A computational study of the relative aromaticity of pyrrole, furan, thiophene and selenophene, and their Diels-Alder stereoselectivity

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ABSTRACT: The collinearity of terminal *p* orbitals of a diene with that of a dienophile is required for an effective overlap to result in σ bond formation during the Diels-Alder reaction. The ease of the DA reaction of a cyclic diene with a given dienophile, therefore, must also depend on the distance between the termini of the diene. A distance larger than the unsaturated bond of the dienophile is expected to raise the energy of activation. This scenario has been amply demonstrated from the study of reactions of several dienes, some designed to serve the purpose, with different dienophiles. The five-ring heterocycles pyrrole, furan, thiophene and selenophene possess varying aromatic character for the varied resonance participation of the heteroatom lone pair with ring π bonds. The aromaticity decreases in the same order due to: (a) the increasing $\sigma_{C\text{-}X}$ (X = heteroatom) bond length lifts the bond uniformity required for ring current, hence aromaticity, such as in benzene and (b) size-mismatch of the interacting lone pair orbital and the ring *p* orbitals, especially in thiophene and selenophene, both allowing poor overlap in the ground state structures. It is demonstrated that increase alone in the activation energies of the DA reactions of pyrrole, furan, thiophene and selenophene cannot be considered a measure of relative aromaticity as often done and even theoretically attempted in many ways to prove just that. The separation of the termini of the diene has a much larger role in the determination of activation energy, especially in thiophene and selenophene, than their aromaticity profile. There cannot be a measure better than the relative intensity of heteroatom lone pair overlap with ring π bonds, giving rise to a six-electron like system in following Hückel's 4n+2 rule, to assess the relative aromaticity.

Keywords: Relative aromaticity, Pyrrole, Furan, Thiophene, Selenophene, Diels-Alder reaction, Stereoselectivity

INTRODUCTION

Aromaticity is an important concept in chemistry.[1] It is not observable and also not a directly measurable quantity, many indices of aromaticity have therefore been introduced. Manogaran and Schaefer recently published an 'Aromaticity Index Based on Interaction Coordinates (AIBIC)' and observed that the relative aromaticity of the five-ring heterocycles followed the order thiophene > pyrrole > furan.[2] This order was previously also observed by the Nucleus-Independent Chemical Shift (NICS) studies carried out by Horner and Karadakov.[3] The Topological Resonance Energy (TRE),[4] Magnetic Resonance Energy (MRE),[5] Ring Current (RC) and Ring Current Diamagnetic Susceptibility (χ_G)[6] are among the other approaches used to determine the degree of aromaticity. Not all indices of aromaticity give consistent results among themselves and sometimes different aromaticity values derived from different indices lead to different aromaticity orders or different predictions.[7] The suitability of the NICS and some other approaches for the prediction of aromaticity has been questioned.[8] The aromaticity, in fact, is a challenge to theoretical and experimental chemists.[9]

The superior aromaticity of thiophene over pyrrole and furan appeared doubtful to us from the following arguments/observations:

(a) The aromaticity accrued to the ring is necessarily due to the conjugative interaction (Figure 1) of the heteroatom lone pair with the π system of the ring to cause a six-electron system, as in benzene, following Hückel's 4n+2 electrons rule for aromaticity.[10]

(b) The conjugative interaction must decrease in about the same order as the increase in the carbon-heteroatom σ bond length. This is so because of the increased size-mismatch of the interacting 3*p* orbital of S and 2*p* orbitals of the ring π system in thiophene. In selenophene, it is *4p* orbital of Se.

(c) The uniformity of bonds,[11] which supports uniform distribution of electrons required for ring-current and magnetic susceptibility[12] to enhance aromaticity, decreases dramatically in thiophene for the relatively long C-S and C-Se bonds in comparison to the C-C bond.

(d) The relative rate of piperidinodenitration of 1-methyl-2,5-dinitropyrrole at 25 ^{0}C is markedly lower than those of 2,5-dinitrofuran and 2,5-dinitrothiophene, the k_{rel}

being 1.0, 2.4 × 10^6 and 4.4 × 10^3, respectively.[13] A less significant difference is found with the rate of 1,4-dinitrobenzene (k_{rel} = 9.6). The rate-depressing effect may derive from the conjugative interaction of the ring heteroatom with the leaving NO_2 group in the ground state. The low reactivity of pyrrole in nucleophilic substitution may, therefore, be mainly interpreted in terms of the stability of the ground state, since a significant conjugative interaction between the electron-releasing ring nitrogen and the nitro group, as occurring in the starting substrate, must be lost in the transition state (TS). Such an interaction is expected to be stronger than that of ring oxygen or sulfur for the stronger tendency of nitrogen to share its electrons, and may well be responsible for the position of the pyrrole system in the rate sequence.[14]

(e) The relative rates of bromination of pyrrole, furan, thiophene and benzene are 3 × 10^{18}, 6 × 10^{11}, 5 × 10^9 and 1.0, respectively.[15] Delocalization of lone pair into the ring decreases likewise.

(f) The study of reactivity of pyrrole, furan and thiophene in electrophilic substitution reactions suggests significant differences. The reactivity falls by approximately 10 orders of magnitude in the series pyrrole >> furan > thiophene, and may be explained by the different conditions for delocalization of ring atom electron density, in the course of which overlap of π orbitals of carbon atoms and lone pairs of the heteroatoms takes place.[16] The delocalization of lone pair of nitrogen in pyrrole with ring π system is clearly far greater than those of the oxygen in furan and sulfur in thiophene.

(g) The pK_a of C2-H (Figure 2) in solvent tetrahydrofuran decreases in the order 39.5 > 35.6 > 33.0 in pyrrole, furan and thiophene, respectively.[17] The measured pK_a values indicate higher electron density on C2 in pyrrole than in furan and thiophene. In other words, electron donation, through resonance, by N in pyrrole is larger than by O in furan and S in thiophene, in that order.

(h) The C3- and C4-Hs appear at ppm 6.20 in pyrrole, 6.25 in furan, and 6.92 in thiophene in ^{1}H NMR spectrum.[18] These chemical shifts demonstrate decreasing resonance donor ability of the heteroatoms. One may be tempted to consider this as a consequence of increasing ring current and, thus, increasing deshielding and increasing aromaticity. The following discussions will make it clear that it is due to the relative resonance donor ability of the heteroatom and not the deshielding effect of increased ring current.

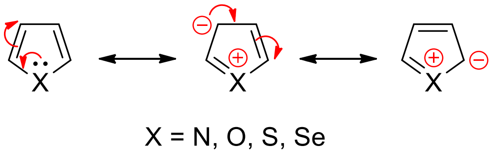


Figure 1. Conjugative interaction of heteroatom lone pair with ring π system

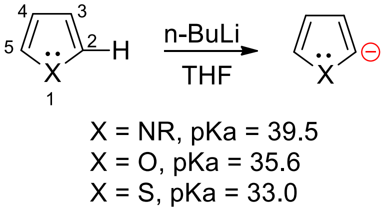
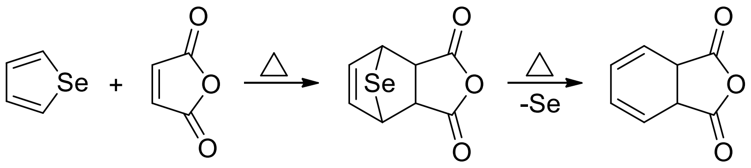


Figure 2. Relative pK_a values of C2-hydrogen in five-ring heterocycles

The above observations point to the order pyrrole >> furan > thiophene for the overall ring electron density and, thus, the relative aromaticity which we wished to investigate herein. The intensely debated notion of superior aromaticity of thiophene over pyrrole and furan stemmed essentially from the failure of thiophene to react with maleic anhydride (MA) in Diels-Alder (DA) manner under the typical thermal alone conditions of the reaction,[19] coupled with the solid understanding that more aromatic the system, larger was the activation barrier as it must overcome the aromatic stabilization. Thiophene, however, does react under high pressure conditions.[20, 21]

Other than the resonance interaction of heteroatom lone pair with ring π bonds to contribute to different reactivity features, including the facility of DA reaction, we proceeded with the very simple premise that as the distance *R* between the termini of the cyclic diene increased with the increased $\sigma_{C\text{-}X}$ (X = heteroatom) bond length, the difficulty in attaining the collinear alignment of the terminal *p* orbitals of the diene with those of the dienophile also increased, and so did the energy of activation. While aware that choosing dienes to test this theorem will be difficult because parameters other than *R* must not change, we proceeded to design and investigate some systems. From here onward, we shall also include selenophene (X = Se) in the discussion. Like thiophene

(X = S), selenophene is also known to react in DA manner under high pressure. The product, however, extrudes selenium in situ to deliver a diene as shown in Scheme 1.[22]



Scheme 1. DA reaction of selenophene with MA followed by Se extrusion

Computational Methods: The geometry optimizations of all the structures studied herein and the TS structure searches were carried out using the quantum chemical method MP2 at 6-31+G(d) and 6-311++G(d,p) levels using Gaussian 16.[23] Optimized structures were verified as minima or first order saddle points on the potential energy surfaces by harmonic vibrational frequency analysis. The effects of solvents on the potential energy profiles of the DA reactions of pyrrole, furan, thiophene and selenophene with MA were estimated using the Conductor Polarized Continuum Model (CPCM).[24] Orbital interactions were estimated by Natural Bond Orbital (NBO) analysis.[25]

RESULTS AND DISCUSSION

The interaction of the heteroatom lone pair (lp) with the π system of the ring, $lp \rightarrow \pi^*_{C=C}$, in the ground state was estimated to be 61.9 kcal/mol in pyrrole, 42.9 kcal/mol in furan, 41.9 kcal/mol in thiophene and 33.0 kcal/mol in selenophene. Since it is this very interaction that confers aromatic character to the ring by making up for the six-electron system, the aromaticity order requires to be pyrrole >> furan > thiophene > selenophene. The relative interaction intensities could be easily gleaned from the molecular orbitals shown in Figure 3.

