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Reaction Coordinate Diagrams

Overview

The basic “experiment” in computational chemistry is to calculate a molecule’s energy from its structure. This computation alone can be enormously useful because many chemical phenomena are controlled by energy. By knowing how energy varies with structure, we can predict a molecule’s preferred structure, its conformational properties, and its tendency to undergo different chemical reactions.

The relationship between energy and geometry can be described in different ways, depending on how much geometrical detail one tries to consider. This handout introduces the simplest picture. Geometry is represented by a single variable so that the relationship between energy and geometry can be portrayed using simple two-dimensional graphs. More detailed relationships will be presented in subsequent handouts.

Why Energy?

The notion that chemistry is controlled by energy may seem peculiar. This is because the chemist’s lexicon is biased in favor of structure, and against energy. A statement like, “methane is tetrahedral” is typical. Energetic factors appear to be irrelevant until the statement is rewritten as, “methane’s minimum-energy structure is tetrahedral.” Now relationships between experimental observation, structure and energy become clear. A methane molecule can and does have many structures, and each has a unique energy. The methane molecules we normally encounter, however, are those that have the minimum-energy structure. “Methane is tetrahedral” is a good, simple expression, but it obscures the important role that energy plays.

Chemists often avoid referring to energy even when talking about chemical reactivity. Consider the following experimental observations:
A chemist might say, “these results show that CH₃ is an activating group, and NO₂ is a deactivating group”, or “CH₃ is an ortho/para director, but NO₂ is a meta director.” These are useful descriptions, and easy to remember, but they fail to show how reactivity is influenced by energy. If we now consider bromination of phenol, C₆H₅OH, we are lost because we may not know the activating and directing properties of OH. An energy-based description is more useful because it shows how we can predict the reactivity of phenol by computing the energies of key intermediates and/or reaction barriers.

These two examples just hint at the role that energy plays in dictating chemical phenomena (and the ways that chemists tend to forget this). The take-home lesson, however, is quite clear: we must think about chemical phenomena in energetic terms if we want to analyze these phenomena computationally. Potential energy surfaces are a particularly convenient device for connecting various phenomena with energy.

**Simple Potential Energy Diagrams**

The simplest tool for describing structure-energy relationships is a simple graph of energy versus geometry. These graphs can describe changes in energy quantitatively, but they are usually limited to qualitative statements about structural changes.

**Multiple Minima/One Structure - Ethane.** Let’s begin with a familiar phenomenon, internal rotation in ethane. The methyl groups rotate with respect to each other about the CC bond axis, changing the molecule’s structure. If we label the hydrogen atoms, and perform one
complete rotation, we generate three distinctly labeled staggered conformers with $H_aCCH_b$ torsional angles of 60°, 180°, and 300°.

![Diagram showing staggered conformers](image)

The structural changes that describe internal rotation are also accompanied by changes in energy. The molecule’s energy smoothly rises and falls during rotation. The staggered conformers are identical in energy, and because they have the lowest energies, collectively represent the molecule’s preferred structure. This structure-energy relationship is conveniently expressed by the following potential energy\(^1\) diagram. The preferred structures, the three staggered conformers, can be identified immediately by looking for the locations of the energy minima on the diagram.

![Potential energy diagram](image)

The diagram also tells us what restrictions are placed on internal rotation. Rotation from one staggered conformation to another requires the molecule to temporarily adopt an eclipsed conformation ($H_aCCH_b$ torsion angles of 0°, 120°, or 240°) with a corresponding increase in potential energy of 2.9 kcal/mol. Conservation of energy demands that this increase in potential energy come at the expense of another type of molecular energy, kinetic or vibrational. Therefore, a staggered ethane must absorb at least 2.9 kcal/mol before it can rotate to another staggered conformation. This turns out to be a very modest restriction at room temperature, and internal rotation occurs more or less freely in all molecules.

