used for the potentiometric titrations, which were automatically conducted under PC control. The electrode was calibrated by aqueous NBS standard buffer solutions. Constant temperature (25 ± 0.1 °C) was provided by a thermostated double-walled glass cell. Difference titrations were carried out in the absence (blank) and presence of ligands. First 1.5 ml of 0.1 M $HClO_4$ solutions were titrated with 0.1 M NaOH. Constant ionic strength of 0.15 M was provided by the presence of $NaClO_4$. Then a ligand was added to the same volume of $HClO_4$ solution and was subsequently titrated with NaOH. The initial concentration of the ligands varied between 1 and 5 mM in the titrations. Non-linear parameter fitting with Origin 8 provided the protonation constants from the volume differences.

2.3. Partition coefficient measurements by the stir-flask method

The distribution coefficients were calculated from the absorbance of the molecules in the aqueous phase before and after partitioning at several octanol/water phase ratios as previously reported (Mazák et al., 2003). For the pH control buffers composed of phosphate and serine; and standardized HCl and NaOH solutions were used with an ionic strength of 0.15 M.

3. Results

3.1. Acid–base equilibria

Morphine in its most basic form bears one negative charge, the addition of one proton will convert this microspecies into a zwitterionic or a non-charged microspecies. The subsequent addition of yet another proton will result in a single, cationic microspecies. The protonation scheme of morphine is depicted in Fig. 1.

Relationships between micro- and macroscopic protonation (proton association) constants have been known since Bjerrum's pioneer work (Bjerrum, 1923), and can be written for morphine as follows:

$$K_1 = k^{N} + k^{O}, \tag{2}$$

$$K_1K_2 = k^{N}k^{O}_{N} = k^{O}k^{N}_{O}, \tag{3}$$

where K_1 and K_2 are the stepwise macroconstants, k^{N}, k^{O}, k^{O}_{N}, k^{N}_{O} are the microconstants, indices O and N designate phenolate and tertiary amino site oxygen and nitrogen atoms, respectively. Superscripts of the microscopic protonation constants indicate the group protonating in the given microequilibrium protonation process, whereas the subscript (if any) stands for the group holding proton during the process.

A review about the physicochemical properties of morphine has recently been published, where we tabulated all the literature data on its acid–base properties and lipophilicity (Mazák et al., 2009a).

Our aqueous protonation macroconstants of morphine, codeine and *N*-methylmorphine are in good agreement with the literature data as reported in Table 1.

There are two fundamental approaches for the determination of microconstants, namely deductive methods and combined spectroscopic-pH-metric methods (Noszál, 1990). The microconstants of morphine have previously been determined by the latter method (Takács-Novák et al., 1994; Schill and Gustavii, 1964) as