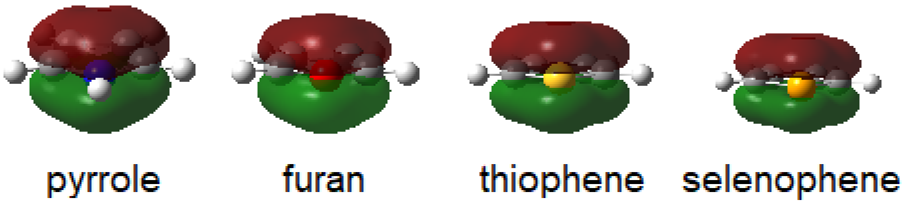


Figure 3. Molecular Orbitals showing interaction of heteroatom lone pair with ring π bonds in pyrrole, furan, thiophene and selenophene at the same isovalue

The interaction intensity decreases from pyrrole to selenophene, the difference between furan and thiophene is rather small.

The activation energy of DA reaction with a given dienophile is expected to rise with the rise in aromatic character of the ring system as the path to TS structure must negotiate with the resonance stabilization. Another important parameter that has largely been overlooked from the general description of relative aromaticity is the separation *R* of the termini of diene in relation to the unsaturated bond in dienophile.[26] *R* controls the efficacy of orbital overlap in TS structure for the emergent σ_{CC} bond formation. It is easy to agree that larger the *R* from the unsaturated bond in dienophile, poorer shall be the collinearity of interaction, leading to higher energy of activation. The separation, enthalpy changes, and activation energies of the *endo*- and *exo*-DA reactions of pyrrole, furan, thiophene and selenophene with MA are collected in Table 1a.

Table 1a. *R* and π bond distances (Å) in the *endo*- and *exo*-TS structures for DA reactions of five-ring heterocycles with MA, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) from gas phase calculations at MP2/6-311++G(d,p) level

Diene	*endo*-TS				*exo*-TS			
	R	π	$\Delta G^{\ddagger}$	ΔG	R	π	$\Delta G^{\ddagger}$	ΔG
X = NH	2.1984	1.4250	22.7	7.3	2.1944	1.4300	21.1	5.6
X = O	2.1492	1.4123	18.5	-0.0	2.1512	1.4117	19.1	-1.7
X = S	2.3940	1.4148	24.6	0.9	2.3930	1.4149	26.0	0.3
X = Se	2.4836	1.4120	24.8	-2.9	2.4805	1.4124	26.9	-0.3

R rises from furan to pyrrole to thiophene to selenophene in both TS structures. The variation in π bond length of MA is relatively very small except in the reaction with pyrrole, where it is the largest. The reason for the largest π bond in reaction with pyrrole alone is probably due to pyrrole's reduced ability to deform in its migration to the TS structure and, hence, enhanced force on the dienophile to allow it negotiate with the diene for the reaction. The reduced ability of pyrrole to deform also translates into its highest aromaticity among the five-ring heterocycles. The activation free energy, $\Delta G^{\ddagger}$, is seen to rise with rise in *R*. *The relatively reduced R and also the π bond in the*

TS structure for the reaction of furan lower the activation energy in comparison to pyrrole. The reduced *R* in furan in comparison to pyrrole is likely due to poorer resonance ability and larger electronegativity of oxygen over nitrogen.[27]

It is significant to note that *R* always contracted in the TS structure from that in the ground state. The distances in the ground state structures are 2.1862 Å in furan, 2.2538 Å in pyrrole, 2.4673 Å in thiophene and 2.5746 Å in selenophene. The contraction in *R* (by 0.0370 Å in furan, 0.0554 Å in pyrrole, 0.0733 Å in thiophene and 0.0910 Å in selenophene) in the TS structure is probably in the effort to ensure best possible collinearity of the interacting terminal orbitals.

The activation energy is not expected to rise linearly with *R* because the facility to push the heteroatom out of the plane of the ring carbons in the TS structure must also rise as the overlap of the heteroatom lone pair with ring π bonds weakens. This could be readily seen from the marginal difference in the activation energies of the reactions of thiophene and selenophene. By taking the activation energy alone, the aromaticity order from both the *endo* and *exo* modes of the reaction is selenophene > thiophene > pyrrole > furan.

Table 1b. *R* and C≡C bond distances (Å) in the TS structures for DA reactions of five-ring heterocycles in reactions with acetylene-1,2-bisnitrile and acetylene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) from gas phase calculations at MP2/6-31+G(d) level

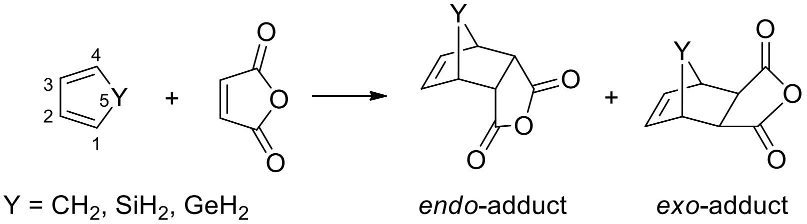
Diene	NCC≡CCN				HC≡CH			
	R	≡	$\Delta G^{\ddagger}$	ΔG	*R*	≡	$\Delta G^{\ddagger}$	ΔG
X = NH	2.1937	1.2898	25.1	2.5	2.1959	1.2715	41.0	12.2
X = O	2.1528	1.2816	23.9	-4.0	2.1530	1.2645	36.7	3.6
X = S	2.3876	1.2837	30.7	-4.1	2.3924	1.2647	44.6	5.3
X = Se	2.4802	1.2803	23.1	-17.7	2.4784	1.2621	40.1	-4.9

We have studied DA reactions of the five-ring heterocycles with weaker-than-MA dienophiles such acetylene-1,2-bisnitrile (NCC≡CCN) and acetylene (HC≡CH) with twin objective to avoid: (a) charge- and electron-transfer considerations[28] and deal with the concerted process alone, and (b) the stereochemical *endo*/*exo* issue. The charge- and electron-transfer mechanisms are more likely between significantly electron-rich and electron-deficient reactants. The results are collected in Table 1b. These results are at slight variance from those in Table 1a. From the activation energy, while the aromaticity order of the five-ring heterocycles is thiophene > pyrrole > furan > selenophene from reaction with acetylene-1,2-bisnitrileis, it is thiophene > pyrrole > selenophene > furan from reaction with acetylene.

We describe below DA reactions of other cyclic dienes to demonstrate the effect of increased *R* on the activation energy to support the *R*-hypothesis.

(1a) **DA reactions of cyclopentadiene, silole and germole with MA**: Cyclopentadiene, silole and germole are expected to behave like normal 1,3-dienes because there is no delocalization of the double bond character within the rings unlike pyrrole, furan, thiophene and selenophene.[29] Rise in *R* is therefore expected to raise the activation energy of the DA reaction.

Table 2a. *R* and π bond distances (Å) in the *endo*- and *exo*-TS structures for DA reactions of cyclopentadiene, silole and germole with MA, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-311++G(d,p) level



Diene	*endo*-TS				*exo*-TS			
	R	π	$\Delta G^{\ddagger}$	ΔG	*R*	π	$\Delta G^{\ddagger}$	ΔG
Y = CH_2	2.3267	1.3870	9.8	-20.4	2.3269	1.3890	12.3	-20.4
Y = SiH_2	2.6370	1.3878	9.6	-23.9	2.6356	1.3906	15.7	-21.2
Y = GeH_2	2.6725	1.3898	10.5	-24.7	2.6704	1.3913	16.4	-21.1

The relevant distances and activation energies are collected in Table 2a. Analysis of the numbers reveals that the activation energy has indeed increased with *R*. The increase in activation energy for *exo* addition is significantly larger than *endo* addition. This is likely due to the interplay of interactions such as maximum accumulation of unsaturation,[30] secondary orbital interactions[31] and dispersion forces[32] in the *endo*-TS structure that are known to significantly influence the activation energy. It may also be that because of these additional interactions the activation energy of *endo* addition of silole is slightly lower than cyclopentadiene. However, the actual reason for the (small) discrepancy with silole only is not clear.

(1b) **DA reactions of cyclopentadiene, silole and germole with acetylene-1,2-bisnitrile and acetylene**: As with the five-ring heterocycles, we have also investigated the DA reactions of cyclopentadiene, silole and germole with acetylene-1,2-bisnitrile and acetylene to avoid the *endo*/*exo* bifurcation and assess how the reaction profiles obeyed the *R*-hypothesis. The results are collected in Table 2b. The results with acetylenes are not the same as with MA. In particular, the activation energies of the reactions of silole and germole decreased, rather than increased, from that of cyclopentadiene. The clean *R*-compliant result from the *exo* addition of MA may, therefore, be fortuitous.

Table 2b. *R* and C≡C bond distances (Å) in the TS structures for DA reactions of cyclopentadiene, silole and germole with acetylene-1,2-bisnitrile and acetylene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-311++G(d,p) level

Diene	NCC≡CCN				HC≡CH			
	R	≡	$\Delta G^{\ddagger}$	ΔG	*R*	≡	$\Delta G^{\ddagger}$	ΔG
Y = CH_2	2.3186	1.2661	14.0	-29.1	2.3166	1.2514	25.5	-19.6
Y = SiH_2	2.6327	1.2630	13.4	-40.1	2.6269	1.2496	22.6	-31.2
Y = GeH_2	2.6682	1.2648	13.9	-41.8	2.6609	1.2510	23.6	-32.7

It is not that the *R*-hypothesis failed because the discrepancy can be explained. The $\sigma_{C5\text{-}H}$ (hydrogen allylic to ring π bond) in each instance is in hyperconjugative interaction with the ring π bonds in the TS structure.[33] In the reaction with acetylene-1,2-bisnitrile, the interactions $\sigma_{C\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}H}$ measure 17.9 and 10.4 kcal/mol in cyclopentadiene, 4.6 and 9.0 kcal/mol in silole, and 4.1 and 7.4 kcal/mol in germole. The combined effect of the two interactions in cyclopentadiene

(17.9-10.4 = 7.5 kcal/mol) is that of net electron donation from $\sigma_{C5\text{-}H}$ to the ring to impart aromatic character. In contrast, the rings are electron-depleted in silole and germole to render them somewhat anti-aromatic. Consequently, cyclopentadiene reacts with higher activation energy in comparison to silole and germole. This argument holds for the reactions with acetylene also as the interactions $\sigma_{C5\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C5\text{-}H}$ measure, respectively, 15.0 and 5.5 kcal/mol in cyclopentadiene, 4.1 and 9.6 kcal/mol in silole, and 3.6 and 8.2 kcal/mol in germole.

