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Theoretical study on water-retaining action of trimethylglycine

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N,*N*,*N*-trimethylglycine (TMG) is one of well-known osmolytes, which are used to protect living cells against osmotic stress. The protection appears as an accumulation of osmolytes in the cell cytoplasm of living organisms with the effect of raising the osmotic pressure when the cells are under the stress. It was considered that the hydration around TMG plays an important role in its function, and many physiological or physicochemical studies on TMG were conducted. In the previous study, a cluster model of trimethylamine-*N*-oxide (TMAO), which is also one of osmolytes, with water molecules was presented as a representative hydration structure of TMAO [1]. We consider that TMG also packs water molecules around it strongly, and has a potential to induce specific hydration structures. In this study, we investigate the hydration structure of TMG.

The geometry of TMG was optimized in the gas phase using *ab initio* MO method. The theoretical level, MP2(full)/aug-cc-pVTZ, was used for the geometry optimization and the vibrational frequency calculation. In aqueous solution, QM/MM-MD simulations were performed for a TMG molecule as QM (HF/6-31G) in a droplet with 216 water molecules as MM (TIP3P). The temperature was set at 298.15 K. The total step numbers were 100000 steps, of which first 5000 steps were used for equilibration and the structures of later 95000 steps were analyzed and averaged.

Figure 1 shows the structures of TMG in the gas phase: conformer-A, B, C, and D. It was confirmed that the conformer-B is the stable structure, and that the other conformers are the transition state structures. In aqueous solutions, QM/MM-MD simulations were performed for each of these four structures using as an initial structure (QM) surrounded by 216 water molecules (MM). Regardless of initial conformation, TMG changed to conformer-B in aqueous solution with occasional appearance of conformer-A. Here, we focus on the first hydration shell of TMG. We found that TMG forms strong hydrogen bonds with water molecules near the carboxylate group. Eleven hydrogen atoms in methyl and methylene groups of TMG are slightly cationic, because of the central cationic nitrogen atom, so that these hydrogen atoms tend to form hydrogen bonds with oxygen atoms of water molecules. Figure 2 shows a snapshot of the hydration networks, which connect the carboxylate group and methyl/methylene groups through water molecules. In average, about 27 water molecules are retained in these networks.

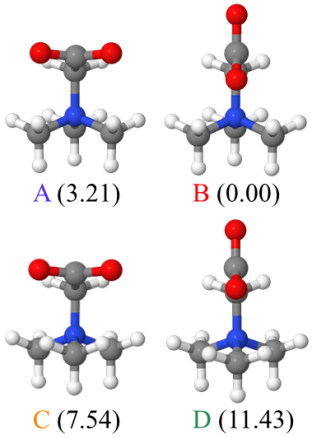

Fig. 1. The conformations of TMG in the gas phase (relative energy in kcal/mol).

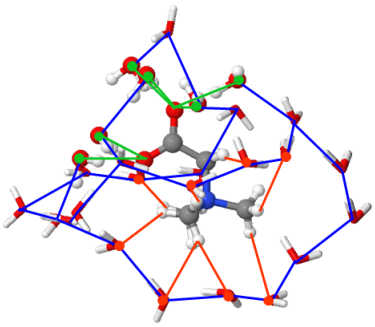

Fig. 2. Hydration networks around TMG (a snapshot in a trajectory).

[1] H. Doi, Y. Watanabe, M. Aida, *Chem. Lett.* **43**, 865 (2014).