



This open access document is posted as a preprint in the Beilstein Archives at <https://doi.org/10.3762/bxiv.2026.39.v1> and is considered to be an early communication for feedback before peer review. Before citing this document, please check if a final, peer-reviewed version has been published.

This document is not formatted, has not undergone copyediting or typesetting, and may contain errors, unsubstantiated scientific claims or preliminary data.

Preprint Title The Geometry of Chemical Reactivity

Authors Simon Gibbons

Publication Date 27 Oct 2026

Article Type Full Research Paper

Supporting Information File 1 Supporting Information.docx; 25.7 KB

ORCID® iDs Simon Gibbons - <https://orcid.org/0000-0003-1587-6809>



License and Terms: This document is copyright 2026 the Author(s); licensee Beilstein-Institut.

This is an open access work under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0>). Please note that the reuse, redistribution and reproduction in particular requires that the author(s) and source are credited and that individual graphics may be subject to special legal provisions. The license is subject to the Beilstein Archives terms and conditions: <https://www.beilstein-archives.org/xiv/terms>.

The definitive version of this work can be found at <https://doi.org/10.3762/bxiv.2026.39.v1>

The Geometry of Chemical Reactivity

Simon Gibbons*

Address:

Centre for Natural Products Discovery (CNPD), School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool L3 3AF, United Kingdom

*Corresponding author

Email: S.Gibbons@ljmu.ac.uk; anabasis@mail.com

Abstract

Chemical reactions often reorganise abruptly with small changes in solvent, catalyst, or excitation, yet such discontinuities are difficult to rationalise using potential energy surfaces alone. Here I show that reactivity is governed by the geometry of constraint-defined state space. In this Boundary Theory (BT) framework, a chemical system occupies an admissible domain whose boundary ($\partial\Omega$) determines which reaction pathways exist. The contrast between *tert*-butyl chloride (S_N1) and methyl bromide (S_N2) shows how curvature on $\partial\Omega$ determines accessible pathways. Deformation of $\partial\Omega$ by external or internal constraints creates or eliminates continuous trajectories, providing a unified geometric explanation for S_N1/S_N2 switching, E1/E2/E1cB behaviour, rearrangement cascades, and pericyclic allowedness. Mechanisms correspond to accessible geodesics on $\partial\Omega$ rather than discrete stepwise sequences. By thinking of chemical reactivity in terms of boundary accessibility, BT offers a general geometric framework for predicting when reactions appear, vanish, or reorganise.

Keywords:

Boundary Theory, Chemical Reactivity, Reaction Mechanisms, Chemical Space, Pathway Accessibility, Mechanistic Switching

Introduction

The dominant language of chemistry remains mechanistic, in which reactions are described as discrete pathways separated by transition states and organised on potential energy surfaces (PES) [1]. However, many recurring experimental observations resist explanation using PES alone. For example, certain reactions occur only under strongly acidic conditions [2], pathways can materialise at catalyst loadings [3], photochemical and thermal reactions can yield divergent outcomes [4], and enzymatic systems frequently exhibit complex cascade rearrangements [5].

Here, I introduce a framework, Boundary Theory (BT), where reactivity is controlled by the geometry of constraint-defined state space and the mathematical formulation of this framework has been described in [6] and briefly in the Supporting Information. Chemical systems are described as domains (Ω) comprising all admissible states, determined by electronic, steric, environmental, and topological constraints. Observable chemistry is restricted to an admissibility boundary ($\partial\Omega$), the subset of states accessible under given constraints. Changes in constraints modify the structure of $\partial\Omega$, thereby determining which reaction pathways occur.

Within this framework, reaction mechanisms are reinterpreted as continuous trajectories (geodesics) on $\partial\Omega$ rather than predefined stepwise sequences. Switching between mechanisms corresponds to deformation of the boundary, rather than competition between independent pathways, and rare or condition-specific reactivity arises when previously inaccessible regions of $\partial\Omega$ become available. BT is formalised as:

Altering constraints deforms the admissibility boundary ($\partial\Omega$), thereby creating or eliminating continuous reaction pathways independently of intrinsic energy surfaces.

Boundary Theory (BT) was first developed by the author as a general framework to describe biological and chemical systems in terms of reachability within constraint-defined state spaces, where admissible domains (Ω), their boundaries ($\partial\Omega$), and constraint-driven deformation govern transitions between states [6]. The framework was subsequently applied to natural product biosynthesis, providing a geometric interpretation of silent and conditionally active biosynthetic gene clusters as boundary-limited systems whose activation depends on deformation of the underlying constraint field [7]. BT has also been extended to antimicrobial activity by the author, where

Gram-negative susceptibility is explained as a boundary-crossing problem governed by permeability, efflux, and intracellular persistence within a common geometric framework [8]. A recent experimental study showed that boundary constraints act as a primary source of positional information, governing the emergence, location, and robustness of developmental patterning by shaping reaction-diffusion signalling dynamics and thereby directing cell fate specification and tissue self-organisation [9].

The present work further develops these concepts by applying BT directly to chemical reactivity and examining how changes in constraints reshape $\partial\Omega$ to create, suppress, or redirect reaction pathways. This perspective suggests that seemingly different forms of reactivity share a common geometric basis. In the following sections, established reaction classes are reinterpreted using BT to illustrate how changes in constraints determine pathway accessibility. A simplified gravity map analogy is introduced to aid visualisation of boundary curvature and accessible trajectories (Figure 1).

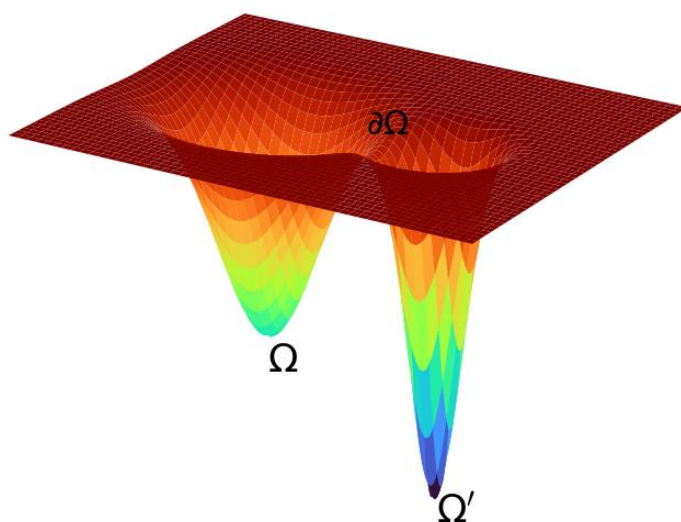


FIGURE 1. Boundary geometry of reaction space. Conceptual representation of the admissibility boundary ($\partial\Omega$) separating accessible and forbidden regions of state space. Distinct basins correspond to mechanistic domains, connected by a ridge defining a transition manifold. Curvature gradients represent variations in accessibility, and representative trajectories illustrate continuous motion constrained to $\partial\Omega$.

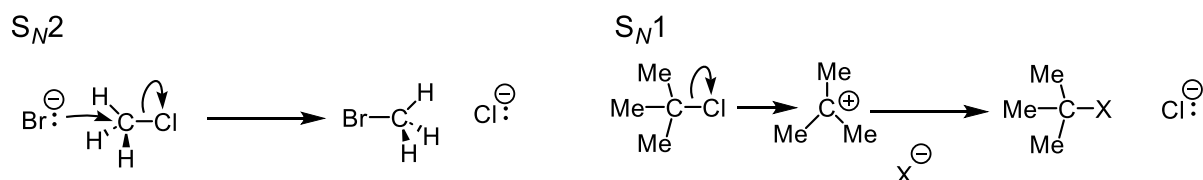
A concise mathematical treatment of Boundary Theory together with a practical Constraint Mapping methodology is provided in Supporting Information File 1.