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\(^1\) “Potential energy”, in this context, is a combination of electrostatic interactions (nucleus-nucleus, electron-electron, and electron-nucleus) and the kinetic energy due to electron motion. Kinetic energy associated with nuclear motion, such as molecular vibration, rotation, and translation, are not included.
Does a molecule have a structure? Ethane’s internal rotation raises an interesting problem. Rotation rapidly changes the molecular structure, yet we regard all of the different conformers as representing “ethane.” Is it reasonable to think of ethane (or any other molecule) as having a unique, well-defined structure? Why do most experimental structure measurements appear to give a well-defined molecular structure for ethane? There are two different ways to approach these questions, both of which rely on energy diagrams.

One answer can be obtained by thinking about the molecules present in a sample at the time of an experimental measurement. Molecules with different structures belong to distinct populations, each of which might respond differently to the conditions of an experiment. Some experimental procedures measure distinct data for each conformer population, but most procedures generate a single set of measurements that contain responses from all of the different populations, i.e., the data is a weighted average. In this case, the data are skewed by the behavior of the molecules in the largest populations, and the structure derived from these data will most closely resemble these molecules.

The size of a conformer population is related to the half-life of the molecules in the population, \( \tau_{1/2} \), and to the free energy barrier for conformational change, \( \Delta G^\ddagger \). The half-life can be calculated from the barrier by means of eq. 1 and 2, where \( k \) is the first-order rate constant for conformational change, \( T \) is the absolute temperature, \( h \) is Planck’s constant, \( R \) is the gas constant, and \( k_B \) is Boltzmann’s constant. The approximate relationship in eq. 2 holds when \( T = 298 \text{ K} \), and \( \Delta G^\ddagger \) is given in kcal/mol.

\[
\tau_{1/2} = \ln \frac{2}{k} = \frac{0.69}{k} \quad (1)
\]

\[
k \text{ (sec}^{-1}) = \frac{k_B T}{h} e^{-\Delta G^\ddagger/RT} \approx 6.21 \times 10^{12} \times 10^{\Delta G^\ddagger/1.36} \quad (2)
\]

Examination of ethane’s energy diagram shows that \( \Delta G^\ddagger = 2.9 \text{ kcal/mol} \) for the staggered conformers.\(^2\) Thus, the half-life of these molecules is only \( 1.5 \times 10^{-11} \text{ sec} \) at 298 K. This is a very short lifetime, but the half-lives of the higher-energy conformers are even shorter. Setting \( \Delta G^\ddagger \) equal to zero\(^3\) gives a half-life of only \( \sim 10^{-13} \text{ sec} \) for the higher-energy conformers. Therefore, the three staggered conformers are much longer-lived than any of the other

\(^2\) Strictly speaking, we cannot equate free energy and potential energy because free-energy, unlike potential energy, depends on entropy and on pressure-volume work. Neither correction should be very important in this case, however.

\(^3\) All of the non-minimum-energy conformers “decay”, i.e., rotate to a more stable structure, without encountering an energy barrier.
conformers; they form the largest populations, and they will be the only conformers detected experimentally.

The same conclusion can be obtained using quantum mechanics, but the reasoning is different. Quantum mechanics states that the probability that a molecule will have a particular structure is proportional to $(\Psi_{\text{nuclear}})^2$, i.e., the square of the wavefunction describing nuclear behavior. The following diagram shows a crude sketch of $(\Psi_{\text{nuclear}})^2$ superimposed on ethane’s energy surface, and it shows quite clearly that the most probable molecular structures are those of minimum potential energy.

![Diagram of energy surface with $(\Psi_{\text{nuclear}})^2$ superimposed](image)

These conclusions can be extended to other molecules. In general, minimum-energy structures are the only ones that can be detected experimentally, even when a molecule undergoes rapid structural change. Therefore, many important chemical properties are the properties of minimum-energy structures, and these are the structures that we need to compute. Structures of higher energy are much shorter-lived and do not form a significant or experimentally detectable population.

