ARTICLE

Rotational Mechanism of Ammonium Ion in Water and Methanol†

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(Dated: Received on June 18, 2018; Accepted on July 25, 2018)

Dynamics of ammonium and ammonia in solutions is closely related to the metabolism of ammoniac compounds, therefore plays an important role in various biological processes. NMR measurements indicated that the reorientation dynamics of \( \text{NH}_4^+ \) is faster in its aqueous solution than in methanol, which deviates from the Stokes-Einstein-Debye rule since water has higher viscosity than methanol. To address this intriguing issue, we herein study the reorientation dynamics of ammonium ion in both solutions using numerical simulation and an extended cyclic Markov chain model. An evident decoupling between translation and rotation of methanol is observed in simulation, which results in the deviation of reorientation from the Stokes-Einstein-Debye rule. Slower hydrogen bond (HB) switchings of ammonium with methanol comparing to that with water, due to the steric effect of the methyl group, remarkably retards the jump rotation of ammonium. The observations herein provide useful insights into the dynamic behavior of ammonium in the heterogeneous environments including the protein surface or protein channels.

Key words: Ammonium, Jump rotation, Hydrogen bond switching, Methanol, Molecular dynamics simulation

I. INTRODUCTION

Ammonium and ammonia is an important media of nitrogen exchange between the life and external environments [1–5]. Many studies were carried out to explore how proteins uptake ammonium produced by glutamine metabolism [5]. It is therefore interesting to study how ammonium [5, 6] moves differently in different dielectric environments (such as in water and in the amphiphilic solvents) [7–9]. An intriguing observation from the nuclear magnetic resonance (NMR) measurements is that ammonium rotates faster in water (viscosity: \(8.95 \times 10^{-4} \text{ Pa} \cdot \text{s}\)) than in a less viscous solvent, such as methanol (viscosity: \(5.41 \times 10^{-4} \text{ Pa} \cdot \text{s}\)) [12–15], which deviates from the seminal Stokes-Einstein-Debye (SED) rule of hydration dynamics predicting that the rotational diffusion constant \(D_R\) of a solute molecule should directly correlate with the solvent viscosity [9–11].

Previous theoretical simulations using classical as well as \textit{ab initio} interaction potentials speculated that in the aqueous solution ammonium cation moves through a consecutive series of discontinuous “jumps”, which possibly leads to its fast reorientation (with respect to water reorientation in the aqueous environment) [16–23]. However, this doesn’t explain why the rotation of ammonium is faster in water than that in methanol, where multiple hydrogen bonds can form between ammonium hydrogen and methanol oxygen as well.

In the past decade, an extended “molecular jump” picture has been adopted to rationalize the reorientation mobility of water. Water reorientation is considered to be contributed by two components in the aqueous solutions: a large-amplitude angular jump during the hydrogen bond switching and a diffusive “frame diffusion” between two consecutive switchings [24]. An extended cyclic Markov chain model is then used to calculate this dynamics in a quantitative way [24]. It has been successfully applied to explain the rotational behaviors of water in various environments, such as the ion effects on the water rotation in the electrolyte solutions [25–30].

In this work, the rotational diffusion constants and the reorientation correlation time of \(\text{NH}_4^+\) in water and methanol at low concentration were calculated using the molecular dynamics simulation and the extended cyclic Markov chain model. The results suggest that the rotational behavior of ammonium in both solvents is similar to that of water in aqueous solutions. Furthermore, the large-amplitude angular jump during the hydrogen bond switching plays the decisive role in determining its overall rotational speed. Due to the lower accessibility of potential hydrogen bond acceptor in methanol
than in water, the rate of the hydrogen bond switching, consequently the jump reorientation, is much lower in methanol than in water, which leads to the slower overall ammonium reorientation measured by NMR.

