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CHEM S445

Advances in Chemical Synthesis (Free Courseware)



香港公開大學
THE OPEN UNIVERSITY
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Chapter 1

Reactivities of chemical reactions

1.1 About this module



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Welcome to this free courseware module 'Reactivities of chemical reactions'!

This module is taken from the OUHK course *CHEM S445 Advances in Chemical Synthesis* (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcGenericPage2010&c=C_ETPU&cid=191149126400&BODY=tcGenericPage2010), a five-credit, Higher level course that is part of the Bachelor of Science in Applied Science (BSc) degree programme offered by the [School of Science and Technology](http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcSubWeb&l=C_ST&lid=191133000200&lang=eng) (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcSubWeb&l=C_ST&lid=191133000200&lang=eng) of the OUHK. *This course* provides you with a firm foundation for understanding synthetic organic chemistry.

CHEM S445 is mainly presented in printed format and comprises five study units. Each unit contains study content, activities, self-tests, assigned readings, etc for students' self-learning. **This module (The materials for this module, taken from the print-based course CHEM S445, have been specially adapted to make them more suitable for studying online. In addition to this topic on 'Reactivities of chemical reactions', which is an extract from Unit 1 of the course, the original Unit 1 also includes the topics 'Reaction mechanisms', 'Valence bond theory', and 'Molecular orbital theory'.) retains most of these elements, so you can have a taste of what an OUHK course is like.** Please note that no credits can be earned on completion of this module. If you would like to pursue it further, you are welcome to enrol in *CHEM S445 Advances in Chemical Synthesis* (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcGenericPage2010&c=C_ETPU&cid=191149126400&BODY=tcGenericPage2010).

This module will take you about **six hours** to complete, including the time for completing the activities and self-tests (but not including the time for assigned readings).

Good luck, and enjoy your study!

1.2 Introduction



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Organic chemistry belongs to a branch of chemistry that is generally associated with compounds containing carbon. It is so important because millions of compounds that contain carbon are related to our daily lives, so organic chemistry has many close connections with living things. For examples, amino acids can react together to form

proteins, which help constitute the essential compounds of muscle, skin and blood. And the DNA in our bodies contain all of our genetic information. A human body is just like a large reaction flask in which many organic reactions occur simultaneously. Those reactions are catalyzed by our enzymes. This is why we refer to carbon-containing compounds *organic*. Many organic compounds also have a wide range of applications in industry and health care, e.g. fuel, oil, detergents, body lotion and cosmetics. Organic chemistry is therefore an important branch of chemistry.

Advanced organic chemistry involves the strategy of organic synthesis, which is a series of chemical reactions for the construction of large, complex organic compounds from small, simple building blocks of starting materials. An organic chemist must develop advanced knowledge of synthetic tools, and learn how to apply these theoretical strategies to real examples.

1.3 Reactivities of chemical reactions



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Different organic compounds have different life-times in nature. For example, methane (CH_4) has a short life-time in the atmosphere: it is easily converted into carbon dioxide (CO_2) via combustion. This makes it useful as an efficient fuel. The life-time length of a particular compound is closely related to its reactivity. The shorter the life-time, the higher the reactivity. The reactivity of a reaction is related to both **kinetic** and **thermodynamic** factors. We therefore need to consider how fast the reaction is, and whether the product is stable to form.

You should note, however, that the term *reactivity* is sometimes restricted to *kinetics*. That is, it refers to the rate at which a chemical substance tends to undergo a chemical reaction in time. For example, the reaction rate of hydrolysis of 1-bromohexane is faster than 2-bromohexane in $\text{S}_{\text{N}}2$ pathway. Hence, the reactivity of 1-bromohexane is higher than 2-bromohexane. The reaction rate is related to a number of factors, including the reactant's physical properties, purity, concentration, temperature and pressure:

- **Physical properties** The *physical properties* of a 'chemical substance' are quite important to its reaction rate. For example, if a reactant is broken down into small pieces, or ground into powder, this increases the surface area and hence can increase the contact area of that reactant, and thus enhance the reaction rate.
- **Purity** Reaction rates can also be affected by the *purity* of the compounds involved. If there are contaminants inside a reactant, the rate of reaction may also be affected. Contaminants can either enhance or reduce a reaction rate, depending on their nature.
- **Concentration** Reaction rate also depends on the *concentration* of the reactants. At a high concentration, the number of molecules in a certain area increases. Since these molecules are closer to each other, the chance of their contact increases, which can also increase the frequency of collisions. As a reaction occurs via the collision of molecules, the reaction rate increases if the frequency of collisions increases.

- **Temperature** *Temperature* is also an important factor. At higher temperatures, molecules have higher thermal energy, which again increases collision frequency, and thus enhances the reaction rate.
- **Pressure** Finally, if *pressure* increases, the reactants are forced into a given area. Again, the collision of molecules can increase and hence increase the reaction rate. This is similar to the effect from concentration.

1.3.1 Self-test 1.1



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List out the factors that can affect the rate of chemical reactions, and suggest how each factor can increase the reaction rate.

1.3.1.1 Self-test 1.1 Feedback



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Factors that can affect the rate of chemical reactions include: purity, concentration, contact area of the reactants, temperature and pressure.

To increase reaction rate, increase concentration, contact area (by grinding the reactant into small pieces), temperature and/or pressure. But note that in the case of purity it is difficult to tell whether high or low purity will lead to a faster reaction rate, because sometimes a contaminant can speed up the reaction, while sometimes it will slow the reaction down. It depends on the nature of the contaminant.

