**Article Title**

Geometry-Controlled Reactivity and Dynamics in Organic Molecules

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**Abstract**

It is well-established that strain in organic molecules is linked to having nonideal bond lengths, bond angles, and unfavourable non-bonded interactions. The constrained geometries of ring systems are particularly predisposed to creating strain. Recently, there has been increased interest in leveraging this property of rings as a synthetic tool by building strain into substrates to activate a desired bond cleavage step. But one could also envisage alternative uses of strain. In this review, we outline how geometry control can be exploited to ‘switch on’ dynamic processes or stabilize reactive transition states. By designing constrained molecular structures that direct strain on particular bonds or functional groups, transformations that are otherwise energetically uphill can become favoured. This phenomenon can subvert our expectations about the reactivity and properties of organic molecules, giving rise to unusual bonding modes.**Introduction**

A molecule’s geometry is governed by the precise balance between optimizing favourable bonding interactions and minimizing electronic repulsion.1 Strain arises in a molecule when deviation from ideal bond lengths, bond angles, or dihedral angles increases its internal energy.2 While strain is rapidly relieved in flexible systems through the low-barrier reorientation of bonds, imposing geometric constraints within a structurally rigid framework (through covalent or noncovalent bonding interactions) enables the isolation of persistently strained molecules.3 In covalent systems, structural rigidity is typically introduced through (i) increasing bond order to restrict conformational freedom, as in alkenes,4 or (ii) annulation to produce mono- or polycyclic ring systems and cages.5

A disparity in strain energy between a substrate and the transition state of a reaction can result in substantial rate modulation, also known as the steric effect.2,6 When programmed into the structure of a substrate,7 this strain greatly enhances reactivity by raising (Fig. 1, Type I) the substrate’s internal energy, thereby lowering the activation energy barrier for a reaction and providing a powerful thermodynamic driving force to effect irreversible transformations without the need for external catalysis.8 Indeed, the principle of strain relief underpins the efficacy of reactions ranging from ring-opening olefin metathesis polymerization9 and cyclopropane radical trapping10 to the β-lactam ring opening responsible for the antibiotic activity of penicillins.11

Though such ‘strain-release’ or ‘strain-promoted’ transformations have a long history, they have garnered renewed interest in recent years, due to their wide synthetic utility.12 As early as 1961, alkynes connected at both ends by a short oligomethylene strap to introduce strain (such as cyclooctyne) were found to undergo rapid [3+2] cycloaddition with phenylazide to quantitatively afford the corresponding triazole.13 Such copper catalyst-free ‘click’ reactions have subsequently been exploited as versatile, biorthogonal methods of cell labelling and drug delivery *in vivo*.14 Similarly, the strain energy stored in the ‘spring-loaded’ C–C and C–N bonds of [1.1.1]propellanes (Fig. 1, Type I), [1.1.0]bicyclobutanes, 1‑azabicyclo[1.1.0]butanes, and housanes has been used to append small-ring bioisosteres to pharmaceutical leads.15,16 Nucleophilic attack selectively cleaves the most strained bond, giving access to bicyclopentane, cyclobutane, azetidine, and cyclopentane groups, respectively. As another example, the geometric constraint of an alkyne moiety within an annulene produces an aryne. Indeed, benzyne is one of the most well-known, strained synthons that has been employed extensively in both pericyclic reactions and nucleophilic additions to access polycyclic aromatics.17 Recently, this synthetic methodology has been extended to strained allenes within a 1,2,3-cyclohexatriene framework.18

Viewed from another perspective, the same design principles can be used to modulate reaction rate by controlling the relative amounts of strain present in a substrate its reaction transition state (Fig. 1, Type II). Most commonly, a molecular structure is designed such that an undesired reaction19 or a conformational change is ‘switched off’ owing to its transition state being energetically inaccessible.20 Dynamic processes, such as ring inversions,21 pyramidal inversions,22 or rotations around a single bond are inactivated,23 resulting in conformationally and configurationally stable molecules. Synthetic chemists have long exploited such molecules as ligands for enantioselective catalysis (e.g., 1,1′-bi-2-naphthol),24 and even leveraged this principle to isolate compounds containing stereogenic oxonium centres.25 The term, ‘molecular strain engineering’ has been proposed recently to describe the use of strain to enforce a certain molecular conformation26 or coordination geometry27 and dictate both the selectivity28 and outcome7,29 of chemical reactions.

Therefore, most discussions on molecular strain are restricted to its ability either to accelerate thermodynamically favoured transformations (Fig. 1, Type I) or to decelerate a dynamic reaction by destabilizing a particular transition state (Fig. 1, Type II deceleration). Yet, the impacts of strain extend beyond the scope of these particular types of steric effects. Strain can be introduced to a substrate to bring it close in energy to an otherwise inaccessible product, switching on a dynamic equilibrium (Fig. 1, Type III).30 Dynamic covalent processes can also be switched on by reducing the energy barrier between molecules in equilibrium (Fig. 1, Type II acceleration).31 In some cases, classical transition state theory alone fails to explain the rate enhancements experienced by these systems as quantum mechanical tunnelling (QMT) is a competing pathway.32 Though typically associated with electron- or proton-transfer reactions, constraining molecules within a rigid geometry can enable heavy-atom tunnelling by restricting the amplitude of atomic motion occurring during a reaction.33 Alternatively, geometry control of a molecular fragment within a larger framework can ‘trap’ transient, high energy structures or even transition states of reactions as stable, observable species (Fig. 1, Type IV). In such cases, the bonding parameters of the ground-state structure can be correlated with properties of the transition state (i.e., the structure–correlation principle), giving access to transition-state analogues.34

**Geometry Control**. In this Review, we define geometry control as strategies that employ strain and/or confinement to enforce certain bond lengths, bond angles and torsion angles in a molecular fragment that effectively ‘trap’ it in a particular (often metastable) conformation. We highlight how geometry control enables unusual and unexpected modes of bonding, dynamics, and reactivity that would otherwise be absent. We also showcase the emergent properties associated with such constrained molecules. In so doing, we have chosen to limit our discussion predominantly to the use of covalent substrate modification to control geometries, although we note that noncovalent bonding interactions, templation effects35–37 and supramolecular confinement38 can also be employed, while molecular machines and switches39,40 can vary the degree of strain present over time through fuelled processes. Note that, in general, geometry control raises the absolute Gibbs energies of the ground-state or transition-state structures (or both) of a reaction compared to their unrestrained analogues. However, for simplicity, our figures depict relative Gibbs energies (*G*rel) for facile comparison of the two reaction profiles.

