



Using Regioselective Formation of Enolates to Compare Kinetic and Thermodynamic Control

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ABSTRACT

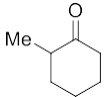
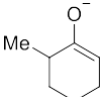
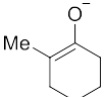
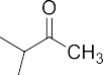
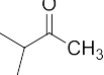
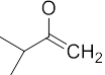
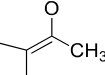
This article provides a clear explanation of how students can easily understand the idea of thermodynamic and kinetic control in the creation of enolates under fundamental conditions. The major goal of this conversation is to provide students with a thorough understanding of this topic while delivering instruction in a familiar and comfortable way.

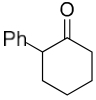
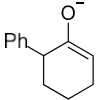
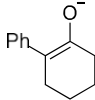



INTRODUCTION

Regioselectivity in the synthesis of enolates and the study of kinetic or thermodynamic control has historically been regarded as two of the most difficult and time-consuming subjects in education. The idea of kinetic vs thermodynamic control of processes has been covered in numerous studies and the majority of undergraduate textbooks^{1-2,3-5} Several papers have also been written that provide organic undergraduate experiments that illustrate this concept.⁶⁻¹⁰ Regarding the exposition of this idea in the lecture hall, Mc Naught has written a note. HgCl₂ and KI react during the experiment.¹¹ With the aid of a perfect gas model, Macomber produced an article on perfect gas behavior to explain the relationship between kinetic and thermodynamic control of a reaction.

A real-world comparison.¹² However, it should be taken into account that this idea might be more difficult for students to understand in the case of enolate formation reactions where other variables are involved, including solvation, rate of interaction with a trapping agent, type of base, and counteraction, and reaction temperature. All of the aforementioned factors could result in a completely different outcome than what would be anticipated (Table 1, entries 2 and 3b, and entry 5a). As a result of these exceptions, teachers may frequently have to field numerous inquiries from their inquisitive students. With the aid of a straightforward invention and a very safe demonstration on this subject, we're going to clarify all the useful and perplexing parameters to students in this section.

Table 1 Lists the Chemical Makeup of Enolate Combinations Created Under Kinetic and Thermodynamic Control

				
	a	Kinetic (LDA, 0°C)	99%	1%
	b	Thermodynamic (NaH)	26%	74%
2				
		(C ₂ H ₅) ₃ N, (CH ₃) ₃ SiOSO ₂ CF ₃ , 2 0°C	84%	16%
3				

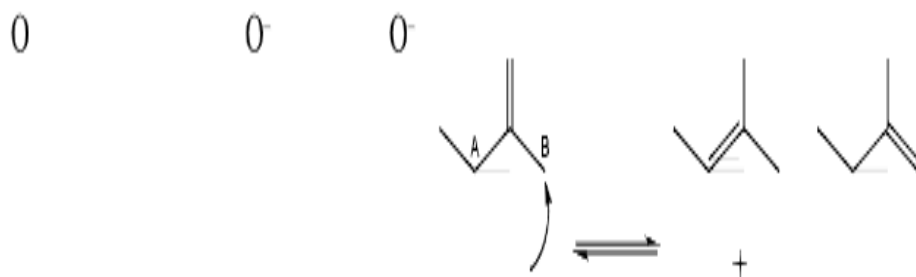
	a	Kinetic(KHMDS, -78°C)	99%	1%
	b	Thermodynamic(KH)	88%	12%
4				
	a	Kinetic(LDA/tetrahydrofuran, -70°C)	Only enolate	
	b	Thermodynamic(KH, tetrahydrofuran)		Only enolate
5				
	a	Kinetic (LDA, 0°C)	14%	86%
	b	Thermodynamic(NaH)	2%	98%

At first glance, the idea of thermodynamic vs kinetic control of enolate production may appear to have a simple definition. However, based on our observations, many students struggle to put this idea into practice since they frequently struggle to grasp ideas like speed and stability. They frequently have the incorrect idea that more stable materials form more quickly. When other factors, such as the solvent, the reaction temperature, the kind of base, and the counteraction are present in reactions like the creation of enolates, the problem is exacerbated. In this situation, pupils may become perplexed and begin to memorize reactions or start showing you exception instances and asking you why a product didn't conform to their learned principles. Students will be shown a straightforward, understandable procedure that takes into account each parameter and how it affects the final result. In order to support the regioselectivity of enolates' formation, we thus use a physical principle. We intend to demonstrate that the faster-forming state is not always the most stable one.

