On the hydration and conformation of cocaine in solution

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Abstract

In order to develop theories relating to the mechanism through which cocaine can diffuse across the blood-brain barrier, it is important to understand the interplay between the hydration of the molecule and the adopted conformation. Here key differences in the hydration of cocaine hydrochloride (CHC) and freebase cocaine (CFB) are highlighted on the atomic scale in solution, through the use of molecular dynamics simulations. By adopting different conformations, CHC and CFB experience differing hydration environments. The interplay between these two factors may account for the vast difference in solubility of these two molecules.

Keywords: Cocaine hydration, atomic scale hydration

1. Introduction

Poor delivery of some drugs hinders the progress in treatment for a number of pathologies.[1] On the contrary, other drugs, such as cocaine, have a high propensity to cross the blood brain barrier (BBB), leading to addiction.[2] Cocaine, like other BBB crossing drugs must be hydrophobic enough to cross the BBB, where a significant amount of cocaine ($\sim$23 % in mice) is thought to enter the brain by virtue of lipid-mediated diffusion.[3] Simultaneously, cocaine is hydrophilic enough to be transported through the blood stream and to avoid sequesteration into the cellular membrane. Understanding the role of water in the hydrophobic/hydrophilic balance in BBB-crossing drugs is important for more effective delivery of pharmaceuticals. In addition, the hydration of a drug has been recognized as important in predicting their ability to bind in vivo. [4, 5, 6, 7] Therefore, details of the

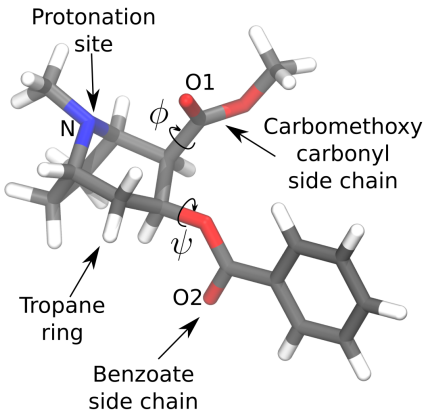

Figure 1: Structure of cocaine with the labels used later in the text. The dihedral angles ϕ and ψ describe the rotation of the carbomethoxy carbonyl and benzoate side chains repectively.

site-specific hydration of cocaine may lead to a better understanding of the role water plays in its ability to bind to a range of sigma receptors.[8, 9]

The work presented here provides a platform for understanding the molecular mechanism by which cocaine is able to diffuse into the brain and the role water has in this process. In the current work, the range of conformations adopted by cocaine in solution and how this affects the hydration has been assessed. Although the conformation of cocaine has been studied for many years,[10] molecular dynamics simulations provide a tool to probe the conformational dynamics of molecules.[11] This enables a more complete understanding of cocaine hydration, providing insight into its balance of hydrophobic and hydrophilic properties that render it an effective BBB crossing drug.

Methods

Molecular Dynamics

Molecular Dynamics (MD) simulations of cocaine were carried out in the LAMMPS simulation package.[12] CHARMM based cocaine parameters were derived using Swissparam [13], and the solvents were modelled using the TIP3P water model [14, 15] and the OPLS-AA chloroform model.[16, 17] It is worth noting at this point that recently other chloroform models have been used as initial parameters for potential refinement simulations.[18] Here

we retain the OPLS-AA based model which we have previously found to be consistent with our neutron measurements.

In order to understand the hydration of both freebase cocaine (CFB) and cocaine hydrochloride (CHC) in different environments, four systems have been investigated here:

1. CHC/water
   3 cocaine hydrochloride (including 3 chloride ions) & 9000 water molecules
2. CFB/water
   3 freebase cocaine & 9000 water molecules
3. CFB/chloro
   8 freebase cocaine & 1600 chloroform molecules
4. CFB/chloro/water
   20 freebase cocaine, 3200 chloroform & 20 water molecules

