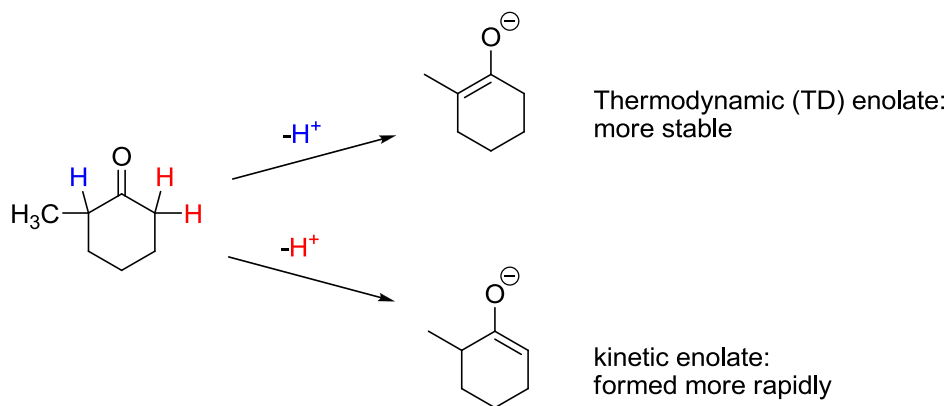


Kinetic vs. Thermodynamic Enolates

An asymmetric ketone with hydrogens at both α -carbons can form two regioisomeric enolates.

If the two α -carbons differ in their degree of substitution, it may be possible to control which of the two regioisomers predominates.



Removal of a proton from the more substituted (and more hindered) α -carbon gives the enolate with the more substituted C=C double bond. This enolate is the more thermodynamically stable, and is referred to as the thermodynamic (TD) enolate. Compare this with Zaitsev's rule, which predicts that reactions that form alkenes favour the production of the more substituted alkene.

Removal of a proton from the less substituted (and less hindered) α -carbon gives the enolate with the less substituted C=C double bond. This enolate is less stable than the TD enolate, but it is formed more rapidly because the hydrogen being removed is more sterically accessible.

In reactions where one product is kinetically favoured and another thermodynamically favoured, the kinetic result is favoured by low temperatures and an irreversible reaction. However, if the reaction is reversible, the kinetic product can revert back to starting material and react again, possibly forming the thermodynamic product. Higher temperatures would then increase the rate at which the two products interconvert.

In the case of enolate formation: if deprotonation is **rapid**, **quantitative**, and **irreversible**, the kinetic enolate predominates because it is formed more rapidly. The pK_a difference between diisopropylamine (36) and a ketone (18-20) indicates that the deprotonation of a ketone with LDA will meet these criteria. Once "locked" as the kinetic enolate, it doesn't matter that it's also

the less stable enolate. Thus **a strong, hindered base like LDA, at low temperatures, typically will favour formation of the kinetic enolate.**

However, if the pK_a difference between the base and the enolate is not great, then enolate formation is reversible. The enolates can interconvert between the TD and kinetic, and over time the more stable TD enolate will predominate. **Weaker bases such as alkoxides or amines, and higher temperatures, favour formation of the TD enolate.**