1.3.2 Rates of chemical reactions



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The rate of a chemical reaction can be defined as the number of starting molecules converted into product in a given time. When a reaction can give more than one possible product, i.e. more than one reaction are occurring simultaneously, these reactions are in competition. The one predominating occurs more rapidly than the others, and hence it reacts preferentially in the reactions. In order to determine which reaction is the most feasible, the term **Gibbs free energy change** (ΔG) must be considered in addition to the chemical kinetics. This is why the term *reactivity* must include both *kinetic* and *thermodynamic* factors, as you learned in the previous section. In fact, ΔG refers to whether a chemical change will take place (related to *thermodynamics*), while *kinetics* just describe how fast the reaction is.

For free energy change:

$$\Delta G = \Delta H - T\Delta S$$

(where ΔG : free energy change; ΔH : **enthalpy change**; T: temperature; ΔS : **entropy change**)

Both kinetic and thermodynamic effects should be considered. Although conditions for a reaction to occur should be favorable if both **enthalpy** and **entropy** are favorable (i.e. a very positive change in entropy and the reaction is highly **exothermic**), the reaction still will not happen if the reaction rate is too slow. Hence, an exothermic reaction does not necessarily lead to a fast reaction. This is because there is a barrier to the chemical reactions (Figure 1.1). Again, reaction rates are not determined by the free energy change (ΔG) between the starting material and the product; they are determined by the height of barrier between the starting material and the transition state.

If a reactant can give two different products via different reaction pathways, the more thermodynamically stable one will usually form, but there are exceptional cases in which the reaction is considered to be kinetically-controlled. In such cases, the less thermodynamically stable product will result in a faster reaction rate. The dichotomy of competition between *thermodynamic* and *kinetic* control reaction will be discussed in a later section.

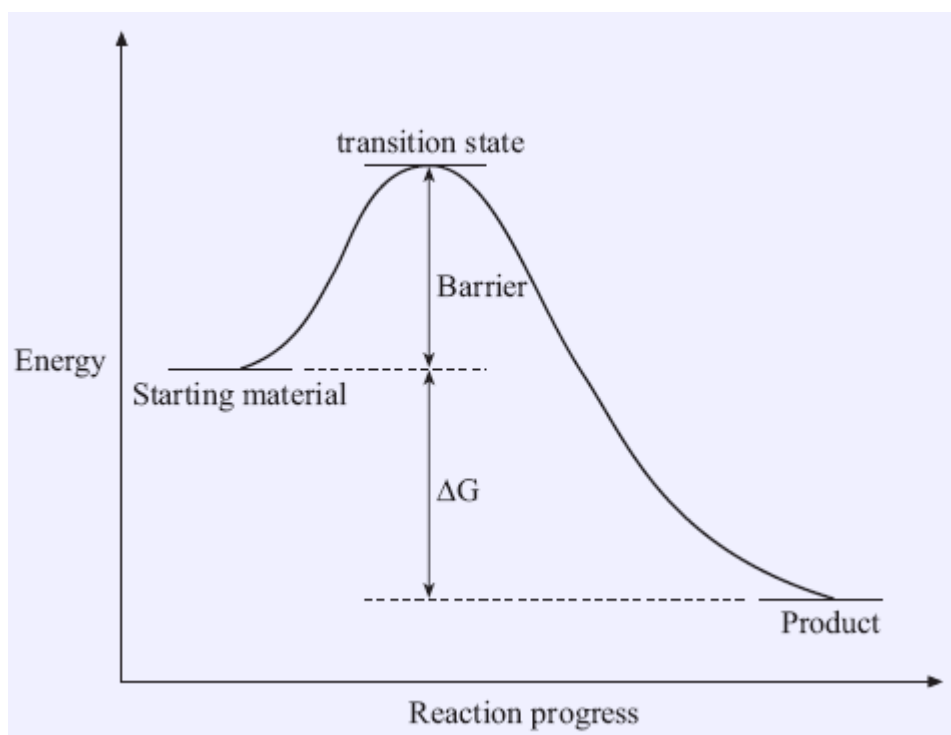


Fig. 1.1: Reaction free-energy diagram for a hypothetical reaction from A to B

1.3.3 Transition states and activation energy



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A reaction starting from reactants that change into products must pass through an unstable state at the highest energy level; this is called a **transition state**. A certain amount of energy is required to overcome the energy barrier, and this energy, called **activation energy**, is represented by ΔG^\ddagger . The magnitude of ΔG^\ddagger determines the rate of a chemical reaction. When ΔG^\ddagger increases, the reaction rate decreases, since more energy is required to pass through the energy barrier. The *double dagger* (\ddagger) symbol is used when a reaction involves transition states. This is different from the *free energy*

change (ΔG) in the previous section. They are illustrated in Figure 1.2 with combustion as an example:

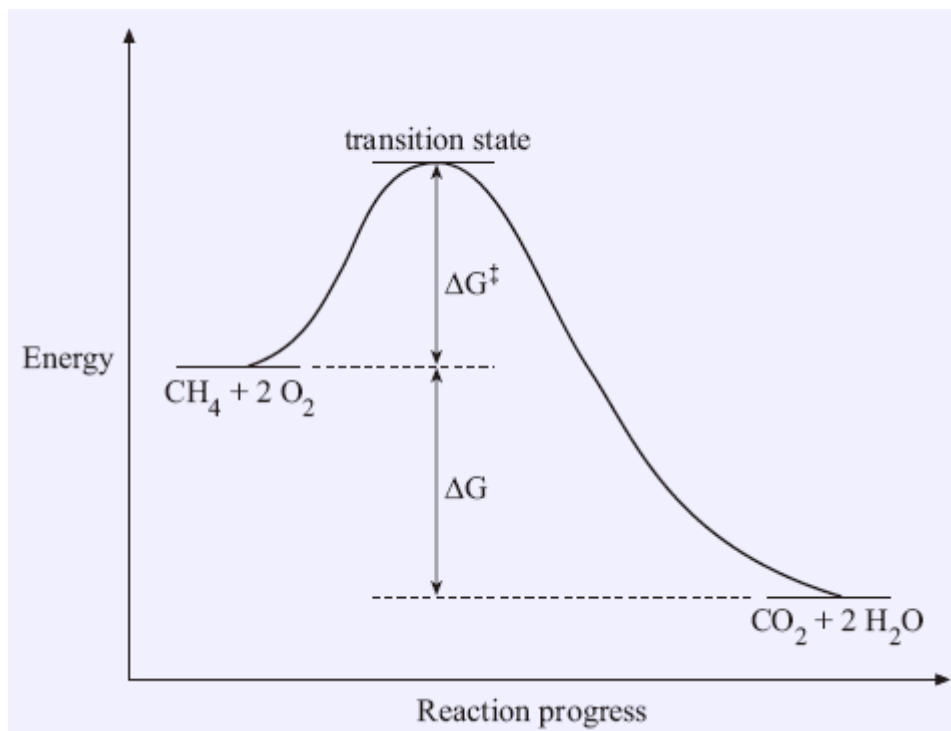
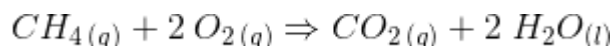
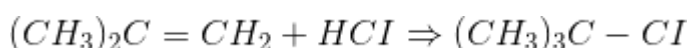


Fig. 1.2: Reaction free-energy diagram for combustion of methane

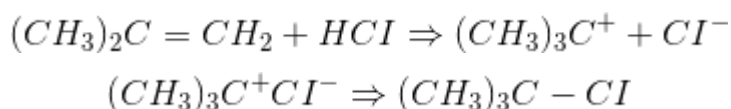
In Figure 1.2, the x-axis is called *reaction progress*, although sometimes it may be written as *reaction coordinate*, while the y-axis is the *energy*.



There are many reactions that take place in more than one step. They involve the formation of reactive intermediates. These reactions can be considered multistep reactions. For example, in the addition of hydrogen chloride to 2-methylpropene:



This can be regarded as a multistep reaction because it involves the following two steps:



Each step has its own reaction rate and transition state. The free-energy diagram is shown in Figure 1.3. For multistep reactions, the slowest step is called **rate-determining step** (or *rate-limiting step*). The reaction rate of the overall reaction is equal to the rate of rate-determining step.

In the example shown in Figure 1.3, there are two transition states. The rate-determining step is the one with the transition state of highest free-energy.

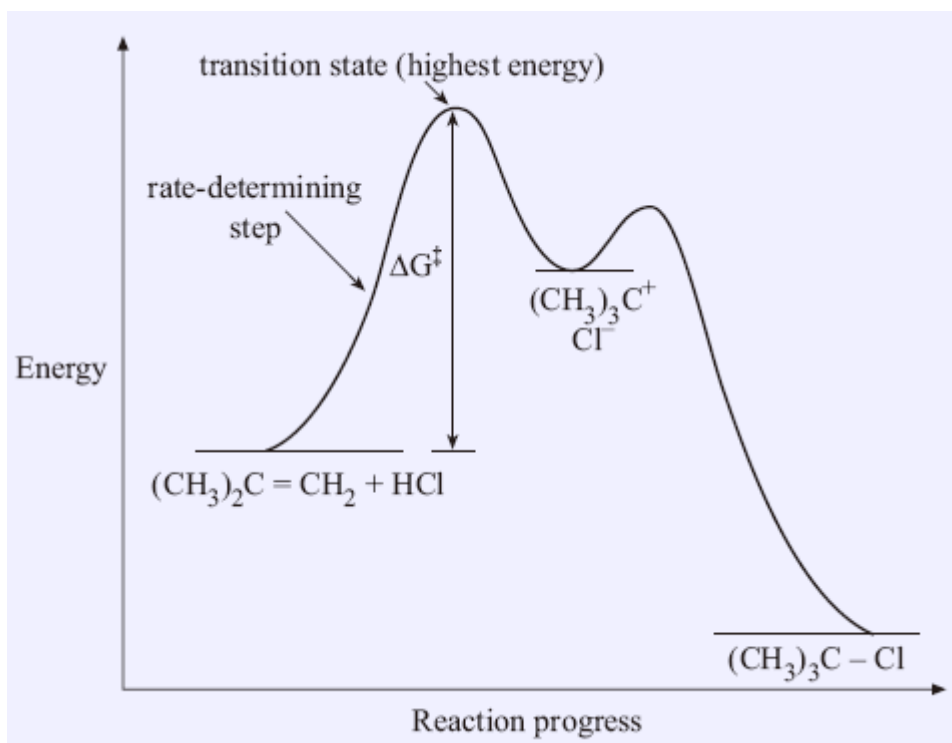


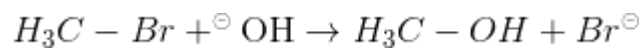
Fig. 1.3: Reaction free-energy diagram for the addition of HCl to 2-methylpropene