**Lowering Transition States versus Altering Conformer Distributions**

The rates of chemical reactions are commonly increased by the action of catalysts, which provide reaction pathways with lower energy transition states than the uncatalyzed alternatives. Geometry control can be thought of as a complementary strategy that, in place of a catalyst, relies on molecular design to provide a low-energy pathway for a reaction, i.e., it is an intramolecular phenomenon that can be invoked by modifying the structure of a substrate. A commonly referenced example of this concept is the Thorpe–Ingold effect (including the *gem*-dimethyl effect). Decreases in bond angles caused by geminal substitution have been implicated in increased reaction rates. However, it is not always clear that these small changes in bond angles actually cause a substantial change in the activation energy. Instead, increases in reaction rate have been attributed to geminal substitution increasing the population of conformers with the geometries required to undergo the reaction, for example, allowing the appropriate orbital overlap for an intramolecular Diels–Alder cycloaddition.41 Care must be taken, therefore, when analysing and describing the effects of geometry control as either a kinetic effect (altering activation energy barriers), a Curtin–Hammett-type phenomenon (altering the proportion of reactive conformers at equilibrium), or a combination of the two.

**Strain-Promoted Electrocyclizations and Sigmatropic Rearrangements**

The influence of geometry control has been prominent in the study of pericyclic reactions. Indeed, it has been shown to be effective in accelerating the rate of irreversible reactions (Type I), lowering transition state energies to establish a dynamic equilibrium (Type II), manipulating equilibrium distributions (Type III), and stabilizing transition states as observable structures or even the energetic ground state (Type IV). In the following section, selected examples are highlighted to showcase the power of geometry control to forge new bonding motifs and enable dynamic behaviour.

Cycloheptatriene (CHT, **1**) undergoes reversible transformation to its bicyclic norcaradiene (NCD) isomer **2** via a 6π-electron electrocyclization. The impact of substituents on the position of this equilibrium and hence the populations of both isomers has been studied extensively (Fig. 2a).42,43 It was hypothesized that the equilibrium populations of **1** and **2** could be altered by attaching a tether across the cycloheptatriene ring (Type III), and this hypothesis was first confirmed during the synthesis of the natural product, colchicine.44 While the acyclic (unstrained) diester **3** was found to exist in the cycloheptatriene form (Fig. 2b), its conversion to the cyclic anhydride **4** imposed additional strain that resulted in complete reversal of the equilibrium and isolation of the NCD isomer exclusively. Notably, the study of this fundamental concept was motivated by close inspection of synthetic intermediates of natural product syntheses, highlighting the fact that synthesis of complex molecules can serve as a vantage point for underlying fundamental principles in organic chemistry.

This initial finding led to a more systematic investigation of the CHT–NCD equilibrium and the discovery of the clamping effect (Fig. 2c),45–47 where annelation of a five-membered ring biases the CHT–NCD equilibrium toward the NCD isomer to relieve strain, whereas larger rings favour the CHT isomer.

In addition to altering equilibria, geometry control has been shown to lower the activation energy barriers for pericyclic reactions. By our classification, such a strategy represents Type II geometry control and—in contrast to previous examples—can lead to rapidly dynamic bonding changes within a molecule. This phenomenon was first investigated using a similar structural motif to the CHT–NCD equilibrium. Starting from the Hardy–Cope sigmatropic rearrangement48,49 between divinylcyclopropane **8** and cyclic diene **8′** (Fig. 2d), it was postulated that the geometry control afforded by tethering the ends the two vinyl groups to the cyclopropane moiety would lower the activation energy barrier to rearrangement.50 The resulting bridged hydrocarbons, semibullvalenes (**9**,**10**), barbaralane (**11**), dihydrobullvalene (**12**), and bullvalene (**13**), have been identified as structures with dramatically reduced activation energy barriers (Fig. 2e).

Systematic shortening of the alkyl group bridging the divinylcyclopropane moiety lowers (Fig. 2e) the rearrangement barrier. Compared to bullvalene (C2 tether), with Δ*G*‡ = 54 kJ·mol−1, barbaralane (C1 tether) has a significantly lower Δ*G*‡ = 32 kJ·mol−1, as determined by 13C NMR experiments.51–60 An even shorter bridge in semibullvalene (**10**) lowers Δ*G*‡ to 26 kJ·mol−1 at 298 K.59 The introduction of additional steric demand by annelation (not shown) or the addition of alkyl substituents stabilizes the transition state further to 21 kJ·mol−1 in 1,5-dimethylsemibullvalene **9**.61

In addition to lowering the activation barrier height, the alkyl groups also have the effect of narrowing the barrier width of the Hardy–Cope rearrangement. Calculations suggest that the change in C–C internuclear distance upon breaking the cyclopropane bond in **10** is a mere 0.75 Å.62 On account of its narrow barrier width and low barrier height, this rearrangement proceeds rapidly at cryogenic temperatures by heavy-atom QMT.63,64 Typically, the contribution of QMT to the overall reaction rate is revealed by (i) the plateauing (Fig. 2f) of its Arrhenius plot at low temperatures (leading—in extreme cases—to temperature-independent rate constants) and (ii) a nonlinear kinetic isotope effect (KIE).33 Experimental evidence for heavy-atom tunnelling in the rearrangement of semibullvalenes was provided by IR spectroscopic analysis of monodeuterated 1,5-dimethylsemibullvalene (*d*-**9**) in an argon matrix from 3–30 K.63,64 While the rearrangement of **9** is degenerate, the monodeuterated analogue interconverts between isotopomers *d*4‑**9** and *d*2-**9** (Fig. 2g) by Hardy–Cope rearrangement. The difference in zero-point vibrational energies between the two introduces a Gibbs energy preference of 0.50 kJ·mol−1 for *d*2-**9**. Despite the lack of thermal energy at these temperatures, a virtually temperature-independent rate constant of ~10−4 s−1 was observed for the conversion of the metastable *d*4‑**9** to *d*2-**9** (τ½ ~1 h), indicating a tunnelling-governed pathway.