The results of DA reactions of cyclopentadiene, silole, and germole with acetylene-1,2-bis nitrile and acetylene using the 6-31+G(d) basis set are collected in Table 2c for a comparison with the results in Table 2b using the 6-311++G(d,p) basis set. The 6-31+G(d) results predict consistent fall in the activation energy from cyclopentadiene to germole. However, the sudden significant fall in activation energy of *endo* addition of acetylene-1,2-bisnitrile to germole is not understood. In the TS structures for the reactions of cyclopentadiene, silole and germole, the interactions $\sigma_{C5\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C5\text{-}H}$ measure, respectively, 16.9 and 8.9 kcal/mol, 4.7 and 10.1 kcal/mol, and 5.0 and 10.1 kcal/mol in reactions with acetylene-1,2-bisnitrile and 17.8 and 15.0 kcal/mol, 4.8 and 15.5 kcal/mol, and 5.4 and 15.2 kcal/mol in reactions with acetylene. This leads to the same scenario as discussed above as it too predicts fall in activation energy.

Table 2c. *R* and C≡C bond distances (Å) in the TS structures for DA reactions of cyclopentadiene, silole and germole with acetylene-1,2-bisnitrile and acetylene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level

Diene	NCC≡CCN				HC≡CH			
	R	≡	$\Delta G^{\ddagger}$	ΔG	*R*	≡	$\Delta G^{\ddagger}$	ΔG
Y = CH_2	2.3175	1.2685	15.3	-29.1	2.3131	1.2540	28.4	-18.2
Y = SiH_2	2.6353	1.2659	14.8	-40.0	2.6253	1.2529	25.5	-29.7
Y = GeH_2	2.6670	1.2647	8.0	-49.5	2.6448	1.2537	22.6	-34.2

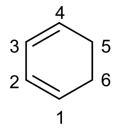
The switch over in the intensities of the $\sigma_{C5\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C5\text{-}H}$ interactions from cyclopentadiene to silole and germole is interesting as it has implications on reaction kinetics.

Also, in the activation energy falling regime under the obvious control of the combined $\sigma_{C5\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C5\text{-}H}$ interactions, it is difficult to assign a role to *R*.

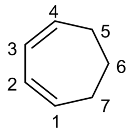
We notice from the above that the study of the effect of changing *R* on the activation energies of DA reactions was complicated for the presence of other forces in the dienes. So, we continued with our search for more dienes to achieve the objective.

(2a) **DA reactions of 1,3-cyclohexadiene and 1,3-cycloheptadiene with MA**: These dienes were considered for the present investigation because the separation of the termini varied from 2.8429 Å in 1,3-cyclohexadiene to 3.1757 Å in 1,3-cycloheptadiene in the ground state structures, and it was anticipated that they will follow the same order in the TS structures in reactions with dienophiles as well. The activation energy was, therefore, expected to rise from 1,3-cyclohexadiene to 1,3-cycloheptadiene.

Table 3a. R and π bond distances (Å) in the *endo*- and *exo*-TS structures for DA reactions of 1,3-cyclohexadiene and 1,3-cycloheptadiene with MA, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level



1,3-cyclohexadiene



1,3-cycloheptadiene

Diene	*endo*-TS				*exo*-TS			
	R	π	$\Delta G^{\ddagger}$	ΔG	*R*	π	$\Delta G^{\ddagger}$	ΔG
Y = $(CH_2)_2$	2.7570	1.3846	16.0	-29.2	2.7570	1.3894	20.2	-27.2
Y = $(CH_2)_3$	3.0121	1.3906	20.1	-31.0	3.0093	1.3970	27.3	-27.3

The relevant parameters for reactions with MA are collected in Table 3a. The activation energies, as expected, rose for both the *endo* and *exo* modes of the addition. The *R*-hypothesis holds.

Scrutiny of orbital interactions in the *endo*-TS structures reveals $\sigma_{C\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}H}$ interactions to be 18.9 and 9.0 kcal/mol in 1,3-cyclohexadiene and 18.9 and 4.2 kcal/mol in 1,3-cycloheptadiene. The differential interaction ($\sigma_{C\text{-}H}$–π^*_{ring})-(π_{ring}–$\sigma^*_{C\text{-}H}$) rose from 9.9 kcal/mol in 1,3-cyclohexadiene to 14.7 kcal/mol in 1,3-cycloheptadiene. Likewise, the $\sigma_{C\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}H}$ interactions in the *exo*-TS structures are 20.3 and 8.4 kcal/mol in 1,3-cyclohexadiene and 21.2 and 5.4 kcal/mol in 1,3-cycloheptadiene. The difference here too has rose from 11.9 kcal/mol in 1,3-cyclohexadiene to 15.8 kcal/mol in 1,3-cycloheptadiene.

The consequence of $\sigma_{C\text{-}H}$–π^*_{ring} > π_{ring}–$\sigma^*_{C\text{-}H}$ is to raise the electron density of the diene and make it more reactive towards dienophiles to lower the activation energy. The activation energy is instead substantially raised from 1,3-cyclohexadiene to 1,3-cycloheptadiene due probably to a strong *R*-effect.

(2b) **DA reactions of 1,3-cyclohexadiene and 1,3-cycloheptadiene with acetylene-1,2-bisnitrile and acetylene**: The reactions of 1,3-cyclohexadiene and 1,3-cycloheptadiene with acetylene-1,2-bisnitrile and acetylene were studied next to bypass the *endo*/*exo* issue as before and assess the effect of increasing *R*. The results are collected in Table 3b. The activation energies have increased with *R*.

Table 3b. *R* and C≡C bond distances (Å) in the TS structures for DA reactions of cyclopentadiene, 1,3-cyclohexadiene and 1,3-cycloheptadiene with acetylene-1,2-bisnitrile and acetylene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level

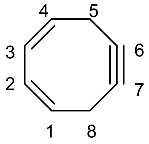
Diene	NCC≡CCN				HC≡CH			
	R	≡	$\Delta G^{\ddagger}$	ΔG	*R*	≡	$\Delta G^{\ddagger}$	ΔG
Y = $(CH_2)_2$	2.7591	1.2661	18.5	-44.6	2.7374	1.2509	31.2	-33.7
Y = $(CH_2)_3$	3.0114	1.2705	22.5	-47.7	2.9851	1.2538	36.0	-36.4

The $\sigma_{C\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}H}$ interactions in the TS structures for reactions with acetylene-1,2-bisnitrile are 19.7 and 8.7 kcal/mol in 1,3-cyclohexadiene and 20.3 and 4.1 kcal/mol in 1,3-cycloheptadiene. The difference ($\sigma_{C\text{-}H}$–π^*_{ring})-(π_{ring}–$\sigma^*_{C\text{-}H}$) has increased from 11.0 kcal/mol in 1,3-cyclohexadiene to 16.2 kcal/mol in 1,3-cycloheptadiene. Likewise, the $\sigma_{C\text{-}H}$–π^*_{ring} and

π_{ring}–$\sigma^*_{C\text{-}H}$ interactions in the TS structures for reactions with acetylene are 16.7 and 9.4 kcal/mol in 1,3-cyclohexadiene and 18.1 and 5.6 kcal/mol in 1,3-cycloheptadiene. The difference of the two interactions here too has increased from 7.3 kcal/mol in 1,3-cyclohexadiene to 12.5 kcal/mol in 1,3-cycloheptadiene. In spite of the net activation energy-lowering $\sigma_{C\text{-}H}$–π^*_{ring} interaction raised, the increase in activation energy from 1,3-cyclohexadiene to 1,3-cycloheptadiene strongly favors the *R*-hypothesis. In other words, when we expect decrease in activation energy for favourable $\sigma_{C\text{-}H}$–π^*_{ring} interaction, we observe increase and this could solely be for the *R*-effect.

(3) **DA reactions of 1,3-cyclohexadiene and 1,3-cyclooctadiene-6-yne with acetylene-1,2-bisnitrile and acetylene**: We have introduced an alkyne bond between C5 and C6 of 1,3-cyclohexadiene to increase the separation of the termini of the diene by taking advantage of the linear alkyne geometry. Indeed, the distance between the termini is 2.8429 Å in 1,3-cyclohexadiene and 3.6348 Å in 1,3-cyclooctadiene-6-yne. Accordingly, the activation energy was expected to rise in DA reactions with acetylene-1,2-bisnitrile and acetylene. The results are collected in Table 3c.

Table 3c. *R* and C≡C bond distances (Å) in the TS structures for DA reactions of 1,3-cyclohexadiene (CHXDN) and 1,3-cycloctadiene-6-yne (COCTDNYN) with acetylene-1,2-bisnitrile and acetylene, activation energies ($\Delta G^‡$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level



1,3-cyclooctadiene-6-yne

Diene	NCC≡CCN				HC≡CH			
	R	≡	$\Delta G^‡$	ΔG	*R*	≡	$\Delta G^‡$	ΔG
CHXDN	2.7591	1.2661	18.5	-44.6	2.7374	1.2509	31.2	-33.7
COCTDNYN	3.3822	1.2734	22.4	-59.7	3.3510	1.2546	35.3	-50.1

The $\sigma_{C\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}H}$ interactions in the TS structures for reactions with acetylene-1,2-bisnitrile are 19.7 and 8.7 kcal/mol in 1,3-cyclohexadiene and 21.8 and 7.3 kcal/mol in 1,3-

cyclooctadiene-6-yne. The difference ($\sigma_{C\text{-}H}$–π^*_{ring})-(π_{ring}–$\sigma^*_{C\text{-}H}$) has altered from 11.0 kcal/mol in 1,3-cyclohexadiene to 14.5 kcal/mol in 1,3-cyclooctadiene-6-yne. Likewise, the $\sigma_{C\text{-}H}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}H}$ interactions in the TS structures for reactions with acetylene are 16.7 and 9.4 kcal/mol in 1,3-cyclohexadiene and 19.4 and 8.8 kcal/mol in 1,3-cycloheptadiene. The difference here too has altered from 7.3 kcal/mol in 1,3-cyclohexadiene to 10.6 kcal/mol in 1,3-cyclooctadiene-6-yne. In spite of the increased net activation energy-lowering $\sigma_{C\text{-}H}$–π^*_{ring} interaction, the raise in the activation energy of 1,3-cyclooctadiene-6-yne could be due only to the *R*-effect.

