Log P as a tool in intramolecular hydrogen bond considerations

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Abstract

Intramolecular hydrogen bonding (IMHB) considerations are gaining relevance in drug discovery and a molecular descriptor which can predict very early the capacity of a compound to form IMHB is needed to speed up the optimization process of drug candidates.

Although log P_{oct} is largely used for optimization purposes, in this paper we firstly use the Block Relevance (BR) analysis to theoretically show how log P_{oct} is not a convenient choice to assess IMHB properties of candidates. Then we discuss the limits of log P_{oct} and introduce Δlog $P_{oct\text{-}tol}$, i.e. the difference between log P_{oct} and log P_{tol} (the logarithm of the partition coefficient in the toluene/water system). Finally, we provided some examples also including bRo5 protease inhibitors, to clarify how to interpret Δlog $P_{oct\text{-}tol}$ values.

a major impact of the HB-related blocks (both the red and the blue blocks are larger) but not a significative decrease of the Size (green block) which remains the most important block.

To limit the impact of Size, a difference between log Ps is expected to provide good results and in fact $\Delta\log P_{oct\text{-}tol}$ (i.e. the difference between log P_{oct} and log P_{tol}) is a clean descriptor of exposed HBD properties [9]. BR analysis supports this expectancy (Fig. 2C) showing that $\Delta\log P_{oct\text{-}tol}$ is mostly influenced by HBD solutes' property (red block, positive sign) and it is poorly influenced by steric descriptors (green block, negative sign) [14]. The presence of IMHBs thus produces low $\Delta\log P_{oct\text{-}tol}$ values.

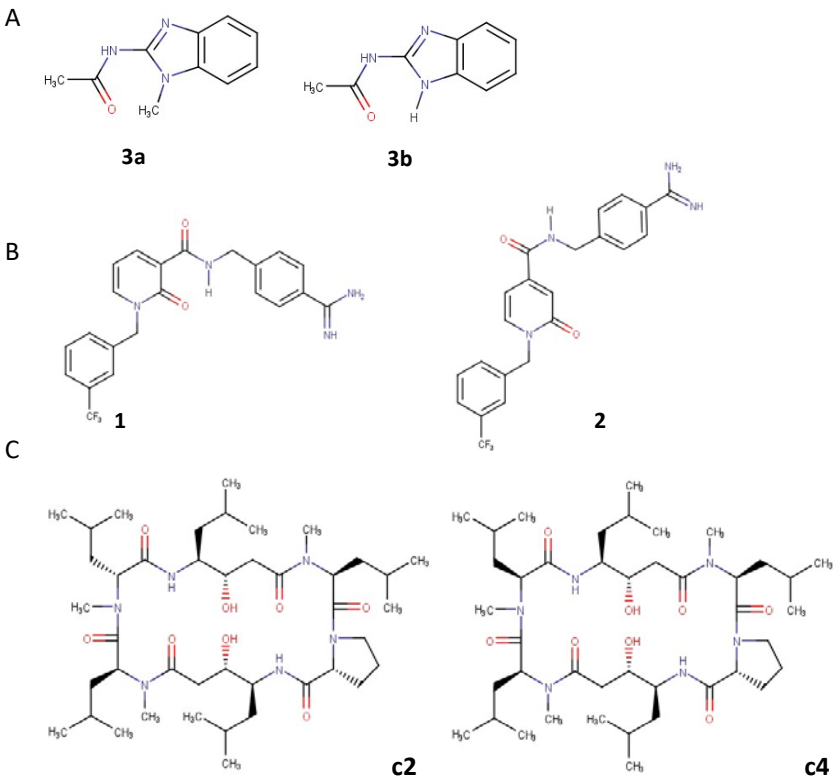
Case studies

As discussed above, the major impact of Size prevents log P_{oct} values from providing clean information about the propensity of compounds to form IMHB and a trick to overpass this issue is pair analysis. This consists in comparing a sample with a substructure prone to IMHB formation along with a control compound with similar structure (and thus Size) but incapable of forming that bond. Two examples are discussed below.

In the first example, we pay our attention on the couple of compounds **3a** and **3b** (Figure 3A) reported in the literature by Kuhn and coworkers [15]. **3b** shows a substructure prone to IMHB formation whereas **3a** (the control) is a compound incapable of forming that bond since a hydrogen atom is substituted by a more lipophilic methyl group. Crystallographic data supported the presence of an IMHB in **3b**. Despite the presence of the N-methyl substituent, log P_{oct} of **3a** (0.68) is lower than log P_{oct} of **3b** (1.39). In **3b** the presence of an IMHB reduces the polarity of the amide and the imidazole N-H and this is revealed by the increase in experimental log P_{oct}. In this case log P_{oct} is in line with NMR data and supports the presence of the IMHB.

In the second example, we focus on compounds **1** (the sample) and **2** (the control). Their chemical structures are in Fig. 3B [16]. EPSA, a supercritical fluid chromatography method specifically developed for the detection of IMHB [17], showed that **1** forms an IMHB. The lipophilicity in octanol/water was described by ElogD, a widely known and validated chromatographic surrogate of log D_{oct} [18]. ElogD is 0.9 for **1** and 0.8 for **2**. These data suggest that two regioisomers **1** and **2** show the same lipophilicity in the octanol/water system and thus this evidence does not support the presence/absence of the IMHB experimentally revealed by another experimental approach.