Combining annelation and alkyl substitution leads to semibullvalene **14** (Fig. 2h) with the lowest reported activation energy barrier (<17 kJ·mol−1).65 X-ray crystallographic studies revealed that the equilibrium was only ‘frozen out’ at temperatures below 40 K in the crystalline solid state.51,56 As predicted by the structure–correlation principle, these structures are also the most promising candidates to stabilize the neutral, homoaromatic transition state of a Hardy–Cope rearrangement—a long sought-after target—as the ground-state structure.45,46,54,55 This approach lies between Types II and IV, in which the geometry of a moiety is altered with the goal of stabilizing the transition state of a reaction. Compound **14** exemplifies geometry control through the clamping effect and steric overcrowding working in unison. While an activation energy barrier to the Hardy–Cope rearrangement has been determined for molecules **9**–**13** in the gas phase, **14** is the first molecule reported to exhibit gas-phase homoaromatic character, marking the experimental realization of Type IV geometry control. It should be noted that the transition state structure of a Hardy–Cope rearrangement in the solution phase has also been stabilized analogously through electronic control.66,67

Overall, pericyclic reactions offer multiple platforms for manipulation by geometry control, which can grant influence over equilibrium populations or create dynamic bonding motifs. The fundamental studies described above pave the way to mobilize otherwise static processes and drive an equilibrium toward an undesired state. The homoaromatic transition state of the Hardy–Cope rearrangement of barbaralane (**11**) bears an internal mirror plane (σ′v) that is not present in the ground state (Fig. 3a).31 Desymmetrizing the core through substitution at the 9-position, for example (Fig. 3b) removes the σ′′v mirror plane present in the ground state (producing a stereogenic centre) but retains the σ′v mirror plane formed in the transition state. As such, the Hardy–Cope rearrangement of **15** enantiomerizes the whole cage, formally inverting the stereochemistry of the C-9 position, by swapping the position of the cyclopropyl and alkenyl groups attached to the stereocentre. Though stereochemical inversions are common in planar chiral motifs, helices, and sp3-nitrogen centres, sp3-carbon centres are generally configurationally stable and require intermolecular reactions to invert. Therefore, the rapid and reversible Hardy–Cope rearrangements of desymmetrized barbaralanes have been investigated because of their unusual dynamic sp3-carbon stereochemistry.31

A stereochemical bias can be imposed by introducing a fixed carbon stereocentre around the fluxional core of **15**; derivatizing the hydroxyl group with (*S*)-Mosher’s acid affords a dynamic mixture of two diastereomers, (*R*,*S*)-**16** and (*S*,*S*)-**16** (Fig. 3c), while (*R*)-Mosher’s acid gives its antipodal mixture (*R*,*R*)-**16** and (*S*,*R*)-**16**. The fixed stereocentre in the (*S*)-Mosher’s ester moiety remotely influences the configuration of the barbaralyl cage, which preferentially adopts its (*S*)-form. The equilibrium for the dynamic rearrangement of the barbaralyl cage is biased toward the (*S*,*S*)-isomer by Δ*G*calc = 4.5 kJ·mol−1 according to DFT calculations. A single crystal obtained from a dynamic mixture of the (*S*)-Mosher’s ester mixture contained (*S*,*S*)-**16** as a frozen, single stereoisomer. An equal and opposite outcome is observed from the (*R*)-Mosher’s ester mixture, giving the enantiomeric (*R*,*R*)-**16** solid-state structure. Analogously, cooling a dynamic mixture of (*S*,*S*)- and (*R,S*)-**16** in solution to 159 K shifts the Boltzmann distribution of isomers exclusively to the lowest-energy (*S*,*S*)-isomer.

**Selective Destabilization of Lower Energy Species**

The strain-promoted dynamics in fluxional molecules described above occur due to equal destabilization of the (often degenerate) isomers present in the equilibria relative to the transition state that connects them. However, one can also imagine cases where energetically inaccessible isomers that lie at high energy could be brought into dynamic equilibrium by selectively destabilizing the lowest energy species (Type III).

Reversible capture and release of singlet oxygen (1O2) has been reported in a series of tethered, highly twisted anthracenes, such as **17** (Fig. 4a).68 Increasing the end-to-end twisting of anthracene **17** by shortening the tether leads to an increase in the rate of Diels–Alder cycloaddition with 1O2 (photosensitized by methylene blue) to form **18**.69 Similarly, the rate of thermal cycloreversion (retro-Diels–Alder reaction) was found to increase by over an order of magnitude at 80 °C when the tether was shortened by two carbon atoms. Notably, the twisted anthracenes showed improved reversibility compared to untethered anthracene. The increased rates of both the forward and reverse reactions upon shortening the tether (and hence, increasing twist) were attributed to (i) increased strain energy bringing the reactant and product closer in energy to the transition state, and (ii) stabilization of the transition state due to an increase in HOMO-coefficients at the 9- and 10-positions. Analogous reports have shown the ability of tethered pyrenes to participate in both Diels–Alder70 and 1,3-dipolar cycloadditions,71 despite the inertness of unrestrained pyrene under these conditions.

