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Massimo D. Bezoari
bezoarim@nsula.edu

Carly Bourgeois
cbourgeois008959@nsula.edu

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Conformational Analysis of Selected [2.2]Heterophanes: A Comparison of Stereochemical Switching Via Computational Chemistry

Massimo D. Bezoari, PhD
Northwestern State University, bezoarim@nsula.edu

Carly Bourgeois
Northwestern State University, cbourgeois008959@nsula.edu

Abstract

Conformational switching of selected [2.2]heterophanes was investigated by computational chemistry. Analyses were carried out by various methods, including Conformational Search in HyperChem, and forced conformational transformations with Energy Profile in Spartan. Stable *anti* and *syn* conformers arising from flipping of aromatic rings within the molecules were observed. The activation energies of the ring flipping process, as well as dipole moments and directions, were obtained by molecular mechanics. The present work shows that simple computational techniques can be employed to screen certain compounds as potential candidates for molecular machinery. Thus, heterophanes demonstrated reversible shifts between two or more configurations which are energetically stable and have different electronic properties, constituting a basic requirement for possible applications as molecular switches.

Keywords

[2.2]Heterophanes, Conformational Search, Molecular Switches, Ring Flipping, HyperChem

Peer Review

This work has undergone a double-blind review by a minimum of two faculty members from institutions of higher learning from around the world. The faculty reviewers have expertise in disciplines closely related to those represented by this work. If possible, the work was also reviewed by undergraduates in collaboration with the faculty reviewers.

Acknowledgments

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Introduction

Since the early 20th century, phane compounds have gained attention for their synthetic challenge, unusual properties (such as aromatic rings that deviate from planarity due to strain), ring current effects, and other transannular interactions that could give rise to charge transfer, and organic conductors (Cram, 1983). Recent reviews demonstrate unabated interest in phane synthesis (Kotha, Shirbate, and Waghule, 2015), as well as known and potential applications in molecular motors, molecular switches, and medicine (Modern Cyclophane Chemistry, 2004; Feringa and Browne, 2011; Zhang *et al.*, 2015).

A phane is a compound having one or more aromatic rings with one or more groups of atoms bridging the rings. In common naming, the term “cyclophane” implies that benzene constitutes at least one of the aromatic rings. The positions of substitution of benzene rings are indicated by the prefixes “ortho,” “meta,” and “para.” Phanes with heteroaromatic rings are called heterophanes, with the prefix “hetero” supplanted by designation of the heteroaromatic ring. Five-membered aromatic rings (e.g. furan, pyrrole, and thiophene) are termed \square -*excessive* due to delocalization of lone pairs of the heteroatoms into the overlapping p-orbital system of the rings, activating them relative to benzene. Benzene is \square -*deficient* relative to non-delocalized \square systems. The number of bridges and the number of atoms in the bridge backbones are indicated in square brackets; the locations of substitution of the aromatic rings are given in rounded parentheses. Thus, [2.2](2,5)furanophane (Figure 1) is a \square -excessive heterophane containing two furan rings, with two bridges, each containing two main-chain carbon atoms, the bridges being bonded at C-2 and C-5 of the furan rings (Smith, 1964). The Systematic naming method (Commission on Nomenclature of Organic Chemistry, 1998) is not used in the present work.

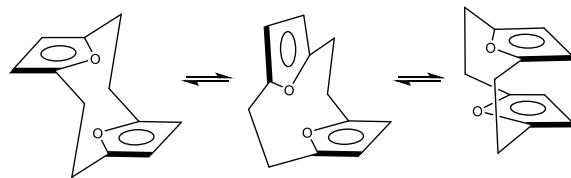
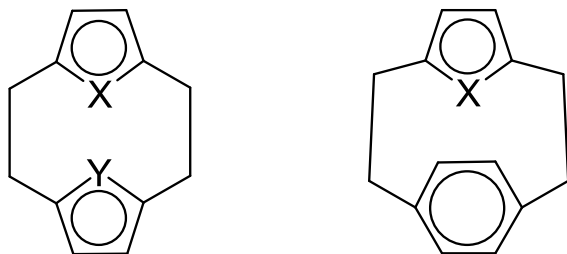


Figure 1. [2.2](2,5)Furanophane Ring Flipping. The *anti* stereoisomer (left structure, with heteroatoms oriented in opposite directions) ring flips to the *syn* stereoisomer (right structure, with heteroatoms oriented in the same direction).

The relative stereochemical directionality of aromatic rings in phanes raises the possibility of molecular switching via ring flips (Figure 1). Ring flipping can be caused by temperature and, perhaps, by other sources of energy that can overcome torsional strain from the bridging methylene groups which rotate as the ring flip occurs, as well as steric hindrance within the cavity of the structure as atoms pass through it (Smith, 1964). A ring flip of [2.2]heterophanes [1]-[10] (Figure 2) will generate two stereoisomers if both rings within the phane are heteroaromatic: the *anti* isomer, having the heteroatoms oriented in opposite directions and the *syn* isomer, having the heteroatoms oriented in the same direction. If either of the rings is symmetrical, as with paracyclophanes [8]-[10] (Figure 2), ring flipping generates identical structures.

The ability of a molecule to change orientation in response to a stimulus satisfies a fundamental requirement of molecular switches (Zhang *et al.*, 2015). Changes in conformation can affect physical properties, such as the dipole moment, promoting the possibility of electronic applications in molecular machinery. The Nobel Prize in Chemistry (2016) was awarded to Stoddart, Sauvage, and Feringa for developments in the field of molecular machines (Feringa, 2017).

The present work describes computational conformational analyses of selected [2.2]phanes (Figure 2). This approach constitutes a simple screening of potential candidates for molecular switches and molecular machinery in general.



- | | |
|---------------------|--------------|
| [1], X = Y = O | [8], X = O |
| [2], X = O, Y = S | [9], X = S |
| [3], X = O, Y = NH | [10], X = NH |
| [4], X = O, Y = NMe | |
| [5], X = S, Y = S | |
| [6], X = Y = NH | |
| [7], X = Y = NMe | |

Figure 2. Selected [2.2]Heterophanes.

The heterophanes that were analyzed include π -excessive Group VI heterophanes (i.e., containing furan, and thiophene) and Group V heterophanes (i.e., containing pyrrole or N-methylpyrrole) [1]-[7], as well as mixed system π -excessive/ π -deficient paracyclophanes [8]-[10].

Initial *anti* or *syn* conformers for phanes are easily constructed in molecular modeling software such as Hyperchem or Spartan as the software permits three-dimensional drawing of molecules, bonds, and bond angles. Thus, an *anti* isomer is drawn by rotating the structure as bonds are added, in order to point the heteroatoms of the constituent rings in opposite directions. The initial structure can then be optimized using various computational approaches. The resulting structure is shown by the computer software and can be examined further.

Geometry optimization is the manipulation of a molecule's 3-dimensional components to obtain the structure corresponding to the energy minimum (Slayden, 2016). The lower total energies indicate the most stable conformers. In molecular mechanics methods, the energy is calculated using classical physics theory and examines changes in the energy and geometry

of a molecule as the atoms are moved to different locations. It treats atoms as spheres and the bonds linking atoms as elastic springs (HyperChem, 2016). The program moves atoms so that bonds between atoms are stretched, compressed, bent, and twisted, changing the energy of the resulting conformation. A simple formula to explain the calculation of a molecule's energy using molecular mechanics is

$$E_{\text{total}} = E_{\text{bond}} + E_{\text{bond angle}} + E_{\text{stretch-bend}} + E_{\text{oop}} + E_{\text{torsion}} + E_{\text{van der Waals}} + E_{\text{electrostatic}}$$

in which E_{bond} is the energy of a bond as the atoms are moved linearly from the expected equilibrium internuclear distance of the bond, determined from experimental measurements of many such bonds. The classical physics Hooke's Law expression for one such bond, between atoms i and j , is

$$E_{\text{bond}} = \frac{1}{2} K_{s,ij} (r_{ij} - r_o)^2$$

in which $k_{s,ij}$ is the stretching force constant for the bond, r_{ij} is the distance between the two atoms, and r_o is the expected internuclear distance. $E_{\text{bond angle}}$ is the energy required to bend a bond from its equilibrium angle, θ_o . Again, this is modeled by a spring, and the energy is calculated using the expression

$$E_{\text{bond angle}} = \frac{1}{2} K_{b,ijk} (\theta_{ijk} - \theta_o)^2$$

in which $K_{b,ijk}$ is the typical bending force constant for atoms i , j , and k , and θ_{ijk} is the bond angle being tested. $E_{\text{stretch-bend}}$ is the stretch-bend interaction energy that calculates the effect of bond angle bending on the bond lengths of the two associated bonds. The expression that calculates the energy of this interaction is

$$E_{\text{stretch-bend}} = K_{sb,ijk} (r_{ij} - r_o) (\theta_{ijk} - \theta_o)$$

in which $K_{sb,ijk}$ is the stretch-bend force for the bond between atoms i and j with the bend between atoms i , j , and k . E_{oop} (where "oop" means "out-of-plane") is the energy required to deform a planar group of atoms from its equilibrium angle of co-planarity, ω_o , usually equal to zero. This force field term is for sp^2 hybridized atoms such as doubly bonded

carbon atoms, and small ring systems. This can be modeled by a spring and the Hookian expression to calculate the energy is

$$E_{oop} = K_{o,ijkl} (\omega_{ijkl} - \omega_o)^2$$

in which $K_{o,ijkl}$ is the bending force constant and ω_{ijkl} is the planarity angle being tested. $E_{torsion}$ is the energy needed to rotate groups about bonds. Torsional energies are usually important only for single bonds because double and triple bonds are too rigid to permit rotation. The expression used to model torsional energy is

$$E_{torsion} = \frac{1}{2} K_{tor,1} (1 + \cos \varphi) + \frac{1}{2} K_{tor,2} (1 + \cos 2 \varphi) + \frac{1}{2} K_{tor,3} (1 + \cos 3 \varphi)$$

in which φ is the dihedral angle about the bond. The constants K are the various torsional constants that relate to the types of bonds being tested. $E_{van\ der\ Waals}$ calculates the energy of interaction of two non-bonded atoms. One form of the expression for the van der Waals energy is

$$E_{van\ der\ Waals} = A/r_{ij}^{12} - B/r_{ij}^6$$

in which A and B are constants that depend on the identities of the two atoms involved and r_{ij} is the distance separating the two nuclei. (This energy is also called the Lennard-Jones potential.) Electrostatic interactions between atoms with partial electrostatic charges (i.e., those in polar bonds) are calculated by $E_{electrostatic}$. A simple electrostatic calculation expression for two atoms is

$$E_{electrostatic} = q_i q_j / \epsilon r_{ij}$$

in which q_i and q_j are the partial atomic charges for atoms i and j separated by a distance r_{ij} , and ϵ is the relative dielectric constant.

The set of constants and parameters used in a molecular mechanics calculation is called a *force field*. Force fields employed in different software may emphasize more greatly or may neglect some intramolecular interactions that contribute to the various energy terms. For example, the MM+ force field differs from AMBER in that it does not include an explicit term to evaluate the contribution of hydrogen bonds to a molecular

structure—in general, hydrogen bond contributions are implicit in the electrostatic energy terms. Each term in a force field may contain additional variables and parameters that account for perturbations and limitations to the basic expressions described above or may use a different term or set of terms to evaluate the same parameter.

Unlike molecular mechanics, quantum mechanical methods involve solving the Schrödinger equation

$$\hat{H} \Psi = E \Psi$$

in which the Hamiltonian \hat{H} , the input, defines every particle of every atom of the system in terms of all the contributions to the energies of those particles, and E , the output, is the system's total energy. The wavefunction, Ψ , expresses all possible positions of each particle (HyperChem, 1996). Such calculations are extremely computer-intensive and require impractical amounts of time for molecules that are not small. *Semi-empirical* methods seek to lessen the computational time of quantum mechanical calculations, by replacing selected interactions with experimental values similar to those used in molecular mechanics, and are useful in evaluating the best structure of a specific isomer. Most molecular modeling is best carried out using molecular mechanics methods, particularly when many larger molecules or many conformers are being analyzed.

In HyperChem, available methods include Geometry Optimization of structures and Conformational Search with Usage Directed and Random Walk combined with an Acceptance Energy Criterion defined by a Maximum Energy of acceptance or a Metropolis Criterion (HyperChem, 2016).

The Conformational Search methods used in HyperChem are variations of Monte Carlo simulations. A Monte Carlo simulation creates random molecular configurations permitted by the energy supplied at the specified temperature. The configurations can be generated in different ways. Beginning from an initial structure, the Metropolis search method in HyperChem selects an atom from

pre-selected torsions and moves it in a random direction, by a random amount. This structure is optimized, employing an energy minimization algorithm (see below) that adjusts all the bond lengths and bond angles, using the various parameters of the force field to obtain the lowest energy molecular configuration resulting from the initial atom relocation. If the resulting energy change is negative, then the new configuration is accepted as a stable conformer. If the energy change is positive, it may be retained, if it falls on a Gaussian distribution curve of the energies being obtained during the sampling. The Metropolis method may be used in two ways: in the Random Walk option, the initial structure for each evaluation step is the previous accepted conformation; in the Usage Directed option the software cycles through each previously accepted conformation as the initial structure for the next step.

Various energy minimization algorithms are available for optimization processes. Each algorithm provides a process of varying the parameters of the force field until a structure with a local energy minimum is obtained. The one employed throughout this research was the Polak-Ribière conjugate gradient algorithm. While it is beyond the scope of the present work to detail the mathematical construct of this algorithm, it is sufficient to understand that the algorithm provides a quicker pathway to find an energy-optimized structure than other known methods and is in general use.

Conformational searches in HyperChem do not yield immediate information regarding the activation energies of ring flips. This can be obtained with further runs at various temperatures, or with molecular dynamics analyses. The present work utilized Spartan's Energy Profile analyses. Here, the user specifies geometric constraints that change in a series of steps, forcing the phane structure to undergo a ring flip. The energy is calculated for each step of the process. The conformers corresponding to each step can be viewed and the highest energy conformer (the

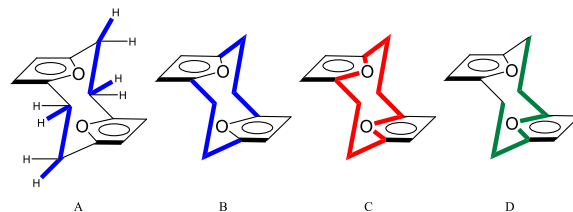


Figure 3. Torsions and rings selected for variation. A and B: HyperChem dihedral selections: to vary torsional angles about bridging C-C bonds; C: internal rings for ring torsion flexing. D: Spartan'18 dihedral selections: to vary torsions about the C-C bond attached to the aromatic ring in each case.

transition state structure) yields the activation energy barrier.

Materials and Methods

HyperChem geometry optimizations were carried out using MM+ or AMBER with the Polak-Ribière conjugate gradient algorithm and 0.01 kcal/mol (0.04 kJ/mol) limiting RMS gradients. The bonds and rings selected for variations are shown in Figure 3.

Conformational searches employed MM+ molecular mechanics. Typical search parameters are summarized in Table 1. Each search was carried out by repeated alternation between Usage Directed and Random Walk methods until no new conformers of lower energy could be obtained. The initial structure was the *anti* stereoisomer but, if a *syn* stereoisomer was not observed after the searches, the experiment was repeated, beginning with the *syn* stereoisomer.

The Spartan'18 Energy Profile experiment was used to simulate the ring-flip process. The calculations employed gas phase transformations using the MMFF94 molecular mechanics force field. Molecular structures were constrained by selecting dihedral angles (Figure 3) that were varied from -120° to $+120^\circ$ in 48 steps, with each step inducing a change of five degrees. These selections forced the molecular structure to undergo a ring flip. In cases where a ring flip could not be induced, the *anti* and *syn* isomers were examined independently.

Setting	Selection
Simultaneous Variations	1 to 12
Acyclic Torsion Variation	± 60 to 180 or ± 0 to 180
Ring Torsion Flexing	± 60 to 180 or ± 0 to 180
Initial Conformations	<i>Anti</i> , with Usage Directed or Random Walk
Acceptable Energy Criterion	Maximum 20 kcal/mol above best
Metropolis Criterion	300 K; 2000 K after 5 repeated or 10 rejected
Optimization Termination	1000 cycles
Randomization	Computer Clock

- HyperChem structure defined as hybrid-type or Kekulé-type.
- Computational Results. 1st number: Molecular Mechanics, MM+; 2nd number: Molecular Mechanics, AMBER99. Numbers in parentheses are C-X-C bond angles

Results and Discussion

Two molecular mechanics methods in HyperChem were screened to determine which computational approach would be best suited for the analyses of heterocyclic aromatic compounds (furan, thiophene pyrrole) by comparison to previous reports of computational and instrumentally based experiments (Tai, Lii, and Allinger, 1989; National Institute of Standards and Technology, 2018; Katrizky, Ramsden, Joule, and Zhdankin, 2010). The results are summarized in Table 2. It is worth noting that the designation of ring systems as being aromatic must be done explicitly for AMBER99 by using hybrid structures (Table 2), which emphasize the p-orbital overlaps, as differences were observed when the Kekulé-type structures were used. Although the molecular mechanics force fields MM+ and AMBER99 gave similar results, AMBER99 gave bond lengths that were slightly closer to the accepted values for the parent heterocyclic compounds. However, in initial HyperChem conformational searches of the heterophanes AMBER99 did not give ring-flipped

conformers, whereas MM+ was more successful. Thus, MM+ was selected as the method of choice for HyperChem.

By using combinations of Random Walk and Usage Directed methods in the Conformational Search of HyperChem, a reasonable examination of the potential energy map for each compound was carried out. For [2.2](2,5) furanophane **[1]**, a *syn* isomer was not discoverable when the initial stereoisomer was the *anti* conformer, even when the parameters (dihedral angles, Random Walk vs. Usage Directed methods, and temperature criteria) were varied. However, both conformers were found when the initial conformer was *syn* (Table 3). This was attributed to a combination of force field and parameter approximations, the number of cycles (limited to 1000 optimizations with 1000 iterations), and the assumptions of the Polak-Ribière algorithm for finding the global minimum. Two mirror-image *syn* isomers were obtained. The mirror images are superimposable indicating that they are identical conformers. The occurrence of mirror images in other analyses has been omitted from further discussion.

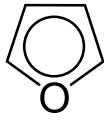
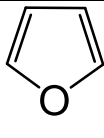
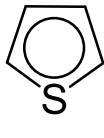
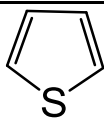

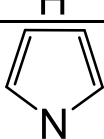
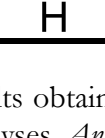
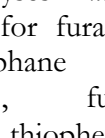
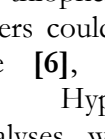
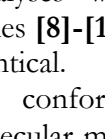
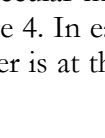

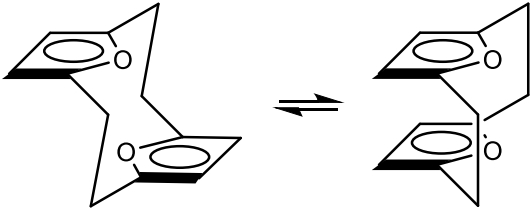
Table 2. Comparison of Experimental and Computational Geometries of Heterocyclic Aromatic Compounds in HyperChem.							
Compound ^a		X1-C2 (Å)		C2-C3 (Å)		C3-C4 (Å)	
		Expt.	Comp. ^b	Expt.	Comp.	Expt.	Comp.
Furan, Hybrid		1.36 (106.5°)	1.23 (108.8°)	1.36	1.39	1.43	1.39
Furan, Kekulé			1.49 (105.2°)		1.40		1.40
Thiophene, Hybrid		1.71 (92.17°)	1.23 (107.5°)	1.37	1.34	1.42	1.34
Thiophene, Kekulé			1.25 (111.6°)		1.34		1.44
Thiophene, Hybrid		1.71 (92.17°)	1.47 (98.26°)	1.37	1.39	1.42	1.39
Thiophene, Kekulé			1.71 (95.54°)		1.40		1.41
Pyrrole, Hybrid		1.37 (109.8°)	1.47 (96.76°)	1.38	1.34	1.42	1.34
Pyrrole, Kekulé			1.80 (93.20°)		1.35		1.40
Pyrrole, Hybrid		1.37 (109.8°)	1.27 (112.7°)	1.38	1.40	1.42	1.40
Pyrrole, Kekulé			1.38 (112.0°)		1.35		1.40
Pyrrole, Hybrid		1.37 (109.8°)	1.27 (111.6°)	1.38	1.34	1.42	1.34
Pyrrole, Kekulé			1.41 (108.3°)		1.34		1.46

Table 4 lists the results obtained from HyperChem and Spartan analyses. *Anti* and *syn* conformers were obtained for furanophane [1], furanothiophenophane [2], furanopyrrolophane [3], furano-N-methylpyrrolophane [4], and thiophenophane [5]. Ring-flipped stereoisomers could not be obtained for pyrrolophane [6], and N-methylpyrrolophane [7]. HyperChem Conformational Search analyses were not carried out for paracyclophanes [8]-[10] as the *anti* and *syn* structures are identical.

In Spartan, forced conformational changes using MMFF94 molecular mechanics yielded data graphed in Figure 4. In each case, the most stable *anti* conformer is at the left of the energy profile.

In those cases in which a ring flip did not occur, as with thiophenophane [5], Energy Profile graphs gave curves that rose exponentially and/or gave sudden zero energies, indicating improper or incomplete energy calculations for highly strained conformers arising in the ring flipping process. As with HyperChem, *anti* and *syn* stereoisomers were obtained for all the furan-containing heterophanes [1]-[4], as well as [8]. A “forced” ring flip could not be induced for pyrrolophanes [6] and [7]. Ring flips were not observed in Spartan for thiophenoparacyclophane [9], and pyrroloparacyclophane [10] (which were not searched in HyperChem). The only apparent disagreement between the HyperChem

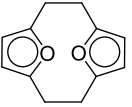
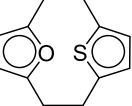
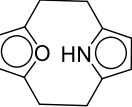
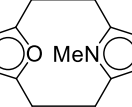
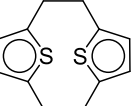
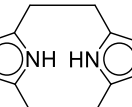

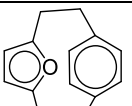
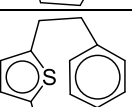
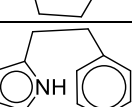
Table 3. Conformational Search Results				
Initial Structure: <i>Syn</i> -[2.2](2,5)Furanophane				
Conformations	3	Iterations	1032	
Lowest E (kcal/mol)	34.59396	Optimizations	1000	
Highest E (kcal/mol)	40.81644			
Conformations Found				
Conformation	Energy	Gradient	Torsion 1 (°)	Torsion 2 (°)
<i>Anti</i>	34.59396	0.00802	-43.44158	43.44035
<i>Syn</i>	40.81644	0.00795	-30.64336	-30.63974
<i>Syn</i>	40.81644	0.00756	30.62112	30.6147
Stereoisomer 1 (<i>anti</i>)				Stereoisomers 2,3 (<i>syn</i>) ^a

Conformational Search and Spartan Energy Profile experiments was for thiophenophane [5], which yielded *anti* and *syn* isomers in HyperChem but could not be induced to undergo ring flipping in Spartan. This is likely due to the extreme bond stretching and angles permitted in the HyperChem Conformational Search that were not allowed in the Spartan Energy Profile experiment.

Reconciliation of our computational results with known variable temperature NMR (VT NMR) experimental analyses is good in some cases. VT NMR experiments with [2.2]heterophanes have been reviewed (Mitchell, 1983; Ernst and Ibrom, 2004; Paudler and Bezoari, 1983; Gault, Price, and Sutherland, 1967). Such analyses faced experimental challenges in controlling and measuring the NMR probe temperatures over wide ranges. The goal of the experiments was to determine energy barriers to ring flipping by observing non-equivalent hydrogen atoms (e.g., those bonded to a bridging methylene), which give distinct, separate signals in a frozen conformation but become indistinguishable during ring flipping. The temperature at which this occurs is the *coalescence temperature*. It is apparent that the barriers to ring flipping in phane structures are due to torsional strain of methylene bridges which must go through

eclipsed conformers, as well as steric strain of atoms passing through the phane cavity. The torsional strain component is common to all the [2.2]phanes, but the steric strain factor differs greatly in the various compounds.

Thus, the relatively small size of the oxygen atom (with an atomic radius of 48 pm) in furanophanes [1]-[4] permits ring flipping of the furan ring with activation energies of about 60 kJ/mol (Table 4) according to the Spartan Energy Profile experiments. These results corroborate to some extent NMR studies (Mitchell, 1983; Paudler and Bezoari, 1983) which showed coalescence temperatures and energy barriers of 63 °C (70 kJ/mol) for furanophane [1], and -40 °C (50 kJ/mol) for furanoparacyclophane [8]. Similarly, a deuterium analog of furanopyrrolophane [3] gave an energy barrier of about 113 kJ/mol (Rosenfeld and Keehn, 1974). However, NMR experiments could not determine coalescence temperatures for furanothiophenophane [2] and furano-N-Methylpyrrolophane [4]. The computational and NMR results are in agreement for thiophenophane [5] and thiophenoparacyclophane [9] in which the larger size of sulfur (atomic radius 87 pm) prevents ring flipping as it cannot pass through the phane cavity. Similarly, pyrrolophane [6]

Table 4. Conformational Analysis ^a of [2.2]Heterophanes.					
Compound	ΔE (kJ/mol, HyperChem) ^b	ΔE (kJ/mol, Spartan) ^c	E_{act} (kJ/mol, Spartan)	Coalescence Temp from NMR (E_{act}) ^d	
1		26	42	63	63°C (70 kJ/mol)
2		30	28	58	>200°C ^e
3		29-35	25	58	>200°C ^e (113 kJ/mol)
4		24	27	54	>80°C ^e
5		41	23	No flip	>200°C ^e
6		No flip	67	No flip	>190°C ^e
7		No flip	55	No flip	unk ^f
8		N/A ^g	N/A ^g	66	-40°C (50 kJ/mol)
9		N/A ^g	N/A ^g	No flip	>150°C ^e
10		N/A ^g	N/A ^g	No flip	105°C

- a. $\square E$: energy difference between *anti* and *syn* stereoisomers. Activation energies (E_{act}) are for interconversions of stereoisomers.
- b. Obtained from the HyperChem Conformational Search.
- c. Obtained from Spartan Energy Profile, or from independent structures.
- d. Obtained by VT NMR spectroscopy.
- e. Highest temperature analyzed; coalescence was not observed.
- f. Unknown, i.e., unmeasured or not reported.
- g. No *anti* or *syn* isomers as they are identical.

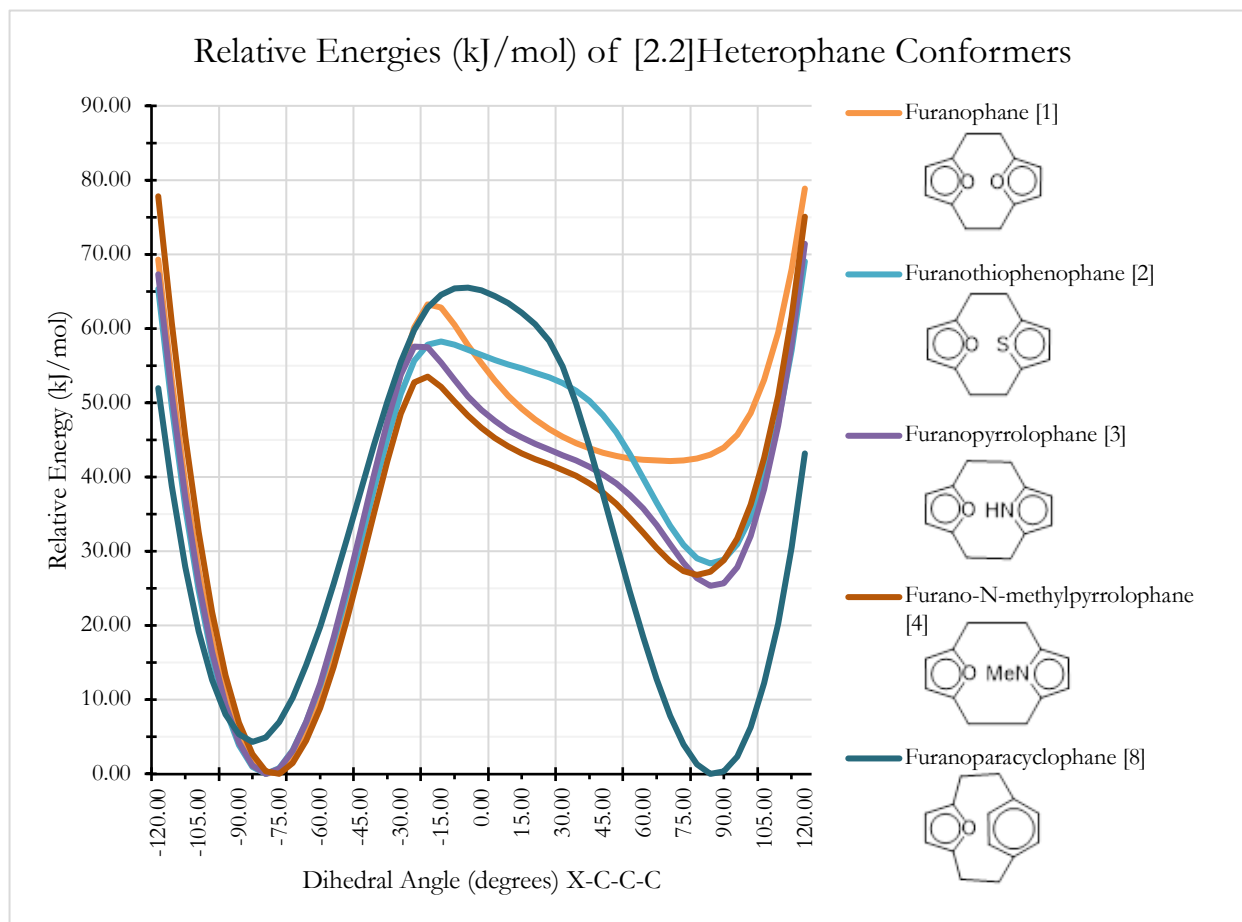


Figure 4. Spartan Energy Profile Conformational Analysis of *Anti*- to *Syn*-Heterophanes. The lowest energies on the left and right correspond to *anti* and *syn* stereoisomers, respectively. The highest energies in the middle correspond to the transition state conformers. Generated from Spartan using molecular mechanics, MMFF94.

and N-methylpyrrolophane [7], in which a nitrogen atom with atomic radius 56 pm as well as an attached hydrogen or methyl group must pass through the phane cavity, did not show any ring flipping computationally or from NMR studies. Computational analysis disagreed with VT NMR results for pyrroloparacyclophane [10]; a ring flip could not be induced computationally, whereas VT NMR gave an apparent coalescence temperature of 105°C (Rosenfeld and Keehn, 1973). It is possible that the experimental difficulty of carrying out VT NMR experiments was a factor. Additionally, temperature variations can cause NMR signals to change appearance or shift to a different

frequency due to other molecular motions, such as sliding or twisting of aromatic rings—the resulting changes in bridging methylene HNMR signals and might be interpreted by investigators as a coalescence of signals due to ring flipping. Also, assumptions inherent in the simple calculations that were used to determine energy barriers from coalescence temperatures may not have been appropriate in some cases (Shoemaker, 2019).

Dipole moment changes for furanophane [1], furanothiophenophane [2], furanopyrrolophane [3], furano-N-methylpyrrolophane [4] and furanoparacyclophane [8] that occurred during the ring flipping process were examined. These are the

compounds that allowed ring flips in the Spartan Energy Profile experiments. The structures for each conformer in the forced ring flips are shown by the software—the results are illustrated in Figure 5. The *anti* and *syn* conformers are in the left and right illustrations, respectively. The middle pictures reveal the highest energy structures, (i.e., transition states) obtained during the ring flip process. In all cases, with the exception of furanoparacyclophane [8], significant changes were observed in magnitudes and directions of dipoles of *anti* vs. *syn* conformers. As noted previously, furanoparacyclophane [8] does not have *anti* and *syn* conformers as ring flipping yields an identical structure. Regardless, the magnitude and direction of the dipole changes during the conformational switch, and the initial and final structures have dipoles that differ in direction. Thus, phane compounds that do not have distinguishable stable stereoisomers may still be appropriate for switching processes if they can be oriented in a suitable matrix.

Conclusions

Computational chemistry approaches were used to investigate conformational switching in strained [2.2]heterophanes [1]-[10].

The results showed that furan-containing [2.2]phanes can switch reversibly between stable conformations, with an

activation energy of about 60 kJ/mol. Agreement between Conformational Search in HyperChem and Energy Profile in Spartan was good. There was limited correlation with previously reported stereoisomeric switching established by VT NMR studies. Apparent discrepancies *within* the NMR studies might be explainable by molecular motions other than ring flipping.

Sources of error in the present computational experiments, other than those inherent in molecular mechanics, include the use of single-molecule, gas-phase approximations for the calculations. The Energy Profile approach used in Spartan imposed five-degree dihedral angle change constraints on the molecular structure that can cause the true conformer to be missed; this is evidenced by the furan ring flip in furanoparacyclophane [8], in which the initial and final structures should have the same structures and energies but were slightly different in the computational simulation (Figure 4).

This work promotes a simple screening method for development of classes of compounds that can change conformations reversibly, and reinforces the possibilities of applications in molecular machinery, molecular switches, and medicinal or other biochemical processes (Zhichang, Nalluri, and Stoddart, 2017).

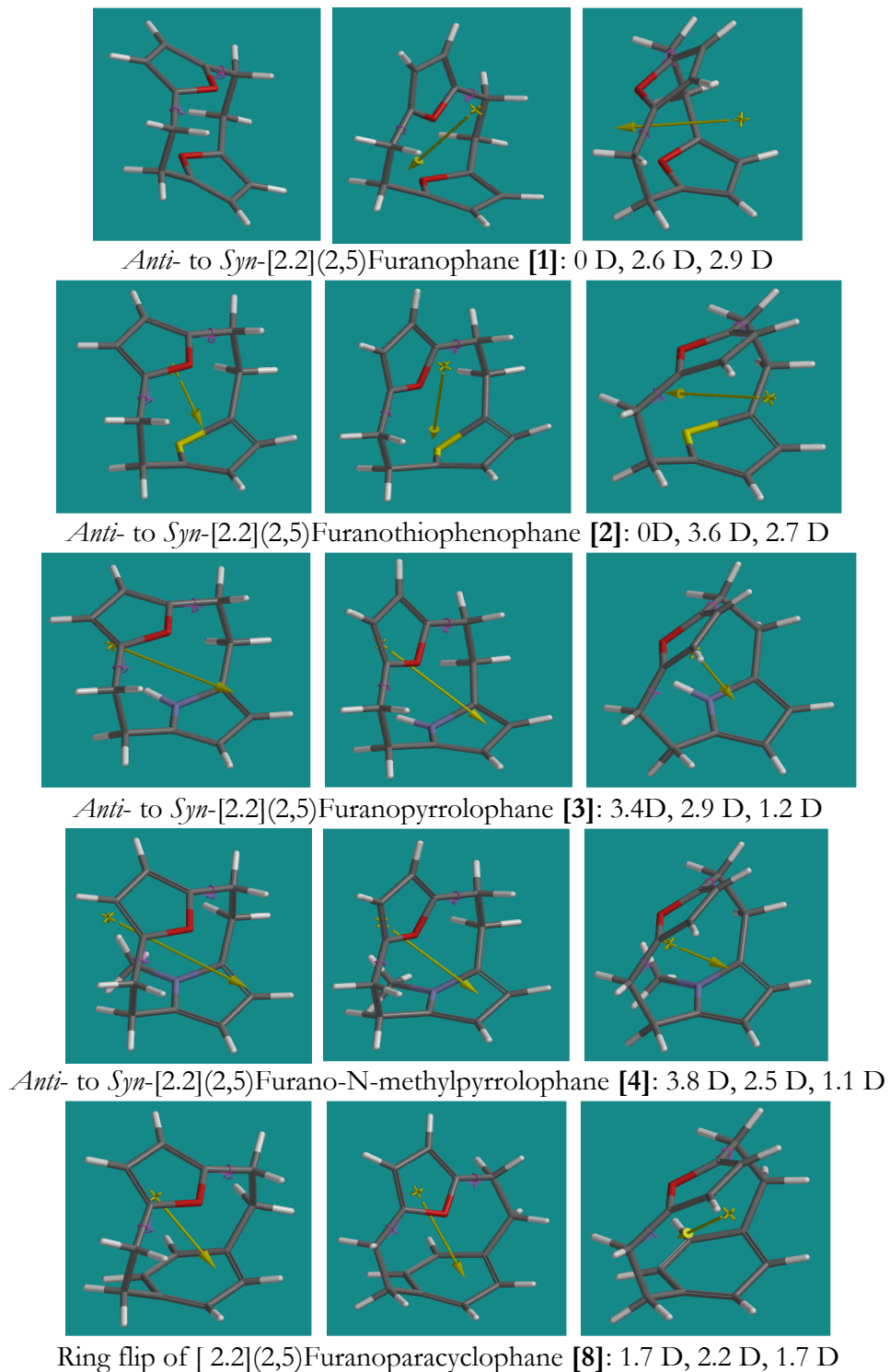


Figure 5. Conformations of Heterophanes and Dipole Moment Changes During Ring Flipping. Left and right structures are the relatively stable *anti* and *syn* conformers. The middle structures show the transition states—the highest energy conformers of the ring flip. Purple “ties” indicate dihedrals that were varied.

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