Results

Ω — Classical Mechanistic Boundaries

S_N1/S_N2 as Curvature-Dependent Geodesics

Nucleophilic substitution reactions are conventionally classified into two distinct mechanistic regimes, S_N1 and S_N2 , based on classical kinetic and mechanistic studies [10]. In the BT framework, these are inferred as alternative trajectories on a common admissibility boundary ($\partial\Omega$). The pathway followed by the system is determined by the local geometric properties of $\partial\Omega$, particularly its curvature under the prevailing constraints.



The S_N2 process corresponds to a continuous, concerted trajectory across $\partial\Omega$. Classically, bond formation and bond cleavage occur simultaneously with inversion of stereochemistry [10]. This behaviour reflects a low-curvature pathway in which the system can move smoothly without encountering intermediate basins. The reaction proceeds as a direct geodesic across the boundary, with no requirement for stabilised intermediate states.

In contrast, S_N1 becomes accessible when this continuous pathway is no longer geometrically favourable. Under these conditions, $\partial\Omega$ curvature increases locally, and the system diverts into a distinct cationic basin corresponding to a carbocation intermediate, followed by subsequent nucleophilic capture [10]. S_N1 corresponds to a trajectory that departs from the low-curvature geodesic into a high-curvature region of $\partial\Omega$.

The transition between S_N2 - and S_N1 -type behaviour is governed by constraints. Parameters such as solvent polarity, nucleophile strength, and leaving group ability collectively determine the geometry of $\partial\Omega$. These factors are well established experimentally to influence substitution pathways [11], but under BT, they are interpreted generally as shaping the curvature landscape that defines pathway accessibility.

This view also accounts for systems that exhibit mixed or intermediate behaviour. Substrates such as benzylic and allylic systems that undergo both S_N1 and S_N2 reactions, correspond to regions of $\partial\Omega$ where multiple trajectories are accessible simultaneously. Rather than representing ambiguous or ill-defined cases, such systems reflect geometries where the admissibility boundary supports more than one continuous pathway. The outcome of the reaction is governed by continuous deformation of $\partial\Omega$ and the resulting redistribution of accessible pathways (Figure 2) and not just discrete switching between mechanisms.

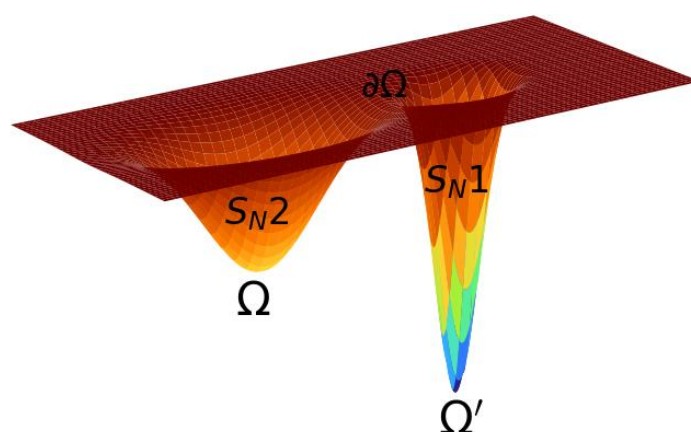
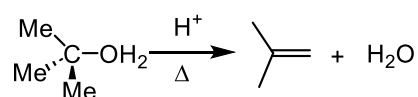


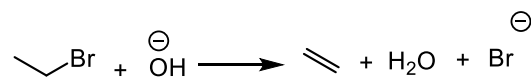
FIGURE 2. Curvature landscape of S_N1/S_N2 reactivity. Low-curvature trajectories correspond to concerted S_N2 pathways, whereas increased curvature leads to diversion into carbocation basins characteristic of S_N1 behaviour. External parameters (e.g., solvent polarity, nucleophile strength, and leaving group ability) modulate the geometry of $\partial\Omega$, shifting the system across regions where multiple trajectories may coexist.

Elimination (E1/E2/E1cB) as a Tri-Basin Geometry

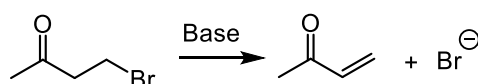
Elimination reactions (E1, E2, and E1cB) are commonly treated as distinct mechanistic classes. Within the framework, these processes are re-explained as trajectories across a shared admissibility boundary ($\partial\Omega$), characterised by three interconnected basins corresponding to cationic, anionic, and concerted regimes of reactivity.

E1

Acid-catalysed dehydration
Carbocation intermediate

E2

Strong base
Concerted elimination

E1cB

Carbanion forms first
Leaving group leaves second

The E1 pathway occurs when the low-curvature route becomes inaccessible. Under these conditions, the system is diverted into a high-curvature cationic basin corresponding to carbocation formation. From this intermediate region, subsequent proton loss allows the system to exit toward product states. Therefore, E1 behaviour reflects a trajectory that departs from the concerted manifold into a confined region of $\partial\Omega$ defined by strong local curvature.

In contrast, the E2 pathway corresponds to a continuous, concerted trajectory across $\partial\Omega$. In classical terms, proton abstraction and leaving group departure occur simultaneously in a single step. However, from the BT perspective, this behaviour reflects a low-curvature geodesic, along which the system can evolve without encountering intermediate basins. The reaction proceeds via a smooth trajectory that maintains continuity on $\partial\Omega$.

The E1cB pathway represents an analogous process occurring through an anionic basin. In this case, proton abstraction precedes leaving group departure, generating a carbanionic intermediate. This corresponds to entry into a high-curvature anionic basin, followed by progression along an accessible exit trajectory. The three elimination pathways may therefore be recognised as motion through distinct, but connected, regions of the same geometric landscape (Figure 3).

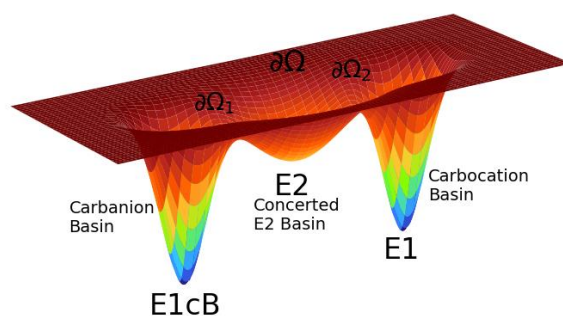


FIGURE 3. Boundary-theoretic representation of elimination mechanisms. E1cB, E2, and E1 correspond to distinct attractor domains embedded within a shared admissibility manifold ($\partial\Omega$). The carbanion basin defines E1cB reactivity, the carbocation basin defines E1 reactivity, and the intermediate E2 basin represents concerted elimination trajectories. Admissibility boundaries $\partial\Omega_1$ and $\partial\Omega_2$ separate the three mechanistic domains and delineate regions of distinct reaction behaviour. Changes in substrate structure, base strength, leaving-group ability, and solvent environment deform the landscape geometry, thereby altering the accessibility and relative stability of the competing elimination pathways.