Figure 3. Compounds taken from the literature to discuss the limits of using log P_{oct} to describe the propensity of compounds to form IMHBs.



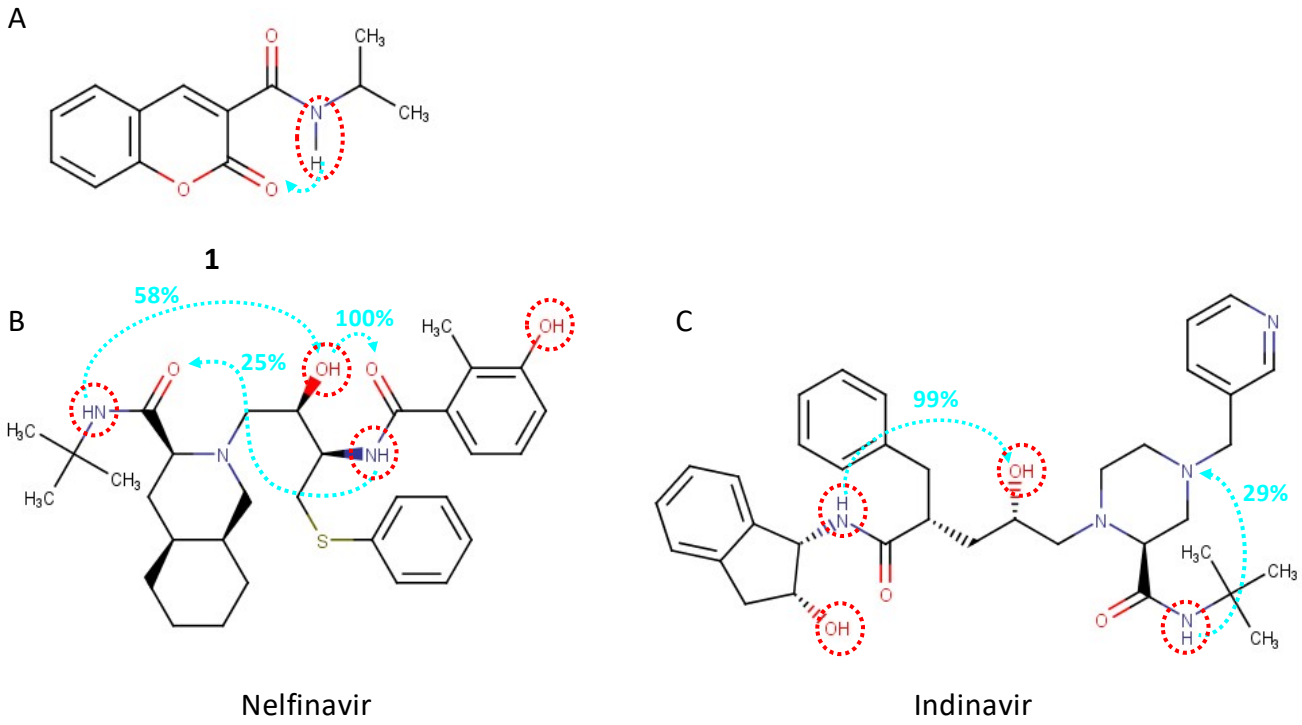
Due to the laboriousness of the experimental measurements, log P_{oct} values are often assessed through calculators. Furthermore, this option is mandatory in very early drug discovery when dealing with virtual structures. A plethora of both commercial and free tools can do that [19]. However, one should be aware that most log P_{oct} calculators are 2D tools and thus cannot be used for investigating IMHB formation which is conformation-dependent. An example is provided by Bockus and coworkers who synthetized a series of cyclic hexapeptide diastereomers containing γ-amino acids and determined lipophilicity and permeability properties [20]. Two compounds **c2** and **c4** are in Fig. 3C and showed identical calculated log P value, 4.60 and 2.48 respectively when MoKa (https://www.moldiscovery.com/) and Marvin Suite (https://chemaxon.com/products/marvin) are used, but their experimental ElogD differs by more than one logarithmic unity (5.7 and 6.9). This difference could be ascribed to different IMHB networks as highlighted by NMR studies.

Overall, examples in Fig. 3 support BR analysis results and show that log P_{oct} is not the most effective tool to predict the capacity of compounds to form IMHBs since log P_{oct} can reveal the presence of some but not all IMHBs. Therefore, its application in drug discovery should be supported by additional descriptors.

As discussed above, BR analysis designates $\Delta\log P_{oct\text{-}tol}$ as a pure descriptor of HBD properties. Therefore, if $\Delta\log P_{oct\text{-}tol}$ can be experimentally obtained (solubility issues can limit the determination of $\log P_{tol}$), it can be used to predict the propensity of compounds to form IMHBs. Some examples are discussed below.