1.3.4 Self-test 1.2



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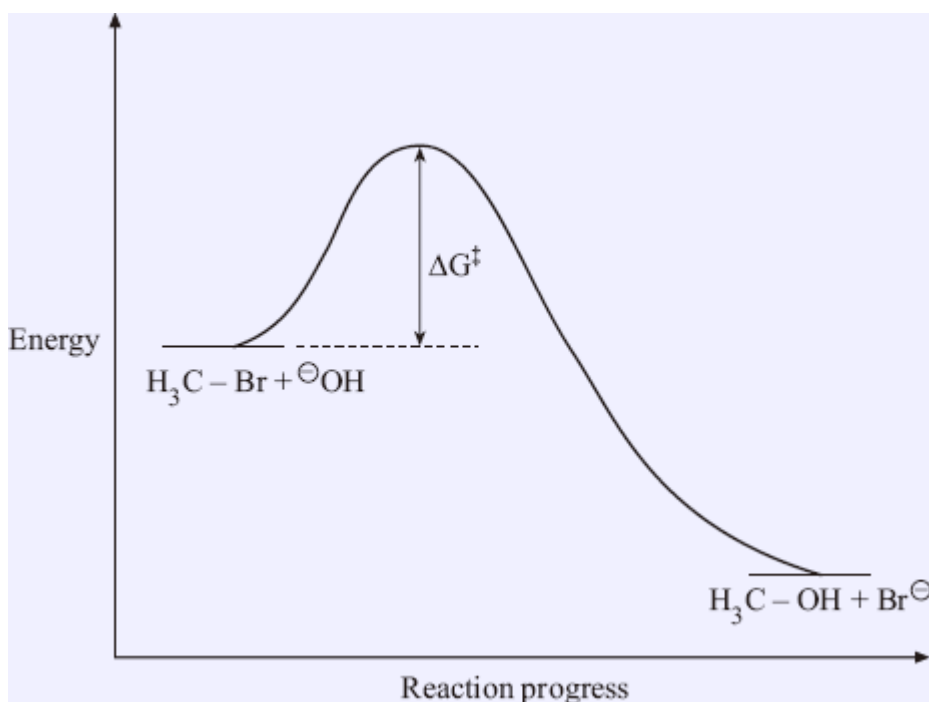
Draw a reaction free-energy diagram for the following S_N2 reaction, and identify the activation energy.



1.3.4.1 Self-test 1.2 Feedback



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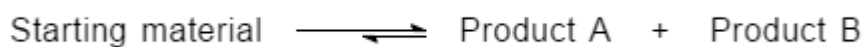


1.3.5 Hammond postulate: kinetic vs thermodynamics



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In this section you will learn how the Hammond postulate helps you understand the relationship between kinetics and thermodynamics in organic reactions. Before we consider the postulate, let's begin by considering a reaction in which two possible products can be formed by the same starting material:



If product A is the major product, we can say that product A is either a more stable product, or it formed at a faster reaction rate. However, there are two factors needed to be taken into account: *thermodynamics* (more stable) and *kinetics* (forms faster). The relative energies of the two products are shown in [Figure 1.4](#).

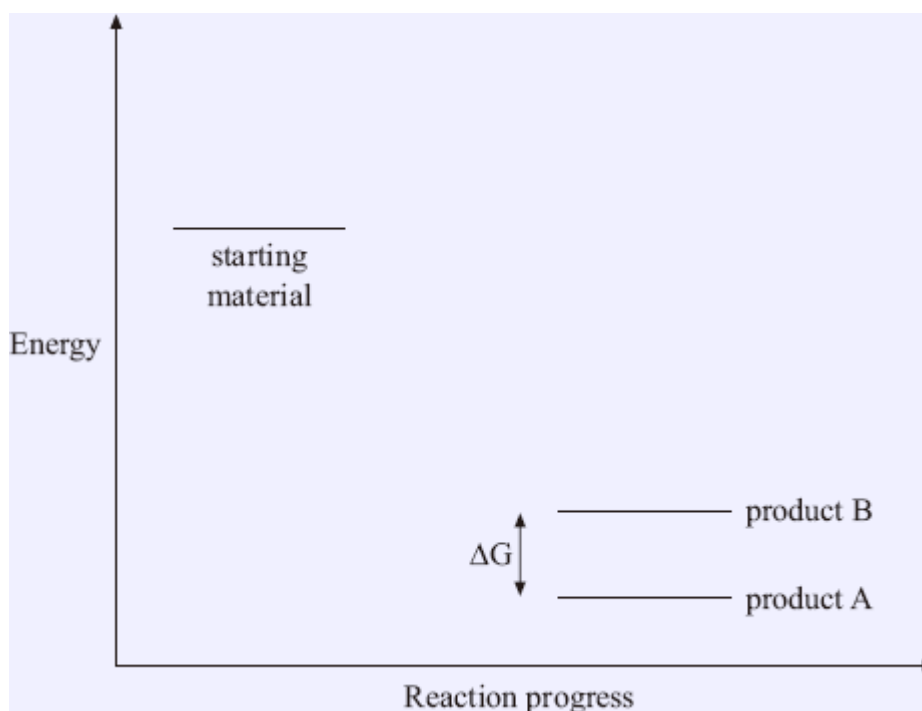


Fig. 1.4: Free energy diagram showing the relative energies of two products

Another diagram (Figure 1.5) shows the formation of a more stable product A in a transition state with a lower energy than that of product B. The activated energy required for the reaction pathway for product A is smaller. Hence, product A can be obtained faster as a more stable major product in this case.

