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Coarctate and Pseudocoarctate Reactions: Stereochemical Rules

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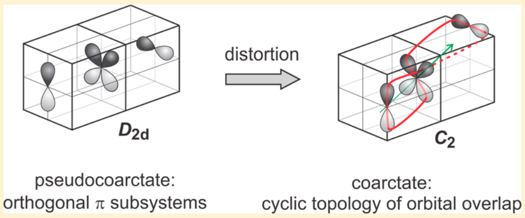
ABSTRACT: Coarctate reactions are a distinct class of concerted reactions. They differ from other concerted reactions, such as S_N2, E2, or pericyclic reactions, in such a way that atoms are involved in the transition state at which two bonds are made and two bonds are broken simultaneously. Similar to pericyclic reactions, an electron count can be used to predict reactivity and stereochemistry. The "coarctate rules" are derived from a topological variant of the aromaticity of the transition state principle. Pseudocoarctate transition states exhibit disconnections in the topology of orbital overlap and do not necessarily follow the coarctate rules.



INTRODUCTION

Reactions in chemistry can be classified according to the number of bonds that are made and broken per atom that is involved in the reaction. Electron transfer reactions are mechanistically the most simple because no bond is made or broken. The majority of organic reactions are characterized by making and breaking one bond at each atom. Prominent examples are polar reactions (e.g., S_N2, E2, Aldol) and pericyclic reactions (e.g., cycloadditions, sigmatropic shift, etc.). The mechanisms are formally written as a linear or cyclic arrangement of electron pushing arrows (Figure 1).

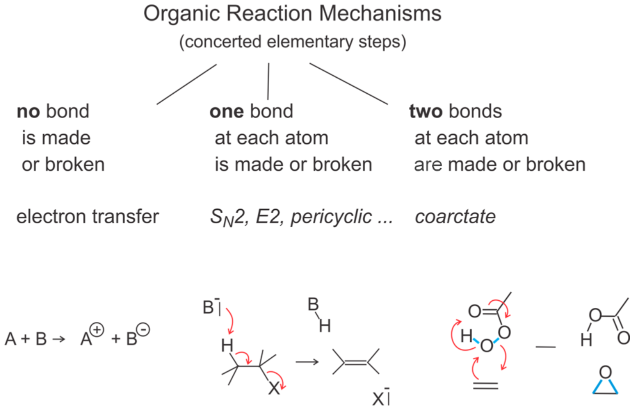


Figure 1. Classification of reactions according to how many bonds are made and broken at each atom involved in the reaction.

There are, however, a few hundred reactions that involve atoms at which two bonds are made and two bonds are broken simultaneously (Figure 2).[1,2]

Different reaction types, such as addition reactions (e.g., epoxidation with peracids or dioxirane), rearrangements (e.g., furfurylidene rearrangement and heteroanaloga), elimination (e.g., of azidopyrazoles, -triazoles, and -isoxazoles), and fragmentation reactions (e.g., of spiroozonides and spirooxazoles), fit in this class. We termed these reactions "coarctate" (lat. coarctare = constricting) and classified them in several categories according to formal criteria.[1,2] Common characteristics of coarctate reactions are that they include one coarctate atom or a string of several coarctate atoms that are terminated by an atom with a lone pair or loops including an odd number of atoms (1, 3, 5, 7,⋯; see Figure 2). These formal relationships can be used to define homology principles for the classification of coarctate reactions. The homology principle in pericyclic reactions is based on the size of the ring of delocalized electrons (e.g., [2 + 2] cycloaddition: 4-membered ring; [4 + 2] cycloaddition: 6-membered ring; etc.). A similar but extended homology principle holds for coarctate reactions. The size of the delocalized system of electrons can be either increased by increasing the size of the terminator loops or by extending the string of coarctate atoms (Figure 3).

These commonalities, in principle, could be fortuitous. However, within the last 20 years since we discovered this type of concerted reactions, we and others have been able to predict and to experimentally verify a number of coarctate reactions.[3,4] Moreover, quantum chemical calculations of several formal coarctate reactions have been proven that they are indeed concerted.

We now present general rules to predict the reactivity (thermo- or photochemical) and the stereochemistry of reactions involving coarctate transition states. To derive generally applicable rules (instead of calculating every specific reaction of interest at a high level of theory), we use a topologically extended approach of the Evans−Dewar−Zimmerman (EDZ) principle of aromatic transition states.[5−7] The EDZ approach has previously been successfully applied to derive the stereochemical rules for pericyclic reactions and is an alternative method to applying correlation diagrams or perturbation theory (frontier orbital method)[8] to derive the Woodward−Hoffmann rules.[9] According to the EDZ approach, the aromaticity principle, which is used to describe the stability