Measurements on these four systems allow for a comparison between the hydration in CFB and CHC, where these two molecules differ with respect to their protonation state in solution. The protonated form of cocaine (CHC) is a weak acid (pKa = 8.61) and the conjugate base (CFB) is a weak base (pKb of 5.59).[19] Using the Henderson-Hasselbalch equation[20], the level dissociation/association can be estimated, giving estimate of 0.04% of CHC molecules deprotonating and 1% of CFB molecules will be protonated. As such, it is reasonable that our model neglects this dissociation/association. Each simulation was run for fifty million 2 fs timesteps, giving a duration of 100 ns for each system at 318 K. The systems were equilibrated using NVE, NVT and finally NPT ensembles for a total of 40 ps, prior to the production calculation. The temperature and pressure (1 atm) were maintained using the Nosé-Hoover algorithm [21, 22] and all hydrogen containing bonds were constrained with the SHAKE algorithm. [23] The electrostatic and van der Waals forces were calculated using a switching function, to reduce the interactions to zero between the cutoffs of 10 and 12 Å, with long range electrostatic interactions calculated using the particle-particle/particle-mesh K-space algorithm [24].

ANGULA

The ANGULA analysis suite was used for generating intra-molecular distance and dihedral distribution plots and spatial density maps (SDMs) - which give the most probable location of water molecules around specific

sites in the cocaine molecules in three dimensions.[25, 26] To generate these SDMs, the orgin of orthonormal coordinate systems were assigned to N, O1 and O2 atoms (Fig. 1) and the benzene ring (details are provided in the Supporting Information). In each case the SDMs have been plotted to encompass the water molecules from 0-8 Å around the specific site depicted. Further, ANGULA has also been used to extract the most probable orientations of water molecules [27] at certain positions around the cocaine molecule.

Water lifetime

In order to assess the stability of water molecules around the cocaine molecules, the water dynamics package of MDAnalysis [28] was used to calculate the survival probability of water molecules [29] around each of the cocaine molecules in the CFB/H_2O and CHC/H_2O systems. The average survival probability is shown below and the standard deviation was used as an estimation of the associated error.

Results and Discussion

Conformation of cocaine molecules

Understanding how molecular conformation affects hydration is an important step towards understanding the behavior of cocaine *in vivo*. Figure 2 shows the intra-cocaine radial distribution function (RDFs) between different atoms on CHC compared with the same RDFs for CFB in each measured solution. From the nitrogen - carbomethoxy carbonyl RDF, CHC and CFB show different distance distributions, with CFB adopting a longer N-O1 distance compared with CHC; CFB shows similar confomations in water, chloroform and chloroform/water solutions. Conversely, the nitrogen-benzoate carbonyl oxygen distance (N-O2) is very similar for both CHC and CFB, where again, CFB shows virtually indentical distances regardless of the solution.

In order to further probe the adopted conformations of CHC and CFB, dihedral angles, used to describe the rotation of the side chains on cocaine are highlighted in Fig. 1. Specifically, ϕ is the H-C-C-O angle for the carbomethoxy carbonyl group and ψ is the H-C-O-C angle form the benzoate side chain. The distribution of these dihedrals for CHC and CFB are shown in Fig. 3. While the benzoate dihedral (ψ) shows a similar distribution of angles for both CFB and CHC in solution, the ϕ angle differs in the two cocaine molecules. Specfically, the most populated angles found for CHC are

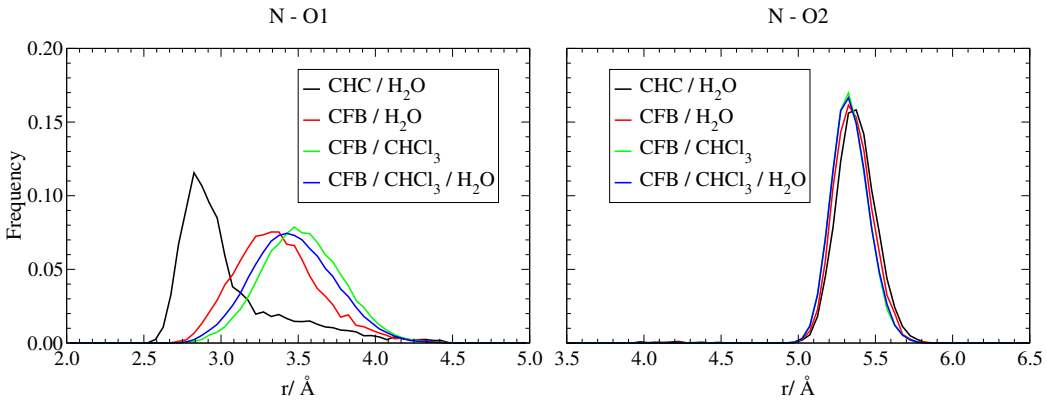

Figure 2: Distribution of intramolecular distances explored by both cocaine freebase and hydrochloride in water.

centred around ∼140°, while in CFB the most likely angle is centred around ∼-140°. This indicates that the carbomethoxy group is tilted towards the tropane ring nitrogen in CHC and is tilting away from the tropane ring nitrogen in CFB. In agreement with Fig. 2, for CFB in all of the measured solutions, there is no significant change in molecular conformation.