A characteristic feature of E2 reactions is the requirement for anti-periplanar alignment of the reacting orbitals. This geometric constraint is well established in classical mechanistic descriptions [12]. In terms of Boundary Theory, such stereoelectronic requirements are explained as conditions that minimise curvature along $\partial\Omega$. Proper alignment of orbitals enables a continuous, low-distortion trajectory, whereas misalignment increases curvature and restricts accessibility to the concerted path.

The BT framework recasts elimination reactions as a unified geometric system. E1, E2, and E1cB processes correspond to alternative regions of $\partial\Omega$ connected through the structure of the admissibility boundary. The pathway followed by the system is determined by local curvature and the imposed constraints, which collectively define whether motion proceeds along a continuous trajectory or through intermediate basins.

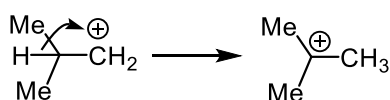
Carbocation Rearrangements

Carbocation rearrangements are traditionally described as processes driven by the formation of more stable intermediates. Under BT, these transformations can be interpreted in terms of the topology and curvature of the admissibility boundary ($\partial\Omega$).

Rather than viewing rearrangements as discrete steps guided by stability, they may be seen as *continuous motion across a landscape comprising multiple connected cationic basins*.

Using this interpretation, several cationic basins can be simultaneously accessible under a given set of constraints. The system evolves along the lowest-curvature trajectories connecting these basins, such that rearrangement reflects the existence of continuous pathways on $\partial\Omega$ rather than discrete, sequential transitions. The observable outcome is thereby determined by the *geometric connectivity of the accessible regions of $\partial\Omega$* .

This interpretation provides a natural description of classical 1,2-shifts, including Wagner–Meerwein rearrangements (in more detail in the next section):



Normally, these rearrangements are depicted as stepwise migrations of hydride or alkyl groups via distinct intermediates [13].

These transformations correspond to continuous trajectories linking neighbouring basins. The system follows a curvature-defined path that smoothly redistributes bonding connectivity. A 1,2-shift can be explained as a single, continuous motion across $\partial\Omega$ rather than as an isolated mechanistic step (Figure 4).

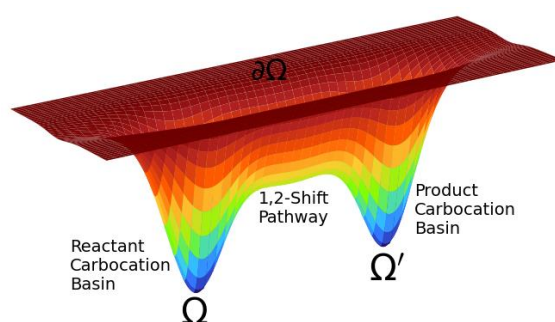


FIGURE 4. Curvature landscape of a carbocation rearrangement. The reactant carbocation basin (Ω) and product carbocation basin (Ω') occupy connected regions of the admissibility manifold ($\partial\Omega$). The intervening 1,2-shift pathway represents a continuous low-curvature trajectory linking neighbouring cationic domains. Within this formulation, rearrangement arises from geometric connectivity between accessible

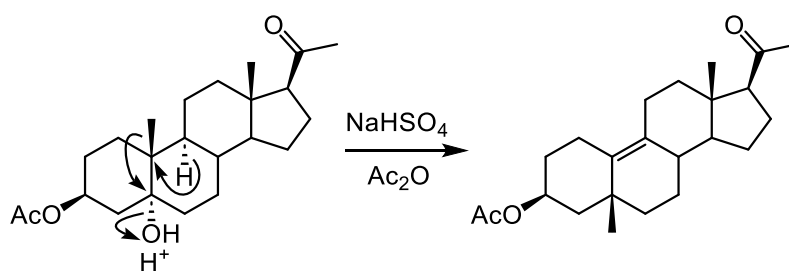
regions of $\partial\Omega$ rather than from discrete, sequential mechanistic steps. The observable product distribution is therefore determined by the topology of the connected cationic landscape.

This framework also affords a natural interpretation of non-classical carbocations. In such systems, cationic character is delocalised over multiple centres, rendering the distinction between individual intermediates increasingly ambiguous. Within the BT formulation, this corresponds to the **coalescence of neighbouring cationic basins into a single extended admissible region of $\partial\Omega$** . The system is no longer restricted to discrete minima but may move freely within a connected domain of admissible states. Non-classical behaviour therefore emerges naturally from the topology of the constraint landscape, where the boundaries separating neighbouring carbocationic configurations become progressively diminished or disappear altogether.

Rearrangement and Migration Manifolds (Ω')

Wagner–Meerwein Rearrangements

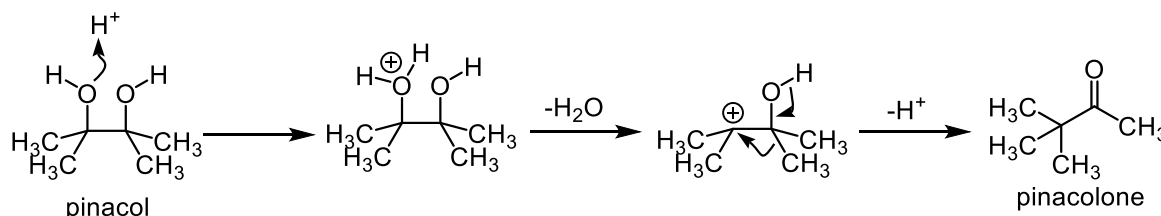
Wagner–Meerwein rearrangements [14] are a canonical example of Ω' behaviour, in which the system is no longer confined to a single region of $\partial\Omega$, but explores a connected manifold of cationic basins. Rearrangement arises when these basins become geometrically connected, allowing continuous trajectories across the boundary. Migration proceeds along lowest-curvature pathways, such that direction and outcome are determined by global topology rather than local energetic considerations.



A notable feature of Ω' systems is that this connectivity is often latent under standard conditions. Changes in constraints, such as strong acid, enzymatic environments, or conformational restriction, deform $\partial\Omega$ and expose previously inaccessible trajectories. Product distributions reflect which pathways remain accessible within this network, rather than the relative stability of isolated intermediates.

Pinacol–Pinacolone Rearrangement

The pinacol–pinacolone rearrangement [15] gives a clear example of how changes in constraints reshape the boundary ($\partial\Omega$) and force the system into a different region (Ω'). The process begins with protonation of one of the hydroxyl groups, which significantly alters the geometry of the system:



In BT terms, this does not just “activate” the molecule, but increases the curvature of the boundary ($\partial\Omega$), destabilising the original diol basin. Protonation increases curvature, pushing the system out of a stable region and the diol basin becomes shallow and no longer readily accessible. The system is therefore forced into a high-curvature region of Ω' . The key step is C–C migration, which occurs because it represents the lowest-curvature pathway available under these conditions.

Reactivity arises from how the surface is reshaped, and the migration step reflects the most accessible route through that reshaped geometry.

Terpene Cyclases as Curvature Engines

Terpene cyclases act as curvature engines, reshaping $\partial\Omega$ into funnels that connect multiple cationic basins. The active site imposes strong geometric and electrostatic constraints, sculpting $\partial\Omega$ into highly curved regions and as the system enters this regime, rearrangement cascades arise without the need for step-by-step control. The sequence of cyclisations, hydride shifts, and rearrangements observed in terpene biosynthesis arises from the topology of the reshaped boundary and is not explicitly programmed [5].

Under BT, enzymes act as *boundary sculptors*, creating high-curvature funnels that make complex rearrangement cascades *inevitable*.