Table 3d. Activation free energies ($\Delta G^‡$, kcal/mol), enthalpy changes (ΔG, kcal/mol), $\sigma_{C\text{-}X}$–π^*_{ring} and π_{ring}–$\sigma^*_{C\text{-}X}$ interactions (kcal/mol) in the *endo*-TS structures for DA reactions of butadiene, 1-Me-butadiene, 1,4-bis-Me-butadiene, 1-CF_3-butadiene, and 1,4-bis-CF_3-butadiene with MA in gas phase at MP2/6-31+G(d) level

X = Y = H, butadiene
X = H, Y = Me, 1-Me-butadiene
X = Y = Me, 1,4-bis-Me-butadiene
X = H, Y = CF_3, 1-CF3-butadiene
X = Y = CF_3, 1,4-bis-CF_3-butadiene

Diene	*endo*-TS			
	ΔG	$\Delta G^‡$	$\sigma_{C\text{-}X}$–π^*_{ring}	π_{ring}–$\sigma^*_{C\text{-}X}$
butadiene	-33.3	16.6	-	-
1-Me-butadiene	-31.2	14.5	9.8	4.6
1,4-bis-Me-butadiene	-28.9	12.4	18.8	9.2
1-CF_3-butadiene	-28.4	19.5	1.8	12.5
1,4-bis-CF_3-butadiene	-23.7	22.3	3.8	22.5

That indeed the allylic hydrogen lowers the activation energies of DA reactions of dienes such as 1,3-cyclohexadiene, 1,3-cycloheptadiene and 1,3-cyclooctadiene-6-yne through $\sigma_{C\text{-}H}$–π^*_{ring} interaction requires to be amply shown. An electron-attracting substituent, on the contrary, is expected to raise the activation energy through π_{ring}–$\sigma^*_{C\text{-}X}$ (X = allylic substituent) interaction.

Unlike the five-ring dienes, these dienes do not acquire aromatic or anti-aromatic character where the effect of the net interaction will be quite the reverse. We have studied the DA reactions of butadiene, 1-methylbutadiene, 1,4-bis-Me-butadiene, 1-CF_3-butadiene and 1,4-bis-CF_3-butadiene with MA. The data is collected in Table 3d.

The activation energy decreases from 16.6 kcal/mol for butadiene to 14.5 kcal/mol for 1-Me-butadiene and 12.4 kcal/mol for 1,4-bis-Me-butadiene as the difference of the electron-enhancing interaction $\sigma_{C\text{-}H}$–π^*_{ring} exceeds the electron-depleting interaction π_{ring}–$\sigma^*_{C\text{-}X/Y}$ by 5.2 and 9.6 kcal/mol, respectively. Contra to this, the activation energy rises from 16.6 kcal/mol for butadiene to 19.5 kcal/mol for 1-CF_3-butadiene and 22.3 kcal/mol for 1,4-bis-CF_3-butadiene as the electron-depleting interaction π_{ring}–$\sigma^*_{C\text{-}X/Y}$ exceeds the electron-enhancing interaction $\sigma_{C\text{-}H}$–π^*_{ring} by 10.7 and 18.7 kcal/mol, respectively.

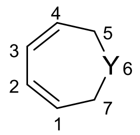
The above discussions substantially supports the *R*-hypothesis, *i.e.*, an increased *R* increases the activation energy of the DA reaction of a diene with a given dienophile. The *R*-hypothesis was floated long ago,[26] but never used in connection with the relative aromaticity of five-ring heterocycles as it is done in here. The *R*-effect and overlap intensity of the heteroatom lone pair with the ring π bonds together determine the activation energy of the DA reaction and the aromaticity order is pyrrole > furan > thiophene > selenophene.

(4) **DA reactions of 6-oxa-1,3-cycloheptadiene, 6-aza-1,3-cycloheptadiene, 6-thia-1,3-cycloheptadiene and 6-selena-1,3-cycloheptadiene with MA**: The idea behind studying these molecules was that the changing $\sigma_{C\text{-}X}$ bond length will also change *R* as in the five-ring heterocycles. Indeed, *R* in the ground state structure changed from 3.1098 Å in 6-oxa-1,3-cycloheptadiene to 3.1422 Å in 6-aza-1,3-cycloheptadiene to 3.2312 Å in 6-selena-1,3-cycloheptadiene to 3.2351 Å in 6-thia-1,3-cycloheptadiene. The *R* changed, respectively, to 2.9673 Å, 2.9868 Å, 3.0933 Å and 3.0554 Å in the *endo*-TSs for DA reaction with MA. It must be noted that the distance in the Se-analog is larger than S-analog by 0.0379 Å in the TS. The distance and energy parameters are collected in Table 4.

The net of interactions $\sigma_{C\text{-}H}$-π^*_{ring} and π_{ring}-σ^*_{CH} in the TS structures measures 10.2 kcal/mol, 11.9 kcal/mol, 12.9 kcal/mol, and 12.6 kcal/mol in the reactions of 6-oxa-, 6-aza-, 6-thia- and 6-selena-

1,3-cycloheptadienes, respectively. This interaction raises the reactivity of the respective diene. Must this interaction be the sole control of the reaction, the reactivity order will be 6-thia- > 6-selena- > 6-aza- > 6-oxa-1,3-cycloheptadiene. Likewise, if *R* alone were the control factor, the reactivity order will be 6-oxa- > 6-aza- > 6-thia- > 6-selena-1,3-cycloheptadiene. However, the reactivity order from the activation energies is 6-aza- > 6-oxa- > 6-selena- > 6-thia-1,3-cycloheptadiene. *R* and the net of the interactions $\sigma_{C\text{-}H}$-π^*_{ring} and π_{ring}-σ^*_{CH} appear to collectively control the reaction.

Table 4. *R* and π bond distances (Å) in the *endo*-TS structures for DA reactions of 6-oxa-1,3-cycloheptadiene, 6-aza-1,3-cycloheptadiene, 6-thia-1,3-cycloheptadiene and 6-selena-1,3-cycloheptadiene with MA, activation energies (Δ*G*‡, kcal/mol) and enthalpy changes (Δ*G*, kcal/mol) from gas phase calculations at MP2/6-31+G(d) level



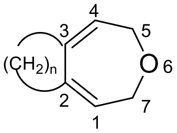
Y = O, 6-oxa-,13-cycloheptadiene
Y = NH, 6-aza-1,3-cycloheptadiene
Y = S, 6-thia-1,3-cycloheptadiene
Y = Se, 6-selena-1,3-cycloheptadiene

Diene	*endo*-TS			
	R	π	Δ*G*‡	Δ*G*
Y = O	2.9673	1.3878	17.1	-33.6
Y = NH	2.9868	1.3864	16.1	-35.4
Y = S	3.0554	1.3892	20.4	-33.1
Y = Se	3.0933	1.3893	18.1	-36.3

(5) **DA reactions of 2,3-cyclopropano-6-oxa-1,3-cycloheptadiene, 2,3-cyclobutano-6-oxa-1,3-cycloheptadiene and 2,3-cyclopentano-6-oxa-1,3-cycloheptadiene with MA**: These molecules were designed to take advantage of the different geometrical constraints of three-, four- and five-membered rings to manipulate *R*, which was expected to decrease in that order. Indeed, *R* varied from 3.3516 Å to 3.2652 Å to 3.1376 Å in the ground state structures of 2,3-cyclopropano-, 2,3-cyclobutano- and 2,3-cyclopentano-6-oxa-1,3-cycloheptadienes, respectively. As above, *R* was

expected to maintain a similar decreasing order in the TS structures for DA reaction with MA. The relevant structural and energy parameters are collected in Table 5.

Table 5. Enthalpy changes (Δ*G*, kcal/mol), activation free energies ($\Delta G^{\ddagger}$, kcal/mol), $\sigma_{\text{C-H}}–\pi^*_{\text{ring}}$ and $\pi_{\text{ring}}–\sigma^*_{\text{C-H}}$ interactions (kcal/mol) in the *endo*-TS structures for DA reactions of 2,3-cyclopropano-6-oxa-1,3-cycloheptadiene, 2,3-cyclobutano-6-oxa-1,3-cycloheptadiene and 2,3-cyclopentano-6-oxa-1,3-cycloheptadiene with MA in gas phase at MP2/6-31+G(d) level



n = 1; 2,3-cyclopropano-6-oxa-1,3-cycloheptadiene
n = 2; 2,3-cyclobutano-6-oxa-1,3-cycloheptadiene
n = 3; 2,3-cyclopentano-6-oxa-1,3-cycloheptadiene

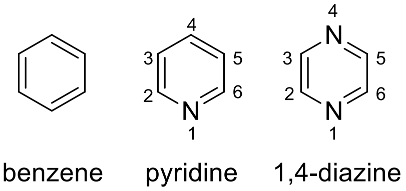
Diene	*endo*-TS				
	R	Δ*G*	$\Delta G^{\ddagger}$	$\sigma_{\text{C-H}}–\pi^*_{\text{ring}}$	$\pi_{\text{ring}}–\sigma^*_{\text{C-H}}$
n = 1	3.1107	-33.3	16.6	8.6	3.9
n = 2	3.0587	-28.0	13.8	12.3	4.6
n = 3	2.9895	-35.8	11.8	14.1	5.6

The activation energy decreased with *R*. The net of the interactions $\sigma_{\text{C-H}}–\pi^*_{\text{ring}}$ and $\pi_{\text{ring}}–\sigma^*_{\text{C-H}}$ increased from 4.7 kcal/mol in cyclopropano-derivative to 7.7 kcal/mol in cyclobutano-derivative to 8.5 kcal/mol in cyclopentano-derivative. The increasing interaction will lower the energy of activation. So, we can safely assume that the fall in activation energy is due to a combined effect of decreasing *R* and the increasing diene-activating $\sigma_{\text{C-H}}–\pi^*_{\text{ring}}$ interaction.