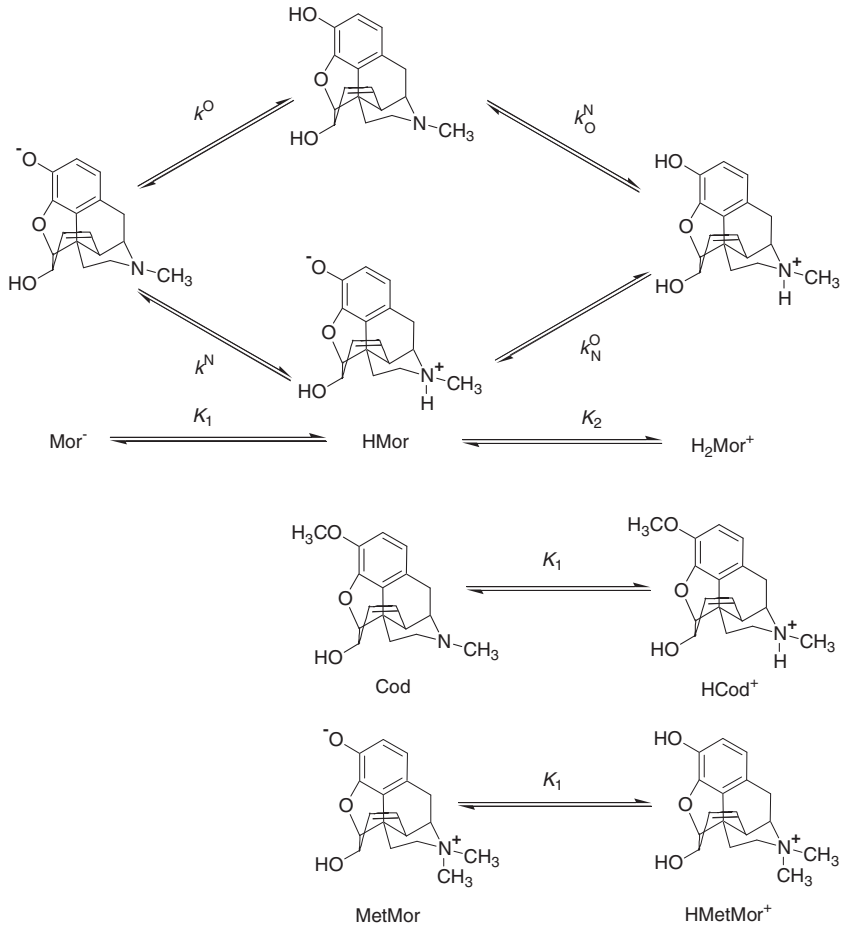

Fig. 1. The protonation equilibria of morphine, codeine and *N*-methylmorphine in terms of macroscopic (K_1, K_2) and microscopic (k^N, k^O, k^O_N, k^N_O) protonation constants.

Table 1
Protonation macro- and microconstants of morphine, codeine and *N*-methylmorphine in aqueous medium. Comparison of our results with literature data. See text for the definition of $\Delta\log k$ and $\log k_z$. The standard deviation of our measurements is in parentheses.

	This work	Takács-Novák and Avdeef (1996)	Avdeef et al. (1996)	Takács-Novák et al. (1994)	Schill and Gustavii (1964)
Ionic strength	0.15 M	0.10 M	0.15 M	0.20 M	0.06 M
Morphine					
$\log K_1$	9.49 (0.03)	9.34	9.26	9.54	9.51
$\log K_2$	8.16 (0.05)	8.18	8.18	8.34	8.31
$\log k^O$	9.36			9.18	9.37
$\log k^N$	8.90			9.29	8.95
$\log k^O_N$	8.75			8.59	8.87
$\log k^N_O$	8.29			8.70	8.45
$\Delta\log k$	0.61			0.59	0.50
$\log k_z$	−0.46			0.11	−0.42
Codeine					
$\log K_1$	8.22 (0.04)	8.25	8.22		8.26
N-Methylmorphine					
$\log K_1$	8.75 (0.03)				8.83

reported in Table 1. Both authors assumed that UV spectroscopy monitors selectively the protonation of the phenolate group. Such assumption is strictly true for cases when isosbestic points occur, e.g., tyrosine. However, the pH-dependent UV spectrum of morphine shows no isosbestic points, making the above assumption arguable. For this reason we chose the deductive method for the determination of microconstants, which requires an appropriate model compound to mimic the minor species (Noszál, 1990; Mazák et al., 1999, 2009b). We used two derivatives of morphine, namely its methyl ether, codeine and *N*-methylmorphine. Both of these compounds contain one functional group only, their protonation scheme is depicted in Fig. 1. This method assumes that the effect of the modified group on the basicity of other groups is equivalent with the protonated form of the original group. The minor protonation pathway proved to be in both cases the one containing the zwitterionic microspecies as opposed to the route containing the non-charged one. The determination of a microconstant related to the minor protonation pathway is more valuable,

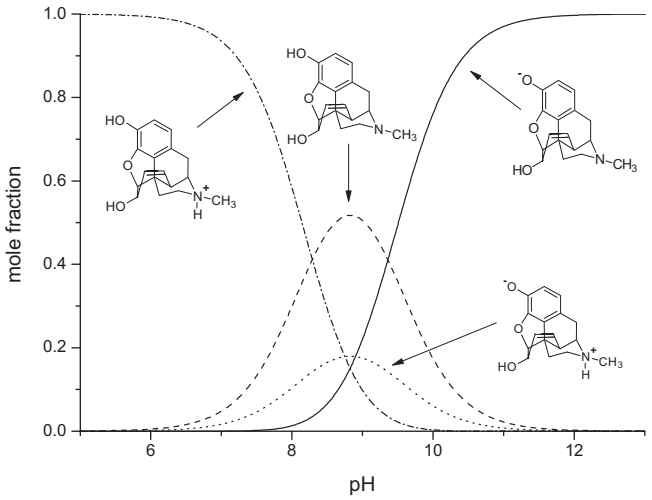

Fig. 2. Distribution of morphine microspecies in aqueous solution.