II. COMPUTATIONAL METHODS

A. Potential models and simulation details

The classical molecular simulations were carried out to explore the properties of NH₄Cl water and methanol solutions with both additive and non-additive force fields. SPC/E (the extended simple point charge model) water [31] and OPLS (Optimized Potentials for Liquid Simulations) ammonium [32] force fields were employed to simulate the interactions. The viscosities of pure water and methanol with SPC/E and OPLS force fields are well consistent with the experiments at ambient conditions [14, 15, 33]. These parameters of additive force fields are listed in Table I. The molecular dynamics simulations were performed with the GROMACS 4.5 software [34].

For the initial simulation systems, the solvent molecule (water or methanol), NH₄⁺ and Cl⁻ were randomly inserted into cubic boxes according to molar ratios of NH₄Cl solvent (1:110 and 1:55) with a fixed number of solvent molecules (1100). The corresponding concentrations of NH₄Cl in both solvents were about 0.5 and 1 mol/L. After initial geometry optimizations and 5 ns pre-equilibration simulation for each system, an extended 4 ns NPT simulations were carried out to obtain the final properties. The equation of motion was integrated by the velocity Verlet scheme with a time step of 2 fs [9]. Temperature and pressure were maintained at 298 K and 1 atm using the Berendsen scheme with weak coupling frequency at 0.1 and 1 ps respectively [35]. The cutoff distances were 14 Å for electrostatic interaction and Lennard Jones interaction. Long-range electrostatic interactions were treated by using the particle-mesh Ewald (PME) summation method [36]. Minimum image conditions were used [9].

B. Rotation and reorientation

The rotational dynamics of single molecule can be described with the rotational diffusion constant and the reorientation time of molecule. The rotational diffusion constant $D_R$ can be obtained by the mean square angle displacements (MSD) of one specified vector of molecule as Eq.(1), assuming that the diffusion of molecule is a stochastic and random motion [37, 38].

$$D_R = \lim_{t \to \infty} \frac{1}{4t} \left( \frac{1}{N} \sum_{i} \left| \varphi_i(t) - \varphi_i(0) \right|^2 \right)$$  \hfill (1)

$$\varphi_i(t) = \int_0^t \delta \varphi_i(t') dt'$$  \hfill (2)

where $\delta \varphi_i(t')$ is the vector angular displacement of $N-H$ bond vector $p_i(t)$ of ammonium $i$ within the interval of $[t', t' + \delta t]$. The vector $\delta \varphi_i(t')$ has the direction of $p_i(t) \times p_i(0)$ with the magnitude $\delta \theta_i$, which is the scanning angle of $p$ during the time interval. The cumulated angular displacement $\varphi_i(t)$ used here can avoid the limitation of the direct angular difference $[p_i(t) - p_i(0)]$ due to the bounded quantity of rotation. The rotational diffusive constants of ammonium ion along N–H bond vector and the normal vector of plane defined by two N–H bonds were calculated.

The reorientational time of molecule can also be used for representation of the rotational mobility of molecule. It can be derived from the reorientation correlation function $C_2(t)$ of molecule along any specified vector $v$, the O–H bond vector for water and N–H bond vector for NH₄⁺ in this work [24–30, 37, 38].

$$C_2(t) = \langle P_l [u(0) u(t)] \rangle$$  \hfill (3)

where $P_l$ is the $l$th Legendre polynomial. In this work, the 2nd rank Legendre Polynomial $P_2(x)=1/2(3x^2-1)$ is used to obtain the rotational correlation time $\tau_2$, which corresponds to the observation quantities of NMR and the ultrafast IR spectrum measurements [36, 37]. The reorientational time by NMR measurements is the integration value of $C_2(t)$. The reorientational time can be derived from the slope of the linear function $ln[C_2(t)]\propto t$, if $C_2(t)$ follows an exponential decay after a short-time libration as previous reports [24–30].

According to the ideal Debye diffusion model, if the reorientational time $\tau_2$ is converted to the rotational diffusion constant $D_R$ by the relationship,

$$C_2(t) = \exp[-l(l+1)/D_R t] = \exp[-t/\tau_2]$$

at long time window [37, 38].

