

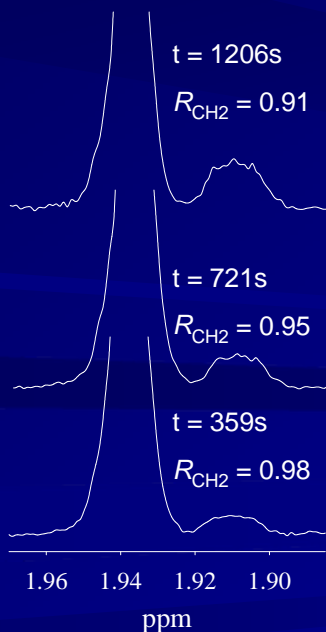
# Ring Strain and Antiaromaticity: Their Effect on the Generation and Reactivity of Enolates in Small-Ringed Ketones



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The fundamental importance of enolates as intermediates in the formation of carbon-carbon bonds is obvious when one considers the amount of space devoted to this topic in Organic Chemistry textbooks. An area of enolate chemistry that has not received as much attention is the effect of ring strain on the generation and reactivity of enolates in cyclic ketones. The strained ring ketones are fundamentally interesting as the induction of strain will result in increased s-character in the C-H bonds thus increasing their acidity, however ring strain should disfavor enolate generation. In the less strained analogs (cyclopentanone and cyclohexanone) the relative reactivity of these compounds to acetone/3-pentanone will provide information about importance of conformational restriction and the orientation of the C-H to the  $\pi$ -system of the carbonyl. These results could have implications in our understanding of many other reactions where strain has been proposed to play a role in the reactivity of the system. An example, would be the induction of strain in substrate molecules and the reduction of degrees of rotational freedom that are often proposed as important modes of lowering the activation energy of enzymatically catalyzed reactions.

The study of enolate generation in strained ring and cyclic ketones by traditional methods is complicated by product stability, and reactivity of the substrate. In our studies enolate generation is followed by performing studies in  $D_2O$  in the presence of general-base catalysts and following deuterium incorporation into the starting material *via*  $^1H$ -NMR. This method circumvents many of the problems traditionally associated with such studies. See figure below of deuterium incorporation into cyclohexanone catalyzed by 3-chloroquinuclidine.



Several compounds have been investigated utilizing this method. For example the  $pK_a$  of benzocyclobutenone has been estimated to be  $\sim 26$  and a  $pK_a$  of 20 has been determined for cyclobutanone. These values are based upon second-order rate constants for the deprotonation of these compounds and estimating the reprotonation rate based upon data from the Bronsted plot.

From the literature, the relative rate of enolization for cyclic ketones is  $C_4 > C_5 > C_8 > C_7 > C_6$  or  $C_4 > C_5 > C_6 > C_7$ , however our results clearly and consistently indicate that this order should be  $C_5 > C_6 > C_4$ . Clearly the effects of strain and the orientation of the alpha protons is more complex than was originally anticipated.

In addition, the synthesis of [4.2.0]-bicyclobutanone and bencyclobutenone derivatives has been undertaken and their rates of enolization will be investigated.

