JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

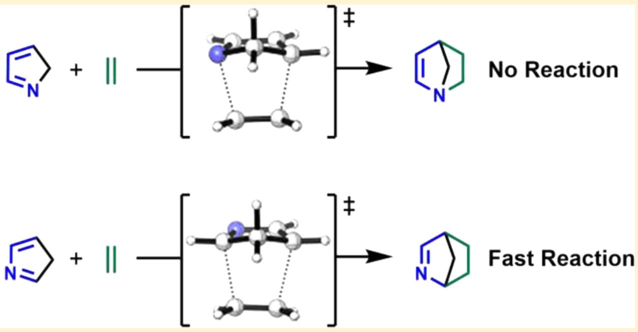
Origins of the Unfavorable Activation and Reaction Energies of 1-Azadiene Heterocycles Compared to 2-Azadiene Heterocycles in Diels–Alder Reactions

Jason S. Fell, Blanton N. Martin, and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Supporting Information

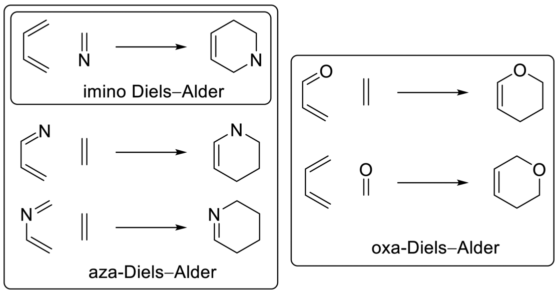
ABSTRACT: The reactivities of butadiene, cyclopentadiene, furan, thiophene, pyrrole, and their 1-aza- and 2-aza-derivatives in Diels–Alder reactions with ethylene and fumaronitrile were investigated with density functional theory (M06-2X/6-311G(d,p)). The activation free energies for the Diels–Alder reactions of cyclic 1-azadienes are 10–14 kcal mol^{-1} higher than those of cyclic 2-azadienes, and the reaction free energies are 17–20 kcal mol^{-1} more endergonic. The distortion/interaction model shows that the increased activation energies of cyclic 1-azadienes originate from increased transition state distortion energies and unfavorable interaction energies, arising from addition to the nitrogen terminus of the C=N bond.



INTRODUCTION

The hetero-Diels–Alder (DA) reaction is a [4 + 2] cycloaddition in which one or more heteroatoms are integrated into the diene or dienophile. These reactions are efficient methods for the synthesis of functionalized heterocycles. Common subclasses of the hetero-DA reaction are the imino-DA involving an aza-dienophile, oxa-DA, and aza-DA reactions, which are shown in Scheme 1.[1]

Scheme 1. Common Subclasses of the Hetero-DA Reactions: Aza-DA, Imino-DA, and Oxa-DA Reactions



The aza-DA reaction has significant synthetic utility in producing nitrogen-containing heterocycles such as piperidines[2] and tetrahydroquinones,[3] which are valuable intermediates for the synthesis of natural products.[4,5] The Povarov reaction involves reactions of 2-azadienes with electron-rich alkenes in the presence of a Lewis acid catalyst (Scheme 2a),[6] and the formation of benzoquinolines (Scheme 2b),[7] tetrahydroquinolines,[8−10] and hexahydropyrroloquinolines.[11] The aza-DA reaction has applications in biorthogonal click chemistry such as tetrazine-alkyne[12] cycloadditions (Scheme 2c) and the Kondrat'eva ligation[13,14] (Scheme 2d). Several recent examples in the literature highlight 2-azadienes in aza-DA reactions to efficiently produce quinolines.[15−20]

While 2-azadienes and oxazoles readily react with numerous dienophiles, DA reactions of 1-azadienes and isoxazoles require high temperatures and catalysts.[21] The 1-aza-DA reactions are much less common than all-carbon DA reactions.[22,23] Scheme 3 highlights earlier experimental aza-DA reactions that attempted to utilize cyclic 1-azadienes but rather isomerized to 2-azadienes before the subsequent cycloaddition reaction could occur.

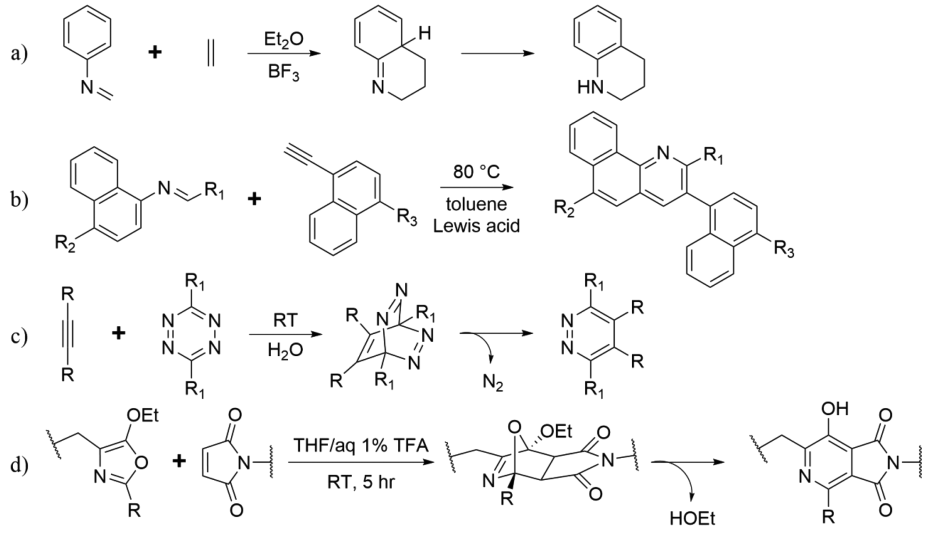
Jung and Shapiro attempted the aza-DA reaction of 2,3,4,5,5-pentachloro-1-azacyclopentadiene with styrene (Scheme 3a), but discovered that the 1-azadiene rearranged to the 2-azadiene, which then undergoes the cycloaddition.[24] They proposed that there is a lower thermodynamic driving force in reactions of 1-azadienes versus 2-azadienes. Vogel et al. studied intramolecular DA reactions of the butenyl pyrroles shown in Scheme 3b. They were only able to isolate the 2-azadiene product and computed this to be favored as well.[25] A theoretical study from our group showed that the reaction of oxazole with ethylene is exergonic while that of isoxazole is endergonic.[21] The unfavorable thermodynamics and lower reactivity of isoxazole were thought to involve the loss of conjugation of the enamine in the bicyclic product from the isoxazole reaction.

