Jurnal Pijar MIPA
https://jurnalfkip.unram.ac.id/index.php/JPM

ISSN 1907-1744 (Print)
ISSN 2460-1500 (Online)

Rethinking Reactivity: How Structure, Energy, and Entropy Drive Chemical Transformations

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Received: March 28, 2025. Accepted: April 24, 2025. Published: June 26, 2025

Abstract: Chemical reactivity has traditionally been analyzed using thermodynamic variables as abstract concepts separate from molecular structure. Bridging structural features with thermodynamic behavior remains a challenge in advancing predictive models and educational clarity. This study presents a novel structural-thermodynamic framework for interpreting chemical and biological reactivity by redefining potential energy and entropy through molecular constitution, configuration, and conformation. Moving beyond conventional models that treat these thermodynamic variables as abstract quantities, this conceptual analysis directly links molecular structure to energy storage and entropic behavior. Using a qualitative, literature-based approach, the paper examines diverse organic mechanisms, including S_N1, S_N2, E1, E2, and Diels–Alder reactions, to demonstrate how structure governs both enthalpic and entropic shifts throughout reaction pathways. The novelty of this framework lies in its ability to unify thermodynamic reasoning with intuitive structural interpretation, offering a predictive tool for reaction outcomes. By connecting spatial and atomic features to thermodynamic properties, this model enhances understanding in areas such as drug design, catalysis, and molecular education, helping students and researchers transition from memorization to mechanistic insight.

Keywords: Duality; Potential Energy; Reaction Mechanism; Reactivity; Thermodynamics.

Introduction

Chemical reactivity is traditionally explained through changes in potential energy and entropy. While these thermodynamic principles are central to understanding reaction spontaneity, they are often taught as abstract quantities, detached from the molecular structure of the reactants and products. This work proposes a new perspective: potential energy and entropy can be directly understood through the physical features of molecules themselves [1].

In classical chemistry, potential energy is commonly defined as the energy stored in chemical bonds, arising from electron distributions and atomic interactions [2]. Bond-breaking absorbs energy and raises potential energy, while bond-formation releases energy and lowers it. These changes are captured in a reaction's enthalpy (ΔH), which quantifies the overall energy transfer [3].

Entropy, meanwhile, is often simplified as a measure of disorder. More precisely, it reflects the number of possible microscopic arrangements or microstates, available to a system [4]. A reaction that produces more mobile species, such as gases or fragmented molecules, generally increases entropy by expanding the number of accessible configurations and motions [5].

Together, potential energy and entropy determine the thermodynamic favorability of a reaction. This relationship is formalized in the Gibbs free energy equation: $\Delta G = \Delta H - T\Delta S$. A process becomes spontaneous when it releases energy ($\Delta H < 0$), increases entropy ($\Delta S > 0$), or both. While this equation is widely taught, it doesn't fully capture the underlying structural logic behind why energy and entropy shift during reactions.

While existing models of reactivity often rely on potential energy surfaces, molecular orbital theory, or statistical mechanics to explain thermodynamic trends, these frameworks typically separate structure from thermodynamic reasoning. In contrast, this work integrates structural identity, constitution, configuration, and conformation, directly into the definitions of potential energy and entropy. This unified perspective shifts the emphasis from abstract variables to tangible, interpretable molecular features that shape energy flow and entropic behavior.

In this study, we explore that structural logic. By analyzing how potential energy and entropy emerge from a molecule's constitution (atomic makeup), configuration (three-dimensional connectivity), and conformation (flexibility and shape) [6], we reveal a deeper connection between structure and thermodynamic behavior. Through this lens, we aim to move beyond rote definitions, and instead offer a unified, intuitive framework for understanding and predicting chemical reactivity.