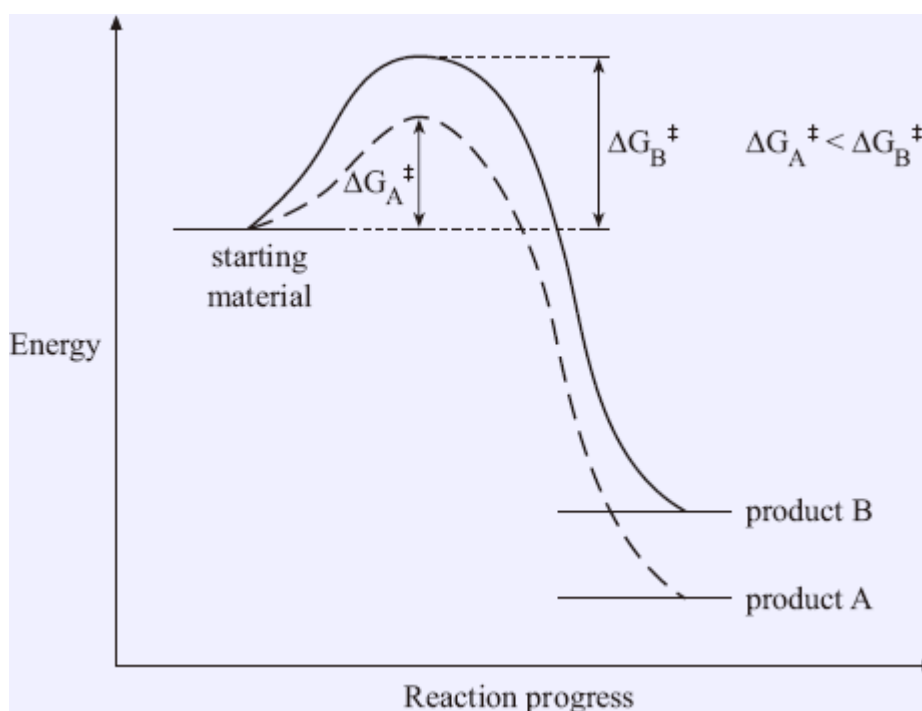


Fig. 1.5: Reaction with the more stable product with a lower transition state, and vice versa

Although product A has lower energy, it will not necessarily form faster than product B. It is possible for the more stable products to have a transition state with higher energy (Figure 1.6). In this case, product B will form faster even though it is the less stable product.

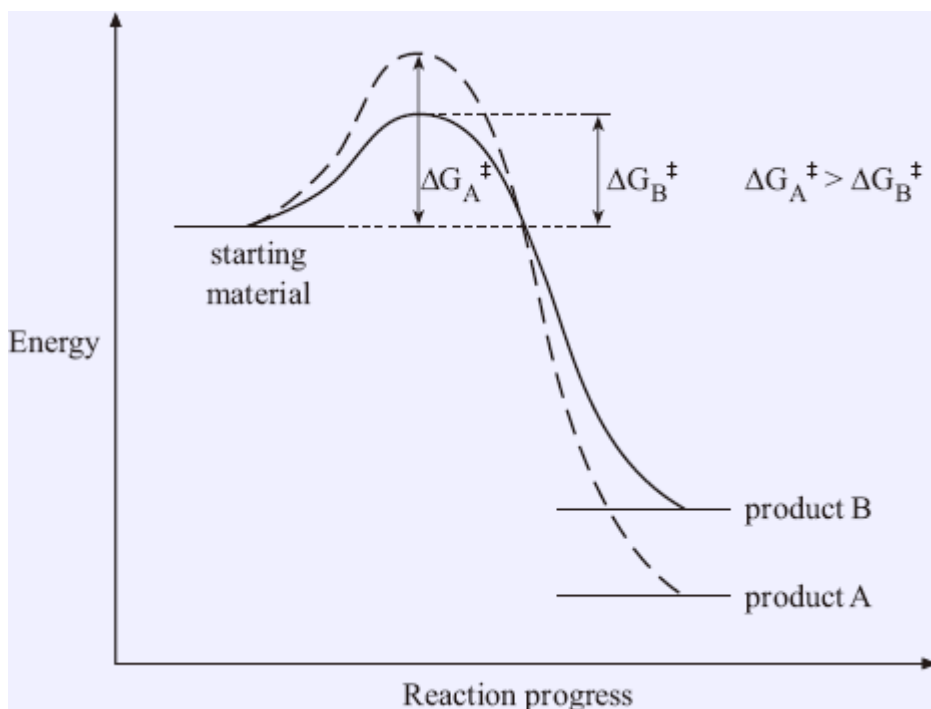


Fig. 1.6: Reaction with the more stable product with a higher transition state, and vice versa

In such cases, the major product of this reaction depends on which factor will win out: *thermodynamic control* or *kinetic control*.