A recent investigation has used periphery overcrowding to balance the strain energy in a series of π‑extended tropylium cations with their aromatic stabilization energy to bring the aromatic tropylium (TP) and nonaromatic ‘Dewar’ (DT) isomers close in energy (Fig. 4b). Periphery overcrowding favours the formation of twisted geometries that resemble the higher energy transition states and intermediates of this isomerization pathway, where the tropylium core adopts a boat-shaped conformation (Fig. 4c). Cations **20**–**23** (Fig. 4d) were chosen as synthetic targets, as they span a wide range of Gibbs energy differences (Δ*G*) between the TP and DT isomers, as predicted by DFT calculations. Single-crystal XRD analysis of tropyliums **20**–**23** reveals that, on one side of the energetic balance point—where aromatic stabilization is greater than strain (as for **20**–**22**)—increasingly twisted tropyliums are observed with end-to-end twists up to 45° (Fig. 4e). The Gibbs energies of the TP and DT isomers are closely matched at this point (15 kJ·mol−1 according to DFT calculations), indicating it is among the most geometrically deformed tropyliums that are synthetically viable. The introduction of further peripheral overcrowding in **23** destabilizes the tropylium isomer beyond the threshold of aromatic stabilization by ~5 kJ·mol−1, leading to the formation of a bicyclic DT.

**Accessing Transition State Analogues**

While confinement through supramolecular encapsulation has been used widely to stabilize reactive intermediates, high-energy conformations, and even transition states,72 covalent geometry control (Type IV) has parallelly emerged as a useful method to ‘trap’ these structures. The forms and properties of transition states have long fascinated chemists, but their fleeting nature (with lifetimes on the femtosecond timescale) has posed great limitations on our ability to observe and study them. Indeed, transition state analogues—molecules that mimic the structure of transition states of metabolic reactions—are an important class of enzyme inhibitors frequently studied as drug leads.73–75 Beyond medicinal chemistry, understanding the structures of transition states and high-energy points on a potential energy surface not only provides invaluable information about the kinetics of a particular reaction, but also offers insight into the elusive modes of bonding that stabilize or destabilize these structures.

For example, the lowest energy pathway for many thermally allowed pericyclic reactions involves an aromatic transition state.76 The exceptional electronic and chemical stability associated with aromaticity is a result of structural features such as bond length equalization and planarization.77 Computational findings indicate that—rather than being the primary driving force—π-delocalization and aromaticity are facilitated by the buttressing effect of σ-electrons, which enforce a rigid, symmetric structure.78 Without this effect, π‑systems tend to localize and prefer bond length alternation. Consequently, despite the extensive aromatic stabilization present in [10]annulene **24**, bond angle strain imposes nonplanar and nonaromatic structures with localized bonds79, rather than its aromatic D10h symmetric form (Fig. 5a). Indeed, the first stable all-*cis* [10]annulene **25** was prepared by modification of the [10]annulene σ-framework through cyclopropenation (to widen bonding angles from 120° to 150°) and the introduction of an alkyne moiety.80,81

Conversely, the σ-framework of benzene is significantly less strained, so it exhibits a planar, aromatic structure. In general, distortions of its σ-framework perturb benzene from its equilibrium geometry, which inevitably impacts its aromatic stabilization and its stability. For example, a Kekulé vibration morphs the minimum energy D6h symmetric benzene (with equal, delocalized bonds) into its hypothetical D3h 1,3,5‑cyclohexatriene form with localized single and double bonds (Fig. 5b).82 While in unrestrained benzene, this cyclohexatriene form is a transient, high-energy species, DFT calculations indicated it can be stabilized to a ground-state structure by annelation of bicyclo[2.1.1]hexane moieties (Fig. 5c).83 The geometry control imposed by the strained σ-framework of the alkyl rings in **26** forces extensive bond localization and bond length alternation of 0.089 Å, as confirmed by single crystal X-ray crystallography.

A similar approach has been used to induce out-of-plane distortions, such as bending or twisting, in aromatic rings. Notably, the geometry control afforded by the alkyl straps in meta-84 and paracyclophanes85 has been used to bend benzene rings into boat conformations. DFT calculations predict out-of-plane angles up to 23° in [5]paracyclophane **27** (Fig. 5d). Metacyclophane **28** (Fig. 5e) exhibits even larger out-of-plane bow and stern angles of 26.8° and 12.0°, respectively, in the solid state. Optical and NMR spectroscopic analyses, in conjunction with computational studies indicate that even severe geometric deformations only cause a minor decline in aromaticity in all three molecules discussed above. The persistence of aromaticity in cyclophanes **27** and **28** has tentatively been attributed to enhanced orbital overlap on the concave side of boat-shaped benzene to counterbalance weaker bonding on the convex face.

Yet, the chemical reactivity exhibited by these systems is unusual for aromatic moieties. Transformations that typically require high temperatures, external catalysis, or highly reactive substrates, such as the epoxidation and Simmons–Smith cyclopropanation of **26**86 and the Diels–Alder cycloadditions of **27** and **28** were shown to proceed under ambient conditions.87,88 These remarkable rate enhancements can be attributed to a combination of (i) strain relief and (ii) the structural similarities between the ground- and transition states of the reaction, allowing for improved orbital overlap. Viewed from this perspective, these geometrically constrained molecules can be considered transition-state analogues.

Unlike benzene, 4n π-electron annulenes do not benefit from aromatic stabilization and adopt nonplanar geometries. Cyclooctatetraene (COT), for example, exhibits a ground-state D2d tub-conformation, which can undergo a tub-to-tub ring inversion via a planar D4h transition state that lies an estimated 42–59 kJ·mol−1 higher in energy (Fig. 5f).89 Following the success of the bicyclic annelation strategy employed to induce bond length alternation in **26**, computational modelling predicted that ‘clamping’ COT with strained cyclobutyl, perfluorocyclobutyl, or [2.2.1]bicyclohexyl rings would trap the core in a D4h transition state.90 Subsequent syntheses and structural analysis confirmed this idea. Compound **29** (Fig. 5g) features a planar COT moiety with alternating bond lengths of 1.33 and 1.50 Å, corresponding to localized double and single bonds.86

By analogy, geometry control has allowed the isolation of transition state geometries of larger polycyclic aromatic molecules, such as corannulene. This geodesic structure (bowl depth 0.87 Å) undergoes rapid, degenerate bowl-to-bowl inversions at room temperature (Δ*G*‡ ~ 43 kJ·mol−1)91, via a planar transition state. A computational study indicated that periphery overcrowding of the corannulene core with bulky thioether groups reduces the bowl depth significantly, bringing the planar and geodesic conformations close in energy. Indeed, the most overcrowded system, decakis(*tert*-butylsulfido)corranulene **30**92 (Fig. 5h) was found to crystallize in two different polymorphs; one exhibits a bowl-shaped core (not shown), with bowl depth 0.56 Å, while the other contains the planar transition state of corannulene as a stable structure (shown).

