A solvent induced mechanism for conformational change†

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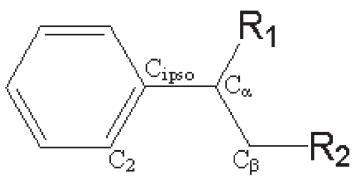
Molecular dynamics simulations have been used to investigate the dynamic behaviour of two small molecule neurotransmitter analogues in aqueous solution, leading to the elucidation of a mechanism for conformational change which is driven by the presence of the solvent molecules.

Whilst the structures of many biologically active molecules in the gas phase are well understood,[1] the solution phase behaviour of the same molecules has received comparatively little attention. Given that the vast majority of biology occurs in aqueous solution, the need to overcome this problem is great, and molecular mechanics simulation offers a viable approach. Of all the small biological molecules available for study, none have attracted more attention than the small molecule neurotransmitters, adrenaline[2] and ephedrine,[3,4] biologically important themselves as well as a source for numerous pharmaceuticals. By the study of simplified analogues of these molecules (Fig. 1), we hope to understand the individual effects that contribute to their solution phase behaviour.

In a recent paper,[5] molecular dynamics simulations (using the CHARMM[6] program with the CHARMM22[7] force field) were used to investigate the effect of solvation on the electronic circular dichroism of 1-(*R*)-phenylethylamine (**1**). In the course of these simulations, a number of observations on the dynamic behaviour of the solute could also be made.

In **1**, there are two dihedral angles about which conformational change can occur, φ (C_2–C_{ipso}–C_α–C_β) and ψ (C_{ipso}–C_α–N–H). We found that whilst φ remains constant throughout the simulations, there is a significant propensity for rotation about ψ. In the unprotonated analogue, where $R_1 = NH_2$, completely free rotation about ψ was observed. The addition of the extra proton to form



1. $R_1 = NH_3^+$, $R_2 = H$, 1-(R)-phenylethylamine
2. $R_1 = OH$, $R_2 = NH_3^+$, 2-amino-1-phenylethanol

Fig. 1 Molecules considered in this study.

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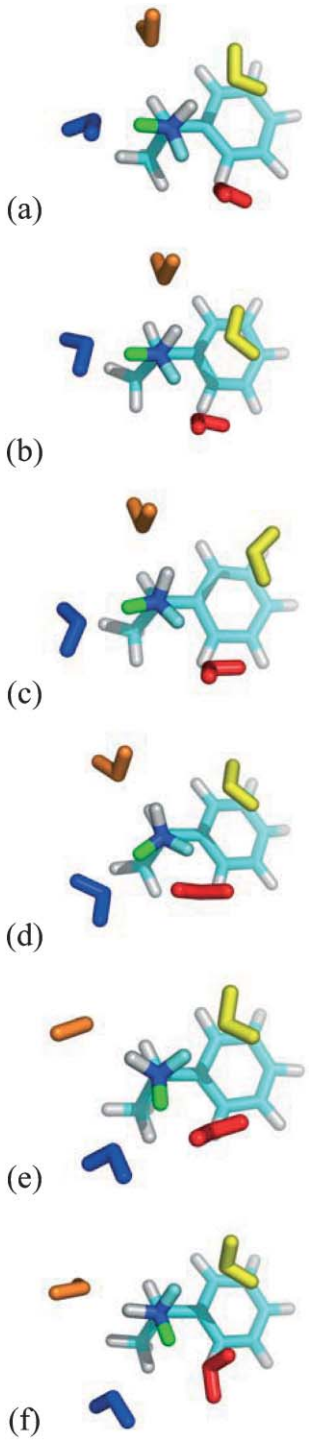

Fig. 2 Mechanism for rotation about ψ in **1**.

the positively charged molecule, however, had a significant effect. Although rotation about ψ was still observed, it occurred relatively infrequently. This difference resulted from the presence of water molecules which bound tightly to each of the three amino proteins, significantly increasing the barrier to rotation.

Further analysis of the rotation of the ψ dihedral reveals that, as well as affecting the energetics of the system, water also plays a significant role in controlling its dynamic behaviour. It has been possible to elucidate the mechanism by which rotation about ψ occurs (Fig. 2), requiring the presence of a single catalytic water molecule which facilitates a stepwise process.

