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Selective formation of bicyclic guanidinium chloride complexes: implication of the bifunctionality of guanidines

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ABSTRACT

Two bicyclic guanidinium chloride structures in the anhydrous and the monohydrated forms were selectively synthesized and characterized, demonstrating the versatile bifunctionality of guanidine molecules.

Guanidine molecules share a Y-shaped CN_3 moiety with high basicity due to the resonance-stabilized guanidinium cation.[1] Guanidine plays important roles in biological functioning, that is, as the side chain functional group found in the amino acid arginine and notably in the nucleic acid nitrogenous base guanine. Arginine is protonated to give the guanidinium species at physiological pH. The protonated cationic side chain of arginine has been identified as a prosthetic group contributing proton source in a concerted protonation reaction of a ferric-peroxo intermediate in the catalytic cycle of cytochrome P450.[2] Moreover, the positive arginine side chain is responsible for electrostatic interaction of the cationic guanidinium with the anionic part of a substrate during binding in the active site of enzymes.

Guanidine organoctatalysts have recently attracted increased attention as they are able to mediate a wide variety of organic bimolecular reactions, such as Diels–Alder reactions,[3] 1,2- and 1,4-addition reactions,[4–14] and ring-opening polymerizations of lactones and lactides.[15,16] It has been proposed that the guanidine molecule may first serve as a Brønsted base to abstract a proton from the substrate to form a guandinium intermediate which might (1) act as a dual hydrogen bond donor to form a complex with the deprotonated substrate to direct the attack of the electrophile,[12–14] or (2) form a hydrogen bond with the substrate as well as the incoming electrophile to generate a pre-transition-state intermolecular complex (Fig. 1).[4] While these two plausible mechanisms are debatable, few kinetic or theoretical studies have been conducted to clarify the exact role of the guanidine catalyst. Complexes of neutral 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and metals, primarily early *d*-block transition metals, have been reported by Coles, Hitchcock and co-workers.[17,18] Ionic forms of guanidine (as guanidinate or guanidinium) have also been investigated and several of such metal compounds have been synthesized and structurally characterized.[19–23]

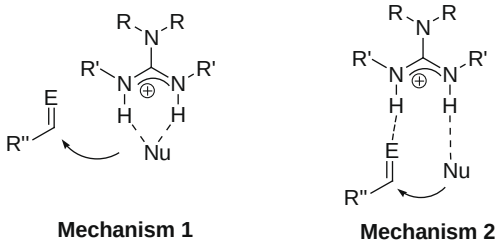

Figure 1. Previously proposed mechanisms for guanidine-catalyzed addition reactions.

During the course of our study, guanidinium chloride structures 1 and 2 were reported by Himmel and co-workers[24] These compounds were obtained as by-products in the synthesis of *cis* and *trans* $(TBD)_2PtCl_2$. Little was discussed about the structure and ideas presented on the mechanistic nature and their relevance to guanidine organocatalysis. Herein, we demonstrate that we are able to tune selectively the reaction conditions to synthesize anhydrous and monohydrated guanidinium chloride compounds from TBD to enable mechanistic investigations.

TBD is a strong Brønsted base because its conjugate acid is resonance-stabilized, an effect known as the Y-aromaticity effect.[25] In an effort to prepare the TBD·HCl complex, we realized that the approx. 5 wt % of water in commercially available TBD could allow stoichiometric control of the formation of HCl upon reaction with Lewis-acidic metal chlorides. The preparation of TBD·HCl (**1**) was achieved by mixing anhydrous $CrCl_3(THF)_3$ and TBD in a 1:2 ratio with THF at room temperature. After removal of THF, the residue was extracted using DMF. Filtration, followed by recrystallization at −35 °C afforded colorless plates suitable for X-ray analysis.

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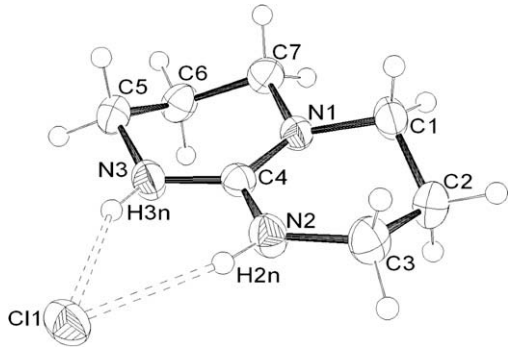