**Different Structures/Different Minima - Butane.** All molecules fall into one of three categories: those with a single minimum-energy structure (e.g. methane), those with multiple identical minimum-energy structures (e.g. ethane), and those with multiple minimum-energy structures, at least two of which are different. Most molecules belong to the third category. The properties of these molecules are more difficult to interpret and predict because the properties of

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4 $\Psi_{\text{nuclear}}$ is usually encountered in connection with vibrational behavior, and an infinite number of vibrational states, each possessing a unique wavefunction, are possible. In practice, most of the molecules lie in the ground vibrational state, so this wavefunction is the most important one for describing molecular structure.

5 One “exception” to this rule is the rare case of a molecule whose energy surface contains a broad, flat minimum. Experimental measurements on such a system cannot be interpreted in terms of a single well-defined structure. Computational study of such systems is still useful, however, because it provides a means for characterizing the shape of the energy surface.
several distinct conformer populations must be considered. We shall see, however, that potential energy diagrams still provide a useful link between energy, structure, and experiment.

One of the simplest organic molecules with multiple minimum-energy structures is \(n\)-butane. Internal rotation about the central bond produces three staggered conformers with different structures and energies, and each is a minimum-energy structure as the following energy surface illustrates.

![Energy Surface of \(n\)-Butane](image)

The three staggered conformers are the only conformers that can be observed experimentally. Two of these are gauche conformers with \(\theta(\text{CCCC}) \approx 60^\circ\) and \(300^\circ\). They have identical energies and can be regarded as a single population. The third conformer is the anti conformer with \(\theta(\text{CCCC}) = 180^\circ\). The anti conformer is the lowest in energy, and is referred to, therefore, as the global minimum of the energy surface (the gauche minima are referred to as local minima).

Since butane has two different minimum-energy structures, a butane sample will normally contain an equilibrium mixture of these two conformers. The relative sizes of the two populations depends on temperature, and is given by eq. 3,

\[ \text{Population Ratio} = \frac{e^{-\frac{E_1}{kT}}}{e^{-\frac{E_2}{kT}} + e^{-\frac{E_3}{kT}}} \]

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6 The total number of butane minima is much higher than the diagram indicates because rotation about the terminal CC bonds has been ignored. Consideration of these rotations leads to 18 identical gauche conformers and 9 identical anti conformers for \(n\)-butane, or a total of 27 (=3×3×3) minimum-energy structures.
where $\Delta G$ is the free-energy difference between the two conformers, i.e., $G_{\text{gauche}} - G_{\text{anti}}$. As we have noted before, free-energy differences are not equal to potential energy differences, but there is usually a close relationship between the two. We shall look at this problem more closely in a later chapter, but for now we will calculate the free-energy difference using $\Delta G = \Delta H - T \Delta S \approx \Delta E - T \Delta S$, where $\Delta E$, the potential energy difference between the two conformers, equals 0.8 kcal/mol. Since $\Delta E$ is small we cannot neglect $\Delta S = S_{\text{gauche}} - S_{\text{anti}}$. In this case, the entropy of the gauche conformer population is higher chiefly because it contains a mixture of two enantiomeric molecules (the 60° and 300° conformers are non-superimposable mirror images), while the anti population contains only one type of molecule. We can estimate $\Delta S$ as $R \ln 2$, which makes $\Delta G \approx 0.4$ kcal/mol at room temperature. Introducing this result into eq. 3 gives the equilibrium composition of butane at room temperature as 66% anti and 34% gauche. This result is typical. The global minimum always defines the largest single conformer population at equilibrium. However, less than half of the molecules may be present at the global minimum if the temperature is sufficiently high, or if the number of other energetically accessible conformers is sufficiently large. For example, in the case of butane, the gauche and anti populations should become equal at ~580 K (307 °C).