Boger et al. reported the first asymmetric aza-DA reaction of *N*-sulfonyl-1-azabutadiene with enol ethers.[26] This reaction of a 1-azadiene occurs at room temperature and without a catalyst; however, this DA reaction is made favorable by the diene being

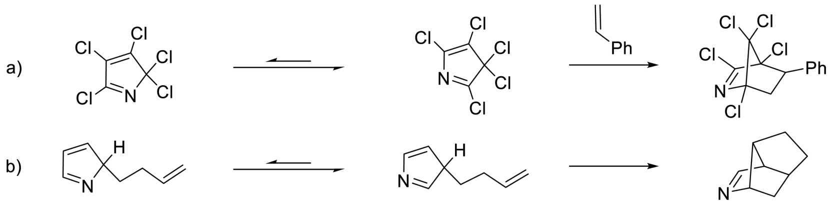
Received: October 17, 2016
Published: February 2, 2017

DOI: 10.1021/acs.joc.6b02524
J. Org. Chem. 2017, 82, 1912–1919

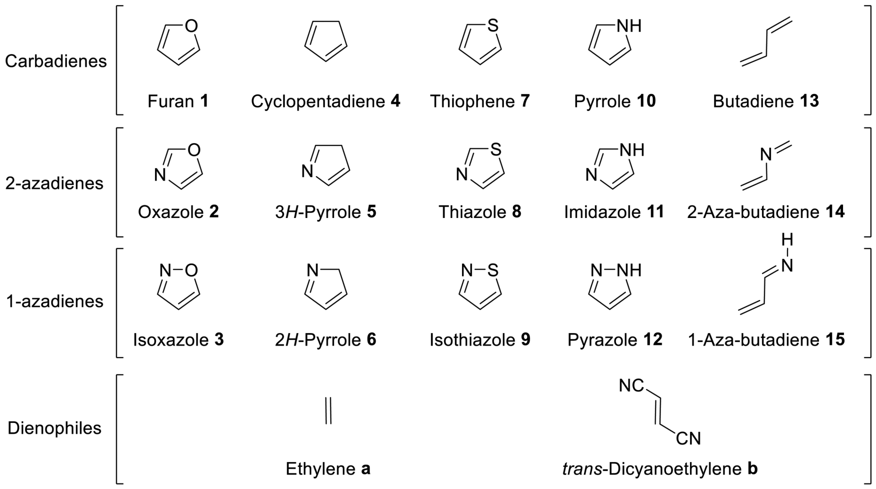
Scheme 2. Examples of Azadienes Utilized in Various Cycloaddition Reactions



Scheme 3. Two 1-Azadienes That Rearrange before Entering into DA Reactions



Scheme 4. Dienes and Dienophiles Studied Here



activated and acyclic and utilizing electron-rich dienophiles. There are recent examples in the literature of unactivated acyclic 1-azadienes that require high temperatures and Lewis acid catalysts to react in cycloaddition reactions.[27−29]

Our group has recently explored the reactivity of benzene and six-membered azabenzenes with ethylene in DA reactions.[30] The activation barriers decrease with each replacement of CH with N, and the reaction becomes highly regioselective to form C−C bonds than C−N bonds. The formation of two C−C bonds is favored by 15 kcal mol^{-1} over reactions where one C−C and one C−N bond are formed, and the formation of two C−N bonds is least favored. The diene becomes less aromatic with each nitrogen replacement, which consequently reduces the energy to distort the diene and increases the interaction energy between the diene and dienophile. Our general interest in understanding cycloaddition chemistry has prompted us to further investigate the effect of introducing a nitrogen atom within five-membered heterocycles.

We have employed density functional theory (DFT) calculations to predict the activation and reaction enthalpies and free energies of the DA reactions involving acyclic and heterocyclic dienes shown in Scheme 4 with ethylene (**a**) and fumaronitrile (*trans*-1,2-dicyanoethylene (**b**)). We have utilized the distortion/interaction (D/I) or Activation Strain model[31−38] to analyze the differences in activation energies between the 1-aza- and 2-azadiene cycloadditions. We report a detailed analysis of the differences in activation and reaction energies of DA reactions of unactivated cyclic all-carbon containing dienes, 1-aza- and 2-azadienes.

■ COMPUTATIONAL METHODS

All calculations were performed with Gaussian 09.[39] Gas-phase ground state and transition state geometries were optimized with Truhlar's M06-2X functional[40] and the 6-311G(d,p) basis set. These have been found by our group to give relatively accurate energies for cycloaddition reactions.[41,42] Vibrational frequencies were computed to determine if the optimized structures are minima or saddle points on the potential energy surface corresponding to ground state and transition state geometries, respectively. Free energies were calculated for 1 atm at 298.15 K. Truhlar's quasiharmonic correction was applied in order to reduce error in estimation of entropies arising from the treatment of low frequency vibrational modes as harmonic oscillations by setting all frequencies less than 100 cm^{-1} to 100 cm^{-1}.[43,44] Molecular structures are displayed with CYLview.[45]

■ RESULTS

We first compared our calculated M06-2X/6-311G(d,p) enthalpies to measured experimental enthalpies of formation. We compared the differences in experimental and calculated enthalpies of formation ($\Delta\Delta H_f°$) of oxazole (**2**), isoxazole (**3**), imidazole (**11**), and pyrazole (**12**), which are shown in Figure 1.