Research Methods

This study adopts a conceptual-descriptive design grounded in interpretive structural analysis [7]. It draws from classical thermodynamics, molecular theory, and mechanistic organic chemistry to develop a unified structural-thermodynamic model [8]. The unit of

How to Cite:
J. Alzeer, "Rethinking Reactivity: How Structure, Energy, and Entropy Drive Chemical Transformations", *J. Pijar.MIPA*, vol. 20, no. 4, pp. 590–597, Jun. 2025. https://doi.org/10.29303/jpm.v20i4.8795

analysis comprises well-characterized reaction types, S_N1, S_N2, E1, E2, and Diels–Alder, chosen for their mechanistic diversity and pedagogical relevance [9]. The analytic method involves deconstructing each mechanism through the structural triad of constitution (atomic makeup and bond types), configuration (spatial and stereochemical arrangement), and conformation (flexibility and motion). These structural features are mapped onto thermodynamic properties such as potential energy and entropy, forming the basis for qualitative comparison. No empirical data collection is involved; instead, the study synthesizes insights from literature and structural logic to build an explanatory model for reactivity [10].

This study is grounded in a conceptual framework derived from the principles of Lifestylopathy, a developing field in medicine that explores health and disease through the interplay of potential energy and entropy. Lifestylopathy proposes that every biological state reflects a balance between stored energy (in various physical, chemical, and psychological forms) and the degree of internal order or disorder. This perspective, while rooted in medicine, offers a powerful lens for reinterpreting chemical reactivity and molecular behavior [11-12].

Result and Discussion

Potential Energy and Entropy in Chemical Reactions

Chemical reactions are driven by a dynamic balance between energy release and the expansion of molecular freedom. These changes are governed by potential energy and entropy, two forces that operate together to shape chemical transformations [13]. Rather than viewing them as abstract thermodynamic variables, this framework treats both as direct outcomes of molecular structure [14].

Reactions often begin with molecules in a more ordered, higher-energy state and proceed toward products that are either lower in potential energy, higher in entropy, or both [15]. For instance, reactions that generate gaseous products lead to a significant entropy increase, not simply because gas is “disordered,” but because gas molecules occupy vastly more microstates than liquids or solids [16]. This structural transition dramatically broadens the system’s energetic possibilities.

At the same time, reactions that release heat (exothermic processes) reflect a drop in potential energy, typically from forming stronger bonds or relieving strain [17]. The thermodynamic favorability of any transformation, captured by the Gibbs free energy equation, $\Delta G = \Delta H – T\Delta S$, depends on how these structural shifts in energy and freedom play out together.

Crucially, this interplay is not random. The structure of molecules, how atoms are arranged, bonded, and able to move, dictates both their internal energy and their entropic flexibility [18]. Molecules with rigid frameworks may store more energy but exhibit low entropy [19]. Flexible structures, in contrast, may have lower energy but access a wider range of conformations [20]. Understanding reactivity, therefore, requires looking at both sides of the thermodynamic equation as structural consequences [21].

Thermodynamic View of Molecular Structure

To fully understand how structure drives chemical behavior, it’s essential to examine how potential energy and entropy emerge from specific molecular features. By viewing constitution, configuration, and conformation as structural levers, we can trace how energy is stored, released, or redistributed, and how entropy arises from the range of motion and spatial possibilities within a molecule [22].

Constitution: Atomic Composition and Energetic Content

Constitution refers to the identity and number of atoms in a molecule. This directly determines the number and types of chemical bonds, which are the primary carriers of potential energy. Molecules with complex constitutions store more energy due to extensive bonding networks. When these bonds break, as in combustion or decomposition, the stored energy is released, often alongside a structural breakdown that raises entropy.

Simpler molecules, though energetically less dense, may generate significant entropy when fragmented further. For example, thermal cracking of heavy hydrocarbons into smaller fragments increases both entropy and molecular motion, even as overall potential energy drops. This interplay illustrates how constitution sets the baseline for both enthalpy and entropic potential.