In the first stage (Fig. 2a) the NH_3 group is solvated by three water molecules, each acting as a hydrogen bond acceptor. A fourth water molecule, in brown, is positioned close to the NH_3 group, but is not involved in hydrogen bonding to any of these groups. A small ($\sim$30°) rotation of the NH_3 group breaks the hydrogen bond formed by NH_{white} to H_2O_{yellow} and eventually shifts it to H_2O_{brown} (Fig. 2b–d). The other two hydrogen bonded water molecules follow the rotation of the NH_3 group. A further small rotation of the NH_3 group takes it through the eclipsed conformation. This rotation shifts the hydrogen bond from H_2O_{red} to H_2O_{yellow} and breaks the H bond between NH_{green} and H_2O_{blue}, the remaining hydrogen bonded water molecule follows the rotation of the NH_3 group (Fig. 2d–e). A final small rotation in the NH_3 group moves the molecule into the new staggered conformation. Once again the process happens as one hydrogen bond shifts between water molecules (in this case from H_2O_{blue} to H_2O_{red}) and the remaining hydrogen bonded water molecules follow the rotation of the NH_3 group (Fig. 2e–f).

To gain further insight into this process, single point *ab initio* energy calculations have been performed on each of the six structures shown in Fig. 2 at the MP2/6-31+G* level of theory,

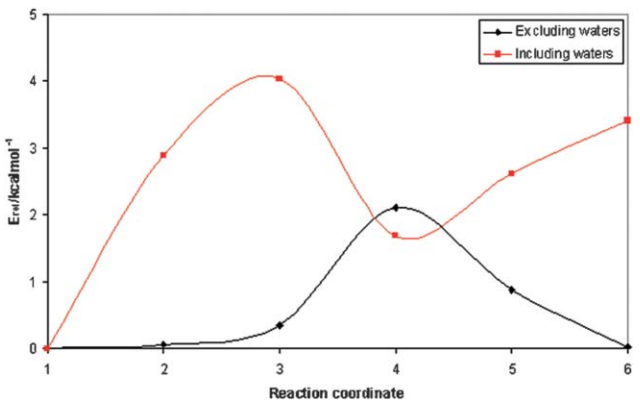

Fig. 3 Energetic profile for rotation mechanism in **1**, calculated at MP2/6-31+G*, energies relative to that of the first structure.

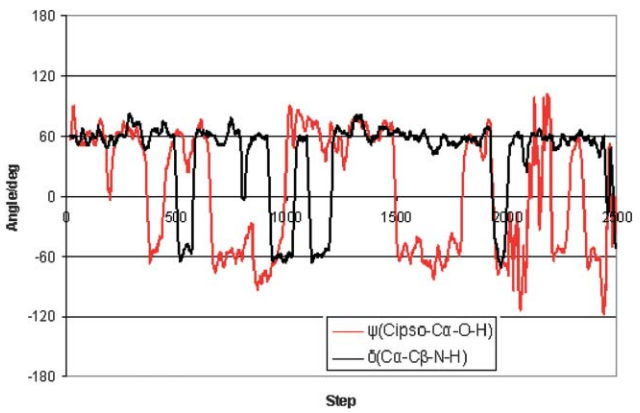

Fig. 4 Monitoring the ψ and δ angles over a molecular dynamics simulation of **2**.