	2	**3**	**11**	**12**
$\Delta H°_f$(Exp.)	- 3.71 ± 0.13	18.78 ± 0.13	30.6 ± 1.8	40.3 ± 2.1
$\Delta\Delta H°_f$(Exp.)	22.49 ± 0.13		12.7 ± 2.8	
$\Delta\Delta H°_f$(Calc.)	25.6		11.8	

Figure 1. Experimental and calculated heats of formation, in units of kcal mol^{-1}.

The calculated $\Delta\Delta H_f°$ for **2** and **3** is 25.6 kcal mol^{-1}, and the calculated $\Delta\Delta H_f°$ for **11** and **12** is 11.8 kcal mol^{-1}. The experimental $\Delta\Delta H_f°$ for **2** and **3** are 22.49 ± 0.13 kcal mol^{-1},[46] and the experimental $\Delta\Delta H_f°$ for **11** and **12** are 12.7 ± 1.4 kcal mol^{-1}.[47] Our M06-2X/6-311G(d,p) calculated enthalpies are in good agreement with the experimentally measured enthalpies. Note the less reactive **3** and **12** are much less stable than the more reactive **2** and **11**!

Figure 2 shows the computed transition structures of the DA reaction of ethylene with dienes **1** thru **15**. The activation free energies and enthalpies are provided below the corresponding transition structure. The top, middle, and bottom rows display the carbadienes, 2-azadienes, and 1-azadienes, respectively.

The activation free energies of the DA reactions of ethylene (**a**) with the carbadienes (**1**, **4**, **7**, **10**, and **13**) range from 30 to 43 kcal mol^{-1}. The introduction of a nitrogen atom at the 2-position within the diene (dienes **2**, **5**, **8**, **11**, and **14**) decreases the barrier by only 1 to 3 kcal mol^{-1}. However, a nitrogen atom at the 1-position of the diene portion (dienes **3**, **6**, **9**, **12**, and **15**) increases the barrier by 9 to 11 kcal mol^{-1} in all five cases.

The transition structures of the DA reactions of ethylene with the symmetrical carbadienes, (**1**, **4**, **7**, **10** and **13**)**a-TS**, are all concerted and synchronous. The transition structures of the 1-aza- and 2-azadienes are also concerted but asynchronous. The asynchronicities of bond formation for (**2**, **5**, **8**, **11**, and **14**)**a-TS** are 0.09 to 0.12 Å, with the shortest forming bond at positions 4 and 5. Transition structures (**3**, **6**, **9**, and **12**)**a-TS** have an asynchronicity of 0.08 to 0.11 Å, with the shortest forming bond at positions 1 and 6; with the exception of **15a-TS** this is synchronous. The forming bonds in the 1-azadiene transition structures are 0.03 to 0.15 Å shorter compared to forming bonds in the transition structures of the carbadienes, which is an indication of later transition states with increased activation energies for those endothermic reactions, in accord with the Hammond Postulate.[48]

We also investigated the free energies and enthalpies of reaction for the DA reaction of ethylene with the dienes. The cycloadducts for each reaction are displayed in Figure 3 with the associated reaction free energy and enthalpy. The top, middle, and bottom rows display the cycloadducts of the DA reaction of ethylene (**a**) with the carbadienes, 2-azadienes, and 1-azadienes, respectively.

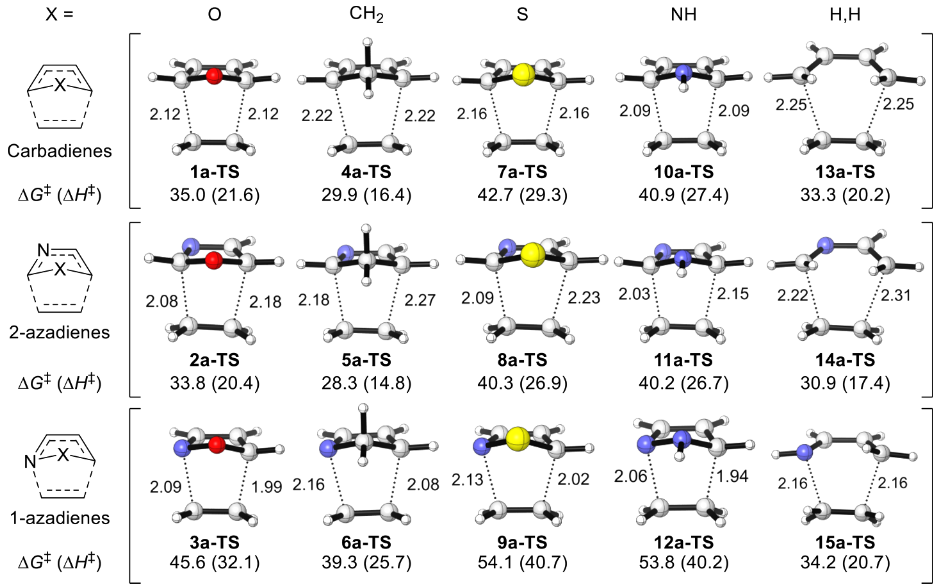


Figure 2. DA transition states of ethylene with each diene in this study displayed with the associated free energies and enthalpies of activation. Energies and distances are in units of kcal mol^{-1} and Å, respectively.

DOI: 10.1021/acs.joc.6b02524
J. Org. Chem. 2017, 82, 1912−1919

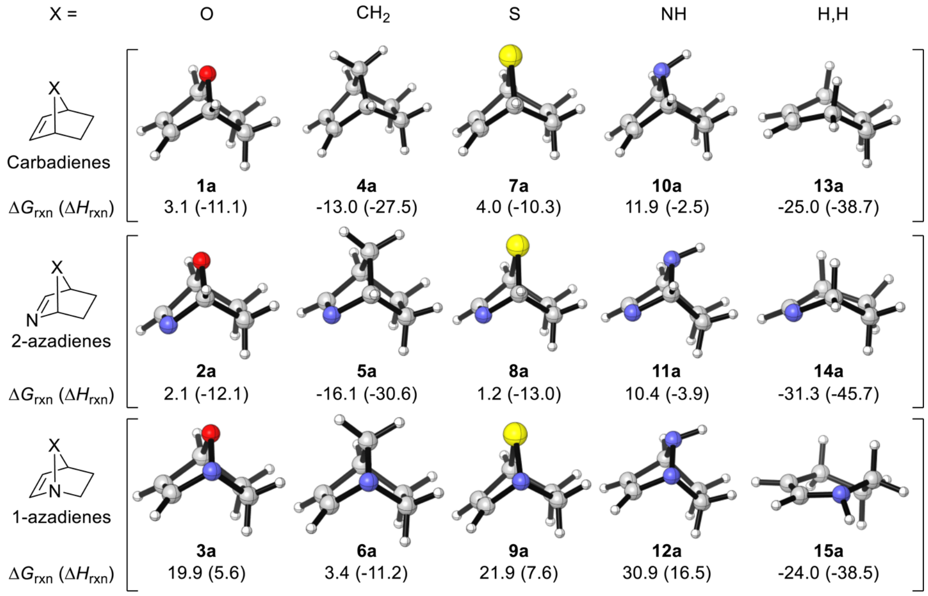


Figure 3. Cycloadducts of the DA reaction of ethylene with each diene in this study displayed with the associated free energies and enthalpies of reaction. Energies and distances are in units of kcal mol^{-1} and Å, respectively.

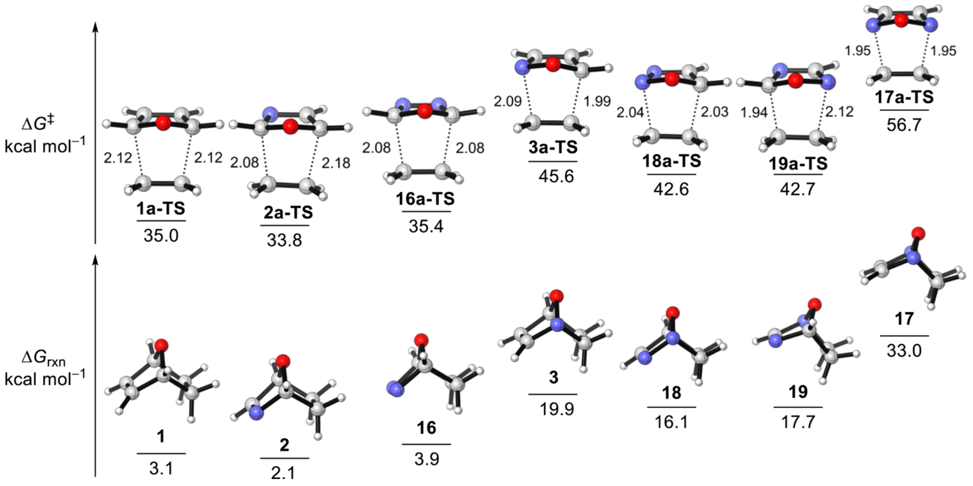


Figure 4. Computed activation and reaction free energies for DA reactions of several N,O-heterocycles with ethylene.

Cyclopentadiene (**4**), butadiene (**13**), 2*H*-pyrrole (**5**), 2-azabutadiene (**14**), and 1-azabutadiene (**15**) are the only dienes in the study with exergonic free energies of reaction. The DA reactions of the 2-azadienes with ethylene have reaction free energies 1 to 3 kcal mol^{-1} more exergonic than the reactions with the carbadienes, while the DA reactions of the 1-azadienes with ethylene are 16 to 20 kcal mol^{-1} more endergonic.

We have also calculated the same free energies using the more realistic dienophile, fumaronitrile (**b**). The results of these calculations are tabulated in the Supporting Information. With fumaronitrile the activation free energy changes range from +1.6 to −11.8 kcal mol^{-1}, while the reaction free energy change between −2.0 to +5.8 kcal mol^{-1}. Although the cyano groups usually increase reactivity as expected, these groups also make the reaction thermodynamics less favorable because the cyanos are removed from conjugation during the reaction.

Nitrogen substitution at either the 1- or 2-position within a diene has a remarkable influence on the activation and reaction free energies for DA reactions. We also studied the influence of multiple nitrogen substitution within a diene. We compared the activation and reaction energies of furan (**1**), oxazole (**2**), isoxazole (**3**), and oxadiazoles (**16**, **17**, **18**, and **19**); Figure 4 shows the respective transition structures and cycloadducts.

The introduction of a second nitrogen atom at the 3-position of oxazole (corresponding to the 2-position of the diene unit, diene **16**) has only a small influence on the energetics. However, introducing a nitrogen at the 2-position of furan (corresponding to the 1-position of the diene unit, dienes **18** and **19**) raises the barrier by 9−11 kcal mol^{-1} and the free energy of reaction by 17−21 kcal mol^{-1} compared to that of dienes **1**, **2**, and **16**. When a second nitrogen is introduced at the 4-position of isoxazole (corresponding to the 1-position of the diene unit, diene **17**), the free energy barrier increase 22 kcal mol^{-1} and the reaction energy is 30 kcal mol^{-1} more endergonic than that of furan.

■ DISCUSSION

To understand these general reactivity trends, we have explored the origins of the low reactivity of 1-azadienes compared to 2-azadienes using the distortion/interaction model.[25] We follow this discussion with an explanation of the reactivity trends observed for different heterocycles based upon reaction free energies and diene aromaticities. We first compare the activation free energy with the reaction free energies for the cyclic dienes. The results are given in Figure 5.

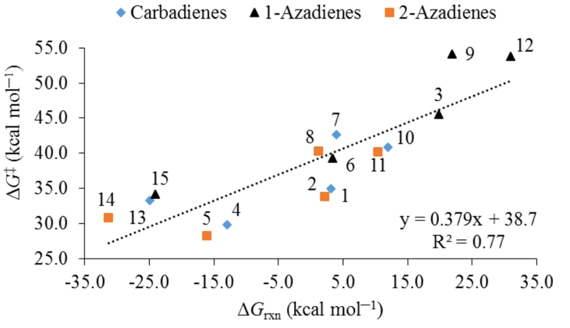
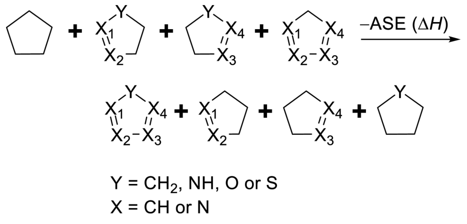


Figure 5. Plot of $\Delta G^{\ddagger}$ vs ΔG_{rxn} for the reaction of ethylene with all of the dienes.

There is a modest correlation (R^2 = 0.77) between the activation and reaction free energies. The slope is near 0.5, expected by Dimroth, Evan-Polanyi, Hammond, and Marcus models.[49] The DA reactions of furan (**1**), oxazole (**2**), cyclopentadiene (**4**), 3*H*-pyrrole (**5**), butadiene (**13**), 2-azabutadiene (**14**), and 1-azabutadiene (**15**) with ethylene are predicted to have similar reactivity. 2*H*-Pyrrole (**6**), thiophene (**7**), thiazole (**8**), pyrrole (**9**), and imidazole (**11**) are predicted to have DA reactions that are endergonic and reaction rates 3 to 5 orders of magnitude slower than the previous group of dienes. The 1-azadienes isoxazole (**3**), isothiazole (**9**), and pyrazole (**12**) (the three black triangles furthest right in Figure 5) are predicted to have DA reactions that are highly endergonic as well as reaction rates 7 to 13 orders of magnitude slower than the first group.

The reaction free energies for the different heterocycles can be correlated with the heterocycle aromaticity. Aromaticity can be quantified in many ways. The aromatic stabilization energy (ASE) is the energy of stabilization arising from cyclic delocalization of π electrons.[50,51] For five-membered heterocycles, Schleyer et al. devised a homodesmotic scheme for calculating the ASE shown in Scheme 5.[51]

Scheme 5. Schleyer's Homodesmotic Scheme for Calculating the Aromatic Stabilization Energy ASE of Heterocycles

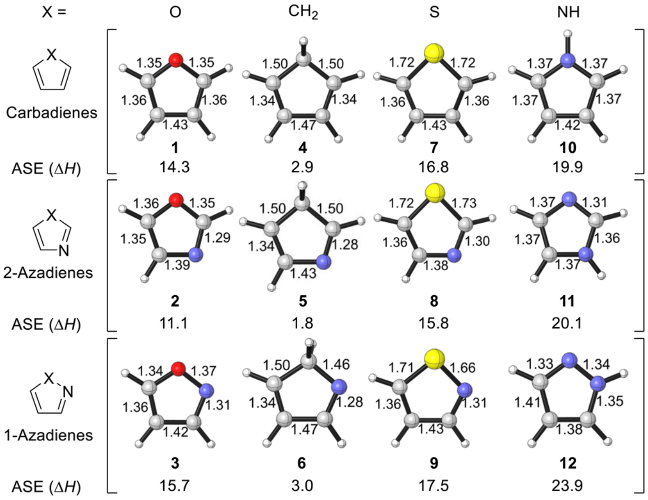


Y = CH2, NH, O or S
X = CH or N

The equation balances the number of single and double bonds on each side of the equation, as well as conjugation, so only the enthalpy (ΔH) gain from cyclic conjugation is measured. The M06-2X/6-311G(d,p) calculated ASE of the cyclic dienes are listed in Table 1 as ΔH.

Figure 6 shows a plot of the ΔG_{rxn} for the DA reactions of the cyclic dienes (**1**–**12**) with ethylene versus the aromaticity (ASE) of the diene.

Table 1. Calculated ASE (Δ*H*) of the Cyclic Dienes Using Schleyer's Homodesmotic Scheme[a]



X =	O	CH$_2$	S	NH
Carbadienes	**1**	**4**	**7**	**10**
ASE (ΔH)	14.3	2.9	16.8	19.9
2-Azadienes	**2**	**5**	**8**	**11**
ASE (ΔH)	11.1	1.8	15.8	20.1
1-Azadienes	**3**	**6**	**9**	**12**
ASE (ΔH)	15.7	3.0	17.5	23.9

[a] The method for calculating energies was M06-2X/6-311G(d,p). The bond distances and energies are reported in units of Ångstroms and kcal mol^{-1}, respectively.

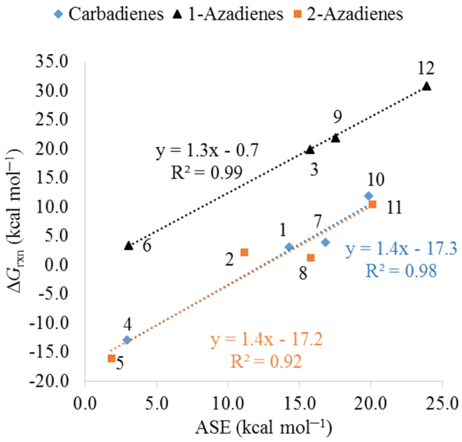


Figure 6. Correlations of ΔG_{rxn} versus cyclic diene aromaticity (ASE) of the carbadienes (blue diamonds), 1-azadienes (black triangles), and 2-azadienes (orange squares).

There is a good correlation between diene aromaticities and the free energies of reactions of each set of dienes. The reaction free energies of 1-azadienes (black triangles) are nearly 16 kcal mol^{-1} higher than the 2-azadienes (orange squares) and the carbadienes (blue diamonds). As each diene becomes more aromatic, the energy of reaction becomes more endergonic.

To understand the origin of the reactivity differences between 1-aza- and 2-azadienes, the activation energies have been analyzed with the D/I (or activation strain[33,34]) model. The D/I model dissects the activation energy ($\Delta E^{\ddagger}$) into two components: the distortion ($\Delta E_d^{\ddagger}$) and interaction ($\Delta E_i^{\ddagger}$) energies.[31,32,52] E is the electronic energy. The $\Delta E_d^{\ddagger}$ is the energy required to distort the reactants into their respective TS‡ geometries. The $\Delta E_i^{\ddagger}$ is a consequence of closed shell repulsions (steric effects), occupied-vacant orbital interactions (charge-transfer), and electrostatic and polarization effects. The D/I model has been used to explain the reactivity of DA cycloadditions.[35−37] Recently we have shown that the poor reactivity of cyclohexadiene and cycloheptadiene relative to that

DOI: 10.1021/acs.joc.6b02524
J. Org. Chem. 2017, 82, 1912−1919

of cyclopentadiene is related to the differences in distortion energies.[38]

Figure 7 shows a plot of the electronic energies of activation versus the distortion energies.

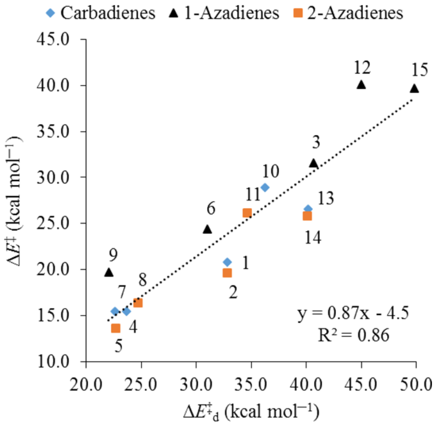


Figure 7. $\Delta E^{\ddagger}$ vs $\Delta E_{d}^{\ddagger}$ for the DA reaction of ethylene with the dienes.

There is a reasonably good correlation between the activation energies and the distortion energies. It is significantly more difficult to distort 1-azadienes as opposed to 2-azadienes or the carbadienes. This was found in studies of DA reactions of benzene and six-membered poly-aza-heterocycles in previous studies by our group.[30,35] It is due to the unfavorable energetics of addition to C=N π bonds and the poorer overlap of orbitals involving N and C in forming a new σ bond.[35] With the exception of the acyclic dienes (**13**, **14**, and **15**), the energy required to distort the cyclic 1-azadienes is 31 to 50 kcal mol^{-1}, while the cyclic 2-azadienes, cyclopentadienes, and monoheterocycles require 23 to 40 kcal mol^{-1} to distort.

In addition to the single-point analysis at the transition state, we have also carried out the D/I analysis along the reaction coordinate for oxazole (**2**) and isoxazole (**3**). The total electronic energy (ΔE), distortion energy (ΔE_dist), and interaction energy (ΔE_int) are plotted versus the average dihedral angle ($\omega_{\text{Ave.}}$) of the bending oxygen atom for oxazole (black) and isoxazole (orange) which are displayed in Figure 8.

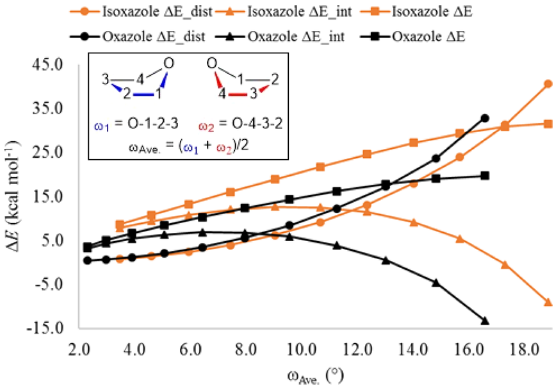


Figure 8. Plots of total energy, distortion energy and interaction energy versus the average dihedral angle of the bending oxygen atom of oxazole (black lines) and isoxazole (orange lines) in the DA reaction with ethylene. The last points to the right are the respective transition states.

The transition state of **2** with ethylene occurs earlier than that of **3**, consistent with the greater exothermicity of the reaction of **2**. The total energies for **2** are always lower along the reaction coordinate than **3**. The change in distortion energy over the reaction coordinate is slightly elevated for **2** compared to **3** until the transition state is reached, where the difference in distortion energies is 7.8 kcal mol^{-1} in favor of oxazole (**2**). Along the reaction coordinate the interaction energy is always more favorable for **2** due to the greater orbital overlap of carbon than of nitrogen and the ethylene p-orbital.[53−55] The interacting p-orbital of nitrogen in **3** is more contracted, resulting in less favorable interaction energy. As we have previously reported in the aza-DA reaction of azabenzenes with ethylene, the replacement of CH with N increases the reactivity of the diene primarily due to more favorable interaction energy along the reaction coordinate.[30] We showed earlier that reaction barriers correlate very closely with distortion energies, but the calculations in Figure 8 showed that the interaction energies influence the position of the transition state.

Another way to look at this focuses on the thermodynamic contribution to the activation barriers. The difference in reaction energies shifts the transition states to favor the oxazole reaction all along the reaction path. To explain the difference in reaction energies for addition to C=C and C=N bonds, we evaluated what bonds are being broken and formed in each DA reaction. A set of isodesmic reactions for each aza-substituted diene are shown in Figure 9.

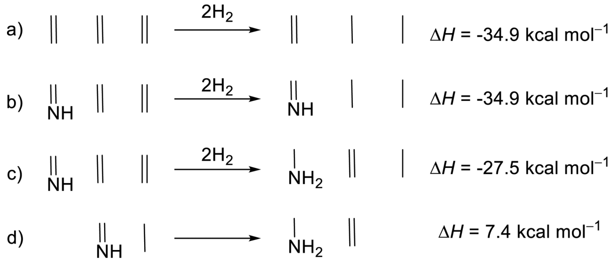


Figure 9. (a) Expressions for bond changes in the DA reaction of ethylene with furan (**1**) and cyclopentadiene (**4**), (b) oxazole (**2**) and 3*H*-pyrrole (**5**), and (c) isoxazole (**3**) and 2*H*-pyrrole (**6**). (d) The energy differences between these reactions can be expressed isodesmically. Computations were performed using M06-2X/6-311G-(d,p).

In the DA reactions with carbadienes three double bonds are converted into two single bonds and one double bond (Figure 9a); calculations on this transformation give a calculated enthalpy of −34.9 kcal mol^{-1}. When 2-azadienes react (i.e., oxazole, **2**, and 3*H*-pyrrole, **5**), one C=N and two C=C bonds are converted to one C=N and two C−C (Figure 9b), which of course has the same enthalpy as the reaction with carbadienes. The reactions of 1-azadienes (i.e., isoxazole, **3**, and 2*H*-pyrrole, **6**) differ in that one C=N and one C=C bond are converted to one C−N and one C−C (Figure 9c); this has an overall reaction enthalpy of −27.5 kcal mol^{-1}. The difference between these reactions can be written as the conversion of one C=N and one C−C to one C−N and one C=C bond (Figure 9d), which has an enthalpy of +7.4 kcal mol^{-1}. The experimental enthalpies of hydrogenation of methanimine and ethylene are −32.5 ± 0.1 and −21.62 ± 0.1 kcal mol^{-1}, respectively.[56−58] The M06-2X energetics (Figure 10) are in agreement with experiment. These two measurements indicate that it is thermodynamically more favorable to convert a C=C

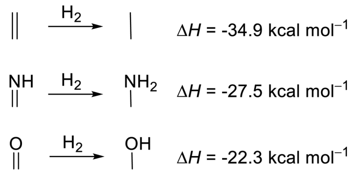


Figure 10. Calculated M06-2X/6-311G(d,p) enthalpies of hydrogenation of simple dienes.

π bond to a C−C single bond as compared to the C═N to C−N transformation.

Bond strength energy is related to the difference in electronegativity of the two atoms involved. This is the basis of Pauling's definition of electronegativity.[59] Pauling, Sanderson, and others have shown that bond energy is proportional to the differences in electronegativity between the constituent atoms in the bond.[59,60] In the cycloadditions, the $C(sp^2)-X(sp^2)$ double bond is being converted to a $C(sp^3)-X(sp^3)$ single bond. Conversion to the more saturated system becomes more difficult as X becomes more electronegative, and as two polar bonds (the double bond) are converted to one polar bond.

An additional contributing factor involves the change in hybridization that occurs upon addition to the N of a C═N double bond. In this process, the sp^2 lone pair on N becomes an sp^3 lone pair: the decrease in s-character is destabilizing as well. This has been discussed previously by Borden et al. in comparing electronic structures and reactions of nitrenes and carbenes.[61]

These energetic trends nicely rationalize why the cyclic 1-azadienes are less reactive than the nonaza- or 2-azadienes. However, we find only small differences for the acyclic cases. This intrinsic difference is counteracted by the stabilizing enamine resonance in the product of the DA reactions of 1-azadienes. We have calculated the enthalpic cost of loss of conjugation in an allylic amine, shown in Figure 11.

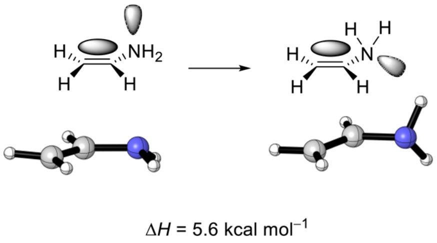


Figure 11. Enthalpy of rotation and deconjugation of nitrogen in acetaldehyde enamine, calculated using M06-2X/6-311G(d,p).

We find there is a 5.6 kcal mol^{-1} enthalpy cost to disrupt the nitrogen conjugation by rotation. This enthalpy cost is present in the product of reaction of all of the cyclic 1-azadienes. In the reaction of **15** and **a**, the enthalpic cost of addition to a C═N bond is mostly counteracted by the nitrogen lone pair conjugation in the nonplanar enamine product. We noted earlier the importance of this factor in causing isoxazole to be far less reactive than oxazole.[21]

■ CONCLUSIONS

The Diels−Alder reactions of a variety of acyclic and substituted heterocyclic dienes with ethylene and fumaronitrile have been investigated using DFT. Activation and reaction energies increase with respective diene aromaticity. The significant difference between the reactivities of 1-aza- and 2-azadienes is related to the thermodynamics of these reactions. Addition to a C═N bond is intrinsically less favorable than addition to a C═C bond, and the former requires more energy to distort in the transition states for 1-azadienes in these DA reactions. In acyclic 1-azadienes there is a compensation due to the conjugation of the developing sp^3 nitrogen lone pair with the double bond, which is not possible in the adducts from cyclic 1-azadienes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02524.

> Additional computational results for the Diels−Alder reaction of the original 15 dienes with fumaronitrile, as well as the geometries and energies for all of the molecules discussed in this paper (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: houk@chem.ucla.edu.

ORCID

Jason S. Fell: 0000-0001-6680-2936
K. N. Houk: 0000-0002-8387-5261

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-1361104) for financial support of this research. High performance computing resources were provided by the UCLA Hoffman2 cluster and the NSF Extreme Science and Engineering Discovery Environment (TG-CHE040013N). We thank Zili Fan and Fang Liu for helpful discussions.

