

BPDCN. This observation probably explains, at least in part, why mutations in the *TET2* pathway are associated with BPDCN.

The authors' findings demonstrate how tissue-specific environmental pressures can drive the evolution of premalignant clones to form a cancer that can affect local (such as skin) and distant (bone marrow) sites. The Darwinian model of cancer evolution is in itself complex and branching in this study across anatomical sites. As evidence grows for the pervasive nature of somatic mosaicism, further investigation is warranted into the interplay between inherited mutations, somatic mosaicism, factors that shape cell survival and, as highlighted by Griffin *et al.*, the role of organ-specific mutations involved in the evolution of disorders arising from clonal-cell lineages.

Given the rise in technologies that can gather data from single cells, it is increasingly possible to find ways of linking diverse measurements of tumour growth. Careful study design, together with the collection of biological samples and the development

of disease models representing each stage of disease evolution, could deepen our understanding of cancer initiation and progression, and also guide the development of surveillance and interception strategies that target the key factors of malignant transformation.

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Organic chemistry

Strain equals gain for organic synthesis

Fahima I. M. Idiris & Christopher R. Jones

Energy released from molecules under strain can promote difficult chemical reactions. A practical method has been developed that uses an overlooked, highly strained compound to rapidly construct complex organic products. **See p. 748**

Organic chemists continually strive to develop methods that enable the preparation of molecules that cannot currently be synthesized, or that allow synthesizable compounds to be made more efficiently. One approach to this is to find ways of promoting reactions that must overcome a large energy barrier to proceed. As with a child trying to scale a high wall to retrieve a ball from a neighbouring garden, there are different options for overcoming the barrier. One option is for the child to start from a point above ground level, such as a nearby tree, and then to drop down over the wall. In a chemical reaction, this equates to starting from a molecule that is much higher in energy than the desired products, and on page 748, Kelleghan *et al.*¹ report an ingenious form of this strategy. They use the high levels of energy stored in a rarely used type of strained organic molecule, known as a 1,2,3-cyclohexatriene, to drive reactions that enable complex chemical synthesis.

Organic compounds known as benzenes, cyclic alkynes and cyclic allenes (Fig. 1) contain a ring of carbon atoms that incorporates either a carbon–carbon triple bond (in the case of benzenes and cyclic alkynes) or two consecutive double bonds (in cyclic allenes). Such double- and triple-bonded systems preferentially adopt linear structures when unconstrained, but are forced to adopt bent structures when accommodated in a ring; the rings, in turn, are also distorted out of a regular arrangement by these bonded systems. The molecules are therefore strained and have high internal energies – much like a rubber quoit becomes strained when one side is pressed flat against a table. Such ring systems react swiftly with other molecules to release strain and generate lower-energy products. These reactions involve the formation of several bonds in a single step, which makes benzenes, cyclic alkynes and cyclic allenes valuable building blocks for the efficient synthesis

From the archive

The architect Christopher Wren uses his astronomy skills to assess an observatory proposal, and questions about cyclones.

100 years ago

“Tom Tower,” Christ Church, Oxford. Some Letters of S^r Christopher Wren to John Fell, Bishop of Oxford — This book was published in honour of the bicentenary of Wren's death ... [T]here are seven ... letters written by Wren ... [T]he sixth and most interesting one ... is a reply to a proposal on the part of the bishop, that the tower should be converted into an observatory. Wren is too polite to reject the proposal altogether, but gives good reasons why it should not be hastily adopted. It would involve a change in the whole design; the bell would have to be lowered so as to heighten the loft, and it might then not be well heard. The Gothic roof, agreeing with the rest of the College buildings, would have to be abandoned ... In addition to these objections from the point of view of an architect, Wren next produces others from the point of view of an astronomer, and here also he could speak with authority, having held the office of Savilian professor of astronomy for twelve years (1661–73) until pressure of other work obliged him to relinquish it ... Oxford did not get an observatory on this occasion (there were only two University Observatories in existence at that time, at Copenhagen and at Leyden), and nearly a hundred years had to pass, before the Radcliffe Observatory was built.