Figure 2. X-ray structure of TBD·HCl (**1**). Relevant dimensions (Å and °): C4–N1 1.331, C4–N2 1.333, C4–N3 1.342, N2–H2n 0.850, N3–H3n 0.874, Cl1–H2n 2.316, Cl1–H3n 2.431, N2–H2n–Cl1 164.30, N3–H3n–Cl1 154.54, N1–C4–Cl1 177.33. CCDC 659357.[24]

The colorless crystals were very hygroscopic and decomposed rapidly upon exposure to air. Selection and mounting of a single crystal onto the glass fiber, therefore, had to be executed quickly followed by sealing the crystal in epoxy glue. The crystal structure confirmed the formation of guanidinium chloride **1** (Fig. 2). The fused bicyclic six-membered rings adopt a '*syn* half-chair' conformation in contrast to those of '*anti* half-chair' conformers observed in most of the other guanidinium complexes in the literature.[26–30] The chloride anion is positioned approximately centrally and symmetric to the guanidinium cation N2–C4–N3 plane with an N1–C4–Cl1 angle of 177.33°. The chloride forms two H-bonds with the two N–H groups (2.316 Å and 2.431 Å for Cl1–H2n and Cl1–H3n, respectively). The H-bonding of this doubly bifurcated H-bond system, in which the guanidinium is a double proton donor while the chloride is a double proton acceptor,[31] is non-linear and thus is not strong. The other weak interaction involved is coulombic attraction due to the opposite charges carried by the chloride and guanidinium.

To investigate the influence of the addition of another hydrogen bonding acceptor on the guanidinium binding geometry, we prepared the guanidinium chloride salt in the presence of additional water. TBD·HCl·H_2O (**2**) was synthesized by treating $CrCl_3·6H_2O$ with 2 equiv of TBD in THF (46% yield). After the removal of THF, the residue was extracted using MeCN. Filtration was followed by recrystallization at −35 °C. Analysis of the crystal structure of **2** revealed that the bicyclic conformation of the guanidinium was intact while one of the N–H bonds is taken over by an incoming water molecule (Fig. 3). Guanidinium chloride **2** has a unit cell size similar to that of **1**, suggesting that the inclusion of water in **2** does not affect the overall crystal system since the guanidinium cation is much larger in size which defines the overall structural system and water only enters the system to take up interstitial space. Nevertheless, these observations are unambiguous evidence of the bifunctional role of guanidine. TBD first served as a Brønsted base (the imine N) to react with HCl and subsequently acted as an acid (one of the two resulting N–H bonds) to bind to a water molecule.

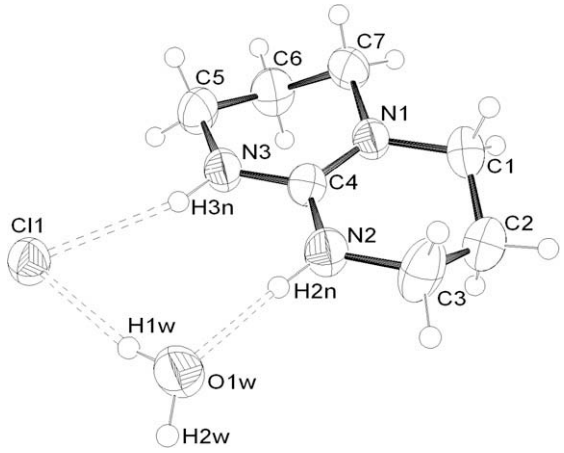

Figure 3. X-ray structure of TBD·HCl·H_2O (**2**). Relevant dimensions (Å and °): C4–N1 1.325, C4–N2 1.343, C4–N3 1.330, N2–H2n 0.883, N3–H3n 0.882, Cl1–H3n 2.374, Cl1–H1w 2.202, O1w–H2n 1.961, O1w–H1w 0.901, N2–H2n–O1w 171.46, N3–H3n–Cl1 161.53, Cl1–H1w–O1w 166.55. CCDC 659356.[24]

In summary, we have tuned the reaction conditions by treating anhydrous and hydrated metal chlorides with commercially available TBD to prepare selectively TBD·HCl (**1**) and TBD·HCl·H_2O (**2**). We have demonstrated that in the absence of other reactants, the guanidinium cation tends to form dual hydrogen bonding with the counter anionic substrate (in this study, chloride). On introduction of a hydrogen bond acceptor, such as a water molecule, the guanidinium complex is able to share one of the hydrogen bonds to include the incoming water molecule into the N(H)–C–N(H) coordination sphere. Kinetic studies and computational modelling of the mechanisms in related guanidine-catalyzed reactions based on these observations are ongoing in our laboratories and will be reported in due course.

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