Wöhler’s synthesis of urea (1) from lead cyanate, reported in 1828,\textsuperscript{1} revolutionized thinking regarding the synthesis of naturally occurring organic molecules. Since then, urea, apart from being a commercially important fertilizer, has been utilized by chemists in innumerable chemical reactions, in host-guest chemistry, and in recent times in catalysis. Its sulfur-containing analog, thiourea (2), has also played a major role in organic chemistry and catalysis. In particular, both have seen extensive application in the newer discipline of organocatalysis.\textsuperscript{2-4}

Relatively speaking, squaramide (3) is a much more contemporary molecule. It can be regarded as a vinylogous amide, and was first synthesized in 1966 from the corresponding ester.\textsuperscript{5} Squaramide has not been as extensively utilized as urea, but it has seen application in host guest chemistry.\textsuperscript{6,7} Very recently, one investigator, Rawal, has begun to champion the use of squaramide derivatives in organocatalysis.\textsuperscript{8-11}

The objective of this seminar is to provide a head-to-head comparison of the relative efficacies of urea- and squaramide-based organocatalysts, particularly in the context of enantioselective carbon-carbon and carbon-nitrogen bond forming reactions.

Urea (1), thiourea (2), and squaramide (3) can be viewed as special types of carboxylic acid amides. In the first two compounds, one carbon atom separates the two nitrogen atoms, and in the last, two carbon atoms. The carbonyl groups can potentially interact with Lewis acids, but the nitrogen atoms do not possess appreciable basicities. However, they can interact with hydrogen bond acceptors, a property that has been extensively established for ureas and thioureas.\textsuperscript{12-14}

The two nitrogen bound hydrogen atoms in 1-3 can effectively act as two-fold hydrogen-bond donors (Figure 1). The presence of two carbonyl oxygen atoms in squaramide 3 makes it a multiple hydrogen bond acceptor as well.\textsuperscript{15} The four membered ring in squaramide is a formal
$2\pi$ electron system, and is thereby aromatic, as verified by Nucleus Independent Chemical Shift (NICS) calculations.\textsuperscript{16}

![Diagram of H-bond acceptor and donor centers](image1)

**Figure 1.** Hydrogen-bond acceptor and donor centers.

From computational experiments, it has been found that the aromaticity of squaramide is enhanced in the presence of hydrogen bond accepting anions or hydrogen bond donating cations.\textsuperscript{15} In the presence of both cations and anions the adduct even becomes comparable to benzene in aromaticity.\textsuperscript{16} These are some of the prime reasons that squaramides have seen utilization in the arena of ion sensing.\textsuperscript{17,18}

![Diagram of modes of activation by hydrogen bonding](image2)

**Figure 2.** Modes of activation by hydrogen bonding

Hydrogen bonding activates various organic substrates as depicted in Figure 2. Curran\textsuperscript{19} first demonstrated an urea based rate enhancement in the condensation shown in Figure 3. Soon, thereafter catalytic enantioselective reactions were developed by Jacobsen\textsuperscript{20} followed by

![Diagram of urea catalyzed reaction](image3)

**Figure 3.** First report of hydrogen bond assisted urea catalyzed reaction.
Takemoto,²¹ Wang,⁴ Berkessel,²² Connon²³ and many more. Hundreds of chiral urea and thiourea catalysts have now been reported.

It represented a breath of fresh air when Rawal, thinking "outside of the box", screened for additional types of two-fold hydrogen bond donors and placed squaramide derivatives onto the chemical podium. Squaramide features a 2.72 Å NH⋯HN distance, ca. ~0.6 Å longer than that in urea (2.13 Å).¹¹ At the same time, the N-H fragments are more convergent. The protons are more acidic because the charge in the conjugate base is better delocalized than in urea.²⁴

These unique features have led Rawal and others²⁵⁻³⁰ to promote chiral squaramide derivatives as useful catalysts for the reactions shown in Figure 4. These include conjugate additions of 1,3-dicarbonyl compounds to β-nitrostyrene and its derivatives,⁸ Michael additions of phosphates to nitroalkenes,⁹ α-aminations of 1,3-dicarbonyl compounds,¹⁰ Friedel-Crafts reactions,¹¹ Michael additions of nitro alkanes,²⁵ conjugate additions of thiols to chalcones,²⁶ and Michael addition of 4-hydroxycoumarins to β,γ-unsaturated α-keto esters.²⁷ Squaramide derivatives have also been used in dynamic kinetic resolutions of racemic azalactones²⁸ and even with suitable substitution as Brønsted acid catalysts.²⁹

Figure 4: Reactions catalyzed by urea(thio) or squaramide along with yield and ee for squaramide catalyzed reactions.

It is hoped that this presentation will clearly compare the pros and cons of the two classes of catalysts, thereby allowing the audience to make independent judgements as to which may best be applied for their purposes and the horse to ride in the future. However, it may require additional time and study for an unambiguous winner in this "Chemical Combat".
References