When a compound has a single HBD group (and at least one HBA), the application of $\Delta\log P_{oct\text{-}tol}$ is straightforward. If $\Delta\log P_{oct\text{-}tol}$ is close to 0 then the compound has high propensity to form IMHBs since this means that the contribution of the red block (i.e. HBD properties) is neglected. This was recently shown by some of us using **1** (Figure 4A, $\Delta\log P_{oct\text{-}tol}$ = 0.10) as an example [9].

*Figure 4. Chemical structures of compounds discussed in the text to highlight how to interpret $\Delta\log P_{oct\text{-}tol}$ values A) **1** ($\Delta\log P_{oct\text{-}tol}$ = 0.10,* [9]*) 2) B) nelfinavir ($\Delta\log P_{oct\text{-}tol}$ = 0.53) and C) indinavir ($\Delta\log P_{oct\text{-}tol}$ = 1.99). Red dotted circles highlight HBD moieties. Cyan dotted lines show the most probable IMHBs in the molecule. In **1** only one IMHB is possible whereas for indinavir and nelfinavir the probability of formation of different IMHBs is reported (see text for details).*



The interpretation of $\Delta\log P_{oct\text{-}tol}$ is more complex when more HBD groups are present in the chemical structure. Nelfinavir (Fig. 4B) is a protease inhibitor which shows a molecular property profile that is generally considered to be disadvantageous for the membrane permeability and drug absorption [21]. It is therefore important to

experimentally verify whether nelfinavir have propensity to form IMHBs which could modulate its ADME behavior.

Using a SiriusT3 instrument (www.sirius-analytical.com) to perform standard potentiometric titrations, we obtained for nelfinavir a value of $\Delta\log P_{oct\text{-}tol}$ = 0.53 (pK_as= 5.96, 11.97, $\log P_{oct}$ = 4.02, $\log P_{tol}$ = 3.49) which suggests that nelfinavir has a high capacity of forming IMHBs (considering the experimental error in the measure of partition coefficients, a value of $\Delta\log P_{oct\text{-}tol}$ close to 0.5 could be regarded as null). Since nelfinavir has 4 HBD groups, conformational analysis is expected to provide further information about the effective involvement of the different HBD moieties in the formation of IMHBs. The conformational sampling was carried out using standard conformational sampling tools, generally available in most molecular modeling packages. A low dielectric constant (ε=2.02) was used to mimic the apolar environment provided by toluene. The percentage of IMHB formed by each HBD group was evaluated weighing the influence of each conformation assuming a Boltzmann-like distribution of the conformers population. Such a percentage could be considered a rough estimation of the effective participation of HBD groups to an IMHB. Fig. 4B shows that for nelfinavir a hydroxyl group is always involved in the formation of an IMHB both as donor (100%) and acceptor group. Moreover, both the amide moieties participate to IMHB formation. Overall, all HBD groups of nelfinavir are significantly involved in the formation of IMHBs and justify a $\Delta\log P_{oct\text{-}tol}$ value close to 0.

Generally speaking, in the presence of more HBD groups, the experimental $\Delta\log P_{oct\text{-}tol}$ is not often equal or near to 0 and it is not trivial to establish a net threshold that discriminates when IMHBs are present or not. For example, indinavir (Fig. 4C) is another antiviral bearing four HBD groups. For indinavir, we measured $\Delta\log P_{oct\text{-}tol}$ = 1.99 (pK_as = 3.87 and 5.68, $\log P_{oct}$ = 2.85, $\log P_{tol}$ = 0.86). The significative difference in $\Delta\log P_{oct\text{-}tol}$ between indinavir and nelfinavir (which bears the same number and types of HBD groups) suggests that nelfinavir has a major capacity of forming IMHBs than indinavir. To verify whether indinavir forms IMHBs or not, conformational analysis was performed and showed that in indinavir (Fig. 4C), only one of the four HBD groups present in the molecule is involved in the formation of an IMHB (the amide moiety) as a donor group, whereas a hydroxyl group is involved in IMHB as an acceptor group (HBA). This example reveals that a value of $\Delta\log P_{oct\text{-}tol}$ about 2 in the presence of more HBD groups does not permit to exclude the formation of IMHBs and other techniques, experimental (e.g. NMR) or theoretical (e.g. conformational sampling), are required to confirm the hypotheses suggested by $\Delta\log P_{oct\text{-}tol}$.

Overall, these examples support that $\Delta\log P_{oct\text{-}tol}$ is a valuable tool to experimentally assess information about IMHB formation. In many cases, from the numerical value researchers can direct evaluate the skill of compounds to form IMHBs. For complex structures, standard conformational analysis can help $\Delta\log P_{oct\text{-}tol}$ interpretation.

Conclusions

Despite its wide application in research programs, the potential of lipophilicity as an elucidator of structural properties is not fully exploited. In this paper we showed that for a more efficient use of lipophilicity in IMHB considerations, the determination of log P_{oct} is not sufficient. Indeed, we need to go beyond the traditional octanol/water system, set-up a second system with a more apolar organic phase (i.e. toluene/water) and calculate Δlog $P_{oct\text{-}tol}$. This latter can provide a significant amount of information about IMHB formation and be used in early drug discovery.

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