Beyond conformational changes and vibrational modes, transition states of bimolecular chemical transformations have also been stabilized as equilibrium geometries. Perhaps the simplest reaction in organic chemistry—an SN2 reaction—proceeds via a trigonal bipyramidal transition state containing a cationic, pentavalent carbon atom with weakly coordinating axial substituents representing the leaving group and the attacking nucleophile. Several groups have leveraged the structural rigidity afforded by planar aromatic frameworks, such as benzene rings or anthracene to immobilize the axial groups, allowing for a hypervalent interaction with a main-group atom positioned between the two.93,94 In keeping with this design principle, a pentavalent carbon was obtained by creating a carbocation at the 9-position of a 1,8-dimethoxyanthracene skeleton in **31** (Fig. 5i). Single crystal XRD analysis reveals the central carbon adopts a planar geometry (sp2-hybridized) with nearly identical C–O distances of 2.43 and 2.45 Å, which are intermediate between that of a covalent C–O bond (1.43 Å) and the sum of their van der Waals radii (3.25 Å). Hence, the geometry of this trigonal bipyramidal carbon centre can be viewed as a ‘trapped’ SN2 transition state.

As discussed above, pericyclic reactions are largely susceptible to the impacts of Type II and Type III geometry control.66,67,95 Taken to the extreme, geometry control can stabilize the charge-neutral, homoaromatic transition states of the Hardy–Cope rearrangements of bullvalenes, barbaralanes, and semibullvalenes (Fig. 2d–f) as energetic ground states. Homoaromatic molecules exhibit the hallmarks of aromaticity (electron delocalization, energetic stabilization, etc.), but possess an interrupted π-system that is bridged by through-space orbital interactions to enable cyclic conjugation. The study of homoaromaticity is of fundamental interest for the understanding of chemical bonding. However, relatively few stable homoaromatic compounds are known.96

Though cycloheptatriene (**1**) has been considered the archetypal neutral homoaromatic compound, there is no conclusive evidence of its homoaromaticity.96 Extension of the 6π system of this ‘homobenzene’ to a 10π-electron system forms a ‘homonaphthalene’ (**32**),97 while formally connecting the two methylene bridges of **32** forms elassovalene (**33**). Both **32** and **33** have been prepared and shown to be non-aromatic.98,99 However, further fine-tuning of the geometry by lengthening the tether by one carbon atom forms **34** (Fig. 6a), which exhibits neutral homoaromaticity in the ground state, as evidenced by experimental and computational analyses.34,100

In order to facilitate a through-space homoconjugative interaction between the carbon atoms in **33**, the distance between the bridging carbons (C4 and C9) needs to be controlled precisely.65,66 The geometry control enforced by the carbonyl bridge in expanded barbaralone **34** lowers the internuclear distance between the methylene bridgehead carbons compared to **33**. StrainViz101 analysis (Fig. 6b) of **33** and **35** revealed that—while **35** experiences greater overall strain—it is distributed across the molecule more evenly, allowing a relaxation of the barbaralone framework and contraction of the central C–C distance.34 Consequently, the through-space interaction that completes the 6π-electron homoaromatic circuit is present in **34**, but not in **33**. NMR spectroscopic data (Fig. 6c) corroborate these calculations. The proton resonances of the 6π-homoannulene moiety in **34** (6.75 and 7.06 ppm) are characteristic of an aromatic system, unlike the corresponding resonances of **33** (6.30 and 6.64 ppm). The structurally related rearranged barbaralone **34** features a bridgehead hydrogen atom that exhibits a marked upfield chemical shift of *δ* = 0.89 ppm, due to its position above the ring current of the 6π-homoaromatic system. By comparison, the analogous hydrogen atom in nonaromatic **33** has *δ* = 1.77 ppm. Finally, X-ray crystallographic analysis (Fig. 6d) of **34** reveals significant bond length equalization of the 6π-homoaromatic moiety (a common hallmark of aromatic delocalization), with single and double bond lengths of 1.36 and 1.42 Å, respectively. Nucleus-independent chemical shifts (NICS)102 and anisotropy of the induced current density (ACID) plots103 confirm the homoaromatic character of **34** and **36**.34

This case study highlights the significant consequences of seemingly minor structural variations through geometry control. Intricate manipulation of internuclear distances by varying the length of a tether positions atoms in closer proximity, which allows them to form a through-space interaction. Overall, this geometry control enables the isolation and observation of a homoaromatic transition state as a stable, ground-state structure. With this class of neutral homoaromatic molecules in hand, systematic deconstruction or alteration of the hydrocarbon framework of **35** can give rise to a deeper understanding of the forces that govern homoaromatic bonding.

**Emergent Phenomena Associated with Geometry Control**

*Accessing New Isomerization Processes of Aromatic Systems*

The altered bonding parameters enforced by geometry control give rise to unusual chemical behaviour on the molecular scale, as well as interesting bulk properties of materials. In this section, we outline key examples of such emergent phenomena demonstrated by the structures described in this Review.

In addition to a local 6π-electron homoaromatic circuit, **34** and **36** also contain a global 10π-electron circuit, albeit to a significantly lower extent, as indicated by ACID calculations. Remarkably, altering the connectivity of the acyl bridge (and hence, the well-defined geometry of the π-system) changes the preferred conjugative pathway from local to the global circuit.34,100 Photoirradiation of **34** (355 nm light) induces (Fig. 7a) this change in connectivity in the form of an unprecedented [1,11] sigmatropic rearrangement to give **37**. The Type IV geometry control afforded by the covalent framework is still present but is able to accommodate the formation of a homoaromatic circuit with a different geometry. Compounds **34** and **37** can be reversibly photoswitched with minor fatigue over at least five cycles. Photoirradiation with a higher wavelength of light (455 nm) reverts **37** to **34**, reinstating the 6π-homoaromatic circuit. This bistable system demonstrates how even subtle changes in strain and molecular structure can profoundly alter a molecule’s characteristics.