Consider two parallel columns (A, B) connected by two gradient stopcocks (D1, D2). Stopcocks slope toward column A, which is longer than column B. An output stopcock (D5, D6) is present in each column. A water reservoir with two stopcocks (D3, D4) is located above the columns (Figure 1). Column B relates to a kinetic product and a state that is wanted in a short period of time, while column A is intended to suggest a more stable state or thermodynamic product. The terms D1 and D2 relate to variables that govern the equilibrium between A and B. D3 and D4 are the initial deprotonation reaction rates. After the synthesis of enolates, the rates of the subsequent reactions are shown by D5 and D6, respectively.

A ketone with the formula displayed in scheme 1 is an example. Two sites for proton abstraction give rise to two distinct enolates (A, B). Does deprotonation at position A or B occur after the addition of any specific base?

Due to gravity, objects frequently fall to the earth. (Now throw a Piece of chalk or a pen and let pupils witness the result). Objects that are close to the ground are more stable than those that are farther away from the. A straightforward tool for grasping the idea of kinetic and thermodynamic control is shown in Figure 1.



The experiment demonstrates that different products could be produced based on the circumstances. It should be observed that product A is more stable since the enolate is more heavily substituted, and from what we know, more substituted alkenes are more stable. Deprotonation of B is, however, significantly easier because of the reduced steric barrier.