If there is enough energy to overcome all the reaction barriers for both products, and the reaction is in equilibrium with the one with lower energy that is more stable, this reaction is regarded as **thermodynamic control**. The ratio of products depends on the ΔG between the two products A and B. On the other hand, if the reaction tends to produce a less stable product as a major product, and the activation energy for this reaction pathway is smaller with a lower transition state, the reaction can be considered as **kinetic control**. The ratio of products depends on the relative difference between their activation energies.

In a reaction free-energy diagram, the transition state has a maximum energy relative to both the reactants and products. It is unstable and cannot be isolated; however, you can imagine that the transition state is a structure that exists somewhere between the reactants and the products, and that all reactions should possess this stage. Usually, the transition involves the process of bond breaking and bond forming. These partial bonds are shown in dashed lines.

For example, in the addition of HCl to 2-methylpropene, the transition state of the first step (formation of **carbocation**) is shown in [Figure 1.7](#).

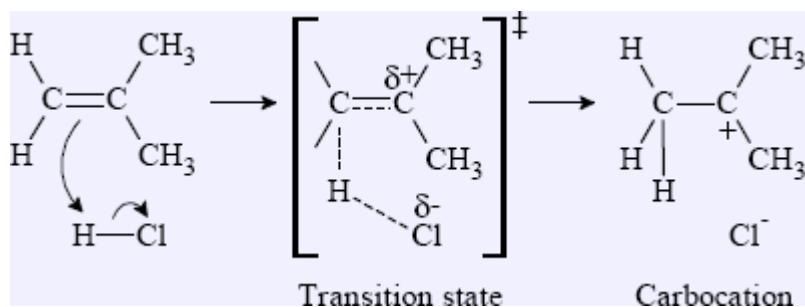


Fig. 1.7: Reaction mechanism for the formation of carbocation from 2-methylpropene and HCl, with the transition state shown in the square bracket.

In the transition state, the π bond of the alkene and the σ bond of H-Cl are breaking, while a C-H σ bond is forming. These partial bonds are represented in dashed lines, with the partial charges $\delta+$ and $\delta-$, which means partial positive and partial negative, respectively. The final product in this reaction is the carbocation and chloride ion with full charges. The major factor that affects the instability of the transition state is the charge separation of the positive and negative charge, and the development of the electron-deficient site.

For the above example, 2-methylpropene is an unsymmetrical alkene which can be protonated at either side of the double bond to give two different carbocations. The free energy diagram is shown in Figure 1.8.

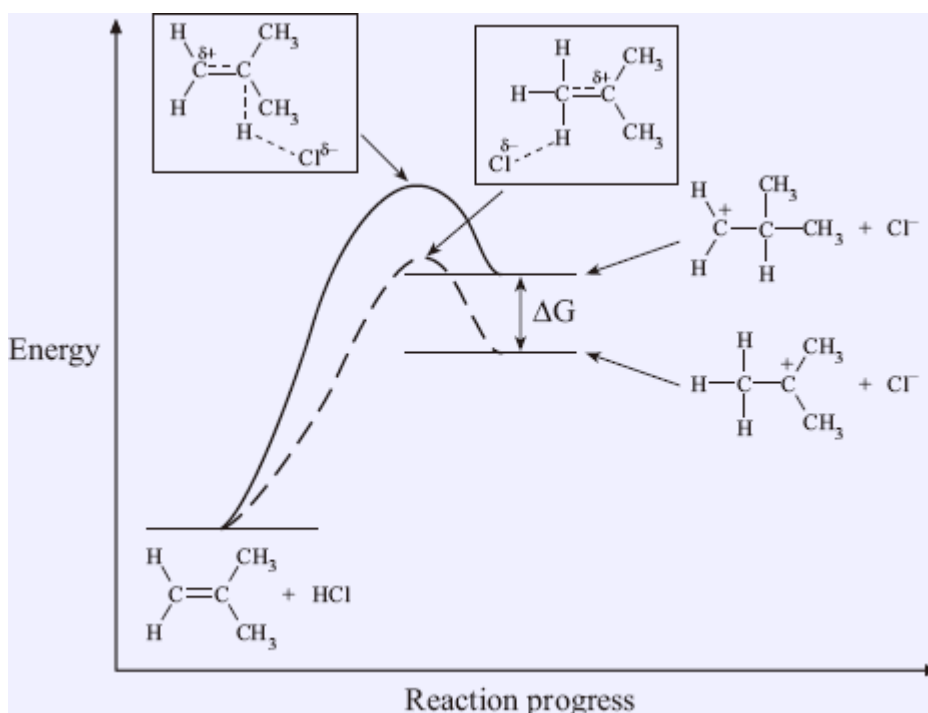


Fig. 1.8: Free energy diagram for the formation of carbocations

The two carbocations have different stabilities. The tertiary carbocation with more substituted (i.e. the lower energy one) is more *thermodynamically* stable than the primary carbocation (i.e. the higher energy one). This is because the substituents stabilize the positive charge on the carbocation by positive inductive effect. The factors that stabilize a full positive charge can be operated to stabilize a partial positive charge. Hence, the transition state for the formation of a tertiary carbocation is more stable than that of a primary carbocation.

An approximation with their structural similarity assumption can be made. This is called **Hammond's postulate**, which is named for George. S. Hammond, who first stated and used it in organic reactions in 1955.

Hammond's postulate

Assume that the transition states for reactions involving unstable intermediates can be closely approximated by their intermediates.