While the Type IV geometry control described above can immobilize an otherwise dynamic system, establishing homoaromaticity, Type III geometry control—typically used to shift equilibrium populations—can introduce dynamic bonding in aromatic systems. At room temperature, **23** undergoes dynamic exchange with its degenerate valence isomer **23′** (Fig. 7b) as confirmed by exchange NMR spectroscopy (EXSY). In doing so, it passes through an aromatic intermediate, **23-TP**, which lies 5 kJ·mol−1 higher in energy than **23**. With the thermal energy available at 298 K, the equilibrium between **23** and **23-TP** is weighted in a ratio of ~90:10 towards the nonaromatic isomer, with an equilibrium constant *K* = 0.12. The presence of a small amount of **23-TP** was confirmed by a hydride ‘trapping’ experiment with NaBH4, which gave a 96:4 ratio of bicyclo[3.2.0]heptadiene **38** and CHT **39**. Computational modelling of aromaticity parameters confirms that even the most deformed tropylium isomers **22** and **23-TP** retain their aromatic character. Overall, therefore, selective destabilization of the tropylium isomer relative to the DT isomer of **23** establishes an unusual strain-promoted dynamic aromatic-to-nonaromatic equilibrium.

*Ambient Temperature Tunnelling Effects*

While heavy-atom QMT is well-explored at cryogenic temperatures, structural rigidification due to geometry control can facilitate tunnelling pathways at ambient conditions.104 To illustrate, enediyne **40** is known to undergo (Fig. 7c) Bergmann cyclization reactions to form biradical **41** at high temperatures. A C4-tether connecting the two alkynyl termini of **40** allows this cycloaromatization to proceed at appreciable rates under physiological conditions (Type I).105 Indeed, the ten-membered (3*Z*)-cyclodec-3-en-1,5-diyne moiety is a common feature in anticancer and antibiotic agents due to its ability to cleave DNA. The cyclic (*Z*)-enyne–allene moiety in **43**—a feature in neocarzinostatin antitumor antibiotics—is known to undergo (Fig. 7d) the Myers–Saito reaction forming biradical **44**.106 Computational studies indicate that the thermodynamic driving force introduced by geometry control also narrows the barrier widths of these cyclizations, enabling heavy-atom QMT. Specifically, the reaction rate of the Bergmann cyclization of **40** was predicted to increase by 38–40% relative to the transition-state theory rate at 37 °C,107 while a 20% rate increase was predicted for the Myers–Saito cyclization at 25 °C.108 These investigations underscore the profound yet unexpected impact geometry control can have on seemingly simple organic reactions.

*Synthetic Applications of Fluxional Molecules*

The reported synthesis of the naturally occurring terpene ocellatusone C gives a noteworthy example of how molecular geometry can be exploited to achieve directed and potentially highly selective functionalizations of a single reactive subunit within a molecule.109 It was shown that enone **46** serves as a key synthetic precursor for a variety of bicyclic hydrocarbon cores. Deprotonation of **46** leads to a dynamic ensemble of shapeshifting anions **47**–**50**, which interconvert between three distinct isomers (Fig. 7e). Of special note are the two constitutional isomers **49** and **50**, in which the bridging C2-unit is formally rotated with respect to the octadienone core. Each isomer of this anion could in principle be exploited for a diverse range of downstream synthetic modification, and thus serves as an ideal starting point for further synthesis. Indeed, depending on the exact reaction conditions, the distinct bicyclic cores of **47**, such as barbaralone **51**, [3.2.2]bicyclononane **52** and—following further synthetic modification—**53**, have been trapped. In this sense, the geometrically constrained barbaralone core grants access to a highly dynamic bishomoallylic anion (Type II/Type III approach) that serves as a branching point for further synthesis through concurrent access to a variety of reactive molecules.

The remarkable divergence in reaction pathways was achieved by modulating deprotonation conditions and subsequent trapping of delocalized anion **47**, demonstrating the synthetic power of this strategy.110 This approach resembles biosynthetic pathways, e.g., terpene biosynthesis, in which a collection of simple building blocks is exploited in a highly divergent manner in a multitude of follow-up pathways.111 In the case of anions **47**–**50**, structurally related intermediates that lie close in energy form structurally diverse products. Such a scenario is an ideal platform to demonstrate the influence of substituents on the population of the isomers in solution and thus the outcome of a subsequent trapping reaction.

Similarly, the rapid Hardy–Cope rearrangements in desymmetrized barbaralanes (Fig. 3a) give rise to the property of dynamic sp3-C stereochemistry. Appending a fixed stereogenic centre to the fluxional core imposes a stereochemical bias, the magnitude of which can be altered or inverted depending on the size and shape of the substituent at the 9-position. A chiral phosphoramidite–alkene ligand112,113 bearing a desymmetrized barbaralyl core (Fig. 7f) showed a 20.2 kJ·mol−1 preference for its *S*,*S* diastereomer (*c.f.* a 3.8 kJ·mol−1 preference for the *R*,*S* diastereomer of **16**).31 Coordination of this ligand to Pd(II) or Ru(II) produces chiral-at-metal complexes **54**, linking the sp3-C configurational inversion to the *A*/*C* isomerism of the distorted trigonal bipyramidal coordination environments. 1H NMR spectroscopic analysis reveals that the chiral information from the fixed stereogenic centre is transmitted through the fluxional barbaralyl framework to bias the chiral-at-metal configuration toward one diastereomer.

In the absence of a fixed stereogenic centre in its ligand structure, cationic metal complex **55** undergoes degenerate enantiomerization. The addition of a chiral counterion such as *Δ*-TRISPHAT or (*S*)-BORBIN establishes an equilibrium mixture containing diastereomeric ion pairs, which becomes enriched in one stereoisomer. Preliminary investigations confirm that this counterion-directed stereomutation can be exploited for enantioselective ion-pair catalysis, giving improved enantiomeric excesses compared to ligands without a fluxional moiety.