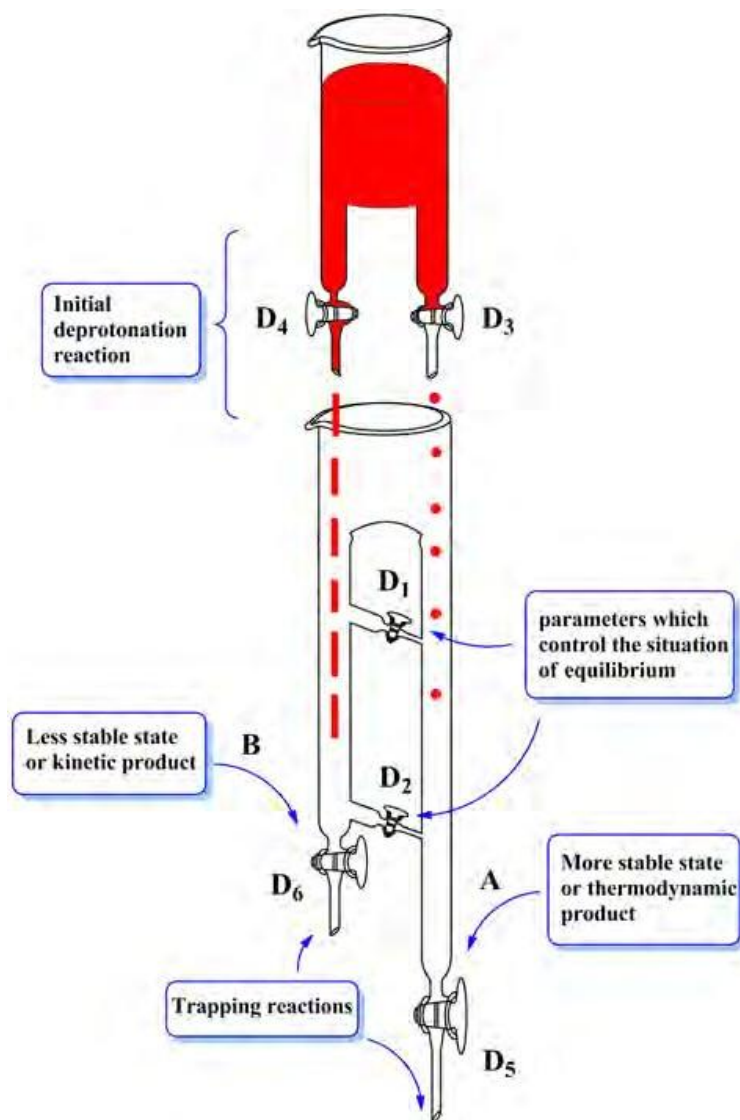


Figure 1. A Simple Apparatus for Understanding Concept of Kinetic and thermodynamic Control

Proton removal at the start of a response can actually be compared to harvesting apples from a tree. Think about which is simpler to pick: an apple hanging from a single branch or an apple passing through a forest of dense branches. If the proton is in a highly substituted position, deprotonation will be more challenging and removal of the proton will be more difficult when bulky bases like lithium diisopropylamide (often abbreviated LDA) are present (Figure 2).

With the use of our suggested apparatus, the rates of competing processes for proton removal from two separate sites may be simulated (Figure 1). As a follow-up question, ask the students if transferring a sizable amount of water from stopcock D4 as opposed to stopcock D3 could serve as evidence that, during the initial stages of this transfer, water exiting from stopcock D4 would place in a more stable position (A: a position that is more close to the ground) than water came out from stopcock D3.

Both kinetic and thermodynamic principles may be used to control the final product's composition. What impact do a system's equilibrium and competitive rates of product production have? With the aid of the aforementioned equipment, we hope to provide a response to this topic here.

Assume that the water trickles slowly through stopcock D3 into the right column while flowing more quickly via stopcock D4 and that both stopcocks are open into the left column via stopcock D4. Which side of the device, A or B, will hold the water supply? Column B would typically be the correct response due to the greater water flow. However, because of the law of gravity, objects gravitate toward the Earth. In this regard, posture A is more stable than position B. Water will flow to the right column if stopcock D2 is opened as a result. Although B is more reachable, A is a thermodynamic product. It is evident that the amount of water generated from D2 stopcocks (equilibrium constant) and competing proton removal processes.

Table 2 lists the optimum parameters for kinetic control of enolate production (HMDS: hexamethyldisilazane). 1

Deprotonation must be	In the Lab.	Reason
Rapid Quantitative Irreversible	Strong and bulky bases (LDA, HMDS)	Removal of less hindered hydrogen is accentuated
	Aprotic solvent	Protic solvents permit enolate equilibration by reversible protonation-deprotonation
	In the absence of excess ketone	Excess ketone leads to equilibration
	Coordination of counterion at oxygen must be tight (Li)	For reducing rate of proton exchange
	Low temperatures	High temperature leads to equilibration

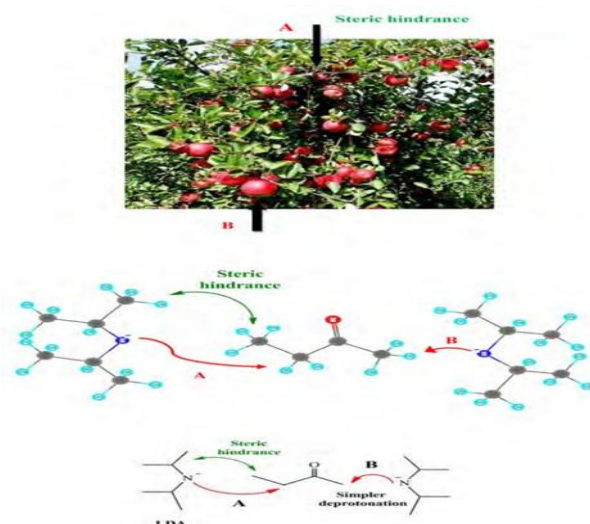


Figure 2 shows a comparison between choosing an apple from a tree's various branches and the rate of proton removal from a ketone's various places.

