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Onset of Nitriles Hydration with an Environmentally Benign Catalyst: in-Water versus on-Water Conditions

Rodolphe Pollet,^{*[a]} Mathilde Andronaco,^[a] and Himansu S. Biswal^[b]

The reaction yield of nitriles hydration using a catalyst depends on the aqueous medium. Using *ab initio* molecular dynamics, we probed whether "in-water" (in bulk medium) or "on-water" (at the interface with vacuum) conditions can change the onset of the reaction. Investigating a hydrogen-bond mediated

mechanism, the lifetimes of the intermolecular interaction between benzonitrile and choline in the two protocols were compared, and the diffusion of the hydroxide anion around the cyano group was discussed.

Introduction

Some of the widely used amide derivatives are Carboxin,^[1] Naropin,^[2] Eulexin,^[3] Nicotinamide,^[4] Paracetamol^[5,6] and Mepronil.^[7] The notable properties of amides that enable them to be one of the desirable functional groups include high stability, polarity, and conformational rigidity. Hence, getting amide functional groups from other functional groups has always been pursued. The synthesis of amides from nitriles is among the most frequently performed organic transformations. One of the most feasible organic transformations to get amides is the hydration of nitriles.^[8,9] On the path toward greener chemistry, this reaction should be based on an efficient yet environmentally benign catalyst. Intermediately between catalyst-free conditions and the use of a transition metal-based catalyst, the use of choline hydroxide (ChOH) as a greener catalyst offers excellent yields with water as a solvent at a temperature of 80 °C, as demonstrated with benzonitrile as a model substrate.^[10] Based on density functional theory calculations with a continuum solvation model, Choudhury et al. attributed the reduction in activation energy by ChOH to the combined abilities of choline to form a hydrogen bond (HB) with cyano nitrogen and of the hydroxide anion to attack cyano carbon. Taking into account environmental solvent effects as represented by explicit water molecules could, however, provide a more complete description of this reaction mechanism. For example, since benzonitrile is only soluble in hot water, the catalysed conversion to the amide could actually take place under "on-water" conditions^[11–13] whereby the

reactant would be partially or totally located on the surface, and choline hydroxide would be more immersed in water owing to its higher solubility. The goal of the present *in silico* study was to test this assumption, namely whether this on-water strategy could facilitate the encounter of the benzonitrile and choline hydroxide molecules in comparison with the "in-water" (or bulk) protocol. With this aim, we performed large scale *ab initio* molecular dynamics (AIMD) simulations at 350 K at the vacuum-water interface (see Figure 1) and in the bulk (see Figure 2). This paper clarifies the influence of these in-water and on-water protocols on the onset of nitriles hydration catalysed by choline hydroxide.

Results and Discussion

We describe structural and dynamical properties, as well as other notable events, first under in-water and then under on-water conditions. In the bulk water simulation, benzonitrile and choline (in its initial *trans* conformation) separated rapidly. We observed a competition between hydrogen bonds attacks onto the nitrile nitrogen either by nearby water molecules or by the choline hydroxyl group, the latter occurring only during the equilibration period for a lifetime of at most 100 fs. The average distance between the hydroxyl hydrogen and the benzonitrile nitrogen atoms was 6.57 Å with a standard deviation of 1.52 Å. After large fluctuations, it eventually oscillated around 4.31 (0.54) Å. The authors infer that the prevalent hydrogen bonding between solvent molecules and the benzonitrile nitrogen atom, but also between water and the hydroxyl oxygen atom, hinders the approach of the catalyst and the formation of the hydrogen-bonded complex according to the currently accepted reaction mechanism.

We also verified that this approach can neither be favoured by any cation- π interaction. The average distance between the ammonium nitrogen atom and the center of the aromatic ring was indeed 6.98 Å, with only some rare configurations where the ammonium cation was on top of the phenyl group with a separation distance less than 4.5 Å. This could be expected since the cation- π interaction is known to be weak (i) for the large ammonium cation, (ii) in polar solvents such as water, and

[a] Dr. R. Pollet, M. Andronaco
Université Paris-Saclay, CEA, CNRS, NIMBE, 91191, Gif-sur-Yvette, France
E-mail: rodolphe.pollet@cea.fr

[b] Dr. H. S. Biswal
School of Chemical Sciences, National Institute of Science Education and Research (NISER), 752050, Bhubaneswar, India
and
Homi Bhabha National Institute, 400094, Mumbai, India