C. The translational diffusion constant

The translational diffusion constant can also be obtained from the time-dependent mean square displacements of the labeled molecule center of mass according

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Atom} & \textbf{$q/e$} & \textbf{$\sigma/\AA$} & \textbf{$\varepsilon/(kJ/mol)$} \\
\hline
\hline
SPC/E & O & -0.8476 & 3.166 & 0.650 \\
& H & 0.4238 & 0.000 & 0.000 \\
& MeOH & O & -0.683 & 3.12 & 0.711280 \\
& H & 0.418 & 0.00 & 0.000000 \\
& C & 0.145 & 3.50 & 0.276144 \\
& H(C) & 0.040 & 2.50 & 0.125520 \\
\hline
NH₄⁺ & N & -0.40 & 3.25000 & 0.1700 \\
& H & 0.35 & 0.000000 & 0.0000 \\
\hline
Cl⁻ & -1.00 & 4.41724 & 0.4928 \\
\hline
\end{tabular}
\caption{The force field parameters.}
\end{table}
to the Einstein relation,
\[ D_t = \langle |r(t) - r(0)|^2 \rangle / 6t \tag{4} \]
where \( r(t) \) is the position vector of the molecular center of mass at time \( t \), and the averaging is performed over all molecules of the same species \([9-11, 37, 38]\).

**D. The extended jump model**

Following the Ivanov jump picture, the second-rank reorientational correlation function \( C_2(t) \) along the hydrogen bonded constrained vector of molecule can be expressed as two independent contributions, the jump correlation function and the frame rotational contributions after a fast libration part. The frame rotation of molecule is a cooperative rotation mode of molecule with intact hydrogen bond pair. If each independent correlation function can be described with a single exponential function, the reorientational correlation time can be obtained from the contributions of them and follows the relationship of Eq.(5) \([24-30]\):

\[ \frac{1}{\tau_2} = \frac{1}{\tau_1} + \frac{1}{\tau_F} \tag{5} \]

where \( \tau_1 \) is the jump rotational time and \( \tau_F \) is the frame rotational time. The overall reorientational correlation function is therefore calculated as (Eq.(1)) \([24-30]\),

\[ C_2(t) = \langle \vec{u}_{OH}(0) \vec{u}_{OH}(t) \rangle = \langle \vec{u}_{OH}(0) \vec{u}_{OH}(t) \rangle \times \langle \vec{P}_2 [\vec{u}_{OX}(0) \vec{u}_{OX}(t)] \rangle \tag{6} \]

with \( \vec{P}_2 \) as the second order Legendre polynomial, \( \vec{u}_{OH} \) being the unit vector of ammonium O–H bond within the local hydrogen bond OX frame and \( \vec{u}_{OX} \) being the orientation of OX frame. X is an acceptor atom.

The jump rotational relaxation time \( \tau_J \) is the function of the average jump angle \( \varphi \) and the hydrogen bond lifetime \( \tau_{HB} \) (1/\( \tau_{HB} \) is the frequency of hydrogen bond switching).

\[ \tau_J = \tau_{HB} \left\{ \frac{1 - 1}{2n + 1} \sin \left( \frac{n + 1/2}{2} \varphi \right) \right\}^{-1} \tag{7} \]

The hydrogen bond lifetime \( \tau_{HB} \) is obtained by fitting the hydrogen bond correlation function of \( C_{HB}(t) = \langle n(0) n(t) \rangle \) with single exponential function \([24]\), \( n_R(0) \) and \( n_F(t) \) are the functions of hydrogen bond state. The value of \( n(0) \) is 1, if ammonium hydrogen atom uniquely forms a hydrogen bond with initial acceptor. Once a new hydrogen bond forms, the value of \( n(0) \) becomes zero after that time.