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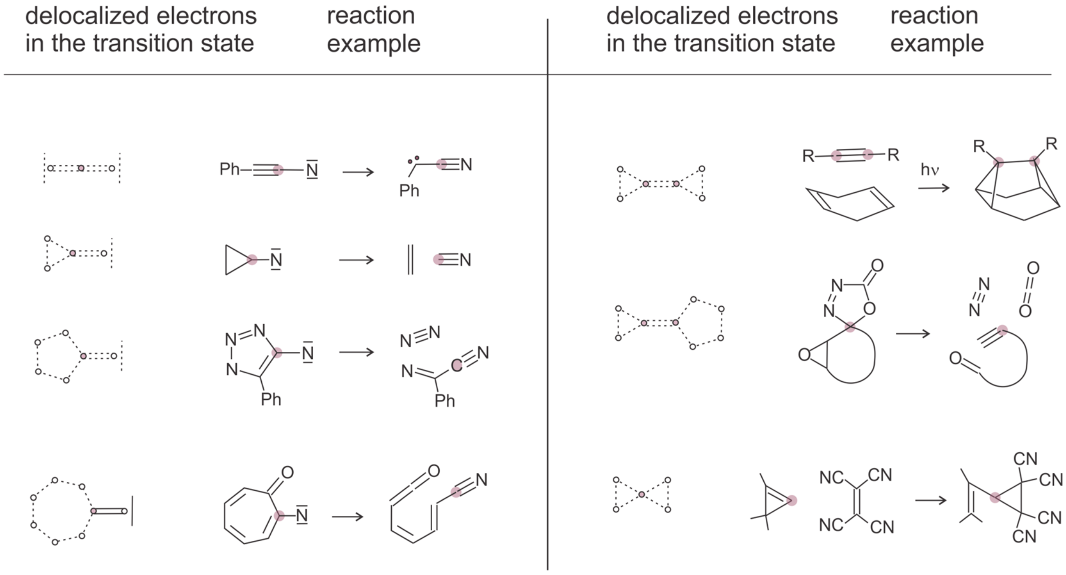

Figure 2. Examples of coarctate reactions. Atoms at which two bonds are made and broken simultaneously (coarctate atoms) are shaded.

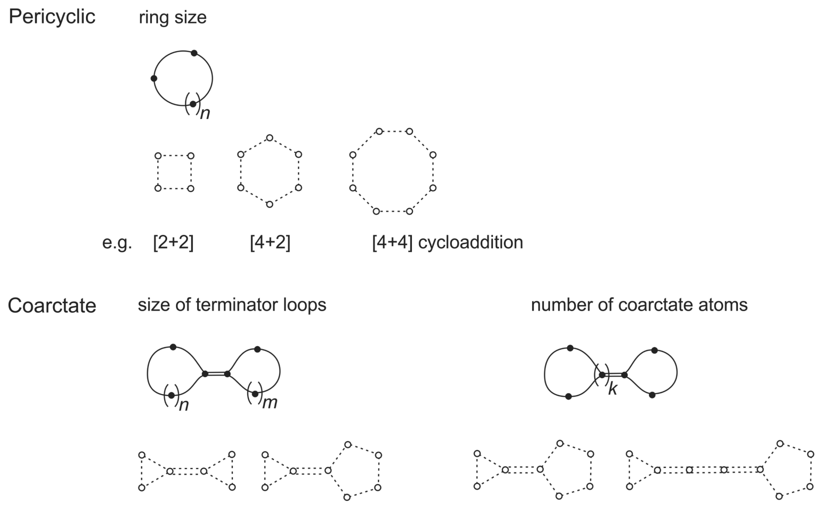

Figure 3. Homology principle of pericyclic reactions (top) and coarctate reactions (bottom).

of ground state molecules like benzene (Hückel rule),[10] can be extended to pericyclic transition states. The delocalized system of electrons in pericyclic transition states can be strongly aromatic. The ring currents in the transition states of the Diels–Alder reaction, 1,5-sigmatropic shift, or the electrocyclization of 1,3,5-hexatriene are almost as strong as the ring current in benzene.[11,12] To describe the aromaticity of transition states, Zimmerman distinguishes between Hückel and Möbius topology. His idea is based on the theoretical work of Heilbronner, who predicted that annulenes with Möbius topology would be aromatic with 4*n* delocalized electrons.[13] Thus, the stereochemical rules for pericyclic reactions can be comprised in one sentence: Pericyclic reactions with aromatic transition states (Hückel 4*n* + 2, Möbius 4*n* delocalized electrons) are favored. Although ground state Möbius systems have been elusive until 2003,[14] a number of Möbius type transition states were known, such as the disrotatory electrocyclization of octatetraene[11,15] and the antarafacial 1,7-sigmatopic shift.[16]

■ RESULTS AND DISCUSSION

Coarctate Reactions. Unfortunately, the EDZ approach cannot be directly applied to coarctate reactions. The Hückel/Möbius electron count can only be applied to simple rings. In qualitative Hückel theory,[17] every individual atom involved in the delocalized system is represented by one basis orbital (one