Configuration: Spatial Arrangement and Stereochemical Influence

Configuration captures the fixed three-dimensional arrangement of atoms, including stereochemistry and chirality. Isomers with the same constitution can vary greatly in both energy and entropy depending on their spatial layout. For example, cis-isomers often experience greater steric repulsion than trans-isomers, resulting in higher potential energy. Likewise, molecules with multiple stereocenters tend to be more ordered and enthalpically rich.

When configuration changes, such as during racemization or isomerization, potential energy typically decreases while entropy increases, as the system moves toward a more statistically probable distribution. These changes are not just geometric; they reflect deep shifts in how energy is stored and how freely the system can evolve [23].

Conformation: Flexibility, Movement, and Entropic Reach

Conformation refers to the shapes molecules adopt through rotations around single bonds. This flexibility is a direct source of entropy. Rigid molecules, due to ring strain, bulky groups, or intramolecular interactions, are locked into limited conformations, resulting in lower entropy and often higher potential energy. In contrast, flexible molecules can access a wide

range of geometries, increasing their entropic richness and spreading energy across more accessible states [24].

In this context, rigidity behaves like a compressed spring, it stores energy that can be released when the molecule relaxes into more favorable conformations. Flexibility, meanwhile, reduces the energetic cost of transition states by offering diverse paths to lower-energy structures. Thus, conformation doesn't just affect shape, it modulates the very thermodynamic landscape the molecule navigates.

Energy and Entropy: Key to Biomolecular Change

Biomolecular transformations vividly illustrate how potential energy and entropy operate together to drive chemical processes in living systems. These processes are not just thermodynamic shifts, they're structural transitions encoded in the molecules themselves [25]. Thermodynamics plays a crucial role in the understanding of energy transformations occurring within complex systems such as living organisms. For instance, the energy transformations in cells are influenced by the intricate balance of entropy and energy availability [26].

Take glucose as an example. It has a defined atomic makeup (constitution), a stable ring structure (conformation), and specific stereochemistry (configuration), characteristics that contribute to its stability and energy richness. The compact, energy-rich molecular structure of glucose can store significant potential energy in its bonds while maintaining relatively low entropy due to its organized form [27]. When glucose undergoes complete oxidation to carbon dioxide and water, that organized structure is dismantled, demonstrating a clear interplay between structure and thermodynamic principles. The stored potential energy is released, captured in ATP or dissipated as heat, while entropy increases dramatically as more mobile molecules are produced. This reaction represents a thermodynamic double-shift, with energy liberation and molecular order giving way to dynamic freedom (Figure 1).

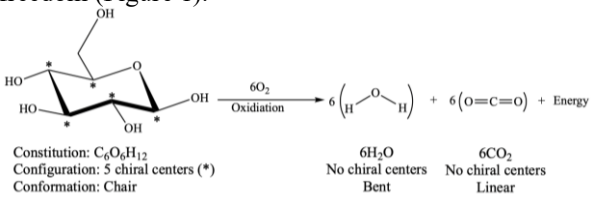

Figure 1. The Chemical Transformation of Glucose During Oxidation in Cellular Respiration

This principle is not unique to glucose; other biomolecules such as proteins, nucleic acids, and polysaccharides exhibit similar behaviors, where their intricate bonding and stereochemical complexity result in high potential energy and low entropy. The breakdown of these biomolecules also contributes to entropy gain and energy release, underscoring fundamental traits of metabolic transformation [28]. ATP offers a particularly rich example of these principles in action. Its dense molecular constitution includes a purine base (adenine), a ribose sugar, and a triphosphate group, which carries substantial electrostatic strain. The configuration of ATP, characterized by defined stereocenters, adds structural precision, and its conformation is restricted due to repulsions between phosphate groups and coordination with magnesium ions. This rigidity creates a high-energy state, akin to a wound spring. Upon hydrolysis to ADP and inorganic phosphate, the molecule relaxes into a more flexible, lower-energy, and higher-entropy state. Importantly, the magnesium ion remains bound, stabilizing the product and supporting further structural roles, illustrating the multifaceted ways that structure and energy management are interconnected in biological systems (Figure 2).