Pericyclic Boundary Traversal ($\partial\Omega$)

Pericyclic Reactions

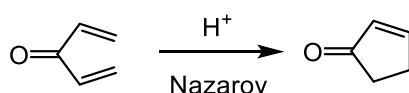
Pericyclic reactions are a special type of reactivity that occur entirely along the boundary ($\partial\Omega$). Unlike substitution or elimination reactions, they do not involve falling into intermediate “bowls.” Instead, they follow a single continuous path (a geodesic) across $\partial\Omega$. In classical chemistry, these reactions are governed by the Woodward–Hoffmann rules, which determine whether a reaction is “allowed” or “forbidden” [4].

The Woodward–Hoffmann rules define which corridors exist on $\partial\Omega$, not detailed step-by-step mechanisms. “Allowed” reactions correspond to smooth, continuous pathways that can exist on the boundary. “Forbidden” reactions correspond to pathways that would require impossible curvature, meaning no continuous route exists on $\partial\Omega$. Under the BT framework, this arises when there are no deep basins along the path, the system never “falls” into an intermediate, but it simply moves continuously along $\partial\Omega$ from reactants to products. “Concertedness” is not a special rule, but is simply the result of a smooth, uninterrupted pathway across the boundary.

Electrocyclisations

Electrocyclisations are a type of pericyclic reaction in which a molecule undergoes a ring opening or ring closing, and in BT, this corresponds to a topological change along the boundary ($\partial\Omega$). Unlike reactions that move between different basins, electrocyclisations involve continuous motion along $\partial\Omega$, but with a key difference in that

the *shape of the boundary itself changes* during the transformation. In classical chemistry, electrocyclisations follow conrotatory or disrotatory pathways, depending on the system and conditions [4]. A representative example is the Nazarov cyclisation, where a divinyl ketone undergoes a conrotatory 4π electrocyclisation to form a cyclopentenone from a cyclopentadienyl cation under acidic conditions:



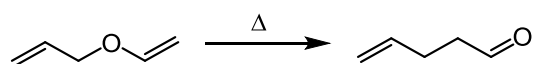
Considering the BT framework, these outcomes are not arbitrary “rules,” but reflect the only geometrically accessible ways to traverse $\partial\Omega$. Conrotatory and disrotatory motions correspond to the minimal-curvature trajectories that preserve continuity of the boundary while satisfying the system’s symmetry constraints. Alternative motions would require distortions that break this continuity and are therefore inaccessible.

Electrocyclic selectivity can again be understood as the consequence of the system following the smoothest admissible path between states.

One of the most striking features of electrocyclisations is that thermal and photochemical conditions give opposite outcomes [4]. This can be appreciated as a change in the curvature of $\partial\Omega$. Under thermal conditions, the boundary has one curvature profile, whereas under photochemical excitation, electronic occupation changes, which inverts the curvature of $\partial\Omega$. This inversion means that the previously smooth path becomes inaccessible and a different pathway (with opposite rotation) now becomes *the lowest-curvature route*. This also explains why conrotatory becomes disrotatory (and vice versa) without needing separate mechanistic rules.

Sigmatropic Rearrangements

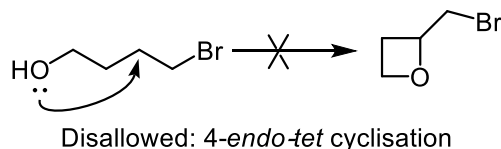
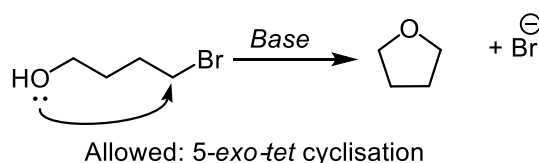
Sigmatropic rearrangements are pericyclic reactions where a σ -bond shifts position across a conjugated system. A classic example of this is the Claisen rearrangement where an allyl vinyl ether is concerted to a γ,δ -unsaturated carbonyl compound by heat:



In classical descriptions, sigmatropic rearrangements occur either suprafacially (same face) or antarafacially (opposite face), depending on orbital symmetry rules [16]. From the perspective of Boundary Theory, these pathways arise from topological constraints on $\partial\Omega$ and the system can only move along paths that maintain continuity of the boundary. Suprafacial motion represents the most natural, low-distortion path in most systems, whereas antarafacial motion requires the boundary to twist more dramatically, and is therefore often harder to achieve. In simple terms, the molecule follows whichever route allows it to stay on $\partial\Omega$ without introducing impossible curvature or breaks in continuity.

Baldwin's Rules as Boundary Accessibility Conditions

Baldwin's rules classify ring closures as "allowed" or "disfavoured," yet the origin of these patterns has remained largely empirical. These rules are cleanly articulated by 5-*exo-tet* cyclisation (allowed) and 4-*endo-tet* cyclisation (disallowed):



The oxetane product is not observed because the *trajectory required to form it (4-endo-tet) is geometrically inaccessible*. From the BT perspective, these rules logically arise from the geometry of $\partial\Omega$. A ring closure is only possible if the bond-forming motion corresponds to a continuous, low-curvature path on the boundary. When the required trajectory forces the system to leave $\partial\Omega$, for example, by demanding an approach angle or torsional alignment that cannot be achieved without distorting the boundary, the closure becomes inaccessible.

Exo-tet, *exo-dig*, and *endo-tet* closures correspond to motions that preserve continuity of $\partial\Omega$, allowing the system to move smoothly toward bond formation. In contrast, disfavoured *endo-dig* or *endo-trig* closures require curvature inversions or geometric compressions that cannot be accommodated within the admissible domain. These reactions are not “forbidden” in a mechanistic sense, but are geometrically impossible under the prevailing constraints, which is consistent with Baldwin’s empirical observations [17]. The rules therefore follow from the geometry of admissible motion on $\partial\Omega$.

Δ — High-Curvature, High-Constraint Manifolds

Radical SAM Enzymes

Radical SAM (S-adenosylmethionine) enzymes operate in some of the most extreme regions of chemical space, corresponding under BT to Δ , high-curvature, high-constraint manifolds. In the Δ -regime, the protein scaffold enforces tight geometric and electronic constraints that bend substrates away from their ground-state preferences, effectively storing reactivity as strain within the manifold. The radical SAM machinery then acts as a controlled release mechanism, using the 5'-deoxyadenosyl radical to project the system across steep energy gradients that would be inaccessible on lower-curvature (Ω or $\partial\Omega$ -like) surfaces. In these systems, the boundary ($\partial\Omega$) is strongly

deformed and tightly confined by the enzyme environment. Unlike classical solution-phase reactions, where one type of intermediate usually dominates, radical SAM enzymes generate conditions in which multiple types of reactive basins coexist and interact.

Because of the high curvature, the system can transition dynamically between radical and cationic character and small movements along $\partial\Omega$ can shift the system from one basin type to another. These transitions do not require large energetic changes, but arise from the tight geometric constraints imposed by the enzyme. This explains why radical SAM enzymes often display complex rearrangements and unexpected transformations that are difficult to rationalise using classical stepwise mechanisms [18].