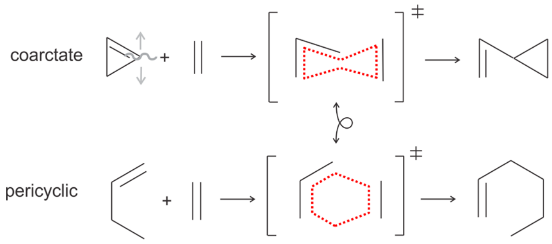

Figure 4. Formal topological equivalence of a coarctate reaction (addition of an olefin to cyclopropene) and a pericyclic reaction (ene reaction). The looped double arrow is the mathematical sign for a homeomorphous relationship (topological equivalence).

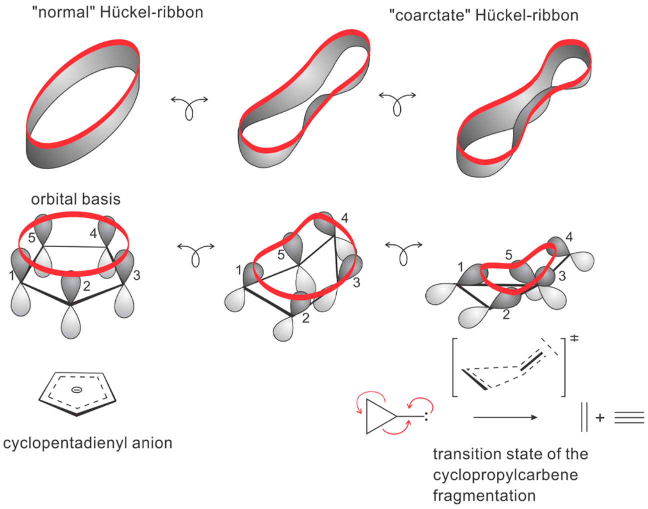

Figure 5. Coarctation (topological transformation) of Hückel systems. Top: general topological transformation of a Hückel ribbon. Bottom: topological transformation of the π system of cyclopentadienyl anion to the orbital basis of the delocalized system in the transition state of the cyclopropylcarbene fragmentation.

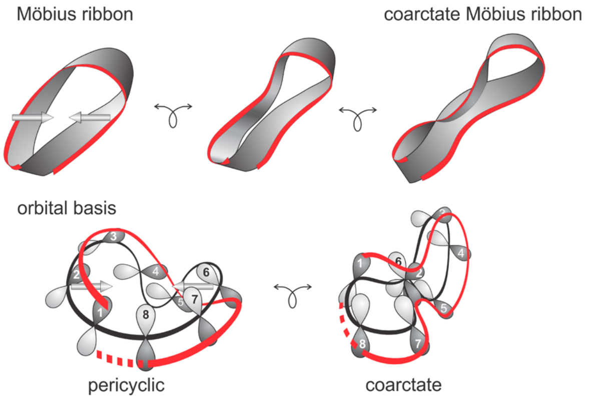

Figure 6. Coarctation (topological transformation) of Möbius systems. Top: coarctation of a Möbius ribbon. Bottom: coarctation of the basis orbitals in the transition state of the conrotatory ring closure of octatetraene. Note that basis orbitals 2 and 6 are orthogonal.

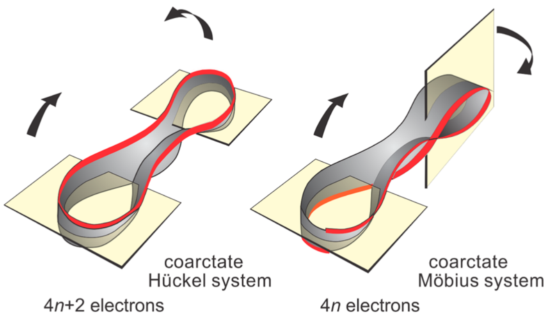

Figure 7. Stereochemistry in coarctate reactions and orientation of the terminator loops.

p orbital at each atom in ground state π systems but also s orbitals in transition states). In coarctate transition states, two orthogonal basis orbitals are needed to describe the simultaneous breaking and making of two bonds at each coarctate atom. At first glance, orbital overlap does not have the topology of a simple ring. However, we have shown that coarctate transition states are topologically equivalent (homeomorphous) to pericyclic transition states. Simple Hückel theory and the EDZ rules (which are derived from Hückel theory) are based on the topology of the basis orbitals involved in the delocalized system of electrons. Thus, topologically allowed (homeomorphic) transformations do not change qualitative predictions, such as aromaticity or antiaromaticity. After