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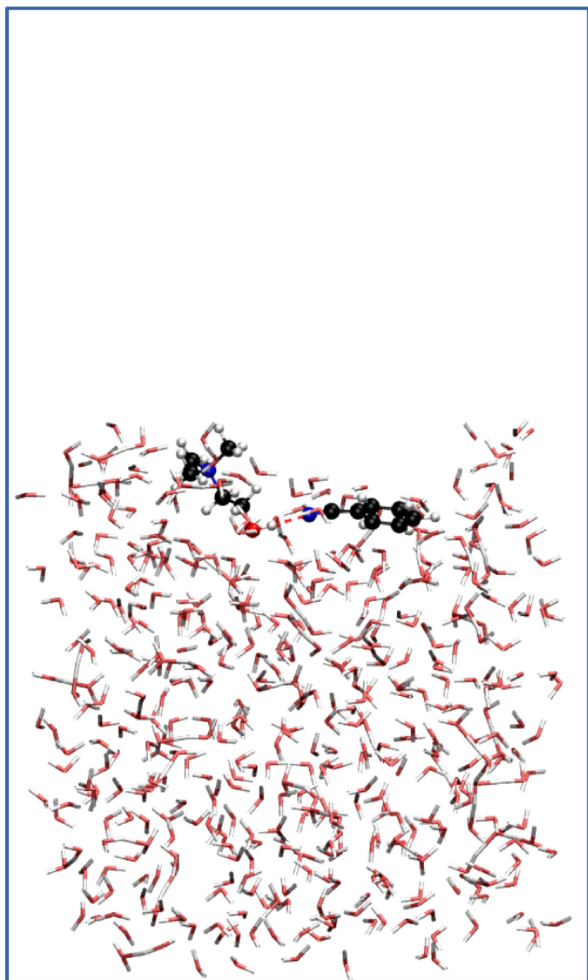


Figure 1. Benzonitrile and choline hydroxide (in CPK representation) at the vacuum-water (in licorice representation) interface. The size of the vacuum separation between slabs is ≈ 25 Å.

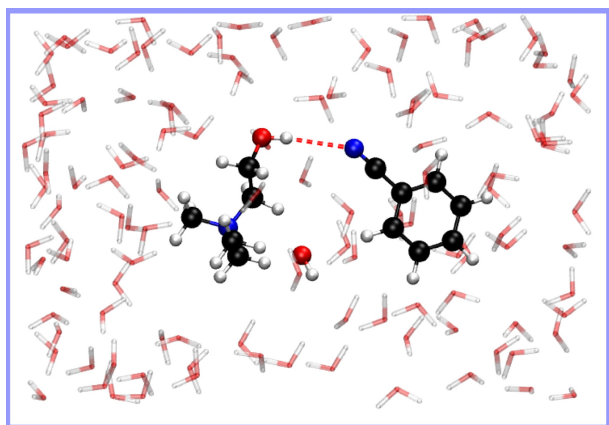


Figure 2. Benzonitrile and choline hydroxide (in CPK representation) in bulk water (in licorice representation) in the initial configuration.

(iii) in the presence of electron-withdrawing groups such as the cyano group.^[14,15]

The hydroxide anion in bulk water diffused according to the well-known structural mechanism.^[16] Starting at 4.49 Å, its

distance to the cyano carbon atom increased by approximately 2.3 Å at the end of the AIMD simulation, after multiple proton jumps. Our trajectory contains both the tetrahedral, with three HB acceptors, and hypercoordinated, with four HB acceptors, solvation structures of hydroxide, thanks to the presence of dispersion corrections to the exchange-correlation approximation^[17] (see Computational Details). The latter structure exhibited a much longer lifetime (typically more than 2 ps) than the former which strongly favoured proton transfers. Again, the spatial separation of the hydroxide anion from the benzonitrile interferes with the proposed reaction mechanism. Consequently, the nitrile bond was not activated at all, exhibiting an almost linear C–C≡N structure, with an average angle of 172°, and bond lengths of 1.43 Å for CC, and 1.17 Å for CN.