*Application of Geometry Control to Macroscopic Properties*

Beyond new synthetic methodologies, low-barrier sigmatropic rearrangements have also been studied computationally within the context of oligomers and polymers known as ‘sigmatropic shiftamers’114,115 which are capable of formally delocalizing a σ-bond within their hydrocarbon frameworks through degenerate sigmatropic rearrangements. These structures serve as a model for how precise control of C–C bond lengths on the molecular scale can translate to unusual properties in the bulk. Indeed, the introduction of moieties that exhibit rapid constitutional dynamics while remaining stable—often termed ‘shapeshifting’116 moieties—has been an area of growing interest.

By including various degrees of shapeshifting bullvalene units (originating from bisboronic acid **56**) in the composition of a polymer **57**, its structural rigidity is diminished (Fig. 7g).117 This phenomenon results in increasingly lower thermal transition temperatures compared to rigid polymers. The facile incorporation of flexible bullvalene units is enabled by the readily accessible bisboronic acid **56**,118 which enables rapid functionalization by cross-coupling reactions. As shown by this example, the targeted implementation of geometry controlled dynamic C–C bonding within a molecule or a material is a viable strategy to systematically influence its properties. Furthermore, it demonstrates that geometry control on the molecular scale can be amplified to a material’s bulk properties on the macroscopic scale.

Readily available multifunctional shapeshifting bullvalene building blocks such as **58** have also found biological utility. In a recent study, two vancomycin units were connected by a fluxional bullvalene core, generating biologically active shapeshifting molecules, such as **58**, that show antibiotic activity.119 Perhaps more importantly, on account of their constitutionally dynamic structures, the vancomycin dimers were less prone to bacterial resistance. This investigation is an early indication that the biological activity of single molecules may be enhanced by introducing dynamic C–C bonding, and thus more flexibility. Recently, constitutionally dynamic bullvalene linkers were also used to create a nanoscale electro-mechanical system. Scanning tunnelling microscopy break junction experiments revealed piezoresistance properties arising from conductance across the constitutionally dynamic bullvalene.120

**Outlook**

Examples of geometry control have been applied to various aspects of organic chemistry throughout the years. The concept first emerged through the physical organic analysis and structural elucidation of simple small molecules and it has since been applied, consciously or otherwise, in the design of increasingly complex molecules and materials that take advantage of dynamic rearrangements and unconventional bonding modes. This article has sought to categorize these examples in order to better define the concept of geometry control. We have outlined how it has been applied to arrive at unusual reactivity, molecular states and bonding. Looking ahead, we envisage that this strategy will continue to be applied by chemists in other ways beyond those discussed here. For example, there is potential to use geometry control in ligand design to investigate distorted binding modes and metal coordination geometries that have not been accessible before. There are already examples of dynamic C–C bonding being exploited in materials and biologically active molecules, which is a trend that is likely to continue. Going even further, by judicious design it may also be possible to purposefully create organic molecules that not only experience low-energy transformations but exhibit heavy-atom QMT that contributes substantially to their reactivity under ambient conditions. Developing these ideas presents an opportunity for cooperation between chemists with varying skills and vantage points. It is no coincidence that many of the examples covered in this review have combined (in almost equal measure) the use of synthesis, modelling and spectroscopy.

**Figure Legends/Captions**

**Fig. 1** | **The design principles of geometry-controlled transformations or molecular conformations.** Type I reactivity describes strain-release transformations, while Types II–IV describe strain-promoted bonding and dynamics. Schematic reaction coordinate diagrams show changes in relative Gibbs energies (*G*rel) of unrestrained molecules (black lines) when subjected to geometry control (red lines). Grey and blue arrows corresponding to changes in barrier heights and widths, respectively, are included to guide the eye. Abbreviations: TS‡ = transition state.

**Fig. 2 | The effect of geometry control on pericyclic reactions**. **(a)** The CHT–NCD equilibrium is heavily weighted toward CHT, but **(b)** the geometry control afforded by a cyclic anhydride tether inverts this preference (Type III).44 **(c)** Annelation of a small ring (n = 1) to CHT stabilizes the NCD isomer, but larger rings (n ≥ 2) retain the preference for a CHT (Type III).45–47 **(d)** The Hardy–Cope rearrangement of divinylcyclopropane **8**.50 **(e)** Experimentally measured activation energy barriers to the Hardy–Cope rearrangements of selected Type II geometry-controlled structures.53,59,60,121 **(f)** The effect of QMT on reaction kinetics manifests as nonlinear (red lines) Arrhenius plots of rate constants (left) and KIE (right).33 **(g)** The Hardy–Cope rearrangement of *d4*-**9** selectively forms *d*2-**9** at cryogenic temperatures.63,64 **(h)** Semibullvalenes (R = Me, Et) with the lowest reported Hardy–Cope rearrangement barriers. Δ*G*‡ values were measured at: *a*298, *b*233, *c*373, and *d*190 K. Abbreviations: Ac2O = acetic anhydride; CHT = 1,3,5-cyclohexatriene; Et = ethyl; KIE = kinetic isotope effect; Me = methyl; NCD = norcaradiene QMT = quantum mechanical tunnelling.

**Fig. 3** | **Dynamic sp3 stereochemistry. (a)** Narcissistic automerization of barbaralane (Type II). **(b)** Desymmetrization of barbaralane produces a pair of enantiomers. **(c)** Addition of a fixed stereocentre (a Mosher’s ester group) remotely biases the stereochemistry of the barbaralyl cage, leading to the selective crystallization of the most thermodynamically stable diastereomer.31 Abbreviations: Me = methyl; Ph = phenyl.

**Fig. 4** | **Type III geometry control examples. (a)** Reversible capture and release of 1O2 by a strapped phenanthrene.68,69 **(b)** Isomerization between tropylium (**19-TP**) and DT (**19-DT**) *via* a Möbius tropylium intermediate (**MT**). **(c)** Boat-conformations adopted by seven-membered rings. **(d)** Peripherally overcrowded tropylium cations **20**–**23** and **(e)** their single-crystal X-ray structures.30 Abbreviations: DT = Dewar tropylium; MT = Möbius tropylium intermediate; Ph = phenyl; TP = tropylium.