Having established the role of *R* and the diene-activating or deactivating orbital interactions, we aimed to study clearly aromatic substrates wherein *R* varied little but there were known differences in the aromaticity to see changes in activation energies of DA reactions. We chose (a) benzene, pyridine and 1,4-diazine, (b) naphthalene, 1-azanaphthalene and 1,4-diazanaphthalene, (c) anthracene, 9-azaanthracene and 9,10-diazaanthracene, and (d) benzene, naphthalene and anthracene, and located the TS structures for reactions with dienophiles. The results are described hereunder.

(6) **DA reactions of benzene, pyridine and 1,4-diazine with acetylene-1,2-bisnitrile and acetylene**: The uniformity of ring bonds is one major requirement for ring current and, hence, aromaticity. Any disruption in bond-uniformity reduces the aromaticity and such is the case with pyridine and 1,4-diazine. Pyridine is known to possess slightly lower resonance energy than benzene.[34] An extension of this argument would make 1,4-diazine possess lower resonance energy than pyridine. For the reactions of pyridine and 1,4-diazine, we chose 1,4-positions for the DA reaction[35] as the nitrogen centre is the source of said non-uniformity of bonds. The relevant structural and energy parameters are collected in Table 6. Surprisingly, the activation energy is seen to have increased in the order the resonance energy decreased. It is equally surprising to note the activation energy decrease for reaction across 2,4-positions of pyridine and 1,4-diazine (see footnotes to Table 6). The noted positional dependence of activation energy may be a good tool to test bond-uniformity.

Table 6. R and C≡C bond distances (Å) in the TS structures for DA reactions of benzene, pyridine and 1,4-diazine with acetylene-1,2-bisnitrile and acetylene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level

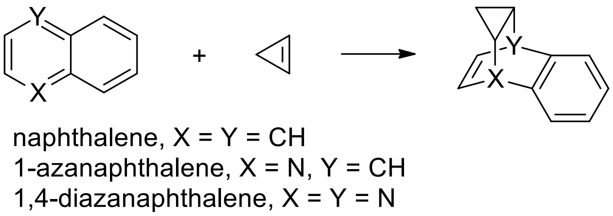


Diene	NCC≡CCN				HC≡CH			
	R	≡	$\Delta G^{\ddagger}$	ΔG	R	≡	$\Delta G^{\ddagger}$	ΔG
benzene	2.6587	1.2848	35.7	1.6	2.6547	1.2655	48.5	12.0
pyridine[a]	2.6529	1.2895	49.2	19.5	2.6529	1.2674	57.7	24.2
1,4-diazine[b]	2.6477	1.2912	64.3	37.4	2.6511	1.2716	69.0	41.6

[a] $\Delta G^{\ddagger}$ = 32.8 kcal/mol for DA reaction across positions 2 and 4 with NCC≡CCN.

[b] $\Delta G^{\ddagger}$ = 29.6 kcal/mol for DA reaction across positions 2 and 4 with NCC≡CCN.

(7) **DA reactions of naphthalene, 1-azanaphthalene and 1,4-diazanaphthalene with cyclopropene**: Naphthalene, 1-azanaphthalene and 1,4-diazanaphthalene are the benzo-derivatives of benzene, pyridine and 1,4-diazine, respectively, and, hence, they will have decreasing resonance energy. We have studied DA reactions of these aromatics with cyclopropene. The reaction was kept *exo* to the benzene ring in each instance as shown in Scheme 2.[36] The relevant structural and energy parameters are collected in Table 7.



Scheme 2. DA reactions of naphthalene, 1-azanaphthalene and 1,4-diazanaphthalene

Table 7. *R* and π bond distances (Å) in the TS structures for DA reactions of naphthalene, 1-azanaphthalene and 1,4-diazanaphthalene with cyclopropene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level

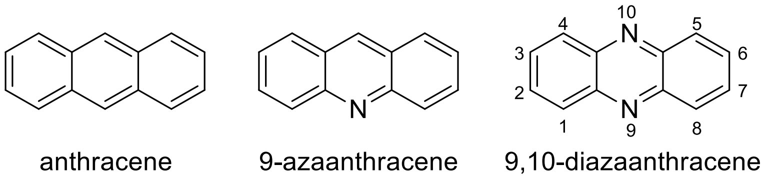
Diene	cyclopropene			
	R	π	$\Delta G^{\ddagger}$	ΔG
naphthalene	2.7315	1.3562	23.0	-19.3
1-azanaphthalene	2.7370	1.3663	28.5	-5.0
1,4-diazanaphthalene	2.7339	1.3787	37.5	10.4

Here also, the activation energy is seen to have risen from naphthalene to 1-azanaphthalene to 1,4-diazanaphthalene concurrent with decline in the resonance energy.

(8) **DA reactions of anthracene, 9-azaanthracene and 9,10-diazaanthracene with cyclopropene**: The DA reactions of anthracene, 9-azaanthracene and 9,10-diazaanthracene with cyclopropene were studied next for further confirmation of the above results. Anthracene has 24 kcal/mol less resonance energy than 3×benzene rings. The 9-azaanthracene and 9,10-diazaanthracene will have further less resonance energy than anthracene for the same reason as for

benzene and pyridine. The relevant structural and energy parameters are collected in Table 8. The activation energy again rose significantly as the resonance energy of the system decreased.

Table 8. R and π bond distances (Å) in the TS structures for DA reactions of naphthalene, 1-azanaphthalene and 1,4-diazanaphthalene with cyclopropene, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level



Diene	cyclopropene			
	R	π	$\Delta G^{\ddagger}$	ΔG
anthracene	2.7595	1.3443	11.9	-43.2
1-azaanthracene	2.7680	1.3550	19.1	-25.5
9,10-diazaanthracene	2.8712	1.3674	27.0	-9.2

(9) **DA reactions of benzene, naphthalene, and anthracene with acetylene-1,2-bisnitrile**: The all carbon systems benzene, naphthalene and anthracene were studied for DA reaction with acetylene-1,2-bisnitrile. Anthracene has 24 kcal/mol less resonance energy than 3×benzene rings. Likewise, naphthalene has 11 kcal/mol less resonance energy than 2×benzene rings. The drop in resonance energy must result in drop in activation energy. The data is collected in Table 9.

Table 9. R and ≡ bond distances (Å) in TS structures for DA reactions of benzene, naphthalene and anthracene with acetylene-1,2-bisnitrile, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) in gas phase at MP2/6-31+G(d) level

Diene	NCC≡CCN			
	R	≡	$\Delta G^{\ddagger}$	ΔG
benzene	2.6587	1.2848	35.7	1.6
naphthalene	2.6858	1.2812	26.4	-13.8
anthracene	2.7124	1.2752	12.3	-37.4

The activation energy is now indeed seen to decrease with the resonance energy from 35.7 kcal/mol for benzene to 26.4 kcal/mol for naphthalene and 12.3 kcal/mol for anthracene. The drop in the activation energy is significantly large, almost as large as the drop in the resonance energy. Indeed, more the resonance energy, more energy is required to deform it for a DA reaction.

We have verified the relationship of resonance and deformation energies by studying the reactions given in Table 9. The difference of the free energies of a reactant in the ground and TS structures constitutes deformation free energy ($\Delta D^{\ddagger}$). We treat the difference of the sum of deformation free energies of the reactants and the actual TS structure free energy as stabilization free energy ($\Delta S^{\ddagger}$) arising from orbital and other interactions. The deformation free energy of each reactant and also the stabilization free energy of the reaction in each instance is collected in Table 10.

Table 10. Deformation free energies ($\Delta D^{\ddagger}$, kcal/mol) and stabilization free energies ($\Delta S^{\ddagger}$, kcal/mol) for the DA reactions of benzene, naphthalene and anthracene with acetylene-1,2-bisnitrile (ABN) in gas phase at MP2/6-31+G(d) level

Reactants	NCC≡CCN			
	$\Delta D^{\ddagger}_{\text{diene}}$	$\Delta D^{\ddagger}_{\text{ABN}}$	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$
benzene + ABN	25.1	20.9	35.7	10.3
naphthalene + ABN	20.2	18.4	26.4	12.2
anthracene + ABN	12.2	14.8	12.3	14.7

The relationship of deformation energy with resonance energy of the aromatic system is very clear from the data. The deformation energy of the aromatic unit decreased with the resonance energy just as the deformation energy of the dienophile decreased with the deformation energy of the aromatic unit. In other words, more the aromatic character, more is the deformation energy of each reactant in the required effort to perturb each other to cause an effective orbital interaction.

In view of the above expected results, it was felt necessary to explore whether a similar relationship existed in DA reactions of the five-ring heterocycles. The relevant data for DA reactions with acetylene-1,2-bisnitrile is collected in Table 11a.