In addition to the dihedral angles, Fig. 3 shows a represententative range of the conformations from the trajectory that CFB and CHC adopt in the pure water solutions, highlighting the conformational difference between these molecules. Interestingly, with the exception of the O1 group rotation, the molecular conformations of both CFB and CHC are somewhat similar, with the benzoate group showing a much higher mobility in both solutions when compared with the other components of cocaine. The orientation of the carbomethoxy side chain relative to the -NH group on CHC is indicative of an internal N-H···O1 hydrogen bond, which has been previously observed in neutron diffraction measurements on CHC in aqueous solution.[27]

Figure 4 shows the RDFs for water around N, O1 and O2 atoms in CHC compared with CFB in water, with the respective coordination numbers shown in Table 1. While the hydration of the benzoate carbonyl O2 (Fig. 1) shows virtually identical hydration in CFB and CHC, CFB shows a higher level of O1 hydration relative to CHC in solution. Although the coordination numbers are similar, the O1-O_w nearest neighbor peak in CFB shows a slightly more narrow range of possible distances. CFB shows a N···Hw hydrogen bond and CHC does not, which is unsurprising given that the tropane

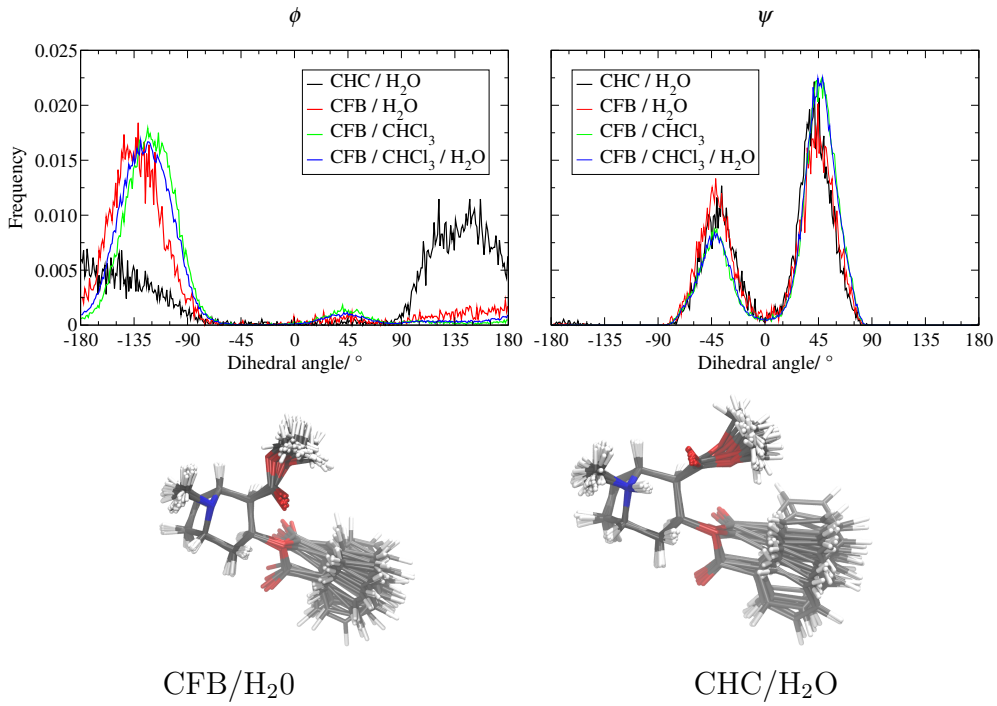

Figure 3: Top: distribution of dihedral angles explored by both cocaine freebase and hydrochloride in water. Bottom: representative snapshots showing the range of conformations adopted by freebase cocaine (left) and cocaine hydrochloride (right) in water. The snapshots are aligned to minimise the square of the deviations of the carbon and nitrogen atoms of the tropane ring.