Experimental measurements made on conformationally mobile molecules are more difficult to interpret than those made on other molecules. In particular, if the data is conformationally-averaged, i.e., if it contains contributions from different conformers, then it cannot be interpreted in terms of any single conformer, not even the global minimum. Conformational averaging is often encountered in NMR spectroscopy, where measured chemical shifts and coupling constants may be averages that reflect the properties of several rapidly interconverting conformers. When such averaging occurs, the observed chemical shift of a particular nucleus, $\delta_{\text{obsd}}$, is given by $\delta_1 X_1 + \delta_2 X_2 + \delta_3 X_3 + \ldots$, where $\delta_i$ is the nucleus' shift in conformer $i$ and $X_i$ is the mole fraction of this conformer. Coupling constants behave the same way. For example, the observation that vicinal $J_{HH} \approx 7$ Hz in acyclic alkyl groups is due to this type of averaging; if rapid internal rotation did not occur or was constrained (as in a cyclic alkane), one would observe significantly different $J$ values. We shall examine more examples of conformational averaging in later chapters, but we note here that computation is an especially

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7 $R \ln 2$ is the entropy of mixing of two equal populations into a single population.
useful tool for studying the properties of conformationally mobile molecules. Structure-energy calculations can locate all of the minimum-energy structures on a given energy surface, determine their relative energies and relative mole fractions, and may even be able to estimate the relevant properties of each conformer, e.g., δᵢ.

So far, we have concentrated on the minimum-energy structures of butane. However, there are also three energy maxima on the energy surface, each corresponding to an eclipsed conformer. The maxima separating the gauche and anti conformers are lower than the maximum separating the two gauche conformers. Consequently, the barrier for gauche→anti rotation is smaller than the barrier for gauche→gauche rotation. Eq. 2 states that there is an inverse relationship between barrier height and rate constant, therefore, the rate constant (and rate) for gauche→anti rotation is larger than the rate constant for gauche→gauche rotation.

**Chemical Reactions: Reaction Coordinate Diagrams.** Two-dimensional energy surfaces are also used to describe the geometry and energy changes accompanying chemical reactions. These surfaces are referred to as *reaction coordinate diagrams*, and consist of a graph of energy versus a geometric coordinate known as a *reaction coordinate*.

Consider the Diels-Alder cycloaddition of butadiene and ethylene. The geometry and energy changes that accompany the reaction are shown by the following energy surface:
two molecules, each of which is at its minimum-energy geometry. The energy of the reactant minimum, then, is the sum of the energies of the two minimum-energy reactant molecules.8

As before, the equilibrium concentrations of the different molecule populations are defined by the temperature of the system and the energy gap between the two minima:

$$\frac{[\text{cyclohexene}]}{[\text{butadiene}][\text{ethylene}]} = K_{eq} = e^{-\Delta G/RT}$$  \hspace{1cm} (4)

where $\Delta G = G_{\text{product}} - G_{\text{reactants}}$, and $K_{eq}$ is the equilibrium constant. It is noteworthy that cyclohexene, the global minimum, need not be the major component of an equilibrium mixture (contrast this result with the earlier discussion of butane’s global minimum). If the initial reaction mixture contains roughly equal amounts of butadiene and ethylene, then cyclohexene will indeed be the major component of the equilibrium mixture. However, if the initial mixture contains a large excess of, say, butadiene, then that species will be the major component of the equilibrium mixture. The cyclohexene population will be smaller, and the ethylene population smaller still.

The energy surface also provides important information about the relative rates at which reactants and product interconvert, although here too, concentration and temperature play a role. The forward and reverse reaction rates are given by eq. 5 and 6 respectively, where the rate constants, $k$, are determined by the temperature

$$\text{forward rate} = k_{\text{fwd}}[\text{butadiene}][\text{ethylene}]$$  \hspace{1cm} (5)

$$\text{reverse rate} = k_{\text{rvs}}[\text{cyclohexene}]$$  \hspace{1cm} (6)

and the appropriate barrier height, $\Delta G^\ddagger$ (eq. 2). Since a larger barrier results in a smaller rate constant (but not necessarily a smaller rate), $\Delta G_{\text{rvs}}^\ddagger > \Delta G_{\text{fwd}}^\ddagger$ implies $k_{\text{rvs}} < k_{\text{fwd}}$.