A spontaneous event in bulk water was the durable change in the choline conformation (see Figure 3): after approximately 14.5 ps, the geometry changed from *trans* to *gauche*, with average NCCO dihedral angles of 182 and of 75°, through an intermediate structure where the angle was 123°. Other structural descriptors, such as the increase in CCO angle (by almost 5°) and decrease in CC distance (by 0.011 Å), are reported in Table 1. Such conformational change is also reflected in the value of the choline dipole moment. Two representative configurations, with NCCO dihedral angles of 175 and 75°, thus exhibited dipole moments of 5.4 D and 2.5 D,

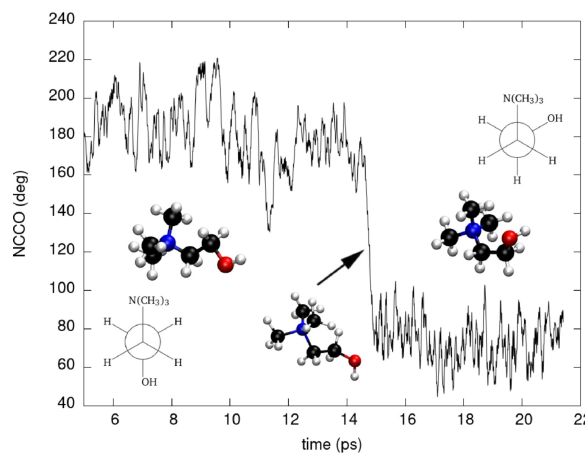


Figure 3. Time evolution of the choline NCCO dihedral angle going from the *trans* to the *gauche* conformation through an intermediate structure during the AIMD simulation in bulk water. Newman projections are shown as insets.

Table 1. Average distances (in Å) and angles (in degrees) in the conformational isomers of choline during the AIMD simulation in bulk water.

	<i>trans</i>	<i>gauche</i>
d(CO)	1.435	1.434
d(CN)	1.532	1.540
d(CC)	1.543	1.532
CCO	108.5	113.4
CCN	115.2	116.3
NCCO	181.9	75.2

as obtained from Wannier localisations and with the centre of mass as the origin. The solvation structures were also different, with the hydroxyl group of the *trans* conformation mainly interacting with two water molecules as HB donor and acceptor whereas we observed only one HB acceptor water molecule in the case of the *gauche* conformation. This atypical stabilisation of a *gauche* conformation with respect to *trans*, where steric strain is reduced (see Newman projections in Figure 3), is called the "gauche effect"^[18] and is the result of electrostatic interactions and intramolecular HB in the case of the choline cation.^[19] For the *gauche* conformation, we indeed observed a short average distance between one of the ammonium methyl hydrogen atom and the hydroxyl oxygen atom, namely 2.48 Å, to be compared with the two other distances of 3.16 and 4.07 Å for the same methyl group.

Taking into account this conformational change, we decided to perform a second AIMD simulation under bulk conditions, starting from a configuration where *gauche* choline was hydrogen-bonded to benzonitrile. Its lifetime increased significantly in comparison with the first simulation, namely 2.7 ps including a brief interruption of 0.7 ps owing to the rotation of the hydroxyl group. During this 10.45 ps long trajectory, its average distance to the benzonitrile nitrogen atom was 4.46 (1.70) Å. Furthermore, stabilisation of the *gauche* conformation could again be related to the HB between the hydroxyl oxygen and one of the methyl hydrogen atoms, with a characteristic length of 2.61 Å. In-water conditions could therefore be favourable to the hydration reaction provided that choline adopts its most stable, i.e. *gauche*, conformation.

In stark contrast to the in-water protocol, the lifetime of the initial HB between nitrile and choline in the *trans* conformation at the vacuum-water interface was much longer. Its breaking, after 2.2 ps, resulted from the formation of a strong HB between a nearby donor water molecule and hydroxyl oxygen followed by the attachment of another, acceptor, water molecule. Concurrently, a third, donor, water molecule from the surface attacked benzonitrile nitrogen with shorter hydrogen-bonding lifetimes (i.e., less than 100 fs). In spite of this moderate lifetime of 2.2 ps, the proximity between the two species decreased once the initial HB was broken. Furthermore, the nitrile group reoriented itself to point away from the surface (that is, toward vacuum), while the choline oxygen was more immersed in water with its molecular axis almost perpendicular to the surface (see Figure 4). Consequently, the distance between nitrile nitrogen and choline oxygen eventually reached 6.61 Å.