■ REFERENCES

(1) Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 11146.
(2) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
(3) Sridharan, V.; Suryavanshi, P. A.; Menendez, J. C. *Chem. Rev. (Washington, DC, U. S.)* **2011**, *111*, 7157.
(4) Girling, P. R.; Kiyoi, T.; Whiting, A. *Org. Biomol. Chem.* **2011**, *9*, 3105.
(5) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.
(6) Domingo, L. R.; Aurell, M. J.; Saez, J. A.; Mekelleche, S. M. *RSC Adv.* **2014**, *4*, 25268.
(7) Mazaheripour, A.; Dibble, D. J.; Umerani, M. J.; Park, Y. S.; Lopez, R.; Laidlaw, D.; Vargas, E.; Ziller, J. W.; Gorodetsky, A. A. *Org. Lett.* **2016**, *18*, 156.
(8) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804.
(9) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598.
(10) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546.
(11) Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. *Chem. - Eur. J.* **2012**, *18*, 5869.
(12) Yang, J.; Seckute, J.; Cole, C. M.; Devaraj, N. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 7476.
(13) Jouanno, L.-A.; Chevalier, A.; Sekkat, N.; Perzo, N.; Castel, H.; Romieu, A.; Lange, N.; Sabot, C.; Renard, P.-Y. *J. Org. Chem.* **2014**, *79*, 10353.

(14) Kondrat'eva, G. Y. *Khim. Nauka Prom-st.* **1957**, *2*, 666.

(15) Yu, X.-L.; Kuang, L.; Chen, S.; Zhu, X.-L.; Li, Z.-L.; Tan, B.; Liu, X.-Y. *ACS Catal.* **2016**, *6*, 6182.

(16) Almansour, A. I.; Arumugam, N.; Suresh Kumar, R.; Carlos Menendez, J.; Ghabbour, H. A.; Fun, H.-K.; Ranjith Kumar, R. *Tetrahedron Lett.* **2015**, *56*, 6900.

(17) Dai, W.; Jiang, X.-L.; Tao, J.-Y.; Shi, F. *J. Org. Chem.* **2016**, *81*, 185.

(18) Min, C.; Seidel, D. *Chem. - Eur. J.* **2016**, *22*, 10817.

(19) Richmond, E.; Khan, I. U.; Moran, J. *Chem. - Eur. J.* **2016**, *22*, 12274.

(20) Muthukrishnan, I.; Vinoth, P.; Vivekanand, T.; Nagarajan, S.; Maheswari, C. U.; Menendez, J. C.; Sridharan, V. *J. Org. Chem.* **2016**, *81*, 1116.

(21) Gonzalez, J.; Taylor, E. C.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3753.

(22) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902.

(23) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259.

(24) Jung, M. E.; Shapiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862.

(25) Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P. A.; Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548.

(26) Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2587.

(27) Tay, G. C.; Sizemore, N.; Rychnovsky, S. D. *Org. Lett.* **2016**, *18*, 3050.

(28) Yan, X.; Ling, F.; Zhang, Y.; Ma, C. *Org. Lett.* **2015**, *17*, 3536.

(29) He, L.; Laurent, G.; Retailleau, P.; Folleas, B.; Brayer, J.-L.; Masson, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11088.

(30) Yang, Y.-F.; Liang, Y.; Liu, F.; Houk, K. N. *J. Am. Chem. Soc.* **2016**, *138*, 1660.

(31) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646.

(32) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187.

(33) van Zeist, W.-J.; Bickelhaupt, F. M. *Org. Biomol. Chem.* **2010**, *8*, 3118.

(34) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114.

(35) Liu, F.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 11483.

(36) Levandowski, B. J.; Zou, L.; Houk, K. N. *J. Comput. Chem.* **2016**, *37*, 117.

(37) Fernandez, I.; Bickelhaupt, F. M. *J. Comput. Chem.* **2014**, *35*, 371.

(38) Levandowski, B. J.; Houk, K. N. *J. Org. Chem.* **2015**, *80*, 3530.

(39) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian Inc.: Wallingford, CT, 2009.

(40) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

(41) Lan, Y.; Zou, L.; Cao, Y.; Houk, K. N. *J. Phys. Chem. A* **2011**, *115*, 13906.

(42) Paton, R. S.; Mackey, J. L.; Kim, W. H.; Lee, J. H.; Danishefsky, S. J.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 9335.

(43) Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813.

(44) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2011**, *115*, 14556.

(45) Legault, C. Y. *CYLview, 1.0b*; Université de Sherbrooke: Canada, 2009; http://www.cylview.org.

(46) McCormick, D. G.; Hamilton, W. S. *J. Chem. Thermodyn.* **1978**, *10*, 275.

(47) Bedford, A. F.; Edmondson, P. B.; Mor-timer, C. T. *J. Chem. Soc.* **1962**, 2927.

(48) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(49) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(50) von Ragué Schleyer, P.; Jiao, H.; Goldfuss, B.; Freeman, P. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 337.

(51) Cyranski, M. K.; Krygowski, T. M.; Katritzky, A. R.; Schleyer, P. v. R. *J. Org. Chem.* **2002**, *67*, 1333.

(52) Fernandez, I.; Bickelhaupt, F. M. *Chem. Soc. Rev.* **2014**, *43*, 4953.

(53) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361.

(54) Fleming, I. *Fronteir Orbitals and Organic Chemical Reactions*; Wiley: London, 1976.

(55) Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, *19*, 1313.

(56) Manion, J. A. *J. Phys. Chem. Ref. Data* **2002**, *31*, 123.

(57) Peerboom, R. A. L.; Ingemann, S.; Nibbering, N. M. M.; Liebman, J. F. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1825.

(58) Aston, J. G.; Siller, C. W.; Messerly, G. H. *J. Am. Chem. Soc.* **1937**, *59*, 1743.

(59) Pauling, L. *J. Am. Chem. Soc.* **1932**, *54*, 3570.

(60) Sanderson, R. T. *J. Am. Chem. Soc.* **1983**, *105*, 2259.

(61) Kemnitz, C. R.; Karney, W. L.; Borden, W. T. *J. Am. Chem. Soc.* **1998**, *120*, 3499.