I: Quantum Mechanical Investigations of Reactions Involved in Natural Products & Organic Materials Formation. II: Synthetic and Theoretical Studies of the Formation and Dynamic Properties of Mechanically Interlocked Molecules.

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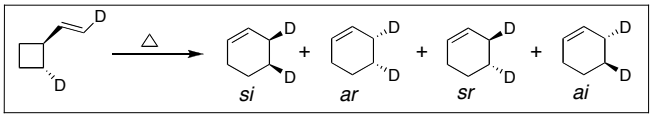
Abstract. Many of the classic and contemporary problems of interest to physical organic chemists require a thorough understanding of 1) the dynamic motions that can dramatically influence both the structure and reactivity of individual molecules, and 2) the subtle but endlessly important noncovalent interactions that play a large role in how molecules interact with each other (intramolecular) as well as with themselves (intermolecular). My PhD. research has focused on using both theoretical and experimental methods to investigate the dynamics and noncovalent interactions that influence and largely dictate the behavior and properties of: small hydrocarbons, dimeric pyrrole-imidazole alkaloids, oligoacenes, bistable rotaxane-based molecular switches, and mechanically interlocked structures possessing complex molecular architectures. The results of these studies have implications in the nature of diradical rearrangements, the formation of natural products, the development of organic materials, the design and function of molecular machines, and the facile construction of highly complex molecular structures reminiscent of those found in nature.

I. [1,3] Sigmatropic Rearrangements of Vinylcyclobutanes.

Though studied for well over 40 years,[1] classical sigmatropic rearrangements such as the [1,3] rearrangement of vinylcyclobutane to cyclohexene[2] continue to be of interest to physical organic chemists on account of their "stereochemical ambiguity." A concerted mechanism, in accordance with orbital symmetry rules,[3] would predict formation of the symmetry allowed products (suprafacial with inversion, *si*, and antarafacial with retention, *ar*) while a fully equilibrated diradical mechanism would predict a statistical mixture of all four possible product stereochemistries (*si*, *ar*, *ai*, *sr*). Experimental studies of a variety of substituted vinylcyclobutanes[4] have consistently shown that neither a concerted nor equilibrated diradical mechanism can account for product stereochemistries, though there is often a preference for the Woodward-Hoffmann allowed products.



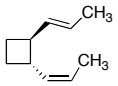
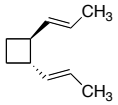
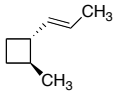
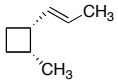
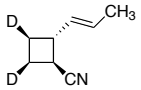
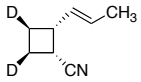
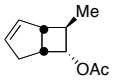
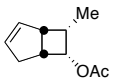
		W.-H. Allowed		W.-H. Forbidden		
		si	*ar*	*sr*	*ai*	(*si*+*ar*)/(*sr*+*ai*)
a)		49 %	3 %	48 %	0 %	1.1
b)		50 %	6 %	41 %	3 %	1.3
c)		58 %	5 %	33 %	4 %	1.7
d)		18 %	11 %	51 %	20 %	0.4
e)		48 %	20 %	27 %	6 %	2.1
f)		13 %	5 %	66 %	16 %	0.2
g)			(*si/sr*) > 9.3			
h)			(*si/sr*) < 0.14			

Table 1. The thermally-promoted [1,3] sigmatropic rearrangement of vinylcyclobutane to cyclohexene can proceed suprafacially (*s*) or antarafacially (*a*) with either inversion (*i*) or retention (*r*) at the migrating carbon, giving rise to four potential product stereochemistries: *si*, *ar*, *sr*, and *ar*. Product distributions and Woodward-Hoffmann "allowed" vs. "forbidden" ratios for rearrangements of a variety of substituted vinylcyclobutane derivatives to substituted cyclohexenes are given.

To gain valuable insight into the mechanism, high-level density functional theory (DFT) and complete active space (CAS) calculations were performed.[5] Computations reveal that the

rearrangement proceeds via short-lived diradical intermediates traversing very flat potential energy surfaces with no minima greater than RT. The lifetimes of these diradicals are on the order of molecular vibrations[6] and the dynamics of bond rotations on flat potential energy surfaces have significant influence on product distributions. The initial trajectories of bond rotations, rather than the total available energy, have the greatest effect on product stereochemistries. The favored pathway for rearrangement is suprafacial with inversion of configuration, but there exist additional stationary points on the computed potential energy surface only slightly higher in energy than the lowest energy pathway. Deviations from the *si* path via these higher energy stationary points explain the experimentally observed stereochemical mix of products. A small preference for the Woodward-Hoffmann[3] "allowed" products arises from orbital interactions that govern the vinylcyclobutane ring opening, but not to an aromatic transition state of a conventional concerted perycyclic process. These orbital interactions and the dynamic motions of diradical species moving along the flat potential surface before ring closure govern the observed stereochemical preferences.[5]

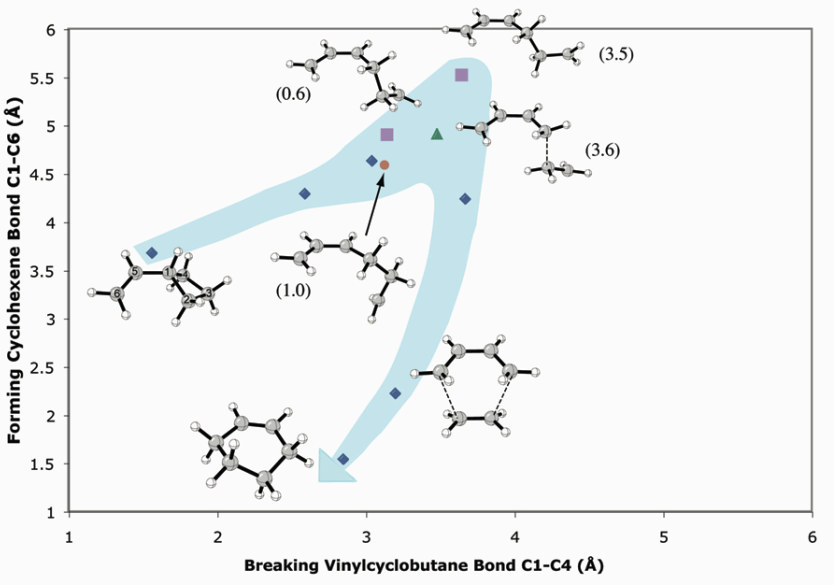
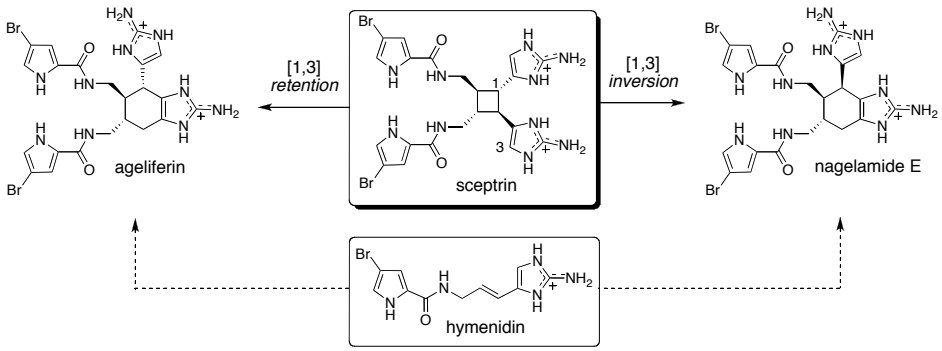


Figure 1. Reaction coordinate for the stepwise diradical *si* rearrangement (◆) of vinylcyclobutane plotted as the lengths of the breaking cyclobutane bond versus the forming cyclohexene bond. Some of the stationary points that are only slightly higher energy than the favored *si* pathway and can account for observed product stereochemistry distributions are also shown (● leads to *sr*, ■ leads to *ar*, ■ + ● lead to *ai*, and ▲ leads to fragmentation to butadiene plus ethylene).

Similar studies were used to determine the mechanism of the recently observed[7] rearrangement of sceptrin to ageliferin and nagelamide E. The reigning biosynthetic hypothesis[8] had been that the antiviral compounds ageliferin and nagelamide E were formed from two equivalents of hymenidin through an enzymatic "Diels-Alderase," though the observation of their formation from sceptrin suggested a vinylcyclobutane[2,4] rearrangement. A thorough investigation[9] of multiple



Scheme 1. Solid arrows: The vinylcyclobutane rearrangements of sceptrin to ageliferin and nagelamide E. Dashed arrows: Hymenidin as a possible precursor to alkaloids ageliferin and nagelamide E by an enzymatic "Diels– Alderase".

mechanistic pathways[10] originating from sceptrin was undertaken to understand the mechanism and to explain the 20:1 preference for formation of ageliferin, which is the symmetry forbidden[3] [1*r*,3*s*] product. DFT calculations demonstrate[9] that sceptrin does rearrange via a diradical mechanism. Hydrogen-bonding interactions present in the 6-*endo-trig* ring-closing transition state favor the formation ageliferin over nagelamide E with a computationally predicted ratio of 22:1. This first observation of a vinylcyclobutane rearrangement of a natural product suggests the possible involvement of a similar process in the biosynthesis of these compounds.

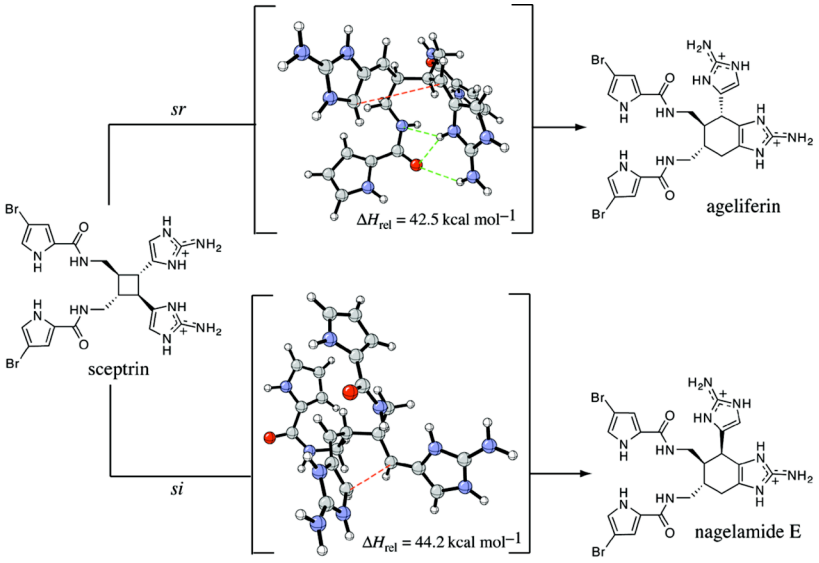
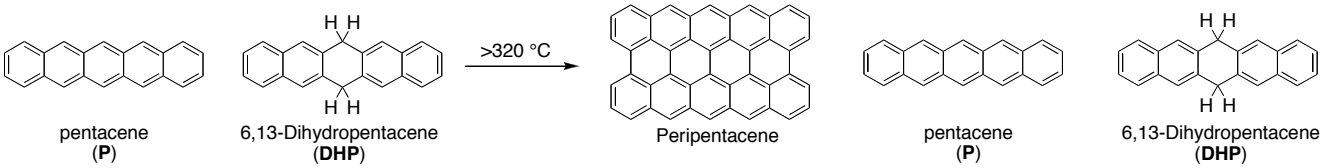


Figure 2. Computed ring-closing transition states leading to ageliferin and nagelamide E. Hydrogen-bonding interactions are highlighted by dashed green lines while dashed red lines indicate the formation of covalent bonds. Computations predict that the transition state leading to ageliferin is 1.7 kcal/mol more stable than that leading to nagelamide E, thus predicting the formation of ageliferin to be preferred to nagelamide E by a ratio of 22:1. The experimentally observed ratio is 20:1.

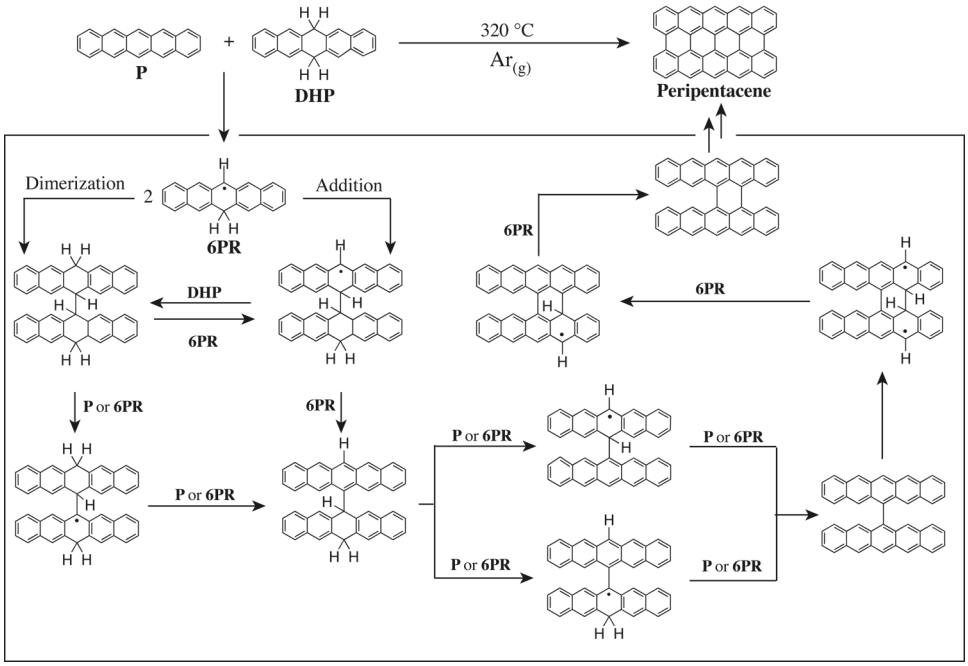
II. On the Mechanism of Peripentacene Formation from Vacuum Sublimation of Pentacene.

There is currently a great deal of interest in the development of organic semiconductors[11] for use in advanced electronic applications[12] such as organic field-effect transistors[13] (OFETs). Pentacene and pentacene derivatives[14] have shown much promise in these endeavors on account of their notable



Scheme 2. The experimentally observed formation of peripentacene along with additional 6,13-dihydropentacene (**DHP**) during high temperature (>300 °C) vacuum sublimation of pentacene in the presence of trace amounts of **DHP**.

semiconducting properties. The purity of pentacene used in organic materials applications can dramatically affect device performance.[15] Recently, Roberson et al. observed[16] that purification of pentacene by vacuum sublimation at temperatures above 320 °C results in the formation of peripentacene – a nanographene[17] – and the process is catalyzed by trace amounts of 6,13-dihydropentacene (**DHP**) present in commercially available pentacene.



Scheme 3. Schematic summary of the many competing H-atom transfer process that can account for the autocatalytic formation of peripentacene from pentacene resulting from reactions between pentacene (**P**), 6,13-dihydropentacene (**DHP**), 6-pentacenyl radical (**6PR**), and dimeric open and closed shell pentacenyl intermediates.

To explain peripentacene formation, a systematic DFT study of the myriad intermolecular hydrogen-atom transfers that may occur between **DHP**, pentacene, and subsequent dimeric pentacenyl intermediates was undertaken.[18] Reaction parameters for hundreds of potential mechanistic pathways were computed and subsequently evaluated with kinetic analysis. From the many possibilities, thirty-five competing reaction pathways were identified that can account for the

formation of peripentacene from pentacene and **DHP**. These results are important not only to the development of pentacene-based materials but to a greater understanding of intermolecular hydrogen-atom transfer processes[19] and the formation of graphenes.[17]

III. Single-Molecule Force Spectroscopy of Synthetic Molecular Motors.

The development of functional molecular machines[20] is a tremendously active area of chemical research. Toward this aim, a number of mechanically interlocked molecular switches[21] have been developed. Switchable, bistable [2]rotaxanes have been likened to linear motors as a result of their ability to undergo redox-controlled mechanical switching wherein the position of a macrocyclic ring can be externally controlled to encircle different recognition sites of a dumbbell-shaped molecule.[21] To demonstrate their potential to do work, self-assembled monolayers of palindromic [3]rotaxane linear motor molecules were shown[22] to be capable of reversibly bending gold-coated cantilevers five orders of magnitude larger than themselves.

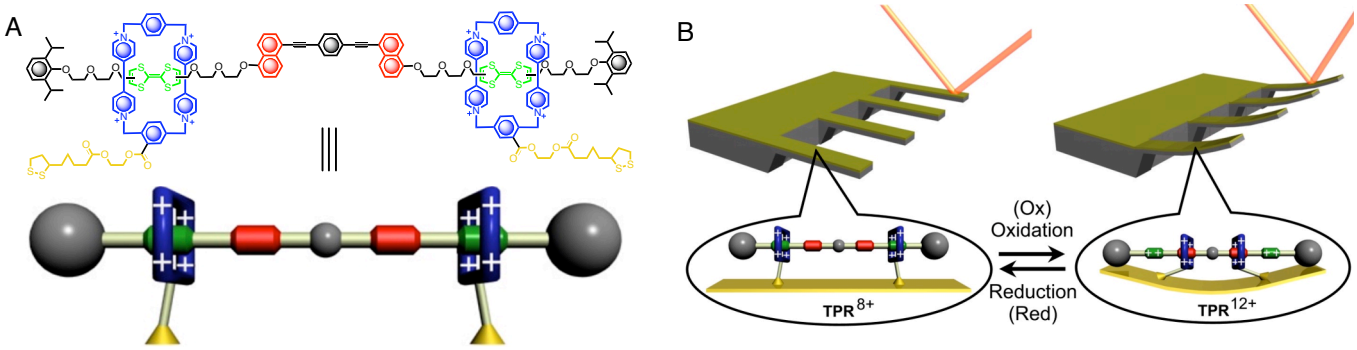


Figure 2. (A) Molecular structure and schematic representation of a palindromic [3]rotaxane molecular muscle capable of reversible, redox-controlled expansion and contraction. (B) Schematic representation of the reversible bending of gold-coated cantilever beams by the collective motions of billions of [3]rotaxane molecular motors.

Additional insight into the capabilities of switchable rotaxanes was then gained through force spectroscopy studies aimed at measuring the energetics of mechanical switching at the single-molecule level.[23] Force measurements were performed by first selectively attaching one end of a specially designed switchable [2]rotaxane to a silica surface and then attaching a gold-coated atomic force spectroscopy tip to it's mobile ring. In conjunction with molecular force field modeling, experiments performed both in the presence and absence of a chemical oxidant allowed for the

repulsive forces that drive mechanical switching to be evaluated. The results, supported by *ab initio* computations, indicate that the energy available[23] to these synthetic [2]rotaxane motor molecules exceeds that available to biomolecular motors[24] by >4.5 times. This study represents the first time the repulsive forces dictating the mechanical switching process in these functional linear motor molecules have been evaluated and further demonstrates their potential to be active components of functional molecular machines.

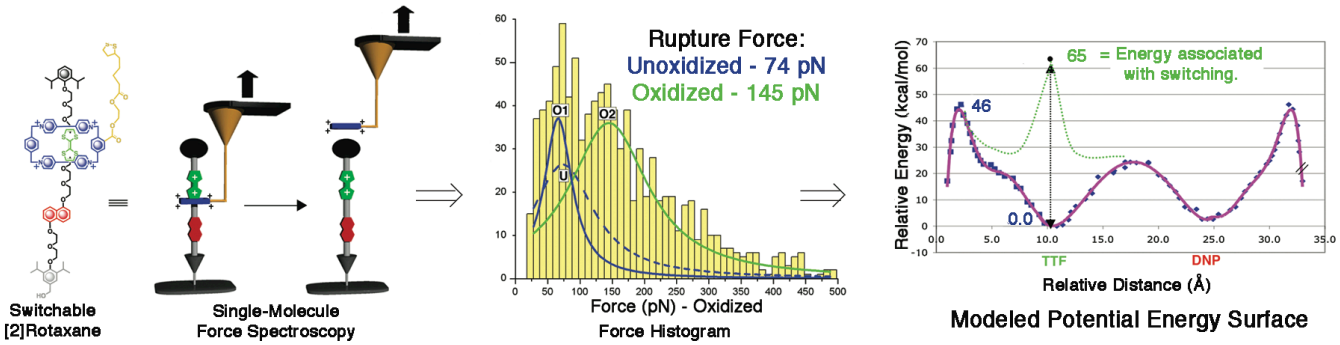
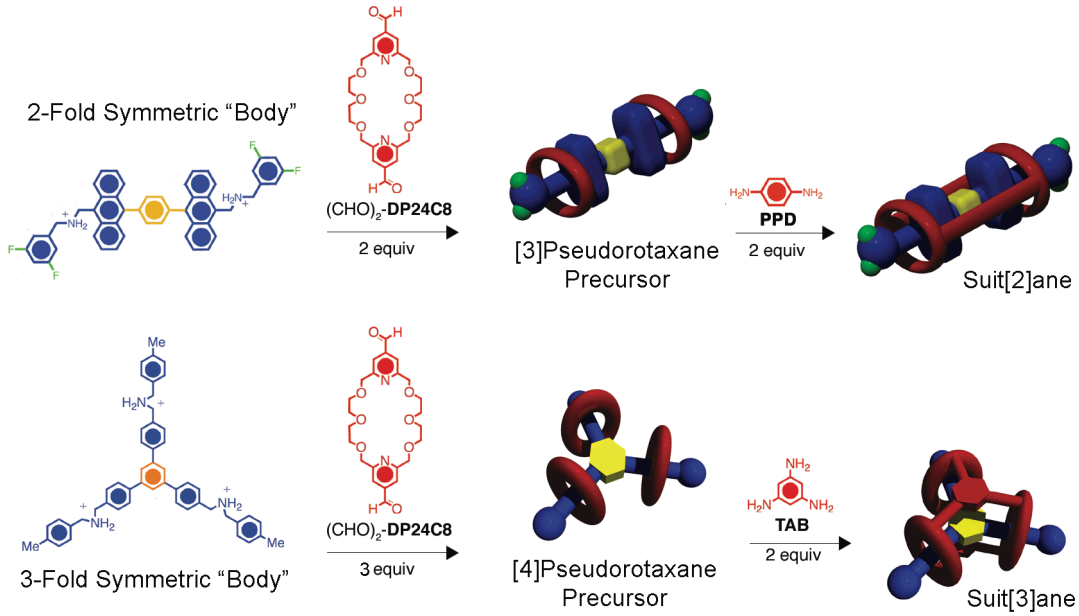


Figure 3. Schematic overview of the multidisciplinary approach – combining synthesis, surface chemistry, force spectroscopy, and computational chemistry – used to quantify, at the single-molecule level, the electrostatic repulsion that drives redox-controlled mechanical switching of bistable [2]rotaxanes.

IV. Introducing "Suitanes" – A New Class of Mechanically Interlocked Molecules.

The development of artificial systems reminiscent of those found in nature requires innovative methods of synthesizing architecturally complex molecules. Self-assembly[25] and dynamic chemistry[26] have emerged as two powerful tools for doing just that. By combining dialkylammonium-crown ether binding[27] with dynamic covalent imine bond formation,[26b] an entirely new class of mechanically interlocked molecules – "Suitanes" – has been developed.[28,29] Suitanes are formed when a rigid "body" with two or more protruding limbs is wrapped-up in a close-fitting all-in-one "suit." The construction of these complex molecular architectures takes advantage of the strong host-guest interactions that hold two[28] or three[29] formyl-substituted crown ethers onto the dialkylammonium limbs of the body, followed by stitching together of the formyl groups with two or three-fold symmetric aromatic amines. Arriving at these interlocked architectures through entirely covalent means would be an incredible challenge, and the ease with which these suitanes can be synthesized reflects the



Scheme 5. Molecular structure of two and three-fold symmetric dialkylammonium "bodies," dipyrido[24]crown-8 macrocycles ($(CHO)_2$-**DP24C8**), and *p*-phenylenediamene (**PPD**) and 1,3,5-triaminobenzene (**TAB**) linkers used in the self-assembly and dynamic covalent construction of new mechanically interlocked suit[2]ane and suit[3]ane molecules.

power of combining self-assembly[25] and dynamic covalent chemistry.[26] Being able to synthesize a molecule within a molecule through noncovalent self-assembly is a prelude to the synthesis of artificial systems similar to the living cell.

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