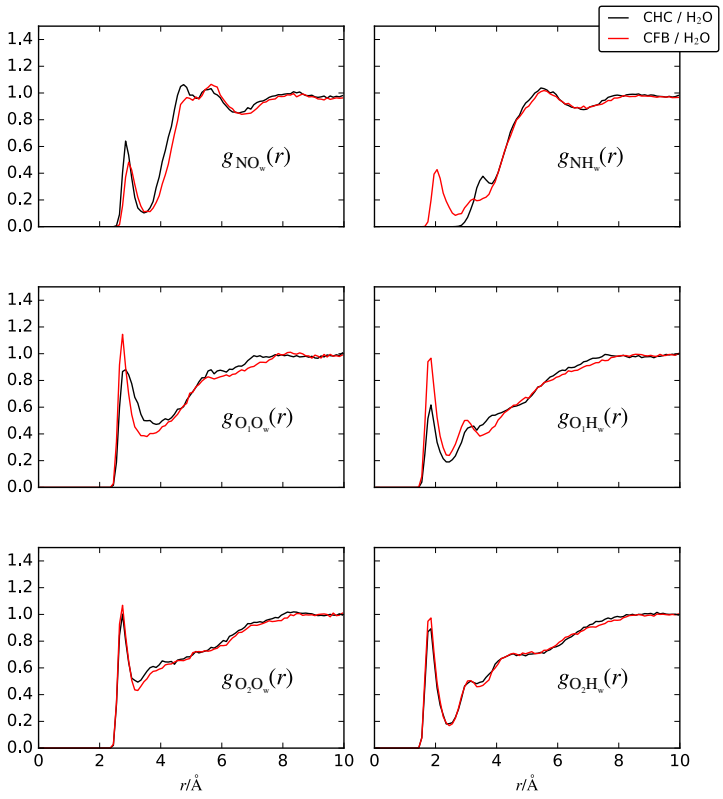

Figure 4: Comparison of the radial distribution functions for the hydration of CFB and CHC in water solutions for N, O1 and O2 atoms as labeled in Fig. 1.

Species	r_{max} /Å	CFB	CHC
NO_w	3.45	0.86	0.95
NH_w	2.65	0.83	0.00
O_1O_w	3.55	2.37	2.63
O_1H_w	2.45	1.52	0.98
O_2O_w	3.25	1.72	1.70
O_2H_w	2.45	1.43	1.34

Table 1: Coordination numbers for water O and H atoms around the nitrogen and carbonyl oxygen atoms of CFB and CHC. r_{max} gives the distance at which the coordination number was calculated.

ring nitrogen is protonated in CHC. What is interesting, however, is that the N-Ow distance remains unchanged from CFB to CHC, despite the N in CHC being a hydrogen bond donor to water and in CFB the N is a hydrogen bond acceptor.

The most probable hydrated locations around cocaine can be shown in three-dimensions by SDMs (Fig. 5). Here the hydration for both CHC and CFB in water are shown along with CFB at lower levels of hydration in the $CFB/CHCl_3/H_2O$ system as a comparison.

For both CFB and CHC the hydration is predominately localized around the tropane ring in front of the N atom in CFB and the -NH group in CHC, which is most easily observed in the xy-plane cross-section on the back panels of the SDM plots. For CFB, the water molecules are more highly localized in an amphiphilic environment which is somewhat expected given the lower abundance of water in the $CFB/CHCl_3/H_2O$ system. Similarly, the most probable benzoate ester (O2; Fig. 1) hydration is similar for CHC and CFB in water, with the hydration density being predominately located above the carbonyl group, rather than coordinating with the C-O-C oxygen, similar to what occurs for other ester linkages in aqueous solution.[30, 31] On the other hand, the hydration around the carbomethoxyether group, while still showing a negligible coordination of water molecules to the ether oxygen, is somewhat different for CHC compared with CFB. O1 shows the most significant level of hydration in both CFB and CHC (see Table 1) but there are differences in the location of the hydrating water molecules around these groups. CFB shows a greater density of water in the -y-direction (towards