These discussions show that energy influences conformational equilibria and chemical equilibria in essentially the same way. A system’s thermodynamic preferences can be investigated and understood by calculating the energies of the relevant minima on the energy surface. Kinetic preferences can be analyzed in a similar fashion, except that one now calculates the energies of both minimum and maximum-energy structures. Both of these situations are elaborated further in the following section.

8 This is true only if the two reactant molecules do not interact at the energy minimum, that is, if the minimum-energy structure for the system corresponds to well-separated molecules.
Competing Chemical Reactions: Chemical Selectivity. Many types of chemical selectivity can be attributed to differences in energy barriers or reaction energies. Therefore, reaction coordinate diagrams are useful tools for describing relationships between energy and chemical selectivity.

Consider the deprotonation of 2-methylcyclohexanone by a strong, sterically hindered base, such as LiN(i-Pr)_2 (LDA). Proton transfer occurs most rapidly at the -CH_2- group giving the less-substituted enolate even though deprotonation of the -CH< group would produce the more-substituted and more stable enolate. The energy surface for both reactions is shown by the following reaction coordinate diagram:

For convenience, the reactants, ketone + LDA, are placed in the middle of the diagram (A). Moving to the left yields the major products (B), the less substituted enolate and diisopropylamine, DA, while moving to the right yields the minor products, the more substituted enolate and DA (C).

By displaying the energy surfaces of both reactions on the same diagram we quickly learn several valuable pieces of information. First, the overall energy change for proton transfer is favorable for both pathways (LDA is a strong base). Second, A→C is more favorable than A→B, that is, the more-substituted enolate is more stable and is thermodynamically preferred. Third, the barrier for A→B is lower than the barrier for A→C. Therefore, A and B equilibrate more rapidly than A and C, and the less-substituted enolate is kinetically preferred. Since the less-substituted enolate and DA are observed experimentally, we must conclude that kinetic preferences define the course of this reaction. (Note that the enhanced rate of A→B is due
strictly to the size of the barrier and not to a concentration effect. Ketone concentration and LDA concentration affect the rates of $A \rightarrow B$ and $A \rightarrow C$ in exactly the same way.)

The outcome of a kinetically-controlled reaction, such as LDA + methylcyclohexanone, is easy to predict as long as the competing reactions are irreversible. The product ratio depends on the energy difference between the two barriers, or more simply, on the difference in the two competing transition state energies (eq. 7).

\[
\frac{[\text{less subst. enolate}]}{[\text{more subst. enolate}]} = \frac{\text{rate (} A \rightarrow B \text{)}}{\text{rate (} A \rightarrow C \text{)}} = \frac{k_B[LDA][\text{ketone}]}{k_C[LDA][\text{ketone}]} = \frac{k_B}{k_C}
\]

\[
= \frac{e^{-\Delta G(AB)^\dagger/RT}}{e^{-\Delta G(AC)^\dagger/RT}} = e^{-\left(\Delta G(AB)^\dagger - \Delta G(AC)^\dagger\right)/RT} = e^{-\left(G_B^\dagger - G_C^\dagger\right)/RT}
\]

(7)

The product ratio also depends on the reaction temperature, and this fact can be used to achieve good selectivity even when energy differences are small. For example, suppose that the energy difference between the two transition states, $G_B^\dagger - G_C^\dagger$, is only $-2$ kcal/mol. If the reaction is run at room temperature, eq. 7 predicts a product ratio of $\sim30:1$. On the other hand, if the reaction is carried out in a dry ice-acetone bath (~78 °C or 195 K), the reaction will be more selective, and the less substituted enolate will be favored $\sim 170/1$. This exquisite sensitivity to temperature means that computational prediction of product ratios will be difficult unless we can compute relative transition state energies with high accuracy.