since conditions of the accurate calculation of the other microconstants are then better (Noszál, 1990). Thus in our case *N*-methylmorphine macroconstants were used as the k_N^O microconstants of morphine.

The microscopic constants determined for this molecule can be seen in Table 1, that also contains the interactivity parameter ($\Delta\log k$, the degree by which protonation at one basic site decreases the basicity of the other site); and the pH-independent $\log k_z$ parameter ($k_z = k^N/k^O$).

To validate our deductive method, we compared the calculated $\log k_O^N$ to the $\log K_1$ of codeine, the difference is only 0.07 log units that shows good agreement.

The determination of microconstants allows the construction of a microspecies distribution diagram (Fig. 2).

3.2. Lipophilicity

Eq. (1) for morphine gets the form as follows:

$$D_{(pH)} = x_{Ani}p^{Ani} + x_{Non}p^{Non} + x_{Zwi}p^{Zwi} + x_{Cat}p^{Cat} \quad (4)$$

where x_i stands for the aqueous mole fractions of the anionic (Ani), non-charged (Non), zwitterionic (Zwi) and cationic (Cat) species.

The aqueous mole fractions include protonation microconstants and acidity values, expressing thus the pH-dependence of the *D* distribution coefficient. For example,

$$x_{Ani} = \frac{1}{1 + (k^N + k^O)[H^+] + k^N k_N^O [H^+]^2} \quad (5)$$

$$x_{Zwi} = \frac{k^N[H^+]}{1 + (k^N + k^O)[H^+] + k^N k_N^O [H^+]^2} \quad (6)$$

The knowledge of each microscopic partition coefficient is especially important for a thorough understanding of the pharmacokinetic and pharmacodynamic properties of drugs acting in the central nervous system, a particularly lipophilic medium. Furthermore, the p^{Non}/p^{Zwi} ratio of the non-charged vs. zwitterionic partition coefficients is an important structural parameter to gain insight into intramolecular effects (Pagliara et al., 1997; Caron et al., 1999).

In order to obtain species-specific $\log p$ values for all the four microspecies, we applied our recently developed method to determine the microscopic partition coefficients (Mazák et al., 2011). We used derivatives of morphine to mimic the two protonation isomers, and finally determined and introduced correction factors to minimize effects of chemical derivatization. For the zwitterionic microspecies the *N*-methyl derivative of morphine was selected as the best choice, while for the non-charged microspecies the methyl ether, codeine, was chosen. The effect of methylation in both model compounds was taken into account by comparing the lipophilicity of the three compounds in their uniformly cationic ionization state, which overwhelmingly exists in sufficiently acidic solutions.

Table 2
$\log D$ values of the investigated compounds in the octanol/water system at pH 0.82 and 13.18 (I = 0.15 M). The standard deviation of the measurements is in parentheses.

Compound	$\log D$ at pH 0.82	$\log D$ at pH 13.18
Morphine	−2.11 (0.10)	−2.01 (0.03)
Codeine	−1.99 (0.04)	1.20 (0.02)
N-Methylmorphine Cl	−2.41 (0.10)	−2.40 (0.12)

We chose a standardized HCl solution of 0.15 M, as the majority of $\log K$ and $\log P$ values are determined at this physiological ionic strength. The results are listed in Table 2, including results obtained with a standardized NaOH solution of 0.15 M.

The determination of $\log D$ values below −2 involves experimental difficulties, namely the octanol/water phase ratio must be very small in the stir-flask experiment. The precision of such data is therefore inevitably poorer than that of routinely measurable $\log D$ values, as reflected by the higher standard deviations. Nevertheless, with the stir-flask method we were able to obtain reliable $\log D$ values. These values would have fallen outside the range of the potentiometric dual-phase titration method (Comer and Tam, 2001).