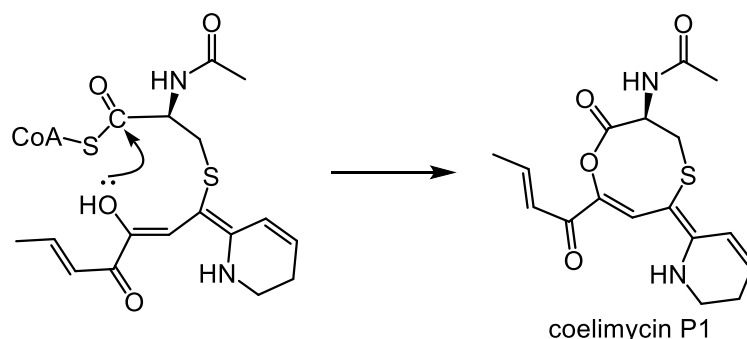
With the framework, this arises from the shape of the constrained region of $\partial\Omega$. The active site enforces a narrow, high-curvature funnel and only a limited set of pathways remain geometrically accessible. Even though many basins are nearby, the system is effectively channelled along specific routes. Selectivity therefore arises from geometric confinement and not solely from differential stabilisation of intermediates.

Polyketide Synthase (PKS) Macrocyclisation

Polyketide synthase (PKS) macrocyclisation presents a contrasting example to radical SAM systems, illustrating how a relatively flat and flexible domain (Ω) can be forced into a high-curvature regime (Δ) by enzymatic constraints. In the early stages, a growing polyketide chain behaves as a highly flexible system, capable of sampling many conformations. The system explores a relatively flat region of $\partial\Omega$, where curvature is low and many states are accessible, and no single pathway is strongly preferred. The macrocyclic product is not yet accessible because the required geometry lies outside the currently reachable region. At this stage, the system is best described as diffuse and unconstrained, with broad access across $\partial\Omega$.

Macrocyclisation occurs when the enzyme imposes strong geometric constraints on the flexible chain and the active site restricts conformational freedom, reshaping $\partial\Omega$. This confinement increases curvature locally, pushing the system toward a high-curvature regime (Δ) and as a result, previously inaccessible regions of $\partial\Omega$ become reachable. An example of where this could occur is in the putative thio-Co-enzyme A coelimycin P1, the precursor to coelimycin P1, a yellow pigment isolated from the

Actinomycete *Streptomyces coelicolor* [19]. Guided by the PKS, this substrate undergoes cyclisation by attack of the hydroxyl group on the carbonyl of the thioester forming the macrolide.



Terpene Cascade Funnels

Terpene cyclases are examples of Δ , with high-curvature, high-constraint manifolds and where reactivity arises from a strongly shaped and constrained boundary ($\partial\Omega$). In these systems, the enzyme does more than facilitate individual reactions, it constructs a curvature funnel that determines the entire cascade. The active site imposes tight geometric and electrostatic constraints, forcing $\partial\Omega$ into a highly curved, directed landscape and this reshaping creates a funnel-like region, where multiple carbocation states and rearrangement pathways become connected. Once the system enters this region, it is effectively locked into a constrained trajectory across $\partial\Omega$. In contrast to classical stepwise descriptions, individual rearrangements in terpene biosynthesis are not independently selected. Instead, they arise because the system is moving through a pre-shaped region where only certain paths exist.

What appears experimentally as a complex sequence of cyclisations, hydride shifts, and carbon migrations is geometrically a single guided trajectory across a highly constrained region of $\partial\Omega$.

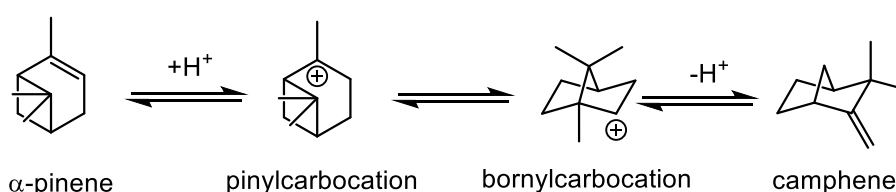
Terpene cyclases are known for producing very specific products, even from similar substrates [5]. A well-known example is (+)-limonene synthase, which converts the same linear precursor (geranyl diphosphate, GPP) into (+)-limonene with high specificity. Closely related terpene cyclases acting on the *same* GPP substrate, however, can instead produce compounds like α -pinene, β -pinene, or myrcene, showing how subtle differences in the enzyme's active-site contour tightly control the cyclisation pathway and final product [20]. Under the BT framework, this specificity

arises because the funnel defined by the enzyme leads toward one dominant basin. Alternative basins may exist nearby, but they are not geometrically accessible within the constrained region. Consequently, the system is therefore guided toward a single global minimum that lies within the reachable region of $\partial\Omega$. Product selectivity is not imposed step-by-step, but appears from the overall shape of the curvature landscape.

Boundary Condition Exemplars

Superacid Reactivity

Superacids show how extreme conditions reshape the boundary ($\partial\Omega$) and reveal entirely new regions of chemical behaviour. In conventional chemistry, many substrates cannot access highly charged intermediates, but superacids change this by introducing extreme curvature into $\partial\Omega$. Strong protonation, where the system is driven far from its equilibrium geometry and cannot easily relax, dramatically increases curvature, pushing it into normally inaccessible regions and as a result, deep cationic basins occur on $\partial\Omega$. These basins correspond to highly reactive species known as superelectrophiles. In this regime, the system is no longer confined to the shallow regions typical of ordinary acid chemistry. Instead, it is forced into high-curvature domains, where multiple rearrangement pathways become available. Superacids can facilitate the formation of carbocations driving rearrangements in monoterpenes:



Once the system enters these deep cationic basins, the surrounding landscape of $\partial\Omega$ becomes steep and highly connected and multiple pathways link the initial state to other basins. The system inherently moves along the available low-curvature exits within this high-curvature region and as a result, rearrangements that might be rare or optional under mild conditions become inevitable outcomes. The molecule is effectively “trapped” in a region where reorganisation is the only way out.

Gas-Phase Rearrangements

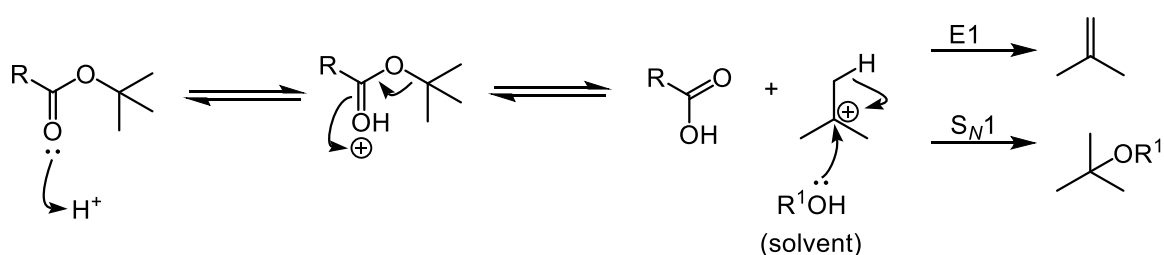
Gas-phase reactions provide a valuable contrast to solution-phase chemistry because they occur without solvent, meaning the boundary ($\partial\Omega$) is not influenced or “smoothed

out” by external interactions. As a result, they reveal the intrinsic structure and connectivity of $\partial\Omega$ more directly. Without solvent, curvature is not flattened or damped by stabilising interactions and the system experiences the full curvature profile of $\partial\Omega$, including sharp features and steep regions. This allows the underlying topology of $\partial\Omega$ to become clearly visible. In solution, solvents stabilise charged species and redistribute energy, effectively smoothing out variations in curvature. In contrast, gas-phase systems reflect the raw geometric landscape, where subtle features play a much larger role.