This means that we can assume the structures of transition states are very similar to those of their intermediates. Since the tertiary carbocation is more stable than the primary carbocation, the transition state leading to the more stable tertiary carbocation should have lower energy, as predicted by Hammond's postulate. Hence, protonation of 2-methylpropene to give a tertiary carbocation proceeds in a pathway with lower activation energy. Therefore, it can be produced at a faster reaction rate.

A complete free energy diagram for the two possible reaction pathways of addition of HCl to 2-methylpropene is shown in Figure 1.9. It should be noted that the stabilities themselves cannot determine which pathway is faster. Only making use of Hammond's postulate can allow us to relate the carbocation energy and transition state energy, and then use the concept of activation energy to determine which one is faster.

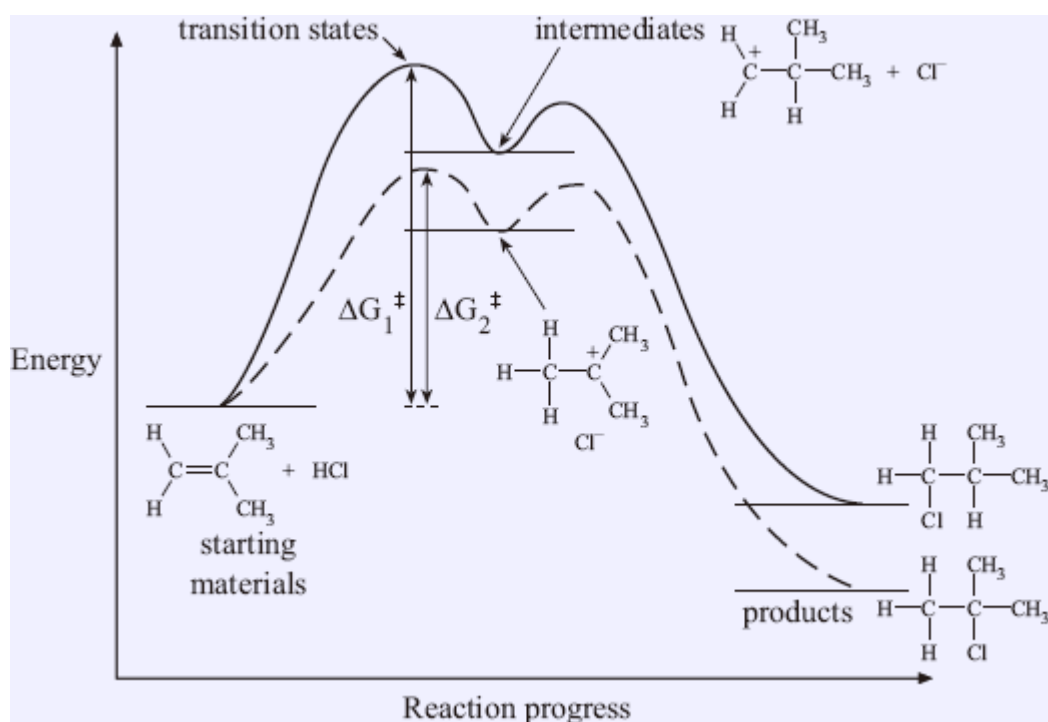


Fig. 1.9: Free energy diagram for the two possible reaction pathways of addition of HCl to 2-methylpropene. Note that Hammond's postulate assumes that the energy of each transition state is similar to that of the corresponding carbocation.

In the above example, the formation of *tert*-butyl chloride is the fastest because it involves the formation of the most stable carbocation, and its transition state should have the lower energy. It then requires less activation energy. Although the structures in transition states are not certain, the structures of the starting materials, products and intermediates can be used in Hammond's postulate, and we can assume that the

transition states and their corresponding reactive intermediates have similar structures.

1.3.6 Activity 1.2



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Suggest a method to obtain a kinetic control product.

(*Hint:* Think about the differences in reaction conditions that can allow us to differentiate the kinetic control and thermodynamic control products.)

1.3.6.1 Activity 1.2 Feedback



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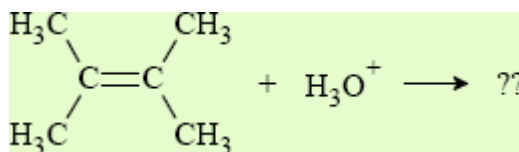
One method to achieve a kinetic control product is to decrease the temperature. Since different products have different reaction pathways, with different activation energies, you can control the amount of energy given to the reaction by controlling the temperature. At a certain temperature, it will only be possible for one reaction to proceed (i.e. you have reached the activation energy of either reaction), but not enough for the other (i.e. you have not reached the activation energy of the other one). By decreasing the temperature, one of the products may have enough energy to overcome the reaction barrier, while the other does not. Hence, the product you can get is the kinetic control product.