The microscopic partition coefficient of the non-charged form of morphine can be calculated from *D* values measured around its isoelectric point, since this species is the predominant one at this pH and it is of the obviously highest lipophilicity, thus the contribution of the second term ($x_{Non}\ p^{Non}$) to *D* in Eq. (4) predominates over all other terms. Measurements at several pH values around the isoelectric gave a $\log p^{Non}$ value of 0.93 (0.03).

Due to the complete predominance of the cation at low pH, the reported $\log D$ values in Table 2 characterize the lipophilicity of the cationic species at the physiological ionic strength. For the same reason, the $\log D$ values in the highly alkaline solution characterize the lipophilicity of the anionic form of morphine, the non-charged one of codeine and the zwitterionic species of *N*-methylmorphine. Based on our data in Table 2, the lipophilicity of the cationic form of morphine is lower than that of its methyl ether, but higher than that of its *N*-methyl derivative; the differences are −0.12 and +0.30 in $\log D$ units, respectively. These differences are valid only for the physiological ionic strength, as the lipophilicity of ionic species depends on the type and concentration of the background electrolyte (Johnson and Westall, 1990; Escher and Schwarzenbach, 1996; Takács-Novák and Szász, 1999; Reymond et al., 2001; Bouchard et al., 2001).

It is plausible that the methylation-derived differences in the lipophilicity of the cationic forms will be very close to the differences between the non-charged forms of morphine and codeine; and between the zwitterionic forms of morphine and *N*-methylmorphine, respectively, at the physiological ionic strength. These differences can serve as appropriate correction factors.

Using the experimentally determined partition coefficients of the model compounds, and taking into account the correction factors, we calculated the logarithm of the microscopic partition coefficients ($\log p$) of the protonation isomers of morphine. For the non-charged form $\log p^{Non}$ is 1.08 = 1.20 ($\log P$ of the non-charged form of codeine) −0.12 (correction factor); whereas for the zwitterionic form $\log p^{Zwi}$ can be calculated as −2.40 ($\log P$ of the *N*-methyl derivative) +0.30 (correction factor) = −2.10.

In order to determine p^{Non}, Eq. (4) had already provided a way for calculation. Since non-charged form is certainly the major

Table 3
The logarithm of microscopic partition coefficients of morphine microspecies in the octanol/water system at 0.15 M ionic strength.

	Our results	Avdeef et al. (1996)
Non-charged	0.93	0.89
Zwitterionic	−2.10	–
Cationic	−2.11	<−2
Anionic	−2.01	<−2

contributor to the overall partition around the isoelectric pH, its microscopic partition coefficient could be calculated in a well-conditioned manner from experimental $D_{(pH)}$ and x_N values. The value obtained and corrected from codeine can serve comparative purposes only. Comparing the two differently obtained $\log p^{Non}$ values for the non-charged species, namely 1.08 (obtained by using model compounds and correction factors) and 0.93 (obtained by calculating from experimental $\log D$ values), there is a 0.15 log unit difference between them, arising partly from the experimental difficulties. The value of 0.93 is certainly the more reliable one, as its determination needed fewer assumptions, while the other one is valuable for verifying purposes. In general, our method of using model compounds and correction factors is still the best experimental determination method for the lipophilicity of microspecies whose concentration and inherent lipophilicity are too low to significantly contribute to the overall partition coefficient of a molecule.

Table 3 shows all the experimentally determined microscopic partition coefficients of morphine.

4. Discussion

4.1. Acid–base equilibria

The microconstants of different sources in Table 1 show that the basicity of the amino and phenolate site is within an order of magnitude. There are approximately three times as many non-charged microspecies than zwitterionic ones, irrespective of the pH of the solution. The interactivity parameter is relatively invariant, because it is an inter-moiety, intramolecular parameter, largely independent of the solution circumstances, and also, it is perturbed to a lesser extent by the protonation and the concomitant electron withdrawing effects of other groups than the microconstants themselves.

Fig. 2 shows that in the pH range 8.30–9.35 morphine mainly exists with mole fraction >0.41 in the non-charged form. In more acidic pH values, the cationic form predominates, its mole percent in the blood plasma (pH 7.40) reaches 85.0%. At the isoelectric point (pH 8.83) the concentration of the zwitterionic form reaches its maximum, amounting to 18%.