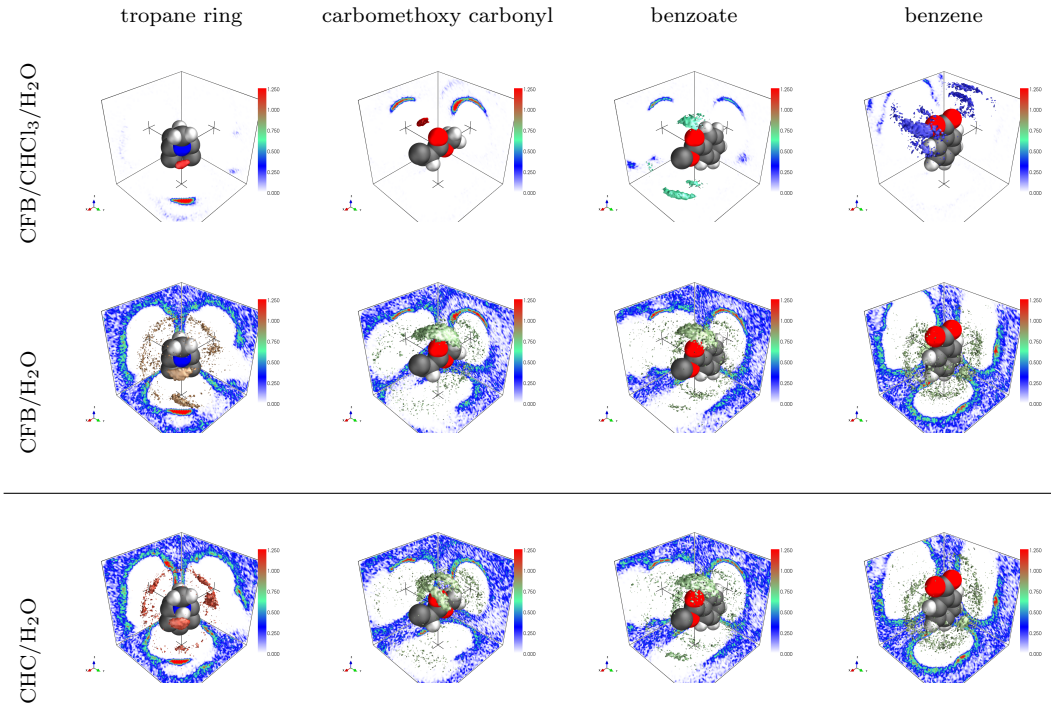

Figure 5: Spatial Density Maps (SDMs) showing the most probable location of water molecules around CFB in both H_2O and $CHCl_3/H_2O$ solutions and for CHC in aqueous solution for four different sites on the cocaine molecule. For each SDM the surface has been calculated such that it surrounds ∼15% and ∼5% of molecules within 0-8 Å for the chloroform and water systems respectively. The panels surrounding the SDMs show the absolute density for each plane, where these panels have been displaced from the origin for clarity.

the nitrogen) than can be seen for CHC. This is consistent with CHC forming an intramolecular hydrogen bond N-H$\cdots$O1. Further evidence of difference is shown in the heathaps in Figures 6 and 7 in the SI.

Both CFB and CHC show a similar hydration pattern around their benzene ring motifs in the water solutions, with water density above and below the surface of the ring, albeit weakly populated with water molecules at this isocontour level. This is similar to what has been observed for many benzene containing systems, where the presence of at least some π-water interactions occur above and below the plane of the benzene ring.[32, 33, 34, 35, 36] Interestingly, for CFB in the $CHCl_3/H_2O$ solution the hydration around the benzene ring has changed from the case of pure water, where the water density has been shifted away from the face of the benzene rings towards the carbomethoxy oxygen atoms. This dehydration is likely due to the fact there is very little water present in the system and water is preferentially bound to the groups with higher partial charges. This suggests that for CFB in an amphiphilic environment that the tropane ring and ester groups are preferentially hydrated over the benzene ring, which is similar to what occurs for the hydration of the benzene ring in indole when transfered from pure water to methanol/water solutions.[35]

Interplay of hydration and conformation

Having identified the regions in which water is most likely to be located, the most probable orientations of these water molecules around specific sites on the molecule can be extracted using ANGULA, this approach has been previously described [36, 37], and the orientational maps used to extract these orientations are shown in the SI. Additionally, by combining the most probable water location/orientation around specific regions in the cocaine molecules (see SI) with the most probable cocaine conformations (Fig. 3), the interplay of hydration with conformation can be assessed. This is shown for both CFB and CHC in Fig. 6, where the most probable water around N are shown in blue and around O1 in red.