From Nature 23 June 1923

150 years ago

We have now reached a point where we can properly and intelligently consider a question that has always baffled meteorologists — the origin of cyclones. The diagnosis of the phenomenon necessarily precedes its explanation. This subject has engrossed many minds, and various have been the ingenious devices for unravelling its mystery. Mr Redfield — the father of storm physics — in his modesty and diffidence ... so keenly felt the need of a more enlarged induction of facts, that he has scarcely left us his opinion.

From Nature 19 June 1873



of structurally complex products^{2–4}.

Because strained ring systems exist only fleetingly, chemists generate them *in situ* from stable precursor molecules during reactions. In 1983, a practical approach for generating benzynes was reported⁵ that has since been adopted for making cyclic alkynes⁶ and cyclic allenes³. These strained ring systems have subsequently been used in the synthesis of a wide range of compounds, such as pharmaceuticals, agrochemicals and materials.

However, another type of strained ring system has been largely overlooked as a building block for synthesis: 1,2,3-cyclohexatriene, a ring of six carbon atoms that contains three consecutive carbon–carbon double bonds (Fig. 1). In the 1990s, three research groups reported independently that 1,2,3-cyclohexatrienes can be reacted with a small number of reaction partners^{6–8}. Despite these enticing findings, the synthetic potential of 1,2,3-cyclohexatrienes has remained unexplored for 24 years.

Kelleghan and co-workers are part of a research group that has been one of the leading exponents of the chemistry of benzynes, cyclic alkynes and cyclic allenes – and of analogous systems that contain atoms other than carbon, such as nitrogen – for the construction of organic molecules^{2–4}. In the current work, the authors hypothesized that 1,2,3-cyclohexatriene should be amenable to taking part in a similar array of reactions.

To achieve this, the authors used a previously reported stable precursor of 1,2,3-cyclohexatriene⁶, from which they generated the strained rings using reaction conditions analogous to those used for benzyne formation⁵. Notably, these conditions are mild – they operate at a moderate temperature of 60 °C and tolerate the presence of a

range of chemical groups in the reactants. The latter is a highly desirable feature, because it means that products can be made that have a variety of physical and electronic properties, and which contain groups that offer scope for further chemical reactions (as needed for multi-step syntheses).

Kelleghan *et al.* reacted 1,2,3-cyclohexatrienes with an array of molecules that result in the installation of rings of different sizes in the products (Fig. 2). Furthermore, like benzyne, 1,2,3-cyclohexatrienes can insert themselves between the carbon atoms of single C–C bonds and undergo reactions with electron-rich molecules known as nucleophiles in a predictable manner. Overall, the authors report reactions involving

“Products can be made that have a variety of physical and electronic properties.”

three different 1,2,3-cyclohexatrienes and 22 reaction partners, thereby generating 29 structurally diverse products in single steps, often in good to excellent percentage yields (greater than 70%).

The 1,2,3-cyclohexatrienes included examples in which the strained ring bears one or two chemical groups (these molecules are said to be mono-substituted or di-substituted 1,2,3-cyclohexatrienes, respectively). The fact that such ring systems can be used as reactants is appealing, because it increases the number of sites in the products at which chemical groups can be added; this is good for applications that require the modular synthesis of structural analogues. However, mono- and di-substituted

1,2,3-cyclohexatrienes have rarely been synthesized^{9,10} and are even less well-studied than is unsubstituted 1,2,3-cyclohexatriene. Kelleghan and colleagues find that reactions of the mono- and di-substituted compounds with nucleophiles have good site selectivity (the reactions occur predominantly at just one position on the strained ring). This is noteworthy for such high-energy molecules, which could potentially react at more than one carbon atom of the triene.

Kelleghan and colleagues also report computational investigations that provide insight into the structure and reactivity of 1,2,3-cyclohexatriene. In these studies, the authors compared the compound's structure with those of benzene (which is an isomer of 1,2,3-cyclohexatriene) and benzyne. Both 1,2,3-cyclohexatriene and benzyne exhibit similar levels of deformation relative to the more-stable structure of benzene. The strain generated by this deformation was calculated to contribute a large amount (about 50 kilocalories per mole) to the overall increase in energy of these molecules, compared with benzene.