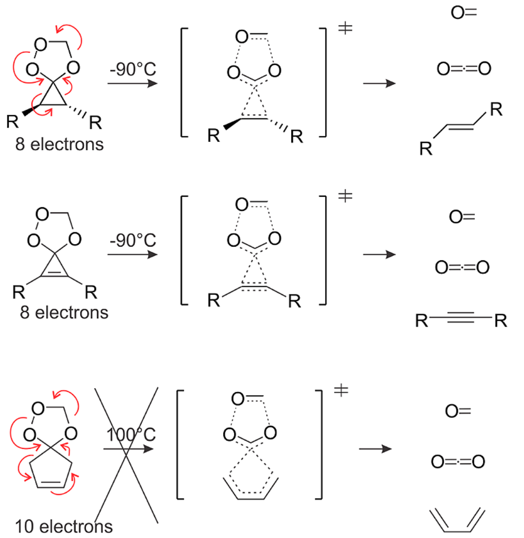

Figure 8. Spiroozonide fragmentation.

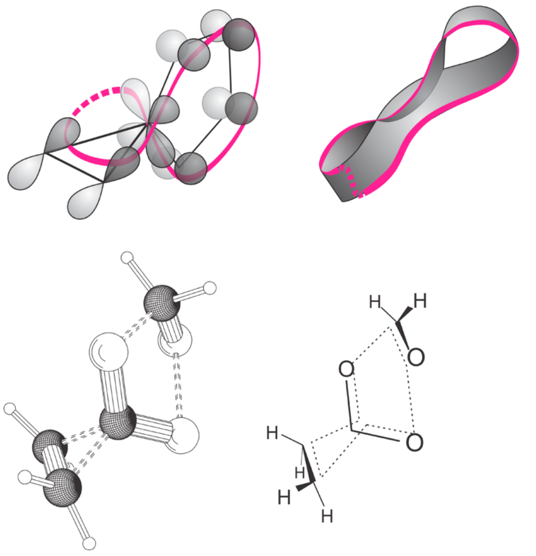

Figure 9. Coarctate Möbius transition state of the spiroozonide fragmentation. Top left: orbital basis of the transition state. Top right: generalized topological "ribbon" representation. Bottom left: calculated (B3LYP/6-31+G*) transition state geometry. Bottom right: structural formula.

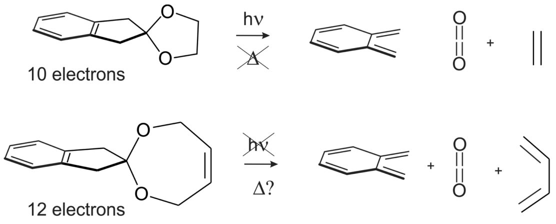

Figure 10. Indanone spiroketal fragmentation.

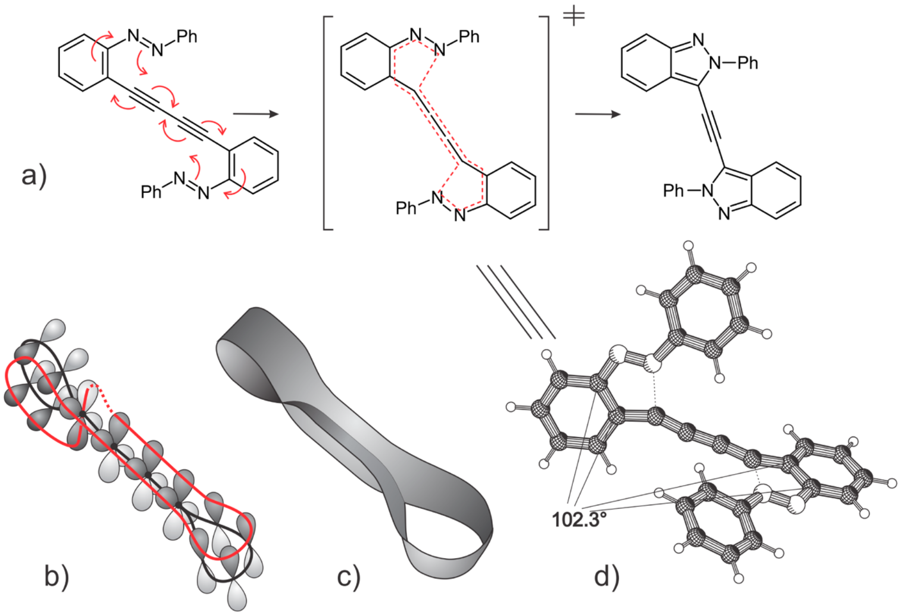

Figure 11. Coarctate (Möbius type) double cyclization: (a) reaction equation, (b) orbital basis of the transition state, (c) simplified ribbon representation of the transition state topology, (d) DFT (B3LYP/6-31G*)-optimized transition structure.