Table 11a. Deformation free energies ($\Delta D^{\ddagger}$, kcal/mol) and stabilization free energies ($\Delta S^{\ddagger}$, kcal/mol) in the TS structures for DA reactions of pyrrole, furan, thiophene, and selenophene with acetylene-1,2-bisnitrile (ABN) in gas phase at MP2/6-31+G(d) level

Heterocycle	NCC≡CCN (ABN)			
	$\Delta D^{\ddagger}_{\mathrm{heterocycle}}$	$\Delta D^{\ddagger}_{\mathrm{ABN}}$	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$
pyrrole	22.2	21.0	25.1	18.1
furan	17.9	17.5	23.9	11.5
thiophene	22.40	18.9	30.7	22.4
Selenophene	22.36	17.9	23.1	17.2

$\Delta SE^{\ddagger} = \Delta DE^{\ddagger}_{\mathrm{heterocycle}} + \Delta DE^{\ddagger}_{\mathrm{ABN}} - \Delta G^{\ddagger}$

Following the deformation energy of the five-ring heterocycle, the resonance energy follows the order thiophene ≥ selenophene ≥ pyrrole > furan. However, following the deformation energy of the dienophile, the resonance energy follows the order pyrrole > thiophene > selenophene ≥ furan. The discrepancy is obvious because the orders are not the same as for benzene, naphthalene and anthracene. *The deformation energy approach is not applicable to the five-ring heterocycles*. *The different heteroatoms allow different flexibility and, hence, deformity during the progress of the reaction*.

We wished to confirm the above deformation energy results by studying *endo*-DA reactions of five-ring heterocycles with MA. The heteroatom in the *endo*-TS structure affects the reaction by impacting the electronics of the diene system but not directly as it may possibly happen in the *exo*-TS structure. The deformation and activation free energy data are collected in Table 11b. The aromaticity order is pyrrole > selenophene > thiophene > furan from the deformation energies of heterocycles and pyrrole > thiophene > furan > selenophene from the deformation energies of dienophile. Other than pyrrole being on the top of the aromaticity order, nothing else is certain.

We noticed above different reactivity profiles and, hence, aromaticity orders from the use of different dienophiles. *The deformation energy approach may, therefore, not be used with confidence to the assessment of reactivity order and, hence, the relative aromaticity of five-ring heterocycles.*

Table 11b. Deformation free energies ($\Delta D^{\ddagger}$, kcal/mol) and stabilization free energies ($\Delta S^{\ddagger}$, kcal/mol) in the TS structures for *endo* DA reactions of pyrrole, furan, thiophene, and selenophene with MA in gas phase at MP2/6-31+G(d) level

Reactants	MA			
	$\Delta D^{\ddagger}_{\mathrm{heterocycle}}$	$\Delta D^{\ddagger}_{\mathrm{MA}}$	$\Delta G^{\ddagger}$	$\Delta S^{\ddagger}$
pyrrole	25.2	17.0	24.2	18.0
furan	19.6	12.9	20.4	12.1
thiophene	23.8	13.7	27.1	10.4
Selenophene	24.7	12.2	21.1	15.8

$\Delta SE^{\ddagger} = \Delta DE^{\ddagger}_{\mathrm{heterocycle}} + \Delta DE^{\ddagger}_{\mathrm{MA}} - \Delta G^{\ddagger}$

(10) **DA reactions of thiophene-1,1-dioxide with MA**: Unlike thiophene, thiophene-1,1-dioxide reacts with MA in DA fashion under the usual thermal conditions. The resonance stabilization due to mixing of sulfur lone pair with the ring π bonds is no doubt lost on oxidation of sulfur and the molecule begins to behave like a normal cyclic 1,3-diene and its reactivity is enhanced. The difference in reactivity of this molecule and cyclopentadiene must, therefore, emanate from two sources: (a) *R* and (b) the allylic interactions, *i.e.*, the interactions of the ring π bonds with C5-substituents.

TABLE 12. *R* and π bond distances (Å) in the *endo*- and *exo*-TS structures for DA reactions of cyclopentadiene (Y = CH_2), thiophene (Y = S) and thiophene-*S*,*S*-dioxide (Y = SO_2) with MA, activation energies ($\Delta G^{\ddagger}$, kcal/mol) and enthalpy changes (ΔG, kcal/mol) from gas phase calculations at MP2/6-31+G(d) level

Diene	*endo*-TS				*exo*-TS			
	R	π	$\Delta G^{\ddagger}$	ΔG	R	π	$\Delta G^{\ddagger}$	ΔG
Y = CH_2	2.3213	1.3890	12.0	-18.6	2.3221	1.3905	14.7	-18.5
Y = S	2.3979	1.4150	27.1	+2.3	2.3958	1.4152	28.7	+2.1
Y = SO_2	2.5343	1.3816	14.7	-30.7	2.5338	1.3849	24.4	-27.1

The relevant parameters for the DA reactions of cyclopentadiene, thiophene and thiophene-1,1-dioxide are collected in Table 12. The larger *R* in the TS structure for the reaction of thiophene-1,1-dioxide must ensure higher activation energy in keeping with the present findings.

The $\sigma_{\text{C5-H}}$-π^*_{ring} and π_{ring}-$\sigma^*_{\text{C5-H}}$ interactions in the reaction of cyclopentadiene with MA are, respectively, 15.9 and 9.3 kcal/mol in the *endo*-TS structure. The net $\sigma_{\text{C5-H}}$-π^*_{ring} interaction therefore is 6.6 kcal/mol and its role is to impart aromatic character to the ring and, thus, raise the energy of activation. Likewise, the $\sigma_{\text{S-O}}$-π^*_{ring} and π_{ring}-$\sigma^*_{\text{S-O}}$ interactions in the reaction of thiophene-1,1-dioxide with MA are, respectively, 1.9 and 12.9 kcal/mol in the *endo*-TS structure. The net π_{ring}-$\sigma^*_{\text{S-O}}$ interaction, therefore, is 11.0 kcal/mol and its role would be to impart anti-aromatic character to the ring and, thus, lower the energy of activation. If the *R*-effect is ignored, for the time being, the activation energy of thiophene-1,1-dioxide would be expected to be lower than that of cyclopentadiene. However, it is not so. The activation energy of thiophene-1,1-dioxide is 2.7 kcal/mol higher than that of cyclopentadiene. More than 2.7 kcal/mol energy will be required to accommodate *R*-effect in allowing thiophene-1,1-dioxide to react.

The $\sigma_{\text{C5-H}}$-π^*_{ring} and π_{ring}-$\sigma^*_{\text{C5-H}}$ interactions in the *exo*-TS structure for reaction of cyclopentadiene with MA are, respectively, 17.8 and 8.4 kcal/mol. The net $\sigma_{\text{C5-H}}$-π^*_{ring} interaction, therefore, is 9.4 kcal/mol and it will impart aromatic character to the ring and raise the activation energy. Similarly, the $\sigma_{\text{S-O}}$-π^*_{ring} and π_{ring}-$\sigma^*_{\text{S-O}}$ interactions in the *exo*-TS structure for the reaction of thiophene-1,1-dioxide with MA are, respectively, 1.9 and 13.0 kcal/mol. The net π_{ring}-$\sigma^*_{\text{S-O}}$ interaction is 11.1 kcal/mol and it would impart anti-aromatic character to the ring and lower the activation energy. However, the activation energy of the reaction of thiophene-1,1-dioxide is 9.7 kcal/mol higher than that of cyclopentadiene. The *R*-effect must contribute a large part of this higher energy demand.

Similar to thiophene-1,1-dioxide, one may expect the presence of lp_{S}-π^*_{ring} and π_{ring}-lp^*_{S} (lp_{S} = lone pair of S) interactions in the TS structures for reaction of thiophene with MA. However, these interactions are absent in both the *endo*- and *exo*-TS structures. In such a situation, the activation energy will depend on *R*, among other factors, and it will be expected to rise from cyclopentadiene to thiophene. Indeed, the activation energy for the reaction of thiophene is a substantial 14−15 kcal/mol above cyclopentadiene.

It is important to note that interactions of the sorts lp_X-π^*_{ring} and π_{ring}-lp^*_X (lp_X = heteroatom lone pair) are also completely absent in the *endo*- and *exo*-TS structures for reactions of pyrrole, furan and selenophene with MA. The interaction $\sigma_{N\text{-}H}$-π^*_{ring} is absent in the reaction of pyrrole. The absence of lp_X-π^*_{ring} interaction in the DA reactions of the five-ring heterocycles clearly suggests that their aromatic characters are fully lifted in the TS structures. On account of ground state aromaticity ensuring planar structures, sufficient energy is required for structure deformation to assume the TS structure.

The activation energy drops from 27.1 kcal/mol for *endo* addition of thiophene to MA to 14.7 kcal/mol for thiophene-1,1-dioxide, which is closer to 12.0 kcal/mol as the activation energy of cyclopentadiene. This drop in activation energy of thiophene-1,1-dioxide from that of thiophene arises from the anti-aromatic character introduced by the net of $\sigma_{S\text{-}O}$-π^*_{ring} and π_{ring}-$\sigma^*_{S\text{-}O}$ interactions in the dioxide.

(11) **DA reactions of *N*-COCF$_3$-pyrrole with MA and comparison with pyrrole and furan**: We considered *N*-trifluoroacetylation of pyrrole to disengage the lone pair from interaction with ring π-bonds in the ground state structure and study its DA reaction with MA to estimate activation energy and compare it with those of furan and the parent pyrrole. Since the lp-π^*_{ring} interaction is also lifted in the TS structure, the role of activation energy is simply to deform the structure to disrupt the lone pair conjugation and, thereby, confer normal diene character to the heterocycle for reaction in DA manner. *N*-trifluoroacetylation was, therefore, expected to lower the activation energy to a level where it may match with that of furan, but for the differences in *R* in the TS structures. This argument will probably not be applicable to *exo*-TS structure because of the apparent steric interactions arising from the COCF$_3$ group.

The TS data is collected in Table 13. Indeed, the activation energy drops from pyrrole to *N*-COCF$_3$-pyrrole by 3.2 kcal/mol and it is now only 0.6 kcal/mol above furan. We must note that *R* is also a bit longer in *N*-COCF$_3$-pyrrole than in furan. *The R-hypothesis appears vindicated*.