It is also important to realize that this same reaction system would behave very differently if it were carried out in a way that allowed complete equilibration of the ketone and both enolates. In this case, the major product would correspond to the more stable energy minimum, $C$, and the nature of the pathway leading to this point would be irrelevant. This kind of system, in which all of the products are in equilibrium, is said to be thermodynamically controlled, and the major product is called the thermodynamic product.

Product concentrations are easily predicted for thermodynamically controlled systems by assuming direct equilibration of major and minor products. For example, for the two enolates we would assume:

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9 Suitable experimental conditions might involve any combination of the following: 1) prolonging the reaction period, 2) raising the temperature, or 3) using slightly less than a full equivalent of LDA so that a small amount of unreacted 2-methylcyclohexanone would remain in the mixture.
Eq. 7 and 8 look quite similar, but where the kinetically controlled product ratio in eq. 7 depends on the difference in transition state energies, $G_B^\ddagger - G_C^\ddagger$, the thermodynamically controlled ratio in eq. 8 depends only on the difference in product energies, $G_B - G_C$. Since the more substituted enolate is more stable, $\Delta G > 0$, the more substituted enolate will be favored under conditions of thermodynamic control.

**Multistep Reactions.** Reaction coordinate diagrams are also useful for analyzing reactions with multistep mechanisms, and they help us understand what is meant by a “step”. Briefly, a multistep reaction mechanism can be thought of as consisting of a series of “elementary steps”, where each elementary step consists of movement on the reaction coordinate from one minimum to the next, with only one energy maximum or transition state intervening. Elementary steps can correspond either to a conformational change or to a chemical reaction, and both kinds of steps are kinetically significant.

The Diels-Alder reaction of butadiene and ethylene, which we previously treated as a one-step reaction, is more correctly viewed as a multistep process. Butadiene normally exists as
a mixture of conformers; the \textit{s-trans} conformer is slightly more stable, but only the \textit{s-cis} conformer has a suitable geometry for Diels-Alder cycloaddition. Therefore, if we think of the Diels-Alder reaction as beginning with the more stable \textit{s-trans} conformer, and proceeding from there to the product, two elementary steps are necessary. In the first step ("reactants" → "intermediates"), \textit{s-trans} butadiene is converted into its "active" form, \textit{s-cis} butadiene. Then, in the second step, ("intermediates" → "product"), \textit{s-cis} butadiene combines with ethylene giving cyclohexene. The energy surface for this reaction contains only three minima because the "product" of the first step is the "reactant" of the second step.

In general, a multistep reaction with \(N\) steps will be described by a reaction coordinate diagram with \(N+1\) minima, where these minima describe the preferred structures of the initial reactant, the final product, and \(N-1\) reaction intermediates. Since reaction intermediates are rarely observed it is easy to confuse them with transition states (which are never observed). There is, nevertheless, an enormous difference between the two. Reaction intermediates, unlike transition states, correspond to energy minima and behave in the same fashion as reactants and products. Thus, intermediates are long-lived molecules, are present in the final reaction mixture,\(^{10}\) and, in principle, are experimentally observable. In reality, however, they usually have much higher energies (and much smaller equilibrium populations) than either the reactants or products. Special experimental techniques are often needed for the detection and characterization of reaction intermediates, and these experiments play an important role in chemical research.

**Summary.** Simple potential energy diagrams surfaces are an excellent tool for describing many types of chemical behavior. They make it easy to compare the energies of different molecules, to understand their conformational preferences, and to predict the rate at which they will undergo conformational change or chemical reaction. Most importantly, they highlight the ways in which energy controls chemical phenomena, and they suggest computational strategies for studying these problems.

The main limitation of these diagrams is that they provide very little detail about molecular structure. Structure is a function of several, usually many, variables, and each variable affects energy differently. Actual computations of geometry and energy must take all of these variables and structure-energy relationships into account, but routine chemical thinking can usually ignore these details.

\(^{10}\) This is certainly the case for the butadiene-ethylene cycloaddition. Any unreacted butadiene will be a mixture of \textit{s-trans} (major component) and \textit{s-cis} (minor component) conformers.