Additionally, the frame rotational time \( \tau_F \) like the total reorientational time as a fitting factor can be derived by fitting their correlation functions with exponential functions as previous studies \([24, 27]\). The hydrogen bond lifetime \( \tau_{HB} \) is obtained by fitting the hydrogen bond correlation function within a single exponential function within linear range according to the stable states pictures \([24]\). The strict hydrogen bond criterion is used to ensure that the hydrogen bond switching happens indeed along the molecular dynamics trajectory \([24, 29]\). For the hydrogen bond donor and acceptor molecules, if \( R_{O-\cdot} < 3.1 \text{ Å}, R_{H-\cdot} < 2.0 \text{ Å} \), and \( \theta_{H-\cdot} < 20^\circ \), the initial and final hydrogen bond acceptors; \( p^+ \): the hydrogen bond donating hydrogen), the hydrogen bond forms for two water molecules. For the hydrogen bond between NH\(_4\) and water or methanol, if the conditions, \( R_{N\cdot-\cdotO} < 3.0 \text{ Å}, R_{H\cdot-\cdotO} < 2.0 \text{ Å}, \) and \( \theta_{H\cdot-N\cdot-\cdotO} < 20^\circ \) are satisfied, we can think the hydrogen bond between them is formed \([29]\).

**III. RESULTS AND DISCUSSION**

The simulated translational diffusion constants of water and methanol in NH\(_4\)Cl water and methanol solutions at 0.5 mol/L are 2.38 × 10\(^{-5}\) and 2.79 × 10\(^{-5}\) cm\(^2\)/s at 298 K and 1 atm with SPC/E water and OPLS methanol non-additive force field. The corresponding experimental values are around 2.3 × 10\(^{-5}\) and 2.4 × 10\(^{-5}\) cm\(^2\)/s for pure water and methanol. Interaction models used in this work are therefore reasonable in describing the dynamic properties of these systems.

The viscosities of SPC/E water and OPLS methanol are 8.95 × 10\(^{-4}\) and 5.41 × 10\(^{-4}\) Pa·s \([14, 15]\). According to the Stokes-Einstein-Debye relationship, the reorientational diffusion constant of ammonium should be smaller in water than in methanol due to higher viscosity of water than methanol. However, the reorientational time of ammonium in water from the nuclear magnetic resonance (NMR) measurements is 0.93 ps, which is much smaller than that of 3.4 ps in methanol \([12, 13]\). The reorientational time of ammonium calculated herein is 2.36 ps in 0.5 mol/L (2.43 ps in 1.0 mol/L) of aqueous solution while 8.20 ps in 0.5 mol/L (9.88 ps in 1 mol/L) of methanol solutions, respectively. The calculated rotational diffusion constants of ammonium are 0.14 × 10\(^{12}\) and 0.07 × 10\(^{12}\) rad\(^2\)/s in water and methanol, which are qualitatively consistent with the experimental values of 0.18 × 10\(^{12}\) and 0.049 × 10\(^{12}\) rad\(^2\)/s (derived from the relationship \( \tau_{cr} = 1/(n(n + 1))D_R \)). Note that the overestimation of the reorientational time of ammonium is probably due to the difference of measurements between the simulation and NMR technique. The integration value of the reorientational correlation is derived from the latter case, which includes the short-time libration contribution.) \([12, 13]\). The 1st and 2nd order reorientational correlation functions \( C_i(t) \) \((i=1, 2)\) of NH\(_4\) along the N–H bond vector and the short-time decays are shown in FIG. 1 (a) and (b). A faster decay is observed for the reorientational correlation function in water than in methanol for ammonium at any order in Eq.(3).

The rotation of ammonium obviously deviates from the Stokes-Einstein-Debye rule, which is observed in wa-
ter and in methanol. At the same time, the translational dynamics of dilute ammonium in both solvents is also decoupled with macroscopic viscosity. The translational diffusion constants of ammonium are $1.62 \times 10^{-5}$ and $0.99 \times 10^{-5}$ cm$^2$s$^{-1}$ (mol/L)$^{-1}$ respectively in water and in methanol of 0.5 mol/L. In this work, we focus on the rotational mechanism of ammonium in water and methanol.