Table 2 discusses the particular circumstances that govern the kinetic control of enolate production. The table indicates that deprotonation needs to happen quickly so that the removal of the hydrogen that is less hindered can be enhanced. The final product should also not converge to the thermodynamic product. It is comparable to a stopcock D4 that is open but D3 and D2 that are almost closed. The majority of the water will therefore enter at position B as it flows. This is exactly what would happen if a powerful base, like LDA, were applied at low temperatures (Table 1; entries 1a and 4a). In other words, a method to regulate the flow of water output from D3, D4 (the rate of water vaporization) is to apply a substantial, strong base at a lower temperature.

Imagine that the stopcock D2 is currently open, but D3 is somewhat more open and D4 is more closed than it was previously. In contrast to the kinetic control example, more water is added to column A as a result. Furthermore, a portion of the water that is being held in column B will flow to column A. In fact, in this instance, we let the system establish the equilibrium. Thus, a product with greater stability will be produced. This is similar to the circumstance in which we apply a weaker and less substantial basis, such as KH. Equation results from this situation. The first step results in the formation of the kinetic product (B), but it quickly comes into equilibrium with A (Table 1; entries 1b and 4b). It should be noted that strong bases have a tendency to abstract the proton quickly, whereas weak bases do not. Therefore, applying weaker bases with less steric hindrance is comparable to the requirement that we give the reaction more time or dictate the reaction pathway to thermodynamic control (opening stopcock D3), and using bulky bases is a tactic to provide the kinetic control conditions (closing stopcock D3).

In order to obtain the kinetic product, the conditions that ensure the reaction is essentially irreversible and suppress the equilibrium are, in brief, as follows:

1. Extremely fast reactions
2. Using aprotic solvents in place of protic solvents
3. A chilly climate
4. Avoid consuming too much ketone.

Each of the aforementioned conditions must be absent in order for stopcock D2 to be open, which is a sign of balance: Enolate's trapping time is extremely significant, as Entry 2 (Table 1) demonstrates. Et₃N is a weak base, but because it is trapped by (CH₃)₃SiOSO₂CF₃ very quickly, there is less of a chance that a thermodynamic product will form. Assume a person is there when water is flowing into columns A and B. To send all the water out and prevent the conversion of B to A, quickly open stopcock D6. More kinetic product is obtained from this person the faster they are. It should be remembered that proton removal from position B is typically quicker. However, in this case, we use a weak base with low steric hindrance at room temperature to open the stopcock D3 a little bit more while the water flow from D4 continues to exceed the stopcock D3. At this point, when the stopcock D6 is fully open, the probability of equilibrium is almost zero because of the quick subsequent reaction.

Here, we give two particular instances to give you a thorough understanding of this idea. The less substituted alkene is created under both kinetic (strong, bulky base at low temperature) and thermodynamic (weaker base at higher temperature), as shown in entry 3 (Table 1). However, more heavily substituted enolate is more stable due to more challenging solvation, even though the main product is the same in both situations. It is comparable to the situation when D2 is closed and stopcock D1 is open. As a result, changing B into A is incredibly tough. With product A being more stable, its anion would also be less solvated. In both cases, the reaction is therefore in favor of the kinetic product. Entry 5 (Table 1) makes the argument that under both kinetic and thermodynamic circumstances, the more strongly substituted product forms. The stopcock D2's full open position is at this moment. This implies that A gets changed into B as soon as B is generated. The main factor, which outweighs steric effects, is the acidification of the vicinal CH next to the pH and the stability of the produced enolate.