What is clear from this figure is how the hydration of the cocaine molecule changes upon a change in conformation from CHC to CFB. The carbomethoxy carbonyl orientation of the two molecules differ in a way that is hydration dependent, specifically in CFB the larger gap between N and O1 can accomodate a water molecule, where the water is oriented such that it bridges between these two sites on cocaine. That this water is bridging is highlighted by the fact that both N and O1 show nearly identical most probable

orientations in CFB. In CHC, the molecular conformation, rather than being controlled by a bridging water molecule, seems to be affected by the presence of an intramolecular hydrogen bond as has been observed previously by neutron diffraction measurements for CHC in aqueous solution.[27]

In contrast to the bridging water molecule [38] observed in CFB, the water molecule in CHC has the O-H bond pointed away from the CHC O1 atom. This can be quantified by considering the hydrogen bond angle, A-H$\cdots$B - where A is the proton donor and B is the proton acceptor. For the interaction of the water around N, the H-bond angles (N-H-Ow) are 163° and 154° for CFB and CHC,respectively. Given that the 'ideal' angle of a hydrogen bond would be close to 180° in both these solutions these water molecules show favorable orientations for hydrogen bonding. The ability of this same most probable water molecule around the N atom (blue, Fig. 6) to bridge to O1 is dependent on the O_w-H_w-O1 angle; which is 137° and 86° for CFB and CHC, respectively. These angles suggest that the nearest neighbor water molecule around nitrogen can form a favourable hydrogen bonded interaction with both N and O1 simultaneously in CFB but not with CHC. Interestingly, the water orientation around the O1 oxygen changes from CFB to CHC, suggesting that the primary binding site for water in both molecules is with the nitrogen rather than the oxygen atoms, consistent with the more localized water density in the SDMs for the tropane ring in Fig. 5.

Hydrating water lifetime

The difference in cocaine conformation changes the landcape of the solvent accessible region between N and O1, which may affect the dynamics of water molecules in this region. The survival probability of water molecules in this region for both CFB and CHC were assessed by calulating the probability of water molecules being retained within a predefined spherical volume with a radius of 3Å, as a function of time throughout the simulation using the atomic coordinates which were saved every 40 ps. This relatively small volume was used to distinguish between these bridging waters and the bulk water environments. The probability data points were fit to an exponential decay which resulted in the following $y = 10^{-1.00x}$ (CFB) and $y = 10^{-0.69x}$ (CHC). That the decay is faster for CFB signifies that the bridging water molecules are less stable in this region for CFB compared with CHC.

This result is somewhat counterintuitive given that the larger N-O1 distance found in CFB seems to facilitate simultaneous hydrogen bonding of