In the meantime, the hydroxide anion at the vacuum-water interface diffused according to the same structural mechanism as in bulk water. Located at 3.6 Å from the cyano carbon atom in the initial configuration, the first jump, away from the water surface, occurred after approximately 1 ps, where hypercoordination was observed. The reverse jump, towards the surface, took place 4 ps later. Interestingly, a previous theoretical study has shown that OH⁻ is slightly more stable on the surface than in the bulk.^[20] Here the proximity of hydroxide to the choline hydroxyl at the interface led to the deprotonation of the latter to form choline alkoxide, 5.7 ps from the start, when OH⁻ captured the hydroxyl hydrogen. The oxygen atom of choline

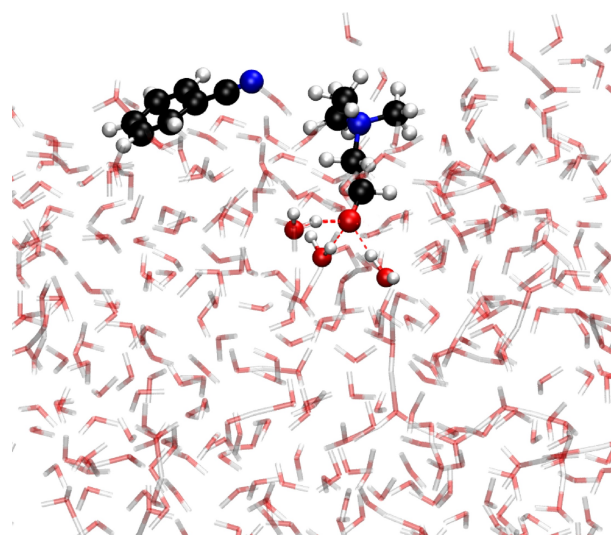


Figure 4. Benzonitrile and choline alkoxide at the vacuum-water interface after their separation and mutual reorientations. Three donor water molecules are also highlighted.

then accepted three stable hydrogen bonds from surrounding water molecules (see Figure 4). After a reprotonation that lasted approximately 1 ps, another water molecule even formed a fourth HB with the bare choline oxygen atom. On the timescale of this AIMD simulation, the hydrogen-bond mediated mechanism therefore appears unlikely under on-water conditions because of the choline deprotonation and the opposite orientations of the reactive sites.

Conclusions

The onset of the benzonitrile hydration catalysed by hydroxide choline was compared in two distinct environments, namely in-water and on-water conditions. In the former protocol, the lifetime of the hydrogen bond between cyano nitrogen and choline oxygen increased significantly when the catalyst exhibited the *gauche* conformation. At the vacuum-water interface, this lifetime was comparable to that of the bulk condition, but both molecules eventually orientated in such a way that the nitrile and hydroxyl groups faced almost opposite directions. In both protocols, the hydroxide anion diffused around the benzonitrile according to a structural mechanism. Despite the low solubility of nitrile in water, our study suggests that in-water conditions may be more favourable for the hydration reaction according to the currently accepted mechanism mediated by a hydrogen bond.^[10] The latter should, however, be re-examined since Choudhury et al. studied it by assuming the *trans* conformation using a continuum solvent model, without taking into account the *trans-gauche* interconversion and explicit solvent effects. Metadynamics simulations are underway in our laboratory to obtain the free-energy landscape for the hydration reaction under such conditions.

Computational Details

The molecules were first solvated with the Packmol software,^[21] which was followed by a classical molecular dynamics equilibration of 1 ns performed with Gromacs.^[22] In the case of the vacuum-water interface, the TIP3P-ST water model fitted to surface tension measurements^[23] was used instead of the popular TIP3P model^[24] to prevent the evaporation of water molecules from the liquid slab. The AIMD simulations were done with the CPMD code (version 4.3).^[25] Stabilisation of the vacuum-water interface required a large supercell (50 Å × 24 Å × 24 Å), so that we used a recent version of this code with much improved performance.^[26] The water slab with its two surfaces in contact with vacuum thus included 468 water molecules, namely almost four times more than in the bulk system, with a cell of 22 Å × 16 Å × 14 Å including 119 water molecules. We used the PBE exchange-correlation approximation^[27] corrected for dispersion effects (D2),^[28] with ultrasoft pseudopotentials^[29] including scalar relativistic effects and allowing a plane wave cutoff of only 30 Ry. CP trajectories used a fictitious electron mass of 700 a.u., a time step of 6 a.u., and Nosé–Hoover chain thermostats^[30] (with a chain length of four) both for ions (with the target temperature set to 350 K and thermostat frequency to 2500 cm⁻¹) and electrons to prevent heat transfer between both subsystems. In addition, hydrogen atoms were replaced by deuterium atoms to maintain adiabaticity. The time lengths of these CP trajectories were 21.2 ps and 10.45 ps for the in-water conditions, and 17.6 ps for the on-water conditions.

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Conflict of Interests

There are no conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Green chemistry · Catalysis · Ab initio calculations · Molecular dynamics

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