These mole fraction values are also indispensable in constructing lipophilicity profiles as discussed in the next chapter.

4.2. Lipophilicity

The bulk pH-distribution profile of morphine and many of its derivatives has already been investigated and microscopic partition coefficients for some of the species have also been reported (Avdeef et al., 1996) that can be seen in Table 3 for comparison. The approximately parabolic pH-distribution profile of morphine in the octanol/water system showed a distribution coefficient (D) maximum at the isoelectric point. In that study potentiometric titrations in the presence of octanol at 0.15 M ionic strength resulted in a $\log P$ of 0.89 for the neutral macrospecies, a composite value, containing the lipophilicity contributions of both the non-charged and the zwitterionic microspecies. The $\log P$ of both the anion and the cation was below the limiting value of −2, while that of the non-charged form of codeine was 1.19. Table 3 shows that our experimentally determined microscopic partition coefficients of morphine are in excellent agreement with the reported results of Avdeef et al. (1996).

Our microscopic partition coefficients in Table 3 allow – for the first time for any compound – to calculate and depict the contribution of each microspecies to the distribution coefficient of the molecule at any pH value (Fig. 3.). The broad black line is the overall lipophilicity profile of the molecule, the sum of the contributions of its four microspecies.

The figure shows that in the pH range 5.26–12.28 the contribution of the non-charged form is dominant, but at lower or higher pH values the monoionic forms prevail the distribution coefficient. The pH-independent contribution ratio of the non-charged to the zwitterionic form is visualized by the parallel lines on the graph.

The log (p^{Non}/p^{Zwi}) value is 3.03 in this study, thus the non-charged microspecies is around 1070 times as lipophilic as its zwitterionic counterpart. Using the mole fractions and microscopic partition coefficients of the non-charged and zwitterionic species, their pH-independent contribution ratio to the distribution coefficient can also be quantified. This

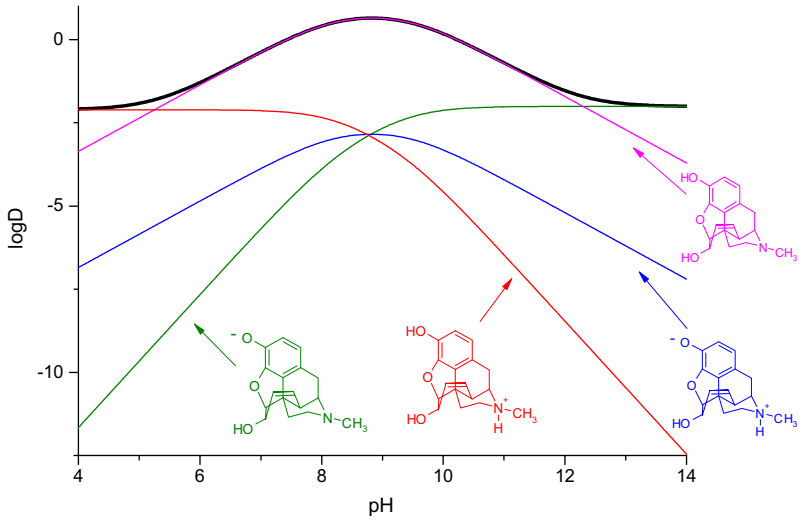

Fig. 3. Contribution of the four microspecies of morphine to the lipophilicity profile (with broad line) of the molecule.

$(x_{Non}\, p^{Non})/(x_{Zwi}\, p^{Zwi})$ value is 3090, which shows that for morphine the contribution of the zwitterionic microspecies is indeed negligible in membrane-penetration and other lipophilicity-related processes.

Thus for morphine the assumptions made by Abraham et al. (1997) to characterize the blood–brain distribution are valid, as around the pH of the blood no species apart from the non-charged one contributes significantly to the distribution coefficient.

Note however, that amphoteric molecules of zwitterionic predominance can take part in partitioning processes in a shared manner, when all the microspecies significantly contribute to the overall partition at the appropriate pH, as niflumic acid exemplified it (Mazák et al., 2011).

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