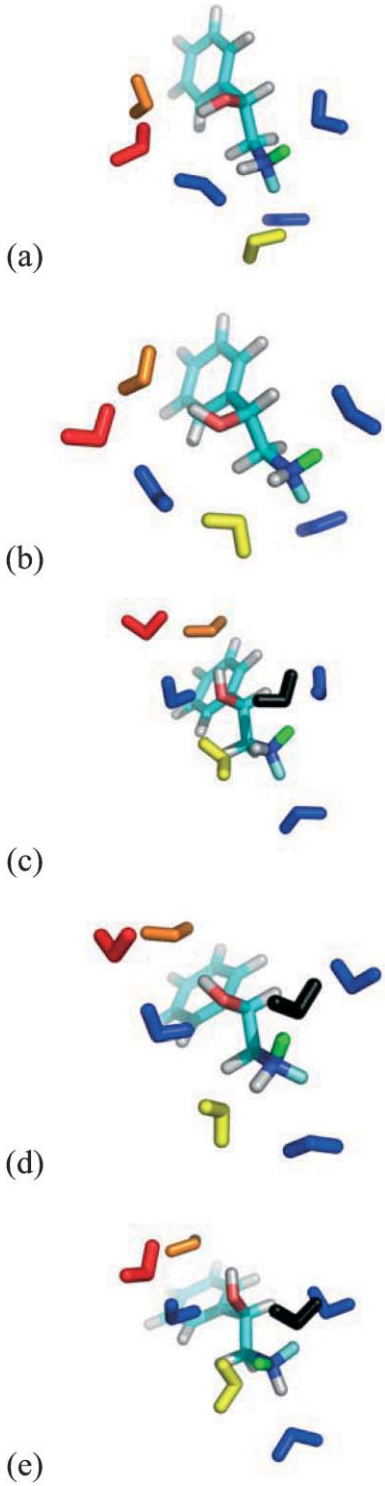

Fig. 5 Mechanism for concerted rotation of ψ and δ in **2**.

with the geometries relaxed to remove the structural distortions arising in the molecular dynamics simulations. For the sake of comparison, the same calculations have been performed on the six structures with the water molecules removed, to measure the underlying energetic barrier to rotation. The results (Fig. 3) reveal that the presence of the water molecules has a substantial effect. In the gas phase, the barrier to rotation occurs when the molecule passes through an eclipsed conformation. In the solvated system, it is the reorganisation of the solvent that gives rise to the energetic barrier for rotation, breaking the H bonding network results in a severe energetic penalty and the height of the barrier is consistent with the energy of a single H bond.[8] The drive to form new hydrogen bonds provides an energetic advantage, however, at exactly the maximum on the barrier to solute rotation, and this facilitates the conformational change. The eclipsed conformation, in which all three ammonium H atoms are hydrogen bonded to a water molecule, is comparatively low in energy. As the NH_3 group again rotates, a H bond is broken, and the energy increases.

To investigate the effect of other functional groups on this mechanism, a set of equivalent molecular dynamics simulations have been performed on **2**. As a direct analogue of noradrenaline, this molecule has received some interest,[9,10] and the effect of water on this molecule has previously been investigated with spectroscopic[11] and computational[12] studies of small hydrated clusters. However, the direct relevance of these studies to fully hydrated systems is still a matter for debate, and the dynamic behaviour of the system is not considered at all.

Although molecule **2** retains the NH_3^+ group of **1**, it also contains a hydroxyl group, which in solution (as in gas phase hydrated clusters[11]) is linked to the amino group *via* the formation of solvent bridges. This results in four, rather than two, dihedral angles about which conformational change can occur, φ (C_2–C_{ipso}–C_α–C_β), ψ (C_{ipso}–C_α–O–H), γ (C_{ipso}–C_α–C_β–N) and δ (C_α–C_β–N–H). Monitoring the ψ and δ dihedral angles in this molecule over the course of this simulation (Fig. 4) reveals that, whilst the amino group is still able to rotate, rotation now occurs in concert with, or slightly after, rotation of the hydroxyl group. The mechanism for this process (Fig. 5) is closely related to that for molecule **1**, but preceded by a shift in the solvent structure that weakens the hydrogen bonded bridge between the two polar groups.

In Fig. 5a we see the three blue water molecules solvating the ammonium group, while the red and orange molecules form a bridge to the hydroxyl group. In Fig. 5b, the yellow water molecule pushes a blue water molecule out of the first solvation shell of the amino group, extending the water bridge, which the hydroxyl group must rotate to maintain. The black water molecule in Fig. 5c then plays the role of the catalytic water molecule that we saw in the case of **1**, allowing for the rotation of the amino group.

These results emphasise the important role that water structure has to play in controlling the conformational behaviour of small molecules, as well as suggesting that the stepwise process involving a single catalytic water molecule is the general mechanism by which rotation of protonated amino groups occurs in aqueous solution.

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