1.3.7 Self-test 1.3

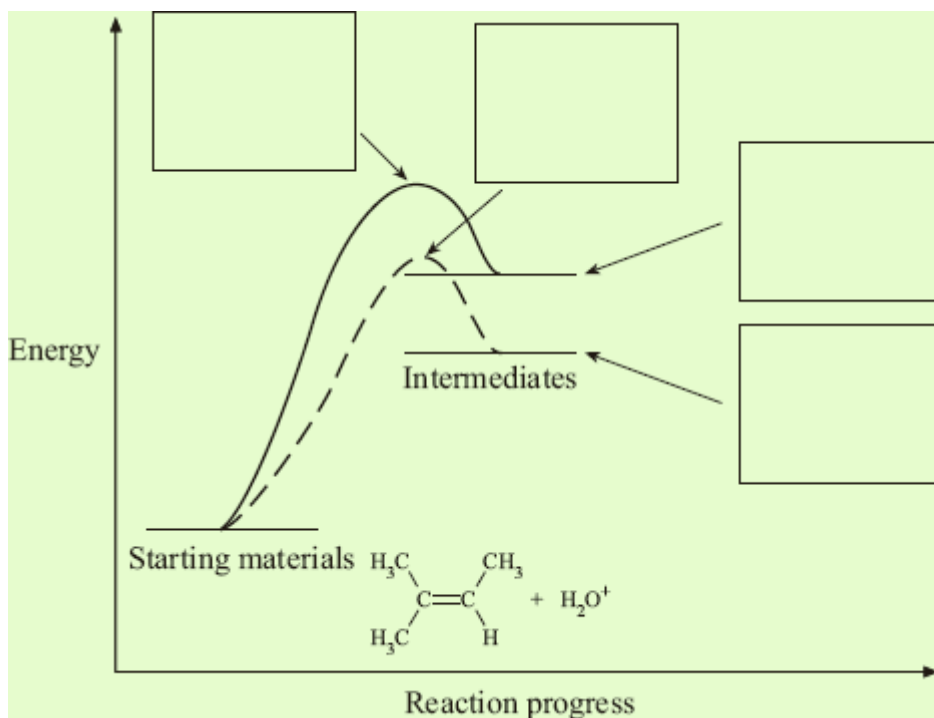


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Consider the following reaction:



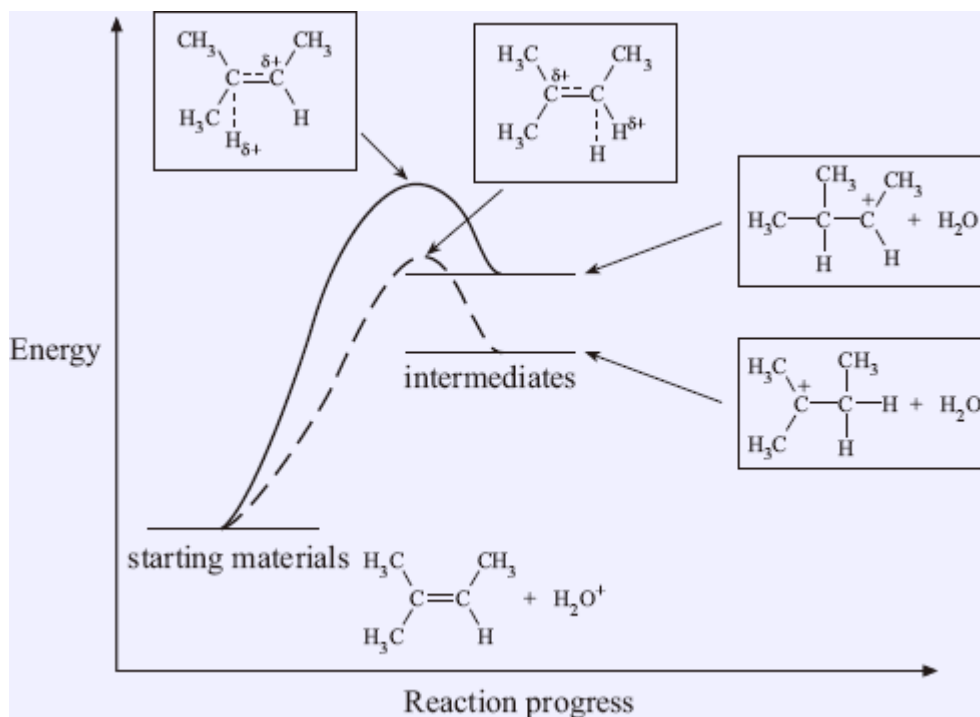
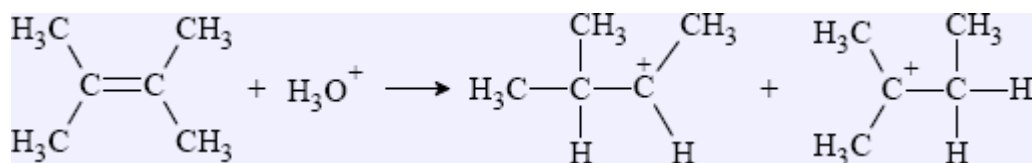
In the following free-energy diagram, write down the transition states and the carbocations formed. Notice the relative stabilities of two transition states and two carbocations.



1.3.7.1 Self-test 1.3 Feedback



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1.4 Conclusion



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Organic chemistry is closely related to our daily lives. We need to use carbon-containing compounds very frequently. In this module you learned how the reactivity of a reaction is related to both kinetic and thermodynamic factors. The energy barrier for a reaction to occur is called activation energy. A reaction may have competition between kinetic control and thermodynamic control. The former considers the reaction that has a lower activation energy that forms faster, while the latter concerns the more stable compound with a lower energy.

If you would like to learn more on this subject, you are welcome to enrol in *CHEM S445 Advances in Chemical Synthesis* (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcGenericPage2010&c=C_ETPU&cid=191149126400&BODY=tcGenericPage2010) offered by the School of Science and Technology (http://www.ouhk.edu.hk/wcsprd/Satellite?pagename=OUHK/tcSubWeb&l=C_ST&lid=191133000200&lang=eng) of the OUHK.