In 2014, workers from the same group as that of Kelleghan *et al.* collaborated with a team of computational chemists to establish a ‘distortion model’ that provided a way of predicting the site selectivity of benzyne reactions¹¹. In the present work, the authors used analogous calculations to design a mono-substituted 1,2,3-cyclohexatriene that exhibits optimal site selectivity in reactions with nucleophiles. In their experiments, small nucleophiles were found to attack the 1,2,3-cyclohexatriene at one position, whereas large nucleophiles attacked at another. This selectivity was correctly predicted by the computational model on the basis of the calculated ring distortion. Having the ability to design substrates and accurately predict their reactivity is an especially powerful tool for organic synthesis.

Importantly, Kelleghan *et al.* find that all 1,2,3-cyclohexatriene reactions consume the molecule's central double bond, yielding products that contain two carbon–carbon double bonds separated by a carbon–carbon single bond (Fig. 2). This arrangement of bonds is known as a 1,3-diene and is a promising starting point for further reactions. The authors exemplify this by showing that a 1,3-diene formed from the site-selective addition of a large nucleophile to a mono-substituted 1,2,3-cyclohexatriene can be transformed in just two steps into a highly topologically complex structure (see Fig. 6b of the paper¹).

Kelleghan and co-workers' detailed study shows the diverse reactivity of 1,2,3-cyclohexatrienes and highlights their huge untapped potential. We expect further investigations into the chemistry of these compounds to follow quickly – applications in catalytic reactions would be particularly interesting,

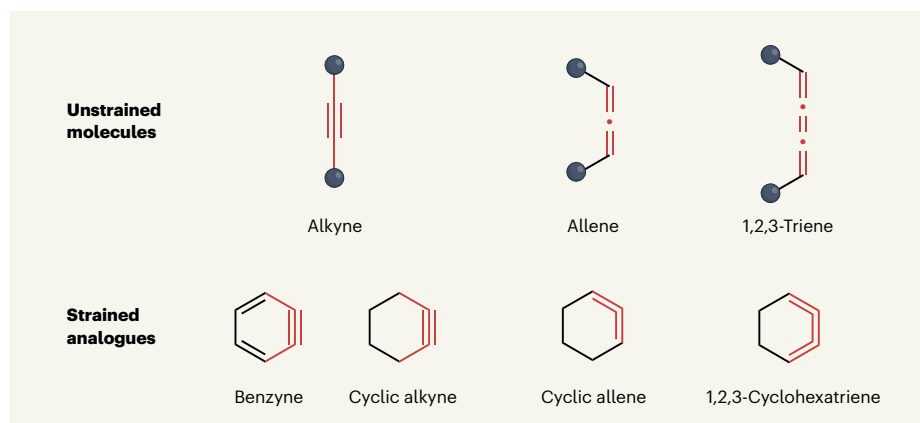


Figure 1 | Strain in organic molecules. Strain occurs in molecules when a stress alters chemical structures in a way that raises the internal energy of the system. For example, alkynes contain a carbon–carbon triple bond, and have the lowest energy when that bond forms a straight line with the adjacent carbon atoms.

When the triple bond is constrained in a ring (forming a benzyne or cyclic alkyne), the adjacent carbons are bent out of alignment, raising the molecule's internal energy and generating strain. Similarly, consecutive carbon–carbon double bonds in allenes and 1,2,3-trienes are at their lowest internal energy when linear, but are forced to bend when constrained in cyclic allenes and 1,2,3-cyclohexatrienes, respectively, generating strain. Black circles represent any chemical group attached to the molecules.