Because $\partial\Omega$ is not modified by solvent, pathways that are normally suppressed or inaccessible become geometrically accessible. Rearrangements can occur that would not be favoured in solution and the system can explore connections between basins that are masked under typical conditions. Gas-phase ions often behave differently from solution-phase species due to absence of solvent and different electrostatic environments [21].

Spontaneous Protecting Group Loss

Spontaneous protecting group loss is often described in classical chemistry as the result of “instability” or unexpected reactivity [22]. Acid-labile protecting groups such as *t*-butyl esters can undergo rapid, condition-sensitive cleavage, even under mildly acidic conditions, reflecting the accessibility of alternative pathways on $\partial\Omega$ once protonation destabilises the protected state [11]:

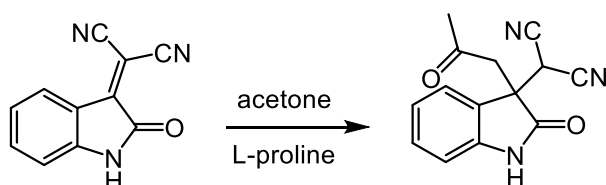


This is a consequence of geometric positioning on the boundary ($\partial\Omega$). Protecting groups are often located at shallow basin edges, rather than deep minima and these regions are only weakly stabilised and sit close to alternative pathways. As a result, their stability depends strongly on the local curvature of $\partial\Omega$. An attribute of these systems is that very small changes in conditions can trigger deprotection, for example, slight changes in solvent, temperature, or conformation, minor alterations in electronic environment or small shifts in steric arrangement can all lead to deprotection.

Within BT, these changes tilt or reshape the local curvature of $\partial\Omega$, reduce the depth of the protecting group basin and eventually cause a collapse of that basin, making it no longer accessible. Once this occurs, the system moves toward a different, more accessible region of $\partial\Omega$.

Catalyst Effects

Catalyst effects, like protecting group loss, show how small changes in constraints can dramatically reshape the boundary ($\partial\Omega$). In many systems, even parts-per-million (ppm) levels of catalyst can alter reaction outcomes, sometimes in ways that appear disproportionate to their concentration [23]. Even extremely small amounts of catalyst can reshape the local curvature of $\partial\Omega$ and this reshaping exposes previously inaccessible pathways. As a result, reactions may occur that would otherwise not be observed at all. Examples include the use of L-proline as a catalyst, not used here for asymmetric induction but for enamine-mediated activation and geometric constraint to form 3,3-disubstituted oxindoles [24]:



In classical terms, catalysts are usually described as lowering activation barriers. In BT, catalysts do not simply speed up reactions; they reshape reachability and thereby determine which pathways become available. The catalyst introduces new interactions that modify the shape of $\partial\Omega$ and this can create new corridors or basins not previously available. The reaction proceeds because a new path has opened and this explains why some catalysts appear to “turn on” reactions entirely, rather than just speeding them up.

The effectiveness of catalysts arises from the high sensitivity of $\partial\Omega$ to local perturbations. Even a small number of catalyst molecules can significantly reshape the boundary at critical points, thereby creating new accessible pathways. Once such a pathway is opened, the system proceeds along it, such that large catalyst concentrations are unnecessary: catalysis operates by modifying geometry rather than stoichiometry. Consequently, the response is nonlinear, with small perturbations producing disproportionately large changes in reactivity.

Dilution-Dependent Rearrangement

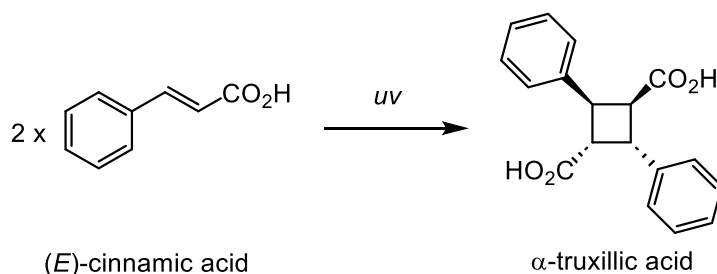
Dilution-dependent rearrangements give an example of how changing concentration alters the structure of accessible regions on the boundary ($\partial\Omega$) [25]. In classical chemistry, concentration is often treated as a kinetic factor. In BT, it defines which domains are geometrically available. Concentration determines whether the system can access single-molecule or multi-molecule regions of $\partial\Omega$. High concentration allows interactions between multiple species, creating additional basins, whereas low concentration restricts the system to isolated, single-molecule pathways [26].

At high concentration molecules are close enough to interact frequently and this creates multibody basins on $\partial\Omega$. Reaction pathways involving association, aggregation, or intermolecular rearrangement become accessible. At low concentration molecules are effectively isolated and these multibody basins disappear. Only single-molecule basins remain accessible.

This represents a change in the dimensionality of the accessible domain, where high concentration leads to a higher-dimensional $\partial\Omega$ (with more degrees of interaction), but a low concentration leads to reduced-dimensional $\partial\Omega$ (restricted to individual molecules). Because different regions of $\partial\Omega$ are accessible at different concentrations, entire reaction pathways may appear or disappear upon dilution and rearrangements that require molecular interaction may be suppressed at low concentration. Intramolecular pathways may become dominant when intermolecular ones are no longer accessible. Reaction outcomes therefore reflect which domains of $\partial\Omega$ are available, not just which pathways are fastest.

Solid-State Reactivity

Solid-state reactions provide an example of how strong spatial constraints reshape the boundary ($\partial\Omega$). Unlike solution-phase systems, where molecules can move and reorganise freely, crystalline environments impose rigid geometric restrictions that fundamentally alter accessible pathways. Crystal packing fixes molecules in specific positions and orientations and this restricts motion and enforces strict geometric alignment [27]. As a result, $\partial\Omega$ is confined into narrow, highly defined regions.



In a crystal, molecules are locked into a repeating lattice structure and only limited motion is possible and consequently, reaction pathways must follow pre-organised geometries dictated by packing [27]. In BT terms, the lattice directly defines which regions of $\partial\Omega$ are accessible. Because of these constraints, pathways that are difficult or impossible in solution can become accessible in the solid state. The imposed alignment creates new curvature corridors on $\partial\Omega$ and at the same time, other pathways disappear because they require motion that is no longer possible [29].

Nicolaou's Epothilone Macrocyclisation

The macrocyclisation step in the total synthesis of epothilones, as reported by Nicolaou and co-workers, gives an obvious example of how reaction success can depend on forcing the system into a specific region of the boundary ($\partial\Omega$) rather than simply optimising traditional reaction conditions [31]. In classical terms,

macrocyclisation is described as a balance between enthalpy and entropy, with large ring formation being entropically disfavoured. However, this explanation does not fully account for why cyclisation sometimes fails under seemingly favourable conditions and succeeds only when specific constraints are applied.

In our BT framework, this behaviour can be interpreted geometrically as the open-chain precursor initially resides in a region of $\partial\Omega$ where the macrocycle basin is not accessible and there is no continuous, low-curvature pathway connecting the linear structure to the closed ring. As a result, the system cannot “find” the cyclisation pathway. Successful macrocyclisation requires conditions that effectively force the system into a different region of $\partial\Omega$. Conformational restriction and reaction conditions reshape the boundary and this deformation increases curvature locally, bringing previously disconnected regions into contact. A continuous pathway to the macrocycle basin therefore becomes available and importantly, the reaction does not proceed simply because the product is favourable, but because a geometric connection is created that did not previously exist.