**Fig. 5 |** **Accessing transition state analogues through Type IV geometry control. (a)** Cyclopropanation and the introduction of an alkyne moiety alter bond angles in unsubstituted all-*cis* [10]annulene **24** to yield the more stable **25**.81 **(b)** Schematic energy diagram for the Kekulé distortion of *D*6h benzene to the *D*3h cyclohexatriene (black line), and the impact of geometry control (red line). **(c)** Solid-state structure of **26**, which exhibits a ground-state cyclohexatriene geometry with alternating bond lengths.83 **(d)** DFT-optimized structure of [5]paracyclophane (**27**)85; **(e)** Solid-state structure of **28**.84 **(f)** Energy diagram for the tub-to-tub inversion of cyclooctatetraene (black line) and the impact of geometry control (red line). **(g)** Solid-state structures of **29**86, which features a planar COT moiety, and **(h)** **30**, which contains a planar carbon framework.92 **(i)** Solid-state structure of a pentacoordinate carbon centre in **31** (resembling the transition state of an SN2 reaction) stabilized within a 1,8-dimethoxy-anthracenyl framework.94 The counterion has been omitted for clarity. Abbreviations: COT = cyclooctatetraene; DFT = density functional theory; Me = methyl; *t*Bu = *tert*-butyl.

**Fig. 6 |** **Neutral homoaromaticity through Type IV geometry control. (a)** Design principles behind neutral homoaromatic **34**.34 **(b)** Comparison of the C2–C11 and C4–C9 internuclear distances, as well as StrainViz analyses of **33** and **35**. **(c)** Selected 1H NMR resonances of **33**, **34**, and **36**. **(d)** C4–C9 internuclear distance and selected bond lengths of the 6π-homoaromatic circuit in **34**. Abbreviations: Me = methyl; NMR = nuclear magnetic resonance; ppm = parts per million.

**Fig. 7 | Emergent phenomena associated with geometry control. (a)** Toggling between 6π- and 10π-electron homoaromatic circuits through a reversible photochemical [1,11] sigmatropic rearrangement.34 **(b)** A dynamic aromatic-to-nonaromatic equilibrium, intercepted by reduction to give a 96:4 ratio of **38** and **39**.30 Reagents and conditions: i) NaBH4, THF, rt, 30 min. **(c)** Bergman107 and **(d)** Myers–Saito cyclizations108 undergo significant QMT under ambient conditions. **(e)** Deprotonation of **46** produces an interconverting mixture of anions **47**–**50**, which exhibit divergent reactivity upon addition of various electrophiles.109,110 **(f)** The stereochemistry of a chiral-at-metal complex with a phosphoramidite–olefin ligand can be biased by adding a fixed stereocentre, as in **54**, or by ion-pairing of **55** with a chiral counterion.31 **(g)** Disubstituted bullvalenes **56**118 are building blocks for flexible polymers **57**.117 **(h)** A vancomycin dimer with a bullvalene backbone **58** exhibits slower antibacterial resistance.119 Abbreviations: aq = aqueous; Bpin = pinacolato boronyl; KHMDS = potassium bis(trimethylsilyl)amide; L = ligand; Me = methyl; Ph = phenyl; QMT = quantum mechanical tunnelling; rt = room temperature; TBS = *tert*-butyldimethylsilyl; TfO = trifluoromethanesulfonate; THF = tetrahydrofuran.

**Box 1**

Definitions of key terms used in this Review are included below:

**Strain.** Strain is the contribution to a molecule’s internal energy arising from nonideal bond lengths, bond angles or dihedral angles.122 This deviation from ideal bonding parameters occurs in order to (i) accommodate otherwise favourable bonding interactions or (ii) minimize unfavourable bonding interactions elsewhere in a molecule. It is an intramolecular phenomenon. Small magnitudes of strain can have relatively subtle consequences, for example, dictating the preferred conformation of a flexible organic molecule or tuning the vibrational energy of a functional group. Higher energy strain can perturb bonding interactions more profoundly, even in relatively rigid molecules. Strain-release reactions take advantage of substrates where a large amount of strain is focused on a particular bond, destabilising it with respect to the transition state of a reaction (Type I). The strain energy in different parts of a molecule can be visualized by comparison to unstrained derivates using computational methods such as StrainViz.101

**Confinement.** In supramolecular systems, confined spaces, such as the binding pockets of a macrocycle, cage, or biological receptor, can limit the movement of encapsulated molecules (i.e., the accessible conformations and their associated bond lengths and angles) relative to a freely solvated species.72,123 When placed under confinement, the interplay of favourable interactions (such as hydrogen bonding or π–π interactions) and unfavourable interactions (such as electrostatic repulsions) can induce nonideal bonding parameters in the bound substrate. The concept of supramolecular confinement—an intermolecular phenomenon—is outside the scope of this Review article. We limit our discussion to unfavourable intramolecular interactions imposed by the covalent framework of a molecule that raise its internal energy.

**Quantum mechanical tunnelling (QMT).** Particles with insufficient energy to cross over a finite potential energy barrier can pass through it by QMT.33 This process is a consequence of the wave nature of matter. The probability of tunnelling is inversely proportional to (i) the square root of the mass of the tunnelling particle(s) and the height of the barrier; as well as (ii) the width of the barrier (*w*) required to convert the geometry of a reactant to that of the product, i.e., the distance travelled by the participating atoms as they react. As tunnelling provides an additional, often lower energy reaction pathway, it generally increases the reaction rate.104

**Structure–correlation principle.** The structural changes that occur during a chemical transformation can be emulated in the ground state of a molecule by controlling its geometry.2,124 The resulting structures resemble the transition state of the reaction, allowing the properties of the ground state (e.g., bonding parameters, energy, etc.) to be correlated with the properties of the transition state.125

**Acknowledgements**

P.K.S. gratefully acknowledges the Engineering and Physical Sciences Research Council (EPSRC) for a Doctoral Training Grant (EP/R513039/1). P.R.M. acknowledges a Leverhulme Trust Research Project Grant (RPG-2023-191).

**Author contributions**

All authors conceived the main outline and idea of the review and contributed to the writing. P.K.S. and T.T.N. prepared the figures.

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