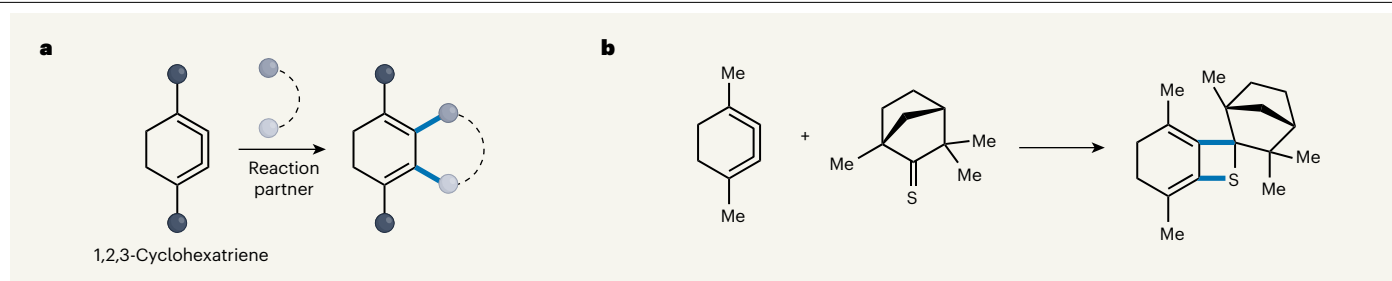


Figure 2 | Single-step reactions of 1,2,3-cyclohexatrienes generate structurally complex molecules. **a**, Kelleghan *et al.*¹ report strain-induced reactions of 1,2,3-cyclohexatrienes with a variety of reaction partners. In this general scheme, black circles represent a small range of groups; grey circles are reactive centres in the partner molecule; and the broken arc represents a diverse range of molecular structures. The reactions result in the formation of two new bonds to the ring (blue). The products also contain two carbon-carbon

double bonds separated by a carbon-carbon single bond (an arrangement known as a 1,3-diene) that is a promising starting point for further chemical reactions. **b**, This specific example shows how structurally complex products can be prepared in one step. Such a capability, combined with the operational simplicity of the chemistry and the diversity of potential reaction partners, makes 1,2,3-cyclohexatrienes powerful building blocks for organic synthesis. Me, a methyl group; S, sulfur.

for example, albeit challenging to develop. The chemistry of related compounds, such as the nitrogen-containing analogues of 1,2,3-cyclohexatrienes, should also be established. In addition, future research will focus on making it easier to synthesize the precursor compounds, and on developing alternative mechanisms for generating 1,2,3-cyclohexatrienes from various precursors. Such work will firmly establish these strained systems as powerful and practical building blocks for the rapid synthesis of structurally complex molecules.

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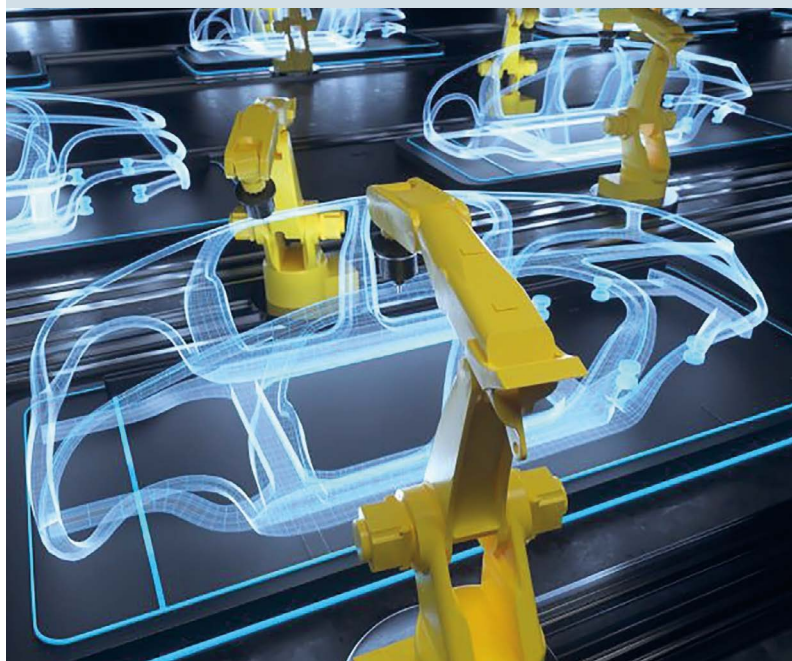
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