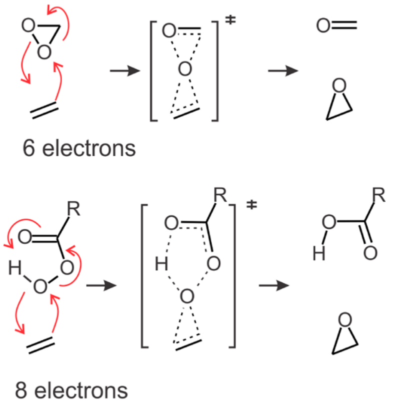

Figure 12. Pseudocoarctate epoxidation reactions.

topological transformation of a coarctate orbital basis to the corresponding pericyclic transition state, the Hückel/Möbius electron count of pericyclic reactions can still be applied. Figure 4 depicts the formal transformation of a coarctate reaction (olefin addition to the "edge" of a cyclopropene (please note that this is an experimentally known reaction)[18−20] to the corresponding pericyclic reaction (ene reaction).

Both reactions involve 6 electrons in a Hückel-type transition state and therefore are thermochemically allowed. There seems to be a complication at the coarctate atom. The system of delocalized electrons seems to have a bicyclic topology. However, the two basis orbitals at this atom are orthogonal, and there is no "shortcut" of the cyclic topology. This is shown in Figure 5 by exemplifying the topological transformation of the orbital basis of the cyclopropyl carbene fragmentation (again a known reaction) to the π system of a cyclopentadienyl anion (note that orbitals 3 and 5 are orthogonal).

The cyclopentadienyl anion is stabilized by aromaticity (6 delocalized π electrons; Figure 5, bottom left). Because the transition state of the cyclopropylcarbene fragmentation is topologically equivalent (Figure 5, bottom right), it should also be aromatic, and the reaction should be favored, which is

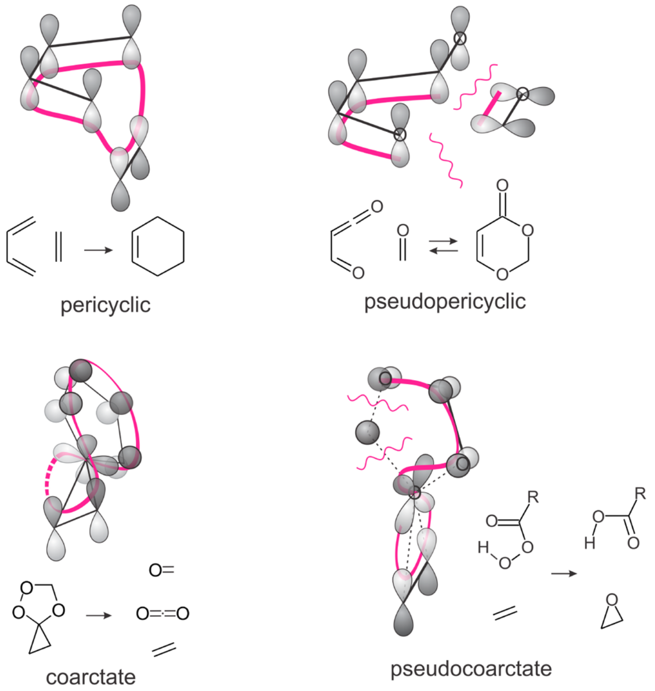

Figure 13. Examples of pericyclic (butadiene + ethylene), pseudopericyclic (formyl ketene + formaldehyde), coarctate (spiroozonide fragmentation), and pseudocoarctate reactions (expoxidation with peracids). There is a contiguous cyclic overlap of basis orbitals in the transition state of pericyclic and coarctate reactions. Their pseudo counterparts, however, exhibit disconnections (wavy lines) in the overlap of neighboring orbitals.

indeed the case. The coarctate fragmentation reaction proceeds readily at room temperature. Quantum chemical calculations predict a concerted mechanism, and the molecular orbitals that can be derived from the orbital basis (Figure 5, bottom right) are qualitatively equivalent with the MOs of the ab initio calculation.[1] Obviously, there is more than just a formal

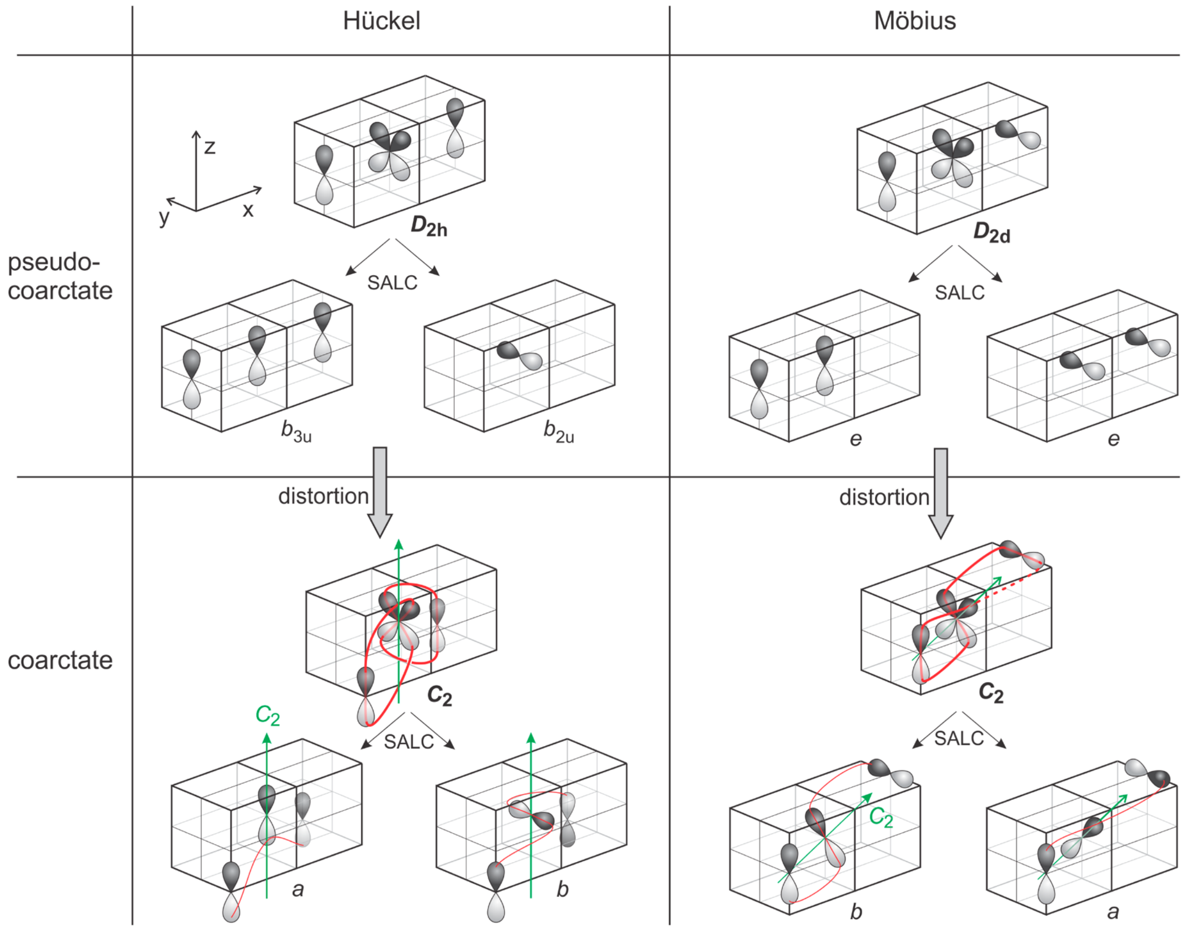

Figure 14. Group theoretical analysis of coarctate and pseudocoarctate Hückel and Möbius transition states. For the sake of simplicity, the smallest conceivable coarctate systems of each type are chosen (one coarctate atom and one atom in each loop), and only two of the four symmetry-adapted linear combinations (SALCs) are shown in each arrangement. The D_{2h} and D_{2d} arrangements (top) generate two independent and orthogonal π systems, whereas the C_2 orbital bases (bottom) cannot be separated into orthogonal subsystems. Orbital overlap is indicated with red lines.

relationship between aromatic π systems or aromatic pericyclic transition states and coarctate transition states.

By topological transformation (coarctation) of a Hückel ribbon, two loops are formed that are in the same plane (Figure 5, top right). Because there are a number of pericyclic reactions with Möbius-type transition states, it is interesting to apply the topological transformation to Möbius systems as well. Figure 6 shows the coarctation of a Möbius band (top) and the coarctation of a Möbius-type pericyclic transition state (conrotatory electrocyclic ring closure of octatetraene) (bottom). Interestingly, the two loops that are formed by coarctation are perpendicular with respect to each other.

On the basis of our topological analysis, we postulate the following rules:

(1) Coarctate reactions with $4n$+2 electrons (Hückel) exhibit coplanar loops.

(2) Coarctate reactions with $4n$ electrons (Möbius) exhibit orthogonal loops.

Figure 7 depicts these stereochemical rules for coarctate reactions.

It is important to note that a tilt or inclination of the loops with respect to each other is allowed without changing the validity of the rules (black arrows in Figure 7). A twist of the loops would be a topologically forbidden operation because it would transform Hückel and Möbius into each other. A simple electron count is sufficient to predict the stereochemistry (coplanar or orthogonal allowed). Electron counting can be performed as in pericyclic reactions by writing down the reaction mechanism with electron pushing arrows. For instance, the two reactions that serve as examples in Figures 4 and 5, the addition of olefins to cyclopropene, and the cyclopropyl carbene fragmentation have to be written with three electron pushing arrows (e.g., Figure 5, bottom). Each electron pushing arrow stands for two electrons. Thus, both reactions involve 6 electrons ($4n$ + 2); they have coarctate Hückel topology, and therefore, the loops are coplanar (slightly tilted, e.g., see Figure 5, bottom right). Quantum chemical calculations confirm these predictions. Other examples are the fragmentations of oxirane-substituted oxadiazolones. These reactions include two coarctate atoms and a three- and a five-membered terminator loop. Ten electrons ($4n$ + 2, Hückel) are involved in the transition state. The fragmentations only proceed if the two loops are fixed in a coplanar orientation by the molecular framework. Meanwhile, a large number of coarctate reactions were discovered. Several reactions have proven to be synthetically useful. The coarctate cyclization of various hetero analogues of 1-ethynyl-2-vinylbenzene are widely used for the synthesis of benzo-annelated heterocycles.[21−23]

Within the last two decades, we predicted and discovered several examples of reactions with coarctate Möbius transition states. We used spiro frameworks to fix the terminator loops in the orthogonal orientation. An impressive example of transition state stabilization by coarctate Möbius aromaticity is spiroozonide fragmentation. The reaction proceeds spontaneously at temperatures below −90 °C (Figure 8).[24,25]

A spiro carbon atom acts as the coarctate atom at which two bonds are made (the π bonds of carbon dioxide) and two bonds are broken (two cyclopropane or cyclopropene bonds). The spiro geometry of the reactant fixes the two terminator loops (three- and five-membered ring) in an orthogonal position and imposes a coarctate Möbius transition state (Figure 9). According to our coarctate stereochemical rules, the fragmentation should be thermochemically allowed if $4n$ electrons (four electron pushing arrows) are involved and forbidden if $4n + 2$ electrons are delocalized in the transition state.

This is in agreement with experimental findings. The fragmention of the spiroozonide of cyclopropanone and cyclopropenone (8 electrons) proceeds spontaneously at very low temperatures, whereas the spiroozonide of cyclopentenone does not react at temperatures up to 100 °C.[30] At higher temperatures or longer reaction times, cyclopent-3-ene-1-one (1,3-dipolar cycloreversion) is formed instead of the forbidden 10 electron coarctate fragmentation to butadiene, carbon dioxide, and formaldehyde (Figure 8, bottom). Density functional theory calculations (B3LYP/6-31+G*) confirm that the 8 electron fragmentation is a concerted reaction (transition structure, Figure 9). Note that the loops (3- and 5-ring) are orthogonal but tilted. The DFT calculations predict a very low activation barrier of only 11.3 kcal mol^{-1}, which is in agreement with the low reaction temperature.

The Woodward−Hoffmann rules state that thermochemical and photochemical pericyclic reactions follow converse stereochemical pathways. This is also the case for coarctate reactions. The fragmentation of indanone spiroketals is isoelectronic to the cyclopentene ozonide. With 10 electrons, it should be thermochemically forbidden but photochemically allowed (Figure 10).

The photochemically (254 nm)-induced fragmentation of indanone 5-ring spiroketal (Figure 10, top) is a very clean reaction.[26] Thermochemical activation by flash vacuum pyrolysis yields a plethora of products. The 7-ring ketal (Figure 10, bottom) upon irradiation does not fragmentate to the products expected from a coarctate reaction. Thus, the experimental observations are in agreement with the coarctate rules.

Coarctate reactions can include a very large system of delocalized electrons in the transition state. During the double ring closure of the diyne-linked bis-azobenzene (Figure 11), 16 bonds are made and broken simultaneously. At first glance, the reaction looks unexpected because azobenzenes are usually very stable compounds. Nevertheless, the reaction proceeds spontaneously at room temperature.[27] Calculations (B3LYP/6-31G*) predict a concerted reaction mechanism with a low lying transition state ($\Delta H^{\ddagger}$ = 14.3 kcal mol^{-1}). The calculated transition structure exhibits orthogonal terminator loops, which is in agreement with a 16 electron ($4n$) coarctate Möbius transition state.

Pseudocoarctate Reactions. Most of the experimentally known reactions comply with the coarctate rules. However, there are exceptions. Formal coarctate reactions in which the coarctate atoms are heteroatoms, such as the epoxidation of olefins with dioxirane or peracids, do not exhibit a clear preference for the orientation of the terminator loops.[28] Both oxygen transfer reactions are known to proceed via concerted mechanisms ("butterfly transition structure") with terminator loops that are orthogonal, and there is only a small energy difference between orthogonal and planar orientation (Figure 12). This is in contradiction with the coarctate rules. The dioxirane epoxidation includes 6 electrons and should be coplanar. The peracid epoxidation is in formal agreement with the coarctate rules, however, the orbital basis cannot be written with a cyclic orbital overlap because the O−H bonds are orthogonal with respect to the C−O bonds that are made and broken. Therefore, the agreement of the transition state structure with the coarctate rules is fortuitous.

Obviously, there is an analogy to pseudopericyclic reactions. We therefore coin these formal coarctate reactions "pseudocoarctate" reactions. The term pseudopericyclic was introduced by Lemal 40 years ago.[29] Since then, these reactions have been thoroughly investigated. Numerous examples have been found,[30−38] and theoretical methods were developed to distinguish between true pericyclic and pseudopericyclic reactions.[39−46] Pericyclic reactions, by definition, include a cyclic system of delocalized electrons. Pseudopericyclic reactions exhibit one or more interruptions (disconnections) in the cyclic overlap of electrons. Orbitals that are involved in bond making and breaking are orthogonal with respect to each other. The Diels−Alder type cycloaddition (cycloreversion) of formaldehyde with formylketene is an illustrative example of a pseudopericyclic reaction[47] (Figure 13, right). The π planes of the two reacting components are orthogonal. Pseudopericylic reactions often have low energy transition states and do not necessarily follow the Woodward−Hoffmann rules (which require a cyclic system of delocalized electrons in the transition state). Similar principles hold for pseudocoarctate reactions. They exhibit disconnections in the orbital overlap in the transition state. A prominent example of a pseudocoarctate reaction is the epoxidation of olefins with peracids[35] (Figure 13, bottom right). The s orbital of the hydrogen atom, which is transferred during the reaction, is orthogonal to the remaining orbitals. The topology of orbital overlap, therefore, is not cyclic, and the coarctate rules do not apply (the agreement in this case is fortuitous).

As in pericyclic reactions, it depends on the geometry of the transition state whether a "formal" coarctate reaction is "truly" coarctate or pseudocoarctate. A straightforward and rigorous method to distinguish coarctate and pseudocoarctate transition states is group theory. The smallest conceivable coarctate system includes one coarctate atom (with two orthogonal basis orbitals) and one atom in each terminator loop (one basis orbital at each atom, Figure 14). The highest symmetry such an arrangement of four orbitals can attain in Hückel topology is D_{2h} and D_{2d} in Möbius topology (Figure 14, top). Note that the rotation of the set of two orthogonal orbitals at the coarctate atom around the long C_2 axis (x axis) is arbitrary. In Figure 14, an orientation of 45° with respect to the xy and xz plane is chosen.

The four basis (atomic) orbitals generate four molecular orbitals (MOs). For the sake of simplicity, only the two lowest MOs (with lowest number of nodes) are shown in Figure 14. The D_{2h} arrangement of orbitals (Figure 14, top left) generates two MOs that transform as the b_{3u} and b_{2u} irreducible representation of the D_{2h} point group. They represent two independent and orthogonal π systems. Hence, a representation of the orbital basis can be chosen that exhibits disconnections in the cyclic overlap similar to pseudopericyclic reactions. We therefore term these reactions pseudocoarctate. A similar separation in orthogonal π systems can be performed with the D_{2d} orbital basis (Figure 14 top, right), which leads to the conclusion that reactions with this transition structure geometry are also pseudocoarctate. The situation changes if the D_{2h} and D_{2d} orbital sets are distorted toward C_2 symmetry (Figure 14, bottom). The corresponding orbital bases cannot be separated into independent orthogonal subsystems. The topology of overlap in the orbital basis (not necessarily in the MOs!) is cyclic (the next neighbor overlaps are indicated with red lines). The corresponding reactions are therefore "truly" coarctate. Analogous symmetry analyses can be performed with larger coarctate systems. For instance, a coarctate transition state with two atoms in each loop can be converted from pseudocoarctate to coarctate if the D_{2h} or D_{2d} arrangement is distorted to C_{2v} or C_{2h} or a lower symmetry. There is an additional analogy to (pseudo)pericyclic reactions. Formal coarctate reactions are often pseudocoarctate if heteroatoms are involved in the making or breaking of a single bond (e.g., cyclization or cycloaddition; see Figure 13). The majority of the known systems are distorted from D_{2h} or D_{2d} to a lower symmetry (e.g., spiroozonide fragmentation, transition structure; see Figure 9). The coarctate rules are valid if the planes of the terminator loops are tilted from a strict coplanarity or orthogonal arrangement, as shown in Figure 7.

CONCLUSIONS

Coarctate reactions are an important and distinct class of concerted reactions. Stereochemical rules can be derived using the Hückel–Möbius method, which had been applied to pericyclic reactions. Similar to pseudopericyclic reactions, pseudocoarctate reactions exist that exhibit disconnections in the cyclic overlap of orbitals in the transition state. Coarctate reactions are not yet thoroughly investigated even though several synthetically powerful methods are based on coarctate processes. They probably often are overlooked because, written down with electron pushing arrows, the mechanisms sometimes look counterintuitive. However, insight into the formal relationships and mechanistic details might lead to a better understanding of the known and the discovery of further examples of coarctate reactions.

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Notes

The authors declare no competing financial interest.

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