

Dr. Brian Goess- Exploring the Chemical and Biological Potential of the Cyclopropane Functional Group

The study of the structure and reactivity of cyclopropanes has yielded significant insights into the nature of the carbon-carbon bond and has led to unique roles for cyclopropanes in chemistry and biology. Since the publication of two complimentary models for bonding in cyclopropane, the first by Förster, Coulson and Moffitt in 1939, and another by Walsh in 1947, chemists have recognized that the enhanced p-character of the strained carbon-carbon bonds of cyclopropane should lead to unusually high alkene-like reactivity (Figure 1).

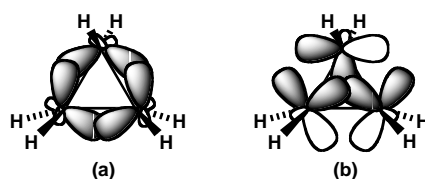
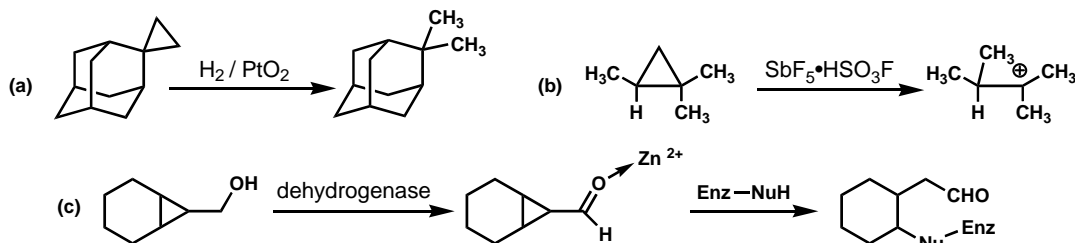


Figure 1. (a) Förster-Coulson-Moffitt model. Carbon-carbon bonds are formed from overlap of “sp⁵”-hybridized orbitals emanating from each carbon atom. (b) Walsh model. Carbon-carbon bonds are formed in part from overlap of unhybridized p orbitals emanating from each carbon atom.

Experimental observations have consistently confirmed this hypothesis. In direct analogy to alkenes, cyclopropanes are susceptible to catalytic hydrogenation to yield acyclic alkanes (Scheme 1(a)), and cyclopropanes can be protonated in strong acid to yield acyclic carbocations (Scheme 1(b)). In recent years, increasingly sophisticated applications of the alkene-like reactivity of cyclopropanes have been disclosed. For instance, mechanism-based inhibitors that rely on the conjugate acceptor-like reactivity of activated cyclopropanes have been designed (Scheme 1(c)).



Scheme 1. Cyclopropanes exhibit alkene-like reactivity in chemical and biological systems.

Advances in the use of the cyclopropane functional group in chemistry and biology will rely on increasing our understanding of the scope of cyclopropane reactivity. The proposals described herein test the boundaries of the cyclopropane/alkene analogy by investigating the reactivity of cyclopropanes in new chemical and biological systems. The results of these studies will provide a series of tools for use in synthetic organic chemistry and chemical biology.

Objectives

The unique reactivity of cyclopropanes provides the opportunity for creative applications of these strained carbocycles as synthesis tools and as probes of biochemical mechanisms.

Furthermore, since the reactivity potential of cyclopropanes has not been fully explored, significant opportunities for methodology development remain. My research program will focus on expanding the known reactivity of cyclopropanes, developing cyclopropane-based methodologies to facilitate the synthesis of substructures commonly found in bioactive natural products, and devising new uses for cyclopropanes as probes of biochemical processes. *Students who join my laboratory will strengthen their skills in organic synthesis, spectroscopy, and reaction development.* Our initial efforts will address the following three objectives:

[1] Expanding the known reactivity of cyclopropanes. The discovery of new reactions facilitates the synthesis of complex organic molecules. We plan to demonstrate the utility of cyclopropanes as homologated π components in sigmatropic rearrangements. Applications to the stereoselective synthesis of functionalized α -amino acids and to the synthesis of enantioenriched amines, both key building blocks of bioactive molecules, will be explored.

[2] Devising new uses for cyclopropanes as probes of biochemical processes. The search for molecules that are highly active and selective anti-cancer agents is a key goal of modern organic chemistry. Many members of the furanosteroid family of natural products possess significant anti-cancer activity. However, their high intrinsic reactivity leads to high toxicity and low enzyme selectivity. We will prepare a cyclopropyl homolog of one member of this family, hisbicone C, in an effort to understand how this type of structural modification affects its chemical reactivity. A biotinylated cyclopropyl homolog of hisbicone C will also be prepared and used in an enzyme binding assay to assess the effect of cyclopropane homologation on its enzyme selectivity.