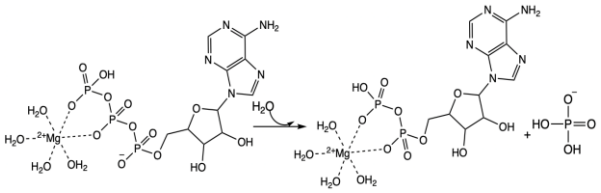

Figure 2. Magnesium-Mediated ATP Hydrolysis: ATP to ADP and Inorganic Phosphate

In this light, ATP transcends the simplistic view of a molecule with "high-energy bonds." It is better understood as a system where constitution, configuration, and conformation collaboratively encode, store, and release energy in a controlled, entropically guided manner [29]. This structural lens offers a unified framework for interpreting energy flow and molecular change, not only in biomolecules but across all of chemistry. It allows us to move beyond isolated ideas of "disorder" or "charge repulsion" and instead focus on how structure encodes thermodynamic behavior.

Duality of Potential Energy and Entropy in Reaction Mechanisms

Understanding chemical reactions requires more than tracking which bonds break or form. Each transformation is shaped by a balance between stored energy (potential energy) and molecular freedom (entropy). These forces work in tandem and are determined by the molecule's constitution, configuration, and conformation [30].

Potential energy increases when structural constraints are introduced, through steric strain, unstable intermediates, or ionic character. Entropy rises when the number of particles increases or when molecular flexibility expands. The reaction mechanism, whether stepwise or concerted, unfolds along a thermodynamic path shaped by these structural and energetic changes [31]

S_N1 Mechanism: Dissociation and Reorganization

The S_N1 reaction illustrates how structural strain and molecular dissociation drive changes in both potential energy and entropy. Tertiary alkyl halides, like tert-butyl bromide, are predisposed to S_N1 due to their crowded configuration. Steric bulk raises potential energy and limits conformational freedom, reducing entropy. The carbon–halogen bond is relatively weak and elongated, particularly with bromine, which contributes to the molecule's high potential energy (Figure 3).

The rate-determining step is ionization: the carbon–halogen bond breaks heterolytically, forming a carbocation and a halide ion. This step requires energy input, raising potential energy, but simultaneously increases entropy. The system shifts from one constrained molecule to two independently moving species, boosting translational and rotational degrees of freedom [32].

The resulting carbocation is high in energy but also gains flexibility, offering multiple conformational and reactive pathways. The subsequent nucleophilic attack is exothermic, releasing potential energy as the carbocation stabilizes. However, entropy decreases again as two species become one product [33].

This reaction pathway reflects a key thermodynamic pattern: bond breaking increases both potential energy and entropy; bond formation reverses both. The S_N1 mechanism succeeds when the initial energy barrier is compensated by an overall gain in entropy and stability of the final product.

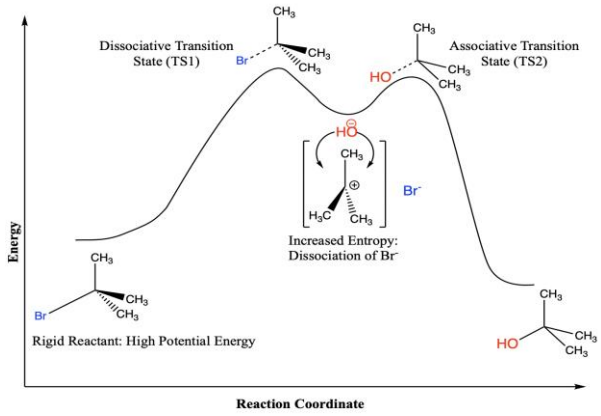

Figure 3. Energy Profile of an S_N1 Reaction Showing Dissociation and Nucleophilic Attack Transition States

E1 Reactions: Stepwise Elimination

The E1 elimination mechanism shares its initial step with S_N1: ionization of the carbon–leaving group bond. However, instead of nucleophilic substitution, the pathway proceeds through deprotonation and alkene formation, making it a powerful example of how entropy and energy collaborate in elimination.

Tertiary and secondary alkyl halides, such as tert-butyl chloride, start in a conformation with high potential energy due to steric strain. Their bulky substituents limit rotational freedom, creating a low-entropy, rigid molecular environment. The carbon–halogen bond is weakened by electronic and spatial factors, which primes it for cleavage (Figure 4).

During the rate-determining step, ionization occurs: the halide leaves, forming a carbocation and a free anion. This bond cleavage raises potential energy but also introduces a significant entropy gain. The molecule transitions from one constrained species to two independently moving particles with increased translational and rotational motion.

Next, a base abstract a β-hydrogen from the carbocation, forming a double bond and yielding a neutral alkene and a byproduct such as HCl [34]. This step is exothermic, lowering potential energy as a π-bond forms and electronic strain is relieved. Entropy increases again slightly due to the production of two neutral species.

E1 becomes more favorable than S_N1 when strong bases are present in the reaction medium, especially if they are sterically hindered and less suited for nucleophilic attack. Elevated temperatures also shift the balance toward E1, as the entropic contribution becomes more significant and elimination pathways benefit from increased thermal energy.

Overall, the E1 mechanism reflects a stepwise redistribution of energy and entropy. It begins with energy input and an entropy surge, followed by energy release and stabilization. Conditions that favor entropy gain, such as heat and the presence of a base, make elimination more likely than substitution [35].

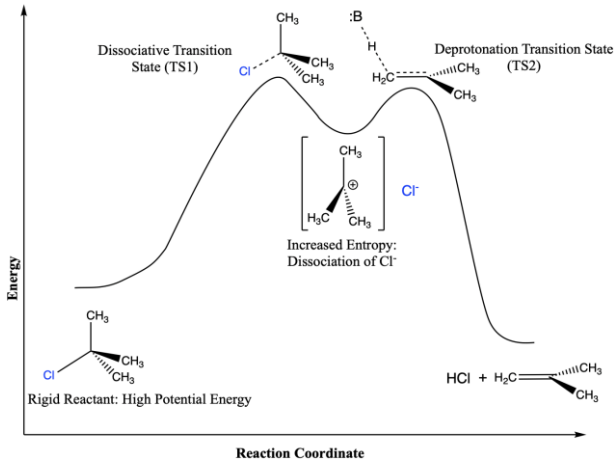

Figure 4. Energy Profile of an E1 Reaction Showing Dissociation and Deprotonation Transition States

S_N2 Mechanism: Alignment and Concertedness

The S_N2 mechanism showcases the delicate coordination between structural alignment, potential energy, and entropy in a one-step reaction. This concerted reaction approach is critical, as it is influenced by several factors, including the sterics and electronic properties of both the substrate and the nucleophile. Primary alkyl halides are ideal substrates due to their minimal steric hindrance. In the initial state, the reactants, a nucleophile and a substrate, exist independently, enjoying high entropy from their translational and rotational freedom. Potential energy is relatively low since both are in stable, unstrained forms [36].

As the reaction begins, the nucleophile approaches the electrophilic carbon from the backside (Figure 5). This leads to a concerted transition state where old and new bonds are partially formed, a fleeting structure with five-coordinated geometry. Achieving this alignment comes at a thermodynamic cost: entropy drops significantly as molecular motion becomes restricted and the system adopts a specific, ordered geometry [37].

Simultaneously, potential energy rises. The strained transition state, with bond reorganization in progress, represents the point of maximum energy. This state is both sterically and electronically unstable, reflecting the energy investment required for reconfiguration.

As the nucleophile completes its bond and the leaving group departs, potential energy is released and

the system relaxes into a stable product. Unlike in E1 or S_N1 reactions, the number of species remains roughly the same before and after the reaction, typically two reactants yielding two products, so there is minimal change in overall translational entropy. The main entropic cost occurs in the transition state, where specific alignment temporarily restricts motion. Once the reaction is complete, molecular freedom is largely restored, and the system returns to a similar entropic state.

The S_N2 mechanism highlights how entropy must temporarily decrease to achieve the ordered transition state, while potential energy peaks due to bond strain. The reaction succeeds when the system can overcome these demands, making minimal steric interference and strong nucleophiles key to success [38-39].

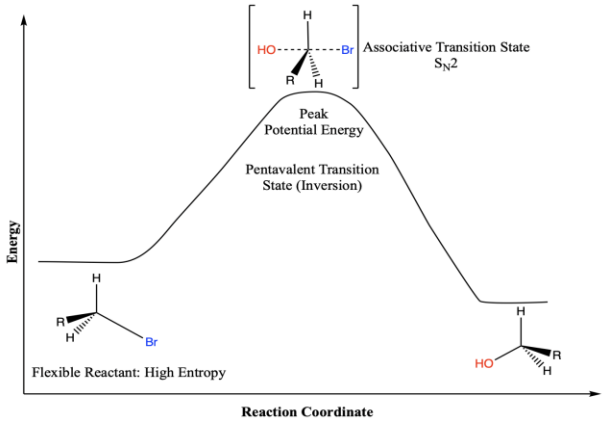

Figure 5. Energy Diagram of an S_N2 Reaction Highlighting the Associative Transition State

E2 Reactions: Concerted Elimination

The E2 mechanism is a single-step elimination reaction that demands strict molecular alignment. It reveals how geometric constraints shape entropy and how bond reorganization drives energy change in real time.

The reaction involves a base abstracting a β-hydrogen while the leaving group departs simultaneously, forming a double bond. For this to occur efficiently, the β-hydrogen and the leaving group must adopt an antiperiplanar geometry, a specific spatial arrangement that enables optimal orbital overlap (Figure 6). This structural requirement sharply reduces entropy, as the molecule must adopt a rare and ordered conformation from among many flexible possibilities [40].

The starting alkyl halide often possesses high entropy due to conformational freedom. But as the molecule adjusts to meet the E2 alignment requirement, entropy drops, and potential energy rises. This energetic cost reflects both the enforced rigidity and the strain involved in reaching the transition state [41].

The transition state itself is a moment of maximum tension, partial bond-breaking and bond-forming occur in concert, pushing the molecule into a high-energy, low-entropy configuration. Once the elimination is complete, the system relaxes into two separate products: an alkene and a leaving group byproduct (often HBr). This bond reorganization lowers potential energy and increases entropy as translational and conformational freedom returns.

E2 is favored over S_N2 when a strong base is present, especially a bulky one that cannot easily approach the electrophilic carbon for substitution. Additionally, secondary and tertiary substrates, which hinder backside attack, further tilt the reaction toward elimination. Elevated temperatures also promote E2 by amplifying entropy's contribution to the reaction drive. While elevated temperatures favor E2, however, in certain sensitive systems, excessive heat may still increase the risk of side reactions or over-elimination. Ultimately, the E2 mechanism exemplifies a delicate balance between the rigid alignment essential for the transition state and the inherent flexibility of molecular structures. This complex relationship allows for alignment that facilitates efficient bond formation and entropy recovery to outweigh the energy costs associated with navigating through the ordered transition state [42].

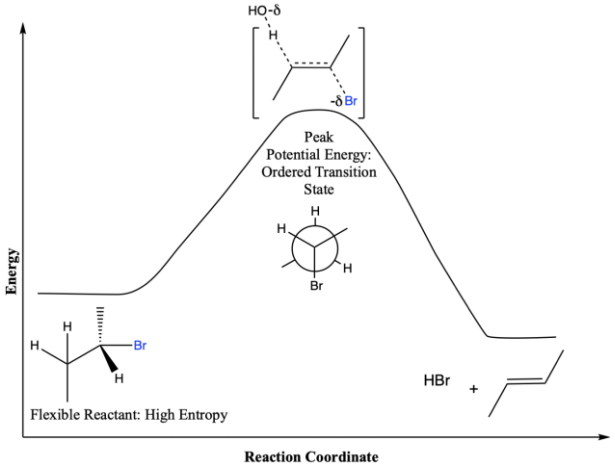

Figure 6. E2 Reaction: Potential Energy and the Ordered Transition State

Diels–Alder Reactions: Concerted Cycloaddition

The Diels–Alder reaction, a [4+2] cycloaddition, elegantly demonstrates how two molecules sacrifice entropy to gain structural stability and lower potential energy. This reaction is concerted, meaning bonds break and form in a single, coordinated step, demanding precise alignment and mutual reactivity [43].

The reaction starts with a diene and a dienophile, each in separate, flexible conformations. At this stage, entropy is relatively high due to the molecules' independent motion and internal flexibility. Their potential energy is moderate, stabilized by delocalized π-electron systems (Figure 7).

As the two species approach, they must adopt specific conformations to achieve the orbital overlap required for bond formation. This spatial demand imposes order, sharply reducing entropy. Simultaneously, π-bonds are strained as new σ-bonds begin to form, raising potential energy and pushing the system toward a high-energy, low-entropy transition state.

The transition state is tightly constrained and geometrically specific, a thermodynamic bottleneck where the energetic cost of bond reorganization is highest. Yet once this state collapses into the cyclic product, the potential energy drops sharply. The

formation of two strong σ-bonds offsets the energy required to distort the starting materials. Entropy partially recovers as the product, though more ordered than the reactants, regains some internal flexibility [44].

This mechanism illustrates a classic thermodynamic exchange: entropy is sacrificed to achieve alignment, energy is invested to reach the transition state, and both are paid back by the formation of a stable, low-energy product. In this way, the Diels–Alder reaction is not just pericyclic, it's a fine-tuned balance of thermodynamic forces written into molecular structure [45].

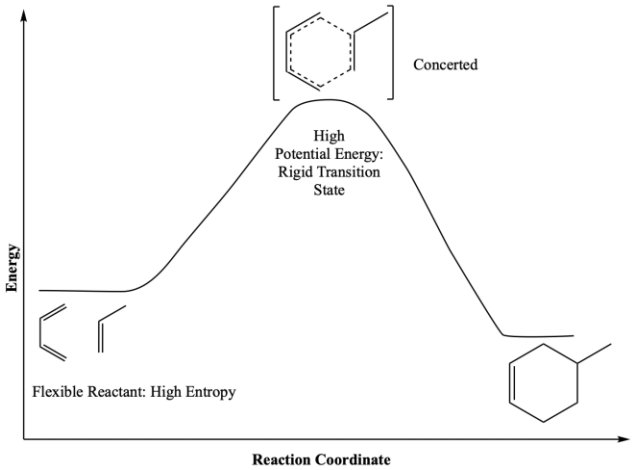

Figure 7. Diels-Alder [4+2] Cycloaddition: High Potential Energy Due to Rigid Transition State

Chemical reactions are often taught as sequences of bond-making and bond-breaking events. However, a deeper understanding emerges when examining these processes through the structural dimensions of constitution, configuration, and conformation, each of which shapes the potential energy and entropy of the system. For instance, potential energy can increase when molecules are forced into strained geometries, unstable intermediates, or charged states. These structural conditions, such as tight configurations, ionic separation, or steric clashes, function to store energy, akin to a compressed spring [46-47]. On the other hand, entropy relates to the system's ability to undergo motion, bend, rotate, and reorganize, rising during bond dissociation, separation of species, or when molecules gain conformational freedom. Conversely, entropy decreases when movement is constrained, as in transition states or tightly bound complexes [48].

When analyzed through this structural lens, each reaction mechanism resembles a thermodynamic pathway where molecules cross energetic peaks and troughs, influenced by structural changes that modulate energy storage and spatial freedom. This framework doesn't just explain known mechanisms, it predicts them. It reveals why a reaction prefers one pathway over another based on how much energy the structure stores, how much entropy it can afford to lose, and whether the overall pathway leads to a more stable, flexible end state. In drug design, this understanding is crucial. Binding affinity isn't just about forming the strongest interactions, it's about achieving them without sacrificing too much entropy. Molecules that are too rigid may bind tightly but pay an entropic penalty. Recognizing this, chemists often adjust scaffolds to strike a balance, optimizing both enthalpic stability and entropic viability.

In catalysis, particularly with organometallic or enzymatic systems, a comprehensive structural-thermodynamic perspective highlights the importance of certain molecular geometries in favoring transition state stabilization and enhancing reaction rates. Factors such as ligand choice, metal coordination, and substrate orientation significantly contribute to this equilibrium between stored energy and freedom of structure. Moreover, in educational contexts, grounding energy and entropy in structure turns abstract definitions into intuitive concepts. Instead of memorizing rules, students can ask: "What part of this molecule is holding energy? What's preventing it from moving? What changes when this bond breaks?" These kinds of questions encourage real chemical reasoning (Table 1).

Table 1. Comparative Summary of Reaction Mechanisms by Structural Influence on Potential Energy and Entropy

Mechanism	Constitution	Configuration	Conformation	ΔPotentia Energy	ΔEntropy	Key Thermodynamic Pattern
S_N1	Moderate	High strain	Low	Increases then drops	Increases then drops	Dissociation-driven entropy spike
S_N2	Low	Minimal strain	Moderate	Peaks at transition	Temporary drop	Concerted reconfiguration
E1	Moderate	Steric hindrance	Low	Similar to S_N1	Dual increase	Sequential energy release
E2	High	Anti-periplanar alignment	Low to moderate	Transition peak	Alignment cost, entropy recovery	Concerted elimination
Diels-Alder	Moderate	π-stacking	Flexible start, rigid TS	Sharp peak, stable drop	Significant loss then partial regain	Entropy-for-stability trade-off

This model also supports advancements in computational and machine learning tools, as the relationships between structure, energy, and entropy can be systematically encoded into algorithms designed to predict reactivity, guide synthesis planning, and refine simulation models [49]. Ultimately, when structural considerations underlie our comprehension of chemical processes, interrelations of energy and entropy become naturally integrated, fostering a unified and enriched understanding of chemistry.

Conclusion

By redefining potential energy and entropy through the lens of molecular structure, this work offers a unified framework for interpreting chemical reactivity. Constitution, configuration, and conformation are not just structural labels, they are thermodynamic forces that determine how molecules store energy and access dynamic freedom. Across diverse reaction mechanisms, from substitution to cycloaddition, we've seen that energy and entropy are not abstract ideas but direct consequences of how molecules are built and behave. This perspective deepens our understanding of stability, reactivity, and molecular design, and opens the door to more intuitive teaching, more predictive modeling, and more purposeful chemistry. Future work may focus on applying this framework in computational chemistry, where simulations could quantify how structural changes influence energy and entropy in real time. It could also be extended into the field of systems biology or medicinal chemistry, offering new ways to analyze biomolecular pathways through structural thermodynamics. Experimental validation, such as observing entropy-driven selectivity under controlled conformational constraints, could further support the model's predictive power.

Acknowledgments
We would like to thank Prof. Loay Awad, Prof. Khaled Abou Hadeed, and Reem Alzeer for their useful discussion and support.

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