Table 13. *R* and π bond distances (Å) in the *endo*-TS structures for DA reactions of pyrrole, *N*-COCF$_3$-pyrrole, and furan with MA, activation energies (Δ$G^‡$, kcal/mol) and enthalpy changes (Δ*G*, kcal/mol) from gas phase calculations at MP2/6-31+G(d) level

Diene	*endo*-TS			
	R	π	Δ$G^‡$	Δ*G*
pyrrole	2.2000	1.4261	24.2	8.4
N-COCF$_3$-pyrrole	2.2374	1.4160	21.0	1.3
furan	2.1601	1.4122	20.4	0.8

TABLE 14. Study of the effects of solvents on the activation free energies (Δ$G^‡$) of the *endo*- and *exo*-DA reactions of pyrrole, furan, thiophene and selenophene with MA and enthalpy changes (Δ*G*, kcal/mol) at the MP2/6-311++G(d,p) level

Diene-Solvent	*endo*-TS		*exo*-TS	
	Δ$G^‡$	Δ*G*	Δ$G^‡$	Δ*G*
Pyrrole-CH$_3$CN	22.04	9.66	22.14	7.04
Pyrrole-Et$_2$O	22.32	9.05	21.90	6.73
Pyrrole-CHCl$_3$	22.30	9.12	21.93	6.77
Furan-CH$_3$CN	18.33	0.37	18.16	-2.13
Furan-Et$_2$O	18.40	0.25	18.49	-1.98
Furan-CHCl$_3$	18.39	0.26	18.46	-1.99
Thiophene-CH$_3$CN	24.56	1.57	25.31	0.31
Thiophene-Et$_2$O	24.60	1.37	25.56	0.36
Thiophene-CHCl$_3$	24.60	1.40	25.54	0.36
Selenophene-CH$_3$CN	24.91	-2.07	26.29	-2.69
Selenophene-Et$_2$O	24.91	-2.30	26.52	-2.69
Selenophene-CHCl$_3$	24.91	-2.27	26.50	-2.69

Having studied the total reaction profiles, we considered it desirable to comment on the stereoselectivity of DA reactions of five-ring heterocycles with maleic anhydride. For all but pyrrole, *endo*-addition is kinetically favored over the *exo*-addition. However, on including the enthalpy change (endergonic/exergonic character) of the processes and also allowing for the imminent reaction equilibration, all the heterocycles except selenophene are predicted for *exo* selectivity. Using the results in Table 1a and the results of solvent study collected in Table 14, the reaction profiles are depicted in Figure 4.

The analysis of data in detail is as follows:

(a) Both the *endo*- and *exo*-additions of pyrrole are endergonic and, hence, the reversal is eminent. The differential activation energy ($\Delta\Delta G^{\ddagger}$) of the reverse reactions is, therefore, more important than those of the forward reactions. Since the reverse reactions are very similar in their activation energies for differing merely by 0.1 kcal/mol from each other, a mixture of products is predicted. The $\Delta\Delta G^{\ddagger}$ for the reverse processes, however, is raised to 2.0 kcal/mol in chloroform as solvent. The reversal of the *exo*-adduct is slower than *endo*-adduct. The *exo*-adduct will therefore accumulate and constitute the major product. The situation remains much the same in solvent ether and also acetonitrile. Specifically, the $\Delta\Delta G^{\ddagger}$ for the reverse processes are 1.9 kcal/mol in ether and 2.7 kcal/mol in acetonitrile. The largest $\Delta\Delta G^{\ddagger}$ in acetonitrile is expected to best promote formation of the *exo* adduct among the solvents investigated herein. The results of the solvent effect on DA reactions of five-ring heterocycles are collected in Table 8.

(b) The energy requirement for *endo* addition of furan is the same as for the reverse reaction. The *exo*-addition is 0.5 kcal/mol higher than *endo*-addition and also the reversal of the *exo*-adduct is 2.2 kcal/mol more difficult than that of the *endo* adduct. Consequently, under thermal conditions allowing *exo*-addition, it is predicted to constitute the major pathway. In acetonitrile, kinetics favors *exo*- over *endo*-addition by 0.2 kcal/mol. Reversal of the *endo*-adduct is faster than its formation by 0.4 kcal/mol and, hence, it must not accumulate. In contrast, reversal of the *exo*-adduct is 2.1 kcal/mol more difficult than its formation, allowing it to accumulate and constitute the predominant product. The overall scenario remains unchanged in solvents ether and chloroform.[37]

(c) The *exo*-addition of thiophene is less endergonic than *endo*-addition by 0.5 kcal/mol. Further, since the reversal of the *endo*-process is faster than forward process by 0.9 kcal/mol, the *endo*-product will not accumulate. The reversal of the *exo*-process is also faster than the forward process but by only 0.3 kcal/mol. Thus, under the reaction conditions that both the *endo* (Δ$G^{‡}$ = 24.6 kcal/mol) and *exo* (Δ$G^{‡}$ = 26.0 kcal/mol) processes could take place, the *exo*-process will predominate. Except for small changes in kinetics, overall scenario remains unchanged in ether, acetonitrile and chloroform.

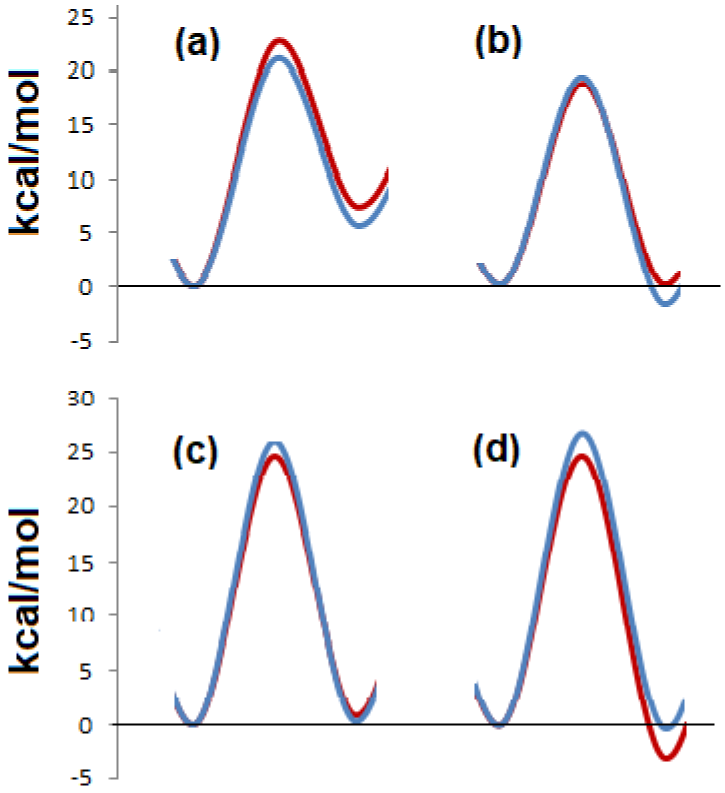


Figure 4. The reaction profiles for the endo (red line) and exo (blue line) Diels-Alder reactions of maleic anhydride with (a) pyrrole, (b) furan, (c) thiophene and (d) selenophene at the MP2/6-311++G(d,p) level

(d) The *exo*-addition of thiophene is less endergonic than *endo*-addition by 0.5 kcal/mol. Further, since the reversal of the *endo*-process is faster than forward process by 0.9 kcal/mol, the *endo*-product will not accumulate. The reversal of the *exo*-process is also faster than the forward process but by only 0.3 kcal/mol. Thus, under the reaction conditions that both the *endo* (Δ$G^{‡}$ = 24.6 kcal/mol) and *exo* (Δ$G^{‡}$ = 26.0 kcal/mol) processes could take place, the *exo*-process will predominate. Except for small changes in kinetics, overall scenario remains unchanged in ether, acetonitrile and chloroform.

(e) Both the *endo* ($\Delta G^{\ddagger}$ = 24.8 kcal/mol) and *exo* ($\Delta G^{\ddagger}$ = 26.9 kcal/mol) additions of selenophene are exergonic by 2.9 and 0.3 kcal/mol, respectively. Since $\Delta G^{\ddagger}$ for the reverse processes ($\Delta G^{\ddagger}_{\text{endo-adduct}}$ = 27.7 kcal/mol and $\Delta G^{\ddagger}_{\text{exo-adduct}}$ = 27.2 kcal/mol) are larger than the corresponding forward processes, the reaction is expected to proceed under kinetic control to allow the *endo*-adduct predominate. The scenario remains unchanged in ether, acetonitrile and chloroform.

Experimentally, pyrrole is reported to undergo DA reaction with maleic anhydride to furnish a mixture (composition not determined) of the adducts,[38] and both furan[39] and thiophene[20] the *exo*-adducts largely. Since the DA adduct formed from selenophene undergoes rapid extrusion of selenium, it prevents comment on the *endo*/*exo* selectivity.[22]

CONCLUSIONS

The order of aromaticity predicted on account of the difficulty of DA reaction and also on account of AIBIC is selenophene > thiophene > pyrrole > furan. This order, however, is pyrrole >> furan > thiophene > selenophene on account of $\text{lp}\rightarrow\pi_{\text{C=C}}$ interaction in the ground state structures. The use of relative DA reactivity as the marker of aromaticity is not appropriate because the reactivity changes substantially with the change in the separation of the termini of the diene for reaction with a given dienophile. A distance larger than π bond of the dienophile lifts the collinearity of the requisite *p* orbitals required for σ bond formation and the activation energy is raised.

Having considered aromaticity as the sole factor for the control of reactivity, one will predict very similar reactivity profiles for both furan and thiophene ($\text{lp}\rightarrow\pi^*_{\text{C=C}}$ = 42.9 kcal/mol in furan and 41.9 kcal/mol in thiophene). However, thiophene reacts only under forcing conditions. This is due to the difference in the distances between the reacting termini of the diene; the substantially large distance in thiophene results in significantly poor collinearity of the terminal *p* orbitals.

The *endo/exo*-selectivities predicted from the combination of differential TS structure energies for forward and reverse reactions and also the enthalpy changes are in excellent agreement with experiments. Among five-ring heterocycles, while furan and thiophene furnish *exo*-adducts, selenophene is predicted for *endo*- and pyrrole for *exo*-addition, depending upon the reaction conditions. Solvents may change the kinetics and also the course of the reaction.

ASSOCIATED CONTENT

Supporting Information (SI)

Cartesian coordinates and Gibbs' free energies of the optimized substrates, products and the transition state structures (PDF, 84 pages).

