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Torquoselectivity Induced by Lone-Pair Conjugation in the Electrocyclic Reactions of 1-Azapolyenes

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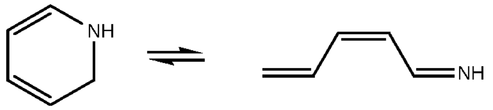
Torquoselectivity in the electrocyclic interconversions of 1-azapolyenes and their heterocyclic isomers was investigated theoretically. The ring openings of 1,2-dihydroazete, 1,2-dihydropyridine, and 1,2-dihydroazocine were examined using HF, MP2, and B3LYP calculations. A large preference for inward rotation of the nitrogen lone pair and outward rotation of the N−H group was found for the four- and six-electron systems. No strong preference was observed for the eight-electron system.

Introduction

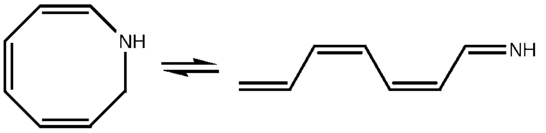
Torquoselectivity is the preference for one of two symmetry-allowed products of an electrocyclic reaction.[1] In the study of many electrocyclic ring openings, it is generally observed that electron-withdrawing groups rotate inward due to a favorable interaction with the breaking σ bond, while electron-donating groups rotate outward due to unfavorable interactions. This effect, first described in the ring openings of 3-substituted cyclobutenes,[2] has been further examined in systems with differing ring sizes, heterosubstitution, charges, and cumulated π bonds.[3] Continuing our studies of pericyclic reactions, we have examined torquoselectivity in the ring-opening reactions of 1,2-dihydroazete (eq 1), 1,2-dihydropyridine (eq 2), and 1,2-dihydroazocine (eq 3). While the six-electron reaction is endothermic and the eight-electron reaction is thermoneutral (vide infra), all three reactions are discussed in terms of ring opening for clarity of presentation.

The electrocyclic interconversions of 1-azapolyenes and their cyclic isomers have been observed experimentally.

1 **2** (1)



3 **4** (2)



5 **6** (3)

N-Substituted 1,2-dihydroazetes can be synthesized and ring opened to form 1-aza-1,3-butadienes.[4] This transformation has been examined computationally using CNDO, HF, and MP2 calculations.[5] Several researchers have utilized the interconversions of substituted 1-aza-1,3,5-hexatrienes and their corresponding 1,2-dihydropyridines.[6] This cyclization is much faster than the

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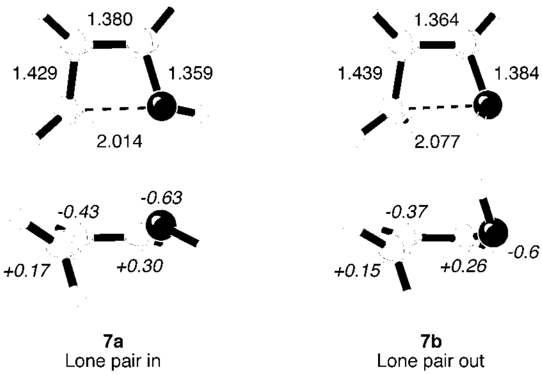
analogous hydrocarbon cyclization of 1,3,5-hexatriene.[6k] 1,2-Dihydroazocine derivatives have been observed to open to 1-aza-1,3,5,7-octatetraenes, which undergo subsequent six-electron ring closure.[7]

Methods

Geometries and energies were obtained for all stationary points in eqs 1−3 using RHF,[8] MP2,[9] and B3LYP[10] methods as implemented in the Gaussian 90, Gaussian 94, and Gaussian 98 programs.[11] The 6-31G* basis set was used with each of these methods.[12] All stationary points were characterized by frequency analysis, and reported energies include zero-point corrections scaled by a factor of 0.9806.[13] ChelpG atomic charges were calculated at each level of theory.[14] Structures, energies, and charges reported in the body of the present text are from the B3LYP calculations, while RHF and MP2 results are provided in the Supporting Information.

Results and Discussion

The electrocyclic ring opening of 1,2-dihydroazete (eq 1) proceeds in a conrotatory fashion, analogous to the opening of cyclobutene.[15] Two diastereomeric transition states are possible—one in which the nitrogen lone pair rotates inward (**7a**) and the other in which the nitrogen lone pair rotates outward (**7b**) (Figure 1). There is a strong preference for inward rotation of the lone pair, with a barrier of 26.4 kcal/mol for reaction via **7a** as opposed to a barrier of 35.0 kcal/mol for reaction via **7b** (Table 1). These are compared to a barrier of 29.6 kcal/mol for the opening of cyclobutene calculated at the same level of theory (Table 2).[16]

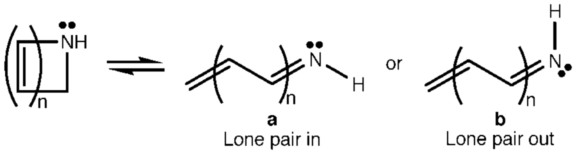


7a
Lone pair in

7b
Lone pair out

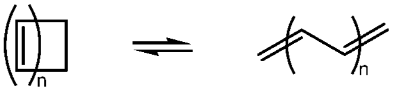
Figure 1. Transition-state geometries for 1,2-dihydroazete ring opening. Selected distances in Å. ChelpG charges on lower views.

Table 1. Ring-Opening Energetics for Equations 1−3 (Energies in kcal/mol)



product	n	lone pair	$\Delta E^{\ddagger}$	ΔE
2a	1	in	+26.4	−23.5
2b	1	out	+35.0	−23.0
4a	2	in	+27.7	+7.1
4b	2	out	+44.7	+7.3
6a	3	in	+19.4	+0.4
6b	3	out	+20.0	+0.7

Table 2. Ring-Opening Energetics for the Hydrocarbon Parent Reactions of Equations 1−3 (Energies in kcal/mol)



n	$\Delta E^{\ddagger}$	ΔE	ref
1	+29.6	−15.1	16
2	+42.9	+12.6	3i
3	+16.5	+0.9	16

The ring opening of 1,2-dihydroazete **1** is highly exothermic (eq 1). Transformation to s-trans product **2a** with the lone pair rotated inward is favorable by 23.5 kcal/mol, while opening to s-trans **2b** is favorable by 23.0 kcal/mol (Table 1). These openings are each more exothermic than the opening of cyclobutene, which is favorable by 15.1 kcal/mol (B3LYP/6-31G*) (Table 2).[16]

The ring opening of 1,2-dihydropyridine **3** (eq 2) is similar to that of cyclohexadiene, also proceeding in a disrotatory manner. Again, there are two possible modes of rotation of the nitrogen lone pair, with a strong

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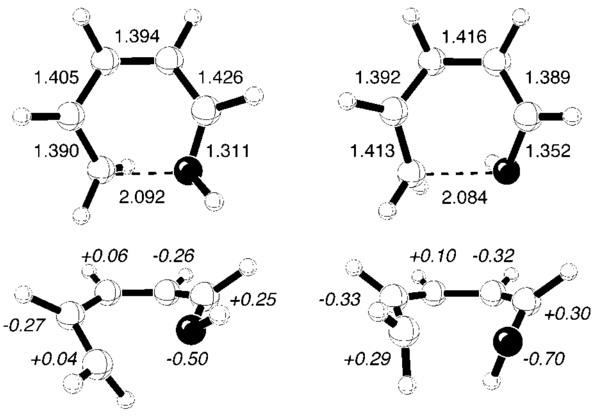
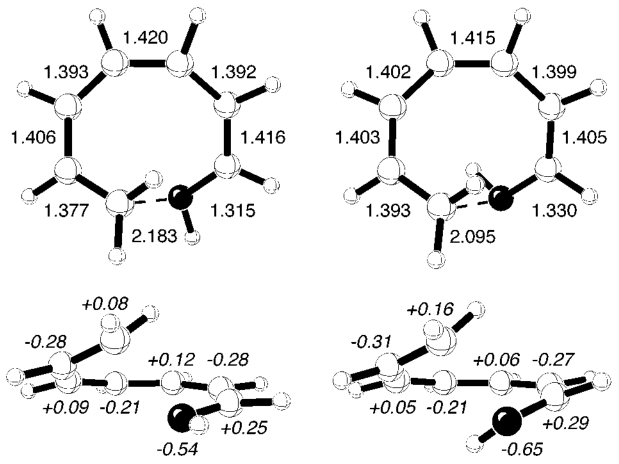


8a
Lone pair in

8b
Lone pair out

Figure 2. Transition-state geometries for 1,2-dihydropyridine ring opening. Selected distances in Å. ChelpG charges on lower views.



9a
Lone pair in

9b
Lone pair out

Figure 3. Transition-state geometries for 1,2-dihydroazocine ring opening. Selected distances in Å. ChelpG charges on lower views.

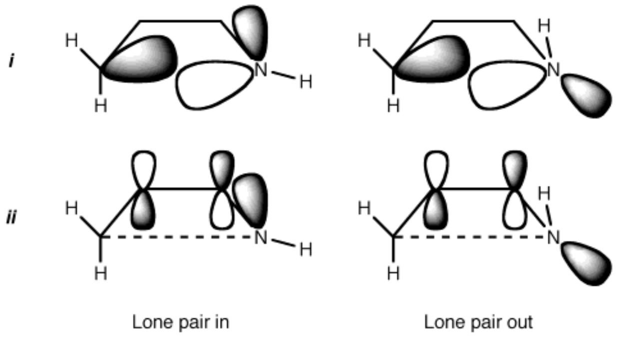


Figure 4. Interactions in the transition state of 1,2-dihydroazete (**1**) ring opening.

preference for inward rotation (Figure 2). Ring opening via transition state **8a** has a barrier of 27.7 kcal/mol while opening via transition state **8b** has a barrier of 44.7 kcal/mol (Table 1). The ring opening of **3** with inward rotation of the nitrogen lone pair is significantly more facile than the opening of 1,3-cyclohexadiene, which has a barrier of 42.9 kcal/mol (B3LYP/6-31G*) (Table 2).[3i]

The six-electron ring opening of **3** is an uphill process (eq 2). This reaction is endothermic by 7.1 kcal/mol in the formation of product **4a** with the lone pair rotated inward and by 7.3 kcal/mol in the formation of **4b** (Table 1). The ring opening of 1,3-cyclohexadiene is endothermic by 12.6 kcal/mol calculated at the same level of theory (Table 2).[3i] Reframing this reaction in the direction of ring closure (the reverse of eq 2), the electrocyclic closures of 1-aza-1,3,5-hexatrienes **4a** and **4b** proceed with barriers of 20.6 and 37.4 kcal/mol, respectively, and are exothermic by 7.0 and 7.3 kcal/mol, respectively (Table 1), compared to a barrier of 30.3 kcal/mol and an overall exothermicity of 12.6 kcal/mol for the closure of 1,3,5-hexatriene (Table 2).[3i]

The ring opening of 1,2-dihydroazocine **5** is an eight-electron and, therefore, conrotatory process (eq 3). Two transition states were located for this opening (Figure 3). Reaction via structure **9a**, with an inwardly rotating lone pair, has a barrier of 19.4 kcal/mol, while reaction via **9b** has a barrier of 20.0 kcal/mol. These openings are less facile than the analogous ring opening of 1,3,5-cyclooctatriene, which has a barrier of 16.5 kcal/mol (B3LYP/6-31G*) (Table 2).[16]

The transformation of 1,2-dihydroazocine **5** to 1-aza-octatetraenes **6a** and **6b** is an essentially thermoneutral process. These openings are calculated to be endothermic by 0.4 and 0.7 kcal/mol, respectively, using B3LYP/6-31G* calculations (Table 1), but MP2/6-31G* calculations predict exothermicities of 0.9 and 0.1 kcal/mol, respectively. The opening of 1,3,5-cyclooctatriene is endothermic by 0.9 kcal/mol (B3LYP/6-31G*) (Table 2).[16]

In the four- and six-electron ring openings of **1** and **3**, there is a strong preference for opening via transition states with inwardly rotating lone pairs (by 8.6 and 17.0 kcal/mol, respectively). This preference is minimized in the eight-electron ring opening of **5**, which has only a 0.6 kcal/mol preference for opening via transition state **9a**. This is similar to trends observed in the torquoselectivities of analogous hydrocarbon ring openings. In four- and six-electron systems, the breaking C$-$C bond is twisted as the reaction proceeds, causing the inward and outward positions to have different interactions with the breaking bond.[2,3a] In eight-electron ring openings, however, the transition state involves a simple stretching of the breaking C$-$C bond, and so inward and outward positions have similar interactions with that bond.[3b]

Bachrach and Liu have also examined a variety of heterosubstituted cyclobutene ring openings, including eq 1.[5c] Their HF/6-31G* and MP2/6-31G* calculations make predictions consistent with those presented above. In particular, they predict a 7.8 kcal/mol preference for ring opening via transition state **7a**, with inward rotation of the nitrogen lone pair. They propose that this selectivity is dictated by a favorable interaction in **7a** between the lone pair and the unfilled σ^* orbital of the breaking C$-$N bond (Figure 4*i*). This differs from known cases of torquoselectivity, in which electron donors prefer outward rotation to minimize a repulsive interaction with the high-lying filled σ orbital of the breaking bond.[1-3] Any stabilization gained from interaction of the lone pair with the unfilled σ^* orbital might be expected to be more than compensated for by the destabilizing interaction between the lone pair and the filled σ orbital of the breaking bond.

We propose an alternative, that the key interaction is between the nitrogen lone pair and the π system (Figure 4*ii*). In the four- and six-electron ring openings, an inwardly rotating lone pair is aligned to overlap with the unfilled π^* orbital, stabilizing these transition states. This interaction is unavailable in the transition states with outwardly rotating lone pairs. Evidence for this interaction can be inferred by an examination of bond lengths and charge distributions (Figures 1 and 2). In each of these cases, lone pair interaction with the π systems has the effect of shortening single bonds and lengthening double bonds for the inwardly rotating transition structures relative to the outwardly rotating structures. This effect is most dramatic in the six-electron system, which also has the greatest preference for inward rotation of the lone pair. For instance, the C_2-C_3 bond of **8a** is 1.426 Å long compared to 1.389 Å for **8b**, and the C_3-C_4 bond of **8a** is 1.394 Å long compared to 1.416 Å in **8b** (Figure 2). There is also an alternating pattern of positive and negative charges in each of these structures that can be attributed to resonance contributions in which the nitrogen lone pair donates into the π system. In each of these cases, inward rotation of the nitrogen lone pair leads to a reaction with a lower barrier than the opening of the hydrocarbon analogue.

A related interaction was proposed to explain anomalous substituent effects in the Nazarov cyclization. Smith and Ulmer observed that β-silyl groups prefer inward rotation, contrary to usual torquoselectivity arguments, and they proposed that this is due to a stabilizing hyperconjugation interaction between the strongly electron donating C−Si σ bond and the cation π system.[17] Denmark, Wallace, and Walker also cited a similar hyperconjugation in related systems.[18] Silyl substituents have also been observed to rotate inward in the ring opening of 3-silylcyclobutenes by Murakami, Miyamoto, and Ito.[19] These authors attributed this torquoselectivity to a stabilizing interaction between an electron-accepting Si−R σ^* orbital on the SiR_3 group and the breaking C−C σ bond. Ikeda, Kato, and Inagaki explain the same phenomenon in terms of electron donation from the C−Si σ orbital and the forming π orbital on the opposing terminus.[20] Hyperconjugation of the C−Si σ bond with the cyclobutene π bond, analogous to our proposed interaction of a nitrogen lone pair with this π bond, could also be responsible for this selectivity.

In the eight-membered case, there is no significant difference between the overlaps of the π systems. There are differences in bond lengths between the transition states with inwardly and outwardly rotating lone pairs, but these are generally less significant than in the four- and six-electron cases. Any gain due to inward rotation of the lone pair may be offset by a repulsive electrostatic interaction between the lone pair and C_7, which has a partial negative charge (Figure 3). This type of repulsive interaction, also observed in hetero Diels−Alder and Alder−ene reactions,[21] may also be the reason the ring opening of 1,2-dihydroazocine **5** is less favorable than that of 1,3,5-cyclooctatetraene.

Conclusion

There is a high degree of torquoselectivity in the ring openings of 1,2-dihydroazete **1** and 1,2-dihydropyridene **3**, which can be attributed to FMO interactions in the transition states. Heterosubstitution makes these reactions both kinetically and thermodynamically more favorable than their hydrocarbon analogues. These effects are minimized in eight-membered 1,2-dihydroazocine **5**, and this ring opening is predicted to have a higher barrier than that of its parent hydrocarbon.

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Supporting Information Available: Geometries and energies for all reported structures are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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