Once this pathway is opened, the macrocycle basin becomes reachable along $\partial\Omega$ and the system can move continuously from the open-chain state into the cyclic product. Cyclisation proceeds as the lowest-curvature accessible path and the key change is not the intrinsic reactivity of the molecule, but the accessibility of the required region of the boundary (Figure 5).

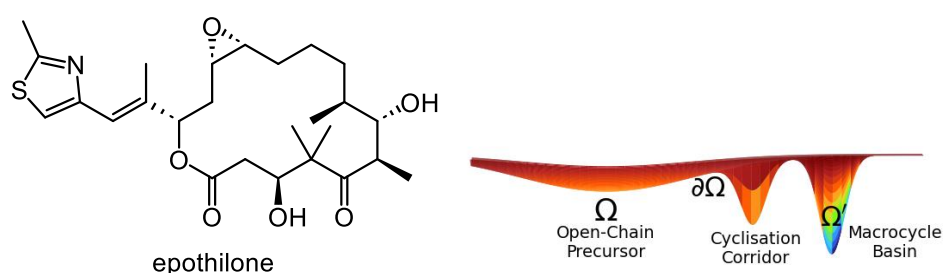


FIGURE 5. Boundary-theoretic interpretation of Nicolaou’s epothilone macrocyclisation. The open-chain precursor occupies a broad admissible region (Ω) from which the macrocycle basin (Ω') is not readily accessible. Conformational restriction and reaction conditions create an accessible cyclisation corridor within the admissibility manifold ($\partial\Omega$), generating a continuous low-curvature pathway to the

macrocycle attractor. Cyclisation proceeds when this geometric connection becomes available, illustrating that reaction success depends on accessibility within $\partial\Omega$ rather than product favourability alone.

Discussion

Boundary Theory predicts that reaction appearance, disappearance, mechanistic switching, catalysis, enzymatic control, and behaviour under extreme conditions arise from changes in accessibility on $\partial\Omega$. Reactivity reflects deformation of boundary geometry rather than competition between fixed mechanisms, with catalysts and enzymes reshaping accessibility and extreme conditions exposing otherwise unreachable regions of chemical space.

Intrinsic parameters as boundary-shaping constraints

Chemical reactivity is governed by the geometry of the admissible boundary ($\partial\Omega$), which determines which trajectories exist under a given set of constraints. While earlier sections focused primarily on external parameters (e.g., solvent, concentration, and catalysis), intrinsic properties of the system itself, most notably charge, mass, and molecular shape, can also be understood as direct contributors to boundary deformation.

Charge introduces an electrostatic field that modifies the curvature and connectivity of $\partial\Omega$. Protonation, ionisation, or polarisation can reshape accessible regions of state space by stabilising or destabilising specific configurations. In geometric terms, charge acts as a field that bends $\partial\Omega$, altering saddle regions and redistributing basin accessibility. This affords a unified description of phenomena such as carbocation rearrangements, changes in substitution pathways, and enzyme-mediated electrostatic steering.

Mass, by contrast, does not directly alter the underlying constraint surface but influences how trajectories evolve upon it. This corresponds to a modification of motion across $\partial\Omega$ rather than deformation of $\partial\Omega$ itself. Heavier atoms, isotopic substitution, and collective modes of motion alter the effective flow through accessible regions, influencing whether trajectories remain confined, transition between basins, or bypass

specific regions entirely. Mass enters the framework through the dynamics of traversal rather than the topology of accessibility.

Molecular shape constitutes the most direct geometric constraint. Steric structure defines which states are admissible, and therefore determines the existence and connectivity of regions of $\partial\Omega$. Stereoelectronic requirements, ring-closure preferences, and enzyme active-site geometries represent manifestations of shape-imposed boundary structure. In this sense, *shape defines the architecture of $\partial\Omega$ itself*.

Charge deforms $\partial\Omega$, shape defines it, and mass governs motion upon it.

Mapping Constraint Geometry and Predicting Reactivity

BT defines chemical reactivity in terms of accessibility on the admissibility boundary ($\partial\Omega$). Chemical systems may therefore be represented as constraint-dependent manifolds:

$$\partial\Omega = f(c_1, c_2, c_3, \dots)$$

where c (a specific constraint) denotes external, environmental, and intrinsic parameters. External variables include solvent (e.g., c_1), temperature (e.g., c_2), pressure (e.g., c_3) and concentration (c_n) while environmental constraints arise from catalysis, enzymatic confinement, or solid-state packing. Intrinsic properties such as charge, steric topology, and conformational flexibility further define the structure of $\partial\Omega$. Collectively, these parameters determine which regions of state space are accessible under a given set of conditions.

Constraint maps may be generated experimentally through systematic variation of these parameters. Classical synthetic practice already exploits such mapping implicitly through solvent variation, dilution studies, catalyst optimisation, and control of reaction conditions that alter pathway accessibility and product distributions [11, 26].

Within such maps, basin accessibility, curvature, and connectivity determine reactivity. Continuous trajectories correspond to accessible transformations, whereas disconnected regions represent geometrically inaccessible reactions irrespective of energetic favourability, consistent with the interpretation of symmetry-forbidden pericyclic processes [4].

Catalysts, concentration changes, environmental perturbations, and molecular constraints may thus be regarded as modifiers of boundary geometry. Changes in these parameters can generate new pathways, suppress existing ones, or alter product selectivity, providing a geometric interpretation of experimentally observed nonlinear responses to catalyst loading and concentration [23, 25].

Constraint mapping therefore provides a framework for predicting pathway emergence, suppression, mechanistic switching, and selectivity. Potential-energy surfaces define the set of possible states, whereas constraint mapping determines which of those states remain reachable under specific conditions. BT therefore complements existing theoretical approaches by introducing a geometric criterion of reachability.

Limitations and Scope

Boundary Theory (BT) describes pathway existence and availability but does not replace energetic analysis. BT is not a theory of fundamental physics; it is a theory of constrained accessibility. Physics defines the underlying state space and governing dynamics available to a system, whereas BT addresses how constraints shape the subset of states and trajectories that remain accessible. Energetics determine rates and competition between admissible trajectories, whereas BT determines which trajectories exist. BT also does not specify the quantitative curvature of $\partial\Omega$, which must be inferred from experiment, computation, or structural constraints. Finally, BT applies to systems in which constraints strongly influence behaviour, including stereoelectronically controlled reactions, topologically restricted systems, enzymatic processes, and symmetry-governed transformations, and is correspondingly less informative in highly unconstrained, high-entropy environments.

Experimental Tests of Boundary Theory

BT generates several falsifiable predictions. Constraint variation (solvent, nucleophile strength, catalyst loading, concentration, irradiation conditions and enzyme active-site geometry) should produce identifiable accessibility transitions rather than smooth changes in rate alone. Mechanistic switching (S_N1/S_N2 , $E1/E2$), catalyst-threshold effects, concentration-dependent pathway appearance or disappearance, thermal-photochemical electrocyclic reversals and selective pathway redirection by active-site mutation are all expected consequences of boundary deformation. Observation of

reproducible accessibility boundaries would support the framework, whereas entirely continuous behaviour without identifiable transitions would argue against it.