A decomposition procedure based on the extended cyclic Markov chain model is then carried out to decompose the overall reorientational time of ammonium in water as well as methanol, and explain the aforementioned seemingly abnormal deviation of rotational mobility from the Stokes-Einstein-Debye rule [9–11]. The motions of ammonium in water and in methanol environments are retarded due to the multiple hydrogen bonds formed between the solute and solvent molecules. Similar to the reorientation of water molecules [24–30], ammonium reorientations should mostly happen as a series of thermally activated “jumps” over the potential barriers. We can consider the consecutive jumps as a cyclic Markov chain, with the characteristics of each jump depending only on the momentary local environment. During the time intervals between the jumps, a slow diffusive (so called “frame”) reorientation occurs. In this picture, jump and frame components of the ammonium reorientation practically do not depend on each other due to their different timescales.

The trajectory of ammonium molecule under investigation is dissected into a group of successive hydrogen bond switching events, and a procedure based on the cyclic Markov chain model was used to quantitatively decompose the difference between the overall reorientations in the two solutions into the jump and frame reorientation contributions during each of the switchings. The overall reorientation correlation function can be calculated using Eq.(7) [24–30]. The overall reorientation time $\tau_{ML}$ is derived from $\tau_J$ (the jump reorientation time) and $\tau_F$ (the frame reorientation time) in Eq.(5). The overall reorientation correlation time, according to Eq.(1), is 2.11 and 6.98 ps in water and 0.5 mol/L methanol, respectively. The Markov chain model calculation qualitatively reproduces the values (2.36 and 8.20 ps) calculated directly from fitting the reorientation correlation function of N–H bond along the trajectories of molecular dynamics simulations. The decomposition analysis of the reorientation correlation function shows that the jump rotation and the frame rotation of ammonium are both retarded in water with respect to those in methanol, while the difference of overall reorientation is mainly caused by the difference in the jump components. In the following, we analyze in detail the mechanisms of jump and frame components, respectively.

Jump reorientation is controlled by two main factors (Eq.(6)): the jump angle and the hydrogen bond life time. The jump rotation of ammonium happens when ammonium switches its donating hydrogen bond from initial hydrogen bond acceptor water O$^a$ or methanol O$^a$ to final hydrogen bond acceptor water O$^b$ or methanol O$^b$ in water or in methanol respectively. The hydrogen bond switching is a cooperative process, which involves the departure of initial acceptor O$^a$ and the approaching of new acceptor O$^b$. The switching event therefore can be described with the reaction coordinates: the distance between ammonium N$^*$ and O$^a$ ($RN_a$–O$^a$), the distance between N$^*$ and O$^b$ ($RN_b$–O$^b$) and the angle ($\theta$) between the project vector of N$^*$–H$^*$ bond on the plane of O$^a$–N$^*$–O$^b$ with the bisector of O$^a$–N$^*$–O$^b$ [24, 27, 29]. The evolutions of these values along the hydrogen bond switching time window are shown in FIG. 2. The time origin is set to the bifurcate hydrogen bond state of N$^*$–H$^*$ with O$^a$ and O$^b$. FIG. 2 indicates that, during the hydrogen bond switching, the angle of O$^a$–N$^*$–O$^b$ nearly does not change, while a sudden and large-amplitude angular rotation of N$^*$–H$^*$ is observed around $t=0$ (73° and 77° in water and methanol respectively). The jump angle therefore has minor influence on the difference of jump rotational time (Eq.(6)) in these two solvents.
The populations of jump angle in water and methanol of 0.5 mol/L are shown in FIG. 3. The population curve of jump angle for ammonium (P_A in FIG. 3(a)) presents near symmetry around the average value, so the average value is used for the calculation of ammonium jump rotational time in Eq.(5). Note the jump angle distribution is related to the structure of transition state during hydrogen bond switching. For instance of the hydrogen bond switching of water hydrogen from initial acceptor water to new acceptor water in current solution, the jump angle distribution for water strongly deviates from the symmetry like in pure water [24]. For the hydrogen bond switching of water with one hydrogen bond between the initial and final HB acceptors at the transition state, the jump angle is about 50° (P_W1 in FIG. 3(b)) [29]. On the other hand, the jump angle is about 70° for the hydrogen bond switching of water without hydrogen bond between the initial and final HB acceptors at the transition state (P_W2). The corresponding population curves P_M, P_M1, and P_M2 for methanol switching its donating hydrogen bond partners from methanol to methanol are also shown in FIG. 3(b) and similar to water. However, one hydrogen atom of ammonium usually switches its hydrogen bonds between two acceptors without hydrogen bonds between two hydrogen bond acceptor molecules at the transition state of hydrogen bond switching. P_M is the dominant contribution to P_A in FIG. 3(a). It is rare event for the hydrogen bond switching with jump angle of 50° (P_M1) as P_M2 and P_W2.

The hydrogen bond lifetime is another factor to determine the jump rotational time of ammonium (Eqs. (6) and (7)). The multiple hydrogen bonds between the ammonium and water were observed by X-ray and vibrational spectroscopy [39]. Our simulations show that 90% and 94% of ammonium forms four donating hydrogen bonds in water and in methanol, respectively. This means that the tetrahedron hydrogen bonding struc-
tation of ammonium is the most popular in water or in methanol. The hydrogen bond lifetime of ammonium-water and ammonium-methanol is obtained by fitting the hydrogen bond correlation function shown in FIG. 4. A good linear behavior is presented for \( \lg[C_{\text{HH}}(t)] \) as a function of \( t \) (FIG. 4). Their hydrogen bond lifetime is 2.70 and 9.67 ps. As a result, the jump rotational time of ammonium in water and in 0.5 mol/L methanol is 2.66 and 9.04 ps, respectively. The difference of hydrogen bond lifetime, that in methanol is more than three times as in water, driving the difference of jump rotational time. The jump rotation of ammonium is heavily retarded by the methanol molecules relative to solvent water.

The dramatic difference of hydrogen bond lifetime in water and in methanol is induced by the excluded volume effect of the methyl group, which dilutes the density of the hydrogen bond acceptor in methanol. The number density of methanol oxygen (the number of oxygen atom divided by the volume of simulation box) is only 14.3 nm\(^{-3}\), which is much lower than that of water of 32.6 nm\(^{-3}\). The decrement of the available hydrogen bond density reduces the rate of the hydrogen bond switching, so that the jump rotation of ammonium slows down.

The frame rotational time of ammonium is derived by fitting the frame rotational correlation function \( C_f(t) \) with single exponential function at a long time scale. The frame rotational correlation functions \( C_f(t) \) are shown in FIG. 4. The frame rotational time of ammonium is 10.35 and 30.64 ps in water and in methanol. The frame rotation is coupled with the global structure relaxation in electrolyte solutions and water-organic solvent mixtures. It has the same tendency with concentration as viscosity. However, the frame rotation in more viscous methanol is slower than in water. According to the Stokes-Einstein-Debye relationship, the rotational mobility is inversely related to the viscosity of solvent and the effective radius of ammonium. The viscosity of methanol is smaller than water, so that the effective radius of the solvated ammonium in methanol is bigger than that in water.

IV. CONCLUSION

The rotational mechanism of ammonium ion is explored by molecular dynamics simulations and the extended jump model. The reorientational correlation time can be well described with the EJM decomposition protocol like water in aqueous solutions. The faster rotation of \( \text{NH}_4^+ \) observed in water than in methanol previous experiments is mainly due to the retardation of the jump rotation of ammonium. The dilution effect of methanol methyl group reduces the density of available hydrogen bond acceptor and retards the jump rotation of \( \text{NH}_4^+ \) motivated by the hydrogen bond switchings. The slow frame rotation of the ammonium in methanol is due to bigger size of solvated ammonium in methanol than in water. The solvation size of ammonium is closely related to the formation of the tetrahedral hydrogen bond structure in both solvents. For the future work, it is also interesting to explore the relationship between the microscopic processes and the macroscopic shear viscosity, so that further insight can be shed on the dynamics of ammonium in various solvents.

V. ACKNOWLEDGEMENTS

This work was supported by the National Key Research and Development Program of China (2017YFA0206801), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000 and XDB10040304), and the National Natural Science Foundation of China (No.21373201 and No.21433014).


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