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REFERENCES AND NOTES

(1) Minkin, V. I.; Glukhovtsev, M. N.; Simkin, B. Y. Aromaticity and Antiaromaticity. Wiley, New York (1994).

(2) Dey, S.; Manogaran, D.; Manogaran, S.; Schaefer III, H. F. Quantification of Aromaticity of Heterocyclic Systems Using Interaction Coordinates. *J. Phys. Chem. A* **2018**, *122*, 6953–6960.

(3) (a) Horner, K. E.; Karadakov, P. B. Shielding in and around Oxazole, Imidazole, and Thiazole: How Does the Second Heteroatom Affect Aromaticity and Bonding? *J. Org. Chem.* **2015**, *80*, 7150−7157. (b) Horner, K. E.; Karadakov, P. B. Chemical Bonding and Aromaticity in Furan, Pyrrole, and Thiophene: A Magnetic Shielding Study. *J. Org. Chem.* **2013**, *78*, 8037−8043. (c) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Homes, N. J. R. v. E. Nucleus-Independent Chemical Shifts: A Simple and Efficient Aromaticity Probe. *J. Am. Chem. Soc.* **1996**, *118*, 6317−6318.

(4) (a) Aihara, J. A new definition of Dewar-type resonance energies. *J. Am. Chem. Soc.* **1976**, *98*, 2750–2758. (b) Gutman, I.; Milun, M.; Trinajstic, N. Graph theory and molecular orbitals. 19. Nonparametric resonance energies of arbitrary conjugated systems. *J. Am. Chem. Soc.* **1977**, *99*, 1692–1704.

(5) Aihara, J.; Kanno, H.; Ishida, T. Magnetic Resonance Energies of Heterocyclic Conjugated Molecules. *J. Phys. Chem.* A **2007**, *111*, 8873–8876.

(6) Aihara, J. Circuit Resonance Energy: A Key Quantity That Links Energetic and Magnetic Criteria of Aromaticity. *J. Am. Chem. Soc.* **2006**, *128*, 2873–2879.

(7) (a) Arkin, R.; Kerim, A. A study on the aromaticity and magnetotropicity of 10π-electron azapentalene derivatives. *Chem. Phys. Lett.* **2012**, *546*, 144–149. (b) Aihara, J. Spherical Aromaticity in Fullerenes and the Nucleus-Indpendent Chemical Shifts at the Cage Centers. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 103–105. (c) Poater, J.; Garcia-Cruz, I.; Illas, F.; Sola, M. Discrepancy between common local aromaticity measures in a series of carbazole derivatives. *Phys. Chem. Chem. Phys.* **2004**, *6*, 314–318. (d) Stanger, A. What is… aromaticity: a critique of the concept of aromaticity−can it really be defined? *Chem. Commun.* **2009**, *15*, 1939–1947. (e) Omelchenko, I. V.; Shishkin, O. V.; Gorb, L.; Leszczynski, J.; Fiase, S.; Bultinck, P. Aromaticity in heterocyclic analogues of benzene: comprehensive analysis of structural aspects, electron decolalization and magnetic characteristics. *Phys. Chem. Chem. Phys.* **2011**, *13*, 20536–20548. (f) Islas, R.; Martinez-Guajardo, G.; Jimenez-Halla, J. O. C.; Sola, M.; Merino, G. Not All That Has a Negative NICS Is Aromatic: The case of the H-bonded Cyclic Trimer of HF. *J. Chem. Theory Comput.* **2010**, *6*, 1131–1135.

(8) For criticism of the NICS approach, see: (a) Lazzeretti, P. Assesment of aromaticity *via* molecular response properties. *Phys. Chem. Chem. Phys.* **2004**, *6*, 217−223. (b) Fias, S.; Fowler, P. W.; Delgado, J. L.; Hahn, U.; Bultinck, P. Correlation of Delocalization Indices and Current-Density Maps in Polyclic Aromatic Hydrocarbons. *Chem.−Eur. J.* **2008**, *14*, 3093−3099. For comments on the reliability of other approaches for aromaticity prediction, see: (c) Najmidin, K.; Kerim, A.; Abdirishit, P.; Kalam, H.; Tawar, T. A comparative study of the aromaticity of pyrrole, furan, thiophene, and their aza-derivatives. *J. Mol. Model.* **201**3, *19*, 3529–3535.

(9) Feixas, F.; Matito, E.; Poater, J.; Sola, M. On the performance of some aromaticity indices: A critical assessment using a test set. *J. Comput. Chem.* **2008**, *29*, 1543–1554.

(10) (a) Hückel, E. Quantentheoretische Beiträge zum Benzolproblem I. Die Elektronenkonfiguration des Benzols und verwandter Verbindungen. *Z. Phys.* **1931**, *70*, 204–286. (b) Hückel, E. Quanstentheoretische Beiträge zum Benzolproblem II. Quantentheorie der induzierten Polaritäten. *Z. Phys.* **1931**, *72*, 310–337. (c) Hückel, E. Quantentheoretische Beiträge zum Problem der aromatischen und ungesättigten Verbindungen. III". Z. Phys. **1932**, *76*, 628–648. (d) Doering, W. v. E.; Detert. F. L. Cycloheptatrienylium Oxide. *J. Am. Chem. Soc.* **1951**, *73*, 876–877.

(11) (a) Kruszewski, J.; Krygowski, T. M. Definition of aromaticity basing on the harmonic oscillator model. *Tetrahedron Lett.* **1972**, *13*, 3839–3842. (b) Krygowski, T. M. Crystallographic studies of inter- and intramolecular interactions reflected in aromatic character of .pi.-electron systems. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 70–78.

(12) (a) Islas, R.; Heine, T.; Merino, G. The Induced Magnetic Field. *Acc. Chem. Res.* **2012**, *45*, 215–228. (b) Poater, J.; Duran, M.; Sola, M.; Silvi, B. Theoretical Evaluation of Electron Delocalization in Aromatic Molecules by Means of Atoms in Molecules (AIM) and Electron Localization Function (ELF) Topological Approaches. *Chem. Rev.* **2005**, *105*, 3911–3947. (c) Chen, Z. F.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. Nucleus-Independent Chemical Shifts (NICS) as an Aromaticity Criterion. *Chem. Rev.* **2005**, *10*, 3842–3888. (d) Merino, G.; Vela, A.; Heine, T. Description of Electron Delocalization via the Analysis of Molecular Fields. *Chem. Rev.* **2005**, *105*, 3812–3841 (e) Lazzeretti, P. Ring currents. *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *36*, 1–88.

(13) Doddi, G.; Illuminati, G.; Mencarelli, P.; Stegel, F. Nucleophilic Substitution at the Pyrrole Ring. Comparison with Furan, Thiophene, and Benzene Rings in Piperidinodenitration. *J. Org. Chem.* **1976**, *41*, 2824-2826.

(14) G. Marino, G. Electrophilic Substitutions of Five-Membered Rings. *Adv. Heterocycl. Chem.* **1971**, *13*, 235−314.

(15) The Chemistry of the Aromatic Heterocycles, Chapter 25, p 1228. https://www.saplinglearning.com/media/loudon/loudon5ech25sec03.pdf

(16) Belen'kii, L. I.; Suslov, I. A.; Chuvylkin, N. D. Substrate and Positional Selectivity in Electrophilic Substitution Reactions of Pyrrole, Furan, Thiophene, and Selenophene Derivatives**.** *Chem. of Heterocycl. Compd.* **2003**, *39*, 36–48; and references cited therein.

(17) Baran, P.; Richter, J. R. https://www.scripps.edu/baran/heterocycles/Essentials1-2009.pdf

(18) The chemical shifts are for the neat liquids with only a small amount of TMS added as a standard. See: Page, Jr., T. F.; Alger, T.; D. M. Grant, D. M. The Carbon-13 Nuclear Magnetic Resonance Spectra of Furan, Pyrrole, Thiophene, and Some of Their Methyl Derivatives. *J. Am. Chem. Soc.* **1965**, *87*, 5333−5339.

(19) Dauben, W. G.; Krabbenhoft, H. O. Organic reactions at high pressure. Cycloadditions with furans. *J. Am. Chem. Soc.* **1976**, *98*, 1992−1993.

(20) (a) Kotsuki, H.; Kitagawa, S.; Nishizawa, H.; Tokoroyama, T. High pressure organic chemistry. 2. Diels-Alder reaction of thiophene with maleic anhydride at very high pressure. *J. Org. Chem.* **1978**, *43*, 1471−1472. (b) Kotsuki, H.; Nishizawa, H.; Kitagawa, S.; Ochi, M.; Yamasaki, N.; Matsuoka, K.; Tokoroyama, T. High Pressure Organic Chemistry. III. Diels-Alder reaction of Thiophene with Maleic Anhydride. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 544−548.

(21) K. Kumamoto, I. Fukada, H. Kotsuki, Diels–Alder Reaction of Thiophene: Dramatic Effects of High-Pressure/Solvent-Free Conditions *Angew. Chem. Int. Ed.* **2004**, *43*, 2015–2017.

(22) Bird, C. W.; Cheeseman, G. W. H.; Hörnfeldt, A.-B. in Comprehensive Heterocyclic Chemistry, 1984, Elsevier, Editors: Katrizky, A. R.; Rees, C. W. https://doi.org/10.1016/B978-008096519-2.00066-7

(23) Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

(24) (a) Barone, V.; Cossi, M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model. *J. Phys. Chem.* A **1998**, *102*, 1995**–**2001. (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. Energies, structures, and electronic properties of molecules in solution with the C-PCM model. *J. Comput. Chem.* **2003**, *24*, 669**–**681.

(25) Reed, A. E.; Curtiss, L. A.; Weinhold, F. Intermolecular interactions from natural bond orbital, donor-acceptor viewpoint. *Chem. Rev.* **1988**, *88*, 899**–**926.

(26) (a) Nyulászi, L.; Schleyer, P. v. R. Hyperconjugative π-Aromaticity: How To Make Cyclopentