# Does Amination of Formaldehyde Proceed Through a Zwitterionic Intermediate in Water? Fragment Molecular Orbital Molecular Dynamics Simulations by Using Constraint Dynamics

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Herein, we present the results of the first full quantum mechanical (QM) molecular dynamics (MD) simulations for the reaction of formaldehyde with ammonia (Scheme 1) in solvent with explicitly considering approximately 200 water molecules. The results of the simulations with constraint dynamics[1] showed that the reaction proceeds through a stepwise mechanism with a zwitterionic species (ZW) as a stable intermediate.
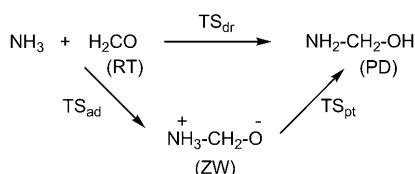
Scheme 1.

Reactions of carbonyl compounds with amine derivatives produce imines, semicarbazones or oximes through carbinolamine intermediates.[2] These amination reactions play key roles for understanding the origin of life. The reactions may be viewed to form carbinolamines (PD) in a stepwise manner[3,4] through addition of nucleophilic amines to carbonyl compounds to give ZW and subsequent water-mediated proton-transfer reactions to yield PD. Alternatively, the reactions may proceed through a concerted mechanism without forming ZW.

Jencks and co-workers explored the mechanism of a series of reactions of substituted benzaldehydes with several nitrogen nucleophiles.[5] The mechanism was found to be complicated because three key bond-formation/cleavage steps at N−C, N−H and O−H occur at different times depending on the substrate structures, the pK_a of the catalysts and the pH of the medium. They reported, for example, that two concurrent pathways occur in the addition of methoxyamine to benzaldehyde, namely, a concerted N−C and O−H bond-formation route and a stepwise route through a ZW intermediate. However, the mechanism for the parent system, ammonia and formaldehyde in pure water, still remains unclear despite the fact that the reaction is taken as the representative of amination reactions.

Molecular orbital (MO) calculations for the reaction of ammonia and formaldehyde have shown that a ZW minimum was not formed in the gas phase.[6–9] However, the analysis of a polar reaction that involves water-mediated proton transfer requires both explicit water molecules and bulk solvent in a self-consistent way. The ideal way to simulate the reaction would be to incorporate a large number of water molecules explicitly, but QM calculations of a system including hundreds of water molecules cannot be performed by conventional methods. The fragment molecular orbital (FMO) method proposed by Kitaura et al.,[10] originally designed for the electronic state calculation of a protein, allows one to treat large systems at a QM level with reasonable computational resources. Furthermore, by combining this FMO method with a MD method, denoted as FMO-MD,[11] simulations of solution reactions can be performed.

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We have previously reported the simulations for the hydrolysis of methyl diazonium cation by using FMO-MD.[12]

The first step of the present study was to carry out MO calculations to confirm that the gas-phase reaction of ammonia and formaldehyde with 0–2 water molecule(s) proceeds by a concerted mechanism. With two water molecules, the activation and reaction energies were 27.7 and −10.4 kcal mol^{-1} at HF/6-31G**, and 10.7 and −12.8 kcal mol^{-1} at MP2/6-31G**. On the other hand, the ZW could be optimised as a local minimum with the polarised continuum model (PCM) with two water molecules. The optimised structures and relative electronic energy (ΔE), enthalpy (ΔH) and free energy (ΔG) for RT, TS$_{dr}$, TS$_{ad}$, TS$_{pt}$, ZW and PD with respect to RT in vacuo and with PCM are listed in Figures S1–S2 and Tables S1–S2 in the Supporting Information. These MO calculations suggested that the results depend on the way of treatment of solvent effect. Thus further rigorous full-quantum simulations with explicit water molecules are required to obtain a realistic picture of the amination reaction in water.

FMO-MD simulations with constraint dynamics were performed at HF/6-31G** by following the sequence below. The reaction coordinate (RC) was defined as $R_{NC}-R_{NH}$, in which R_{NC} is the distance between the nitrogen and the carbon and R_{NH} is the distance between the nitrogen and one of the hydrogen atoms that is bound to it. By constraining RC, structural changes of the substrate in MD simulations are confined on the line that has the slope = 1 and intercept = RC in a More O'Ferrall–Jencks-type diagram (Figure 1),[13] in which the abscissa is R_{NH} and the ordinate is R_{NC}. It is expected that the substrate structure converges in the most stable one on the line of given RC after enough simulation time. After similar analyses with different RC values, the minimum energy reaction pathway is obtained by connecting all converged points. If the plots thus obtained are on a diagonal line on the diagram (represented by ▲ Figure 1), it shows the completely concerted mechanism, including the formation of N–C bond and the proton transfer from nitrogen to oxygen, whereas the plots represented by ● in Figure 1 exhibit the stepwise mechanism through a ZW intermediate. Based on this idea, three initial structures were prepared (Figure 1), namely, a zwitterion-like structure (A), a reactant-like structure (B) and a concerted TS-like structure (C).

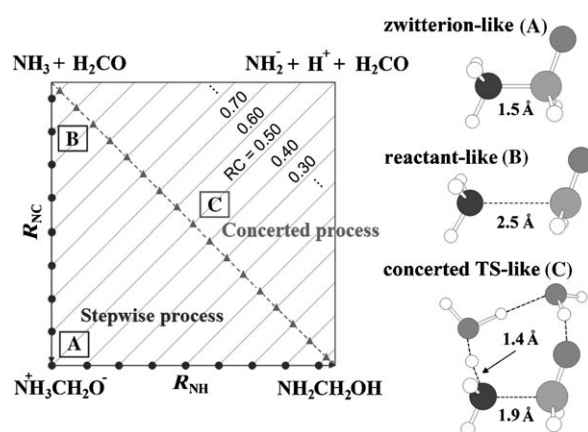The structures A and B were prepared by HF/6-31G** optimisation in vacuo with fixed

Figure 1. Schematic representation of the More O'Ferrall–Jencks-type diagram of carbinolamine formation from formaldehyde and ammonia.

$R_{NC}=1.5$ Å for A and 2.5 Å for B. Then water molecules (193 for A and 231 for B) were generated in a spherical shape around the substrate. Following equilibration of the initial structures with the fixed substrate structures by means of classical MD for 1.0 ns, 0.6 ps FMO-MD with fixed RC = 0.40 for A and 1.50 for B at 300 K were performed. After this initial minimisation, equilibrating (0.3 ps) and sampling (0.3 ps) with fixed RCs were carried out. In the series of simulations, the RC was changed by 0.10 from −0.30 to 0.90 for A, which covers from a middle to a later part of the reaction, and 0.90 to 1.80 for B, which scans the region from reactant to ZW. The time averages of R_{NC} and R_{NH} are summarised in Table S3 in the Supporting Information and the reaction profile with error bars (standard deviation) is shown in Figure 2. Figure 2 shows that the reaction
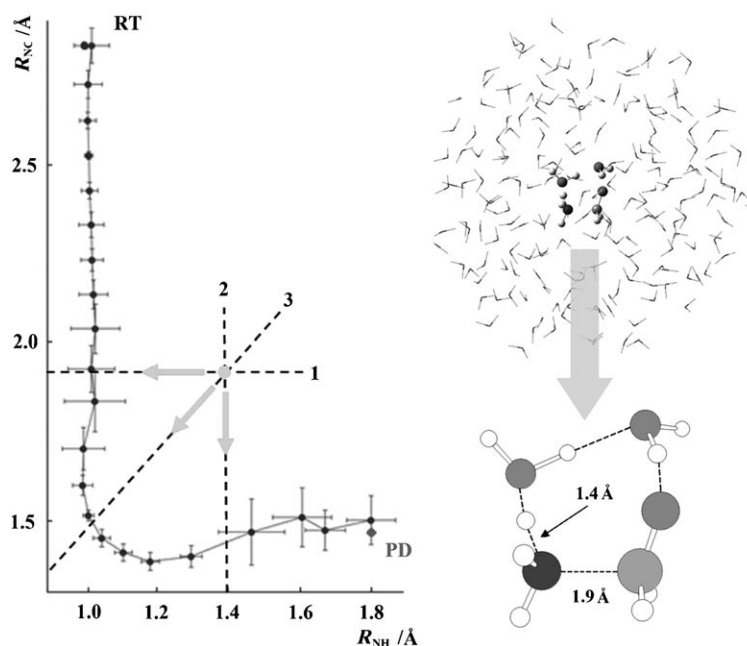

Figure 2. Reaction profile obtained by FMO-MD simulations (with error bars showing the standard deviation) and the concerted TS-like initial structure.

of ammonia and formaldehyde favours the stepwise mechanism and the ZW is stable in water at 300 K. This was confirmed by free MD simulations at 500 K and 700 K, in which the zwitterion persisted for more than 1 ps despite the fact that the high kinetic energy was injected. Note that the two water-catalysed proton transfers leading to carbinolamine were observed during the simulations at the product regions of RC = −0.30 to −0.10. The snapshots of the substrate with two catalysing water molecules at RC = −0.30 are shown in Figure S3 in the Supporting Information. The proton transfer was very fast and was completed within approximately 100 fs.

The analyses above suggested that the reaction of ammonia and formaldehyde favours the two-step mechanism. However, the ZW may have been too stable at the given temperatures to leave the ZW region, or the surrounding solvation shell may have prevented the substrate from translating to another region. To confirm that the reaction does not proceed through a concerted region, a concerted TS-like initial structure in which $R_{NC} = 1.9$ and $R_{NH} = 1.4$ Å, together with two water molecules catalysing the reaction, was prepared by MO calculation, and water molecules (191) were generated in a spherical shape around it (Figure 2). After similar equilibration steps mentioned above, three different trajectories were calculated: 1) $R_{NC} = 1.9$ Å fixed, 2) $R_{NH} = 1.4$ Å fixed and 3) RC ($= R_{NC} - R_{NH}$) = 0.50 fixed. These trajectories 1–3 correspond to the restricted substrate structures varying on the lines $R_{NC} = 1.9$, $R_{NH} = 1.4$ and $R_{NC} - R_{NH} = 0.50$ in the reaction diagram, respectively (Figure 2). The results of the analyses were summarised in Figure 3. Figure 3a shows the change in R_{NH} obtained from the trajectories 1, in which the R_{NH} decayed from 1.4 to approximately 1.05 Å, a normal N−H bond length, as the simulation time increased, and the substrate became a reactant–complex-like structure after 1.0 ps. Similarly, Figure 3b shows that the R_{NC} decayed to a N−C bond length in carbinolamine (≈ 1.45 Å), and carbinolamine was formed through water-mediated proton transfers after 1.0 ps. The simulation 3, with constraining RC = 0.50 from the concerted TS-like structure, resulted in ZW production after 1.0 ps (Figure 3c). Thus, these three trajectories starting from the concerted TS-like structure all left the concerted region, and converged to the stepwise region, eliminating the possibility of the concerted mechanism.

In conclusion, the present FMO-MD simulations clearly show that the reaction of ammonia and formaldehyde produces carbinolamine by the stepwise mechanism through the ZW intermediate, not by the concerted mechanism. Although there are many subjects to be refined, such as calculation levels, boundary conditions and relaxation time, simulations including hundreds of explicit water molecules at a full QM level as presented here will be a promising method to provide molecular level information in both organic and biological chemistry.
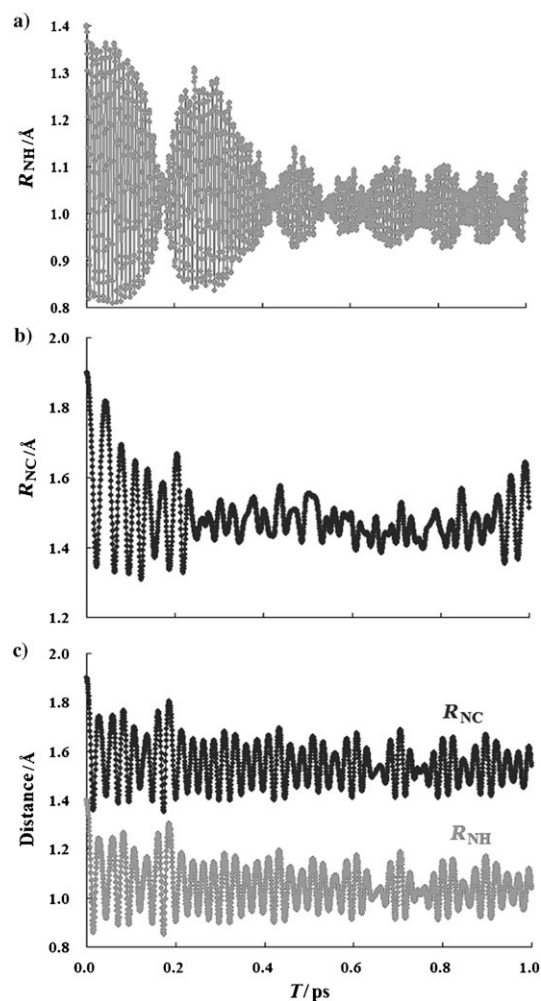

Figure 3. Change in R_{NC} and R_{NH} for 1.0 ps FMO-MD simulations with the following constraints: a) $R_{NC} = 1.9$ fixed, b) $R_{NH} = 1.4$ fixed and c) $R_{NC} - R_{NH} = 0.50$ fixed.

[1] H. C. Andersen, *J. Comput. Phys.* **1983**, *52*, 24–34.
[2] R. W. Layer, *Chem. Rev.* **1963**, *63*, 489–510.
[3] T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper & Row, New York, **1987**.
[4] W. P. Jencks, *Acc. Chem. Res.* **1976**, *9*, 425–432.
[5] S. Rosenberg, S. M. Silver, J. M. Sayer, W. P. Jencks, *J. Am. Chem. Soc.* **1974**, *96*, 7986–7998. J. M. Sayer, B. Pinsky, A. Schonbrunn, W. Washtien, *J. Am. Chem. Soc.* **1974**, *96*, 7998–8009.
[6] I. H. Williams, *J. Am. Chem. Soc.* **1987**, *109*, 6299–6307.
[7] K. Y. Burshtein, A. N. Isaev, *THEOCHEM* **1985**, *133*, 263–268.

[8] D. Courmier, F. Gardebien, C. Minot, A. St-Amant, *Chem. Phys. Lett.* **2005**, *405*, 357–363.

[9] D. E. Woon, *Icarus* **1999**, *142*, 550–556.

[10] K. Kitaura, E. Ikeo, T. Asada, T. Nakano, M. Uebayasi, *Chem. Phys. Lett.* **1999**, *313*, 701–706.

[11] Y. Komeiji, T. Ishikawa, Y. Mochizuki, H. Yamataka, T. Nakano, *J. Comput. Chem.* **2009**, *30*, 40–50. Y. Komeiji, Y. Mochizuki, T. Nakano, D. G. Fedorov, *THEOCHEM* **2009**, *898*, 2–7.

[12] M. Sato, H. Yamataka, Y. Komeiji, Y. Mochizuki, T. Ishikawa, T. Nakano, *J. Am. Chem. Soc.* **2008**, *130*, 2396–2397.

[13] R. A. More O'Ferrall, *J. Chem. Soc. B* **1970**, 274–277; W. P. Jencks, *Chem. Rev.* **1972**, *72*, 705–718.