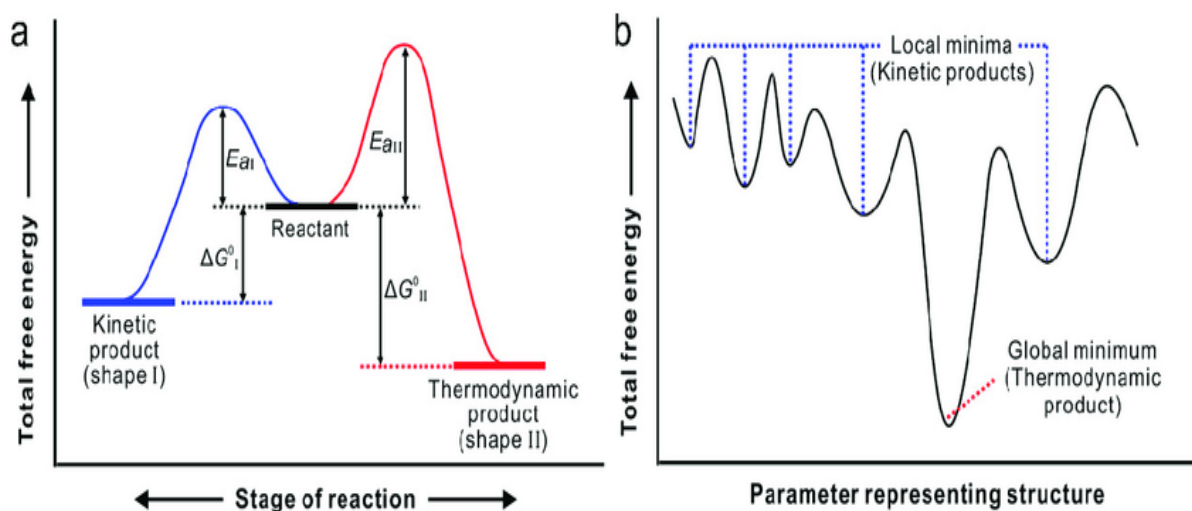


Figure 3 depicts the energy diagrams for three fictitious examples, and Figure 1 compares these diagrams to the suggested system that was previously presented in order to better teach kinetic and thermodynamic control to students. Examples of kinetic and thermodynamically controlled processes are shown in Figure 3.2

The scenario in example 1 is depicted in the diagram, in which the competing products of A and B cannot be converted into the reactant (R). The ratio of products A and B at the end of the reaction depends less on their rapid creation than it does on their stability. In other words, water trickles into the right column while flowing quickly into the left. D1 and D2 are nearby stopcocks.

Case 2 shows that it is possible to produce the desired product by altering the reaction circumstances. For instance, at higher temperatures, products A and B achieve equilibrium, resulting in the production of product A, which is the more stable product. Read more kinetic product might be possible under certain conditions. It appears as though someone would be in charge of stopcock D2. As soon as it opens, water will start to flow into the neighbouring column and will keep doing so until equilibrium is reached (Pascal's law). Equilibrium would be more challenging to achieve if the stopcock D2 was closed.



Case 3 demonstrates how temperature and environmental changes have no impact on the final product's composition since product B has reached equilibrium with A as it forms. In the same way as when stopcock D2 is fully open. As a result, the composition of the finished product is unaffected by the rate of water output from stopcocks D3 and D4. Reaction 5 in Table 1 serves as an example of this circumstance.

CONCLUSION

The demonstration for the organic chemistry II course was successfully implemented. Students could have trouble understanding this notion when enolate reactions and kinetic and thermodynamic control are explained. Different parameters have an impact on these reactions, as was explained in table 2. At first, this topic could seem unclear. However, in a short amount of time, we can describe how different parameters affect the creation of enolates using the water system mentioned earlier. This strategy may be very effective at teaching this idea, according to our prior experience.

Additionally, as water is the only material utilized, the demonstration is very safe. It is important to note that our goal can only be achieved by using the projection of our suggested method rather than the actual equipment in the classroom. In addition, this approach demonstrates to the students how a chemist may create the required synthesis, much like a civil engineer creates a structure, according to our observations.

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