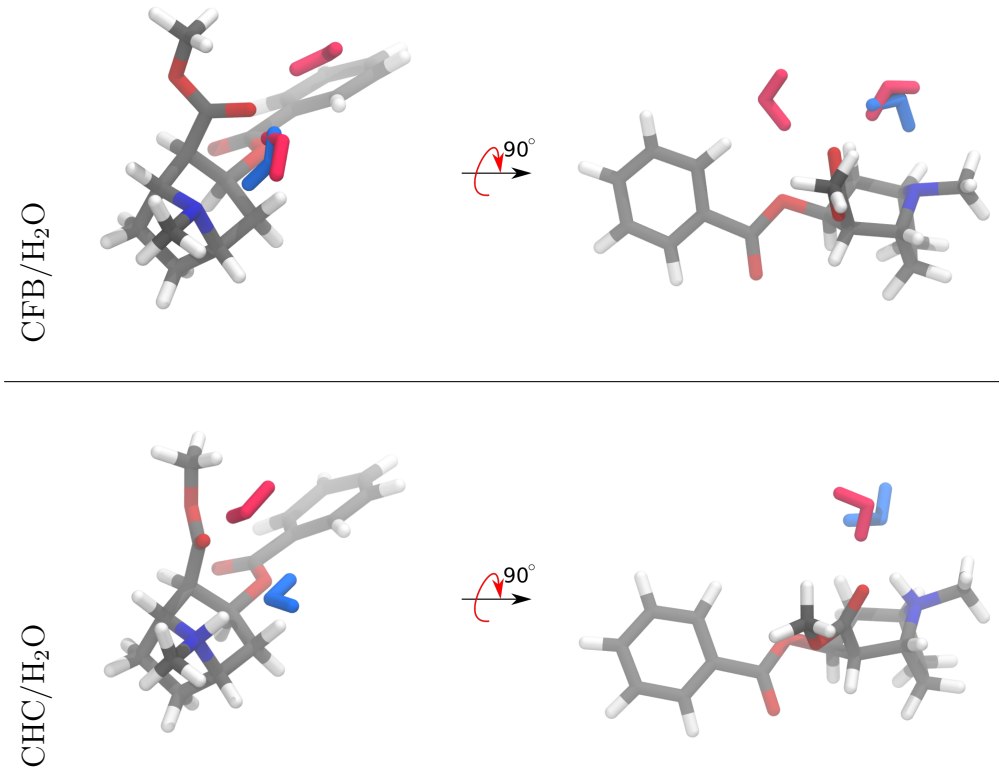

Figure 6: The location and orientation of the most probable water molecules around the different parts of freebase cocaine (left) and cocaine hydrochloride (right) in water (1:3000). Here the location of the most probable water molecules around each of the different regions of cocaine are superimposed on top of one another. The most probable water around nitrogen is shown in blue and the carbomethoxycarbonyl in red. The benzoate side chain has been removed for ease of viewing.

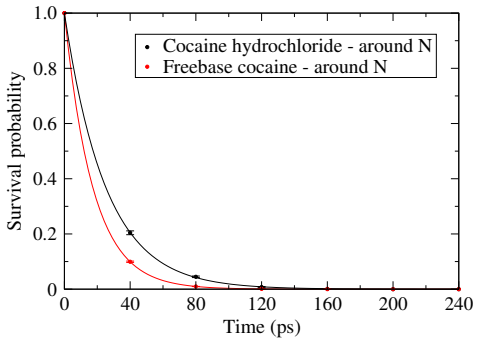

Figure 7: Survival probability of water in a 3Å radius of the nitrogen of cocaine for both the freebase and hydrochloride forms.

the water to both N and O1 as shown in Fig. 6, while in CHC the water molecules appear to bridge concomitantly with the formation of a internal hydrogen bond between O1 and N and as such it might be predicted that water would be less stable, or rather more easily exchanged in CHC compared with CFB. It may be, however, that overall the charge density is more localized in CHC with respect to both water and the internal O1-N hydrogen bond compared with CFB. This could result in the ability of water molecules to bind more easily to both -NH and C=O motifs in cocaine in a shorter distance range given their proximity to one another in the molecule compared with CFB. This view, may go some way to explaining the differences in solubility observed for these two forms of cocaine, with CHC being highly soluble (2.5 g mL^{-1}) and CFB only sparingly soluble in water (1.7 mg mL^{-1}).[19]

2. Conclusions

The analysis of conformation and hydration of the protonated (CHC) and deprotonated (CFB) forms reveal how the solvent accessibility is adjusted within the cocaine molecules in aqueous solutions. This ability to accomodate water molecules slightly differently, appears to stem from a seemingly minor rotation in the carbomethoxy carbonyl side chain, which leads to more dramatic changes in nearest neighbor hydration of the cocaine molecules. The larger N-O distance in CFB due to this carbomethoxy side chain rotation, results in water molecules that sit closer, being able to bridge to the N atom on the tropane ring. Interestingly, this conformation appears to result in two preferential water locations for water around O1 and overall the hydration

of this atom is higher in CFB compared with CHC. However, the lifetime of these water molecules around this site in CFB is reduced compared with the same site in CHC. In CHC, although less water molecules are present around O1, these molecules appear to bridge concomitantly with an internal hydrogen bonding motif within cocaine and have a much higher survival probability of being associated with CHC molecules at this location. The more permanent presence of a water molecule at this site in CHC would, perhaps, aid in keeping CHC soluble in a bulk water solution, as CHC is more highly soluble than CFB in pure water.

The change in the solvent accessible surface of this region of cocaine may be pivotal to its behavior *in vivo*, in terms of solubility, receptor binding and transport. The simple protonation and deprotonation of cocaine does not appear to be the only factor to its dramatic change in solubility, but rather it seems that a modification of the molecular conformation and how this affects the hydration of cocaine is a significant factor. Understanding the solubility of cocaine is of critical importance when trying to understand how the cocaine molecule can penetrate the blood brain barrier. Previously it has been suggested that a protonation/deprotonation event could be critical to the transport of cocaine across the BBB.[39] However recent findings have suggested that conformation may also has an important role to play.[27] The findings here present a third option - that the interplay between both aspects may provide a mechanism for passage.

3. Acknowledgement

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