Conclusion

Reactivity reflects both the energetic landscape and the accessibility of pathways within it. By defining chemical systems in terms of constraint domains (Ω) and their boundaries ($\partial\Omega$), transformations arise as curvature-driven transitions, rather than as discrete mechanistic choices between predefined alternatives. Within this framework, traditional distinctions between mechanisms become secondary descriptions of a deeper principle. What is commonly deduced as a “mechanism” corresponds to a particular accessible pathway on $\partial\Omega$, and shifts in reactivity reflect changes in boundary shape, not intrinsic changes in chemical identity. Boundary Theory (BT) therefore offers a unified way to understand phenomena that are otherwise treated as unrelated, including as shown above, rearrangements, pericyclic reactions, catalysis, enzymatic cascades, and environment-dependent reactivity.

Crucially, this perspective explains how reactions proceed and why they appear or fail to appear under different conditions. Reactions begin when new regions of $\partial\Omega$ become accessible, disappear when those regions are removed, and reorganise when the connectivity between them changes. In this way, chemical behaviour is not governed by energetic preference alone, but by the structure and *reachability* of the boundary itself. This geometric interpretation does not replace the potential energy surface (PES), but rather subsumes it within a higher-order framework. The PES describes the energetic landscape of a given system, while the BT determines which parts of that landscape are actually reachable. Together, they provide a more complete description: ***energy defines possibility, whereas geometry defines accessibility.***

Viewed through BT, chemistry becomes the study of how constraints determine which states can actually be reached. From simple substitution reactions to complex enzymatic cascades, reactivity reflects the same underlying principle: *the geometry of $\partial\Omega$ determines the pathways that exist.*

Supporting Information

The brief mathematical framework and a protocol for Constraint Mapping as a Tool for Determining Reaction Feasibility and Completion are provided in Supporting Information File 1.

Funding statement

The author received no funding for this work.

This article has no primary data

All conceptual and theoretical results are contained within the manuscript.

Author Contributions

Simon Gibbons: conception; writing – original draft; writing – review & editing.

ORCID® IDs

Simon Gibbons - <https://orcid.org/0000-0003-1587-6809>

Competing interests statement

The author declares that they have no competing or conflict of interest.

Acknowledgement

Prof Dr Heinz Falk of Johannes Kepler University Linz is thanked for his very kind and careful suggestions in the preparation of this manuscript.

References

1. Atkins, P. W.; De Paula, J. *Atkins' Physical chemistry*, 10th ed. ed.; Oxford University Press: Oxford, 2014; Fukui, K. *Accounts of Chemical Research* **1981**, *14* (12), 363-368; Marcus, R. A. *Angewandte Chemie International Edition in English* **1993**, *32* (8), 1111-1121.
2. Olah, G. A. P., G. K. S.; Molnár, Á.; Sommer, J. Chapter 1: General Aspects. In *Superacid Chemistry*, 2nd ed.; Wiley: Hoboken, NJ 2009; pp 1-34.
3. List, B. *Chemical Reviews* **2007**, *107* (12), 5413-5415.
4. Woodward, R. B.; Hoffmann, R. *Journal of the American Chemical Society* **1965**, *87* (2), 395-397.
5. Davis, E. M.; Croteau, R. Cyclization Enzymes in the Biosynthesis of Monoterpenes, Sesquiterpenes, and Diterpenes. In *Biosynthesis: Aromatic*

- Polyketides, Isoprenoids, Alkaloids*; Leeper, F. J.; Vederas, J. C., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, 2000; pp 53-95.
6. Gibbons, S. *Phytochemistry Letters* **2026**, 76, 104251.
 7. Gibbons, S. *Phytochemistry Letters* **2026**, 75, 104228.
 8. Gibbons, S. *Phytochemistry Reviews (under revision)* **2026**.
 9. Loo, Y. T.; Chen, J.; Harrison, R.; Rito, T.; Theis, S.; Charras, G.; Briscoe, J.; Saunders, T. E. *Development* **2026**, 153 (13).
 10. Hughes, E. D.; Ingold, C. K. *Journal of the Chemical Society (Resumed)* **1935**, (0), 244-255, 10.1039/JR9350000244.
 11. Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; OUP Oxford: 2012.
 12. Carey, F. A.; Sundberg, R. J. *Molecules* **2001**, 6 (12), 1015-1016.
 13. Olah, G. A. *Angewandte Chemie International Edition in English* **1995**, 34 (13-14), 1393-1405.
 14. Meerwein, H.; Bodenbenner, K.; Borner, P.; Kunert, F.; Müller, K. W.; Sasse, H. J.; Schrod, H.; Spille, J. *Angewandte Chemie* **1955**, 67 (14-15), 374-380.
 15. Song, Z. L.; Fan, C. A.; Tu, Y. Q. *Chem Rev* **2011**, 111 (11), 7523-56.
 16. Salem, L. *The Molecular Orbital Theory of Conjugated Systems*; Benjamin: 1966.
 17. Baldwin, J. E. *Journal of the Chemical Society, Chemical Communications* **1976**, (18), 734-736, 10.1039/C39760000734.
 18. Broderick, J. B.; Duffus, B. R.; Duschene, K. S.; Shepard, E. M. *Chem Rev* **2014**, 114 (8), 4229-317.
 19. Gomez-Escribano, J. P.; Song, L.; Fox, D. J.; Yeo, V.; Bibb, M. J.; Challis, G. L. *Chemical Science* **2012**, 3 (9), 2716-2720, 10.1039/C2SC20410J.
 20. Hyatt, D. C.; Youn, B.; Zhao, Y.; Santhamma, B.; Coates, R. M.; Croteau, R. B.; Kang, C. *Proceedings of the National Academy of Sciences* **2007**, 104 (13), 5360-5365.
 21. Garver, J. M.; Fang, Y.-r.; Eyet, N.; Villano, S. M.; Bierbaum, V. M.; Westaway, K. C. *Journal of the American Chemical Society* **2010**, 132 (11), 3808-3814.
 22. Liang, Z.; Koivikko, H.; Oivanen, M.; Heinonen, P. *Beilstein Journal of Organic Chemistry* **2019**, 15, 746-751.
 23. Liu, C.; Wang, L.; Ge, H. *Chemical Science* **2025**, 16 (27), 12449-12454, 10.1039/D5SC02745D; Horbaczewskyj, C. S.; Fairlamb, I. J. S. *Organic Process Research & Development* **2022**, 26 (8), 2240-2269.
 24. Nichinde, C. B.; Patil, B. R.; Chaudhari, S. S.; Mali, B. P.; Gonnade, R. G.; Kinage, A. K. *RSC Adv* **2023**, 13 (19), 13206-13212.
 25. Sarkar, S. *Physical Review X* **2020**, 10 (4), 041032.
 26. Henstridge, M. C.; Davies, S. G.; Thomson, J. E.; Compton, R. G. *Tetrahedron Letters* **2014**, 55 (11), 1886-1889.
 27. Biradha, K.; Santra, R. *Chemical Society Reviews* **2013**, 42 (3), 950-967, 10.1039/C2CS35343A.
 28. Bertmer, M.; Nieuwendaal, R. C.; Barnes, A. B.; Hayes, S. E. *The Journal of Physical Chemistry B* **2006**, 110 (12), 6270-6273.
 29. MacGillivray, L. R.; Papaefstathiou, G. S. *Solid-State Reactivity/Topochemistry In Encyclopedia of Supramolecular Chemistry*; Atwood, J. L.; Steed, J. W., Eds.; Marcel Dekker: New York 2004; p 1316-1321.
 30. Schmidt, G. M. J. *Journal of the Chemical Society (Resumed)* **1964**, (0), 2014-2021, 10.1039/JR9640002014.
 31. Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angewandte Chemie International Edition in English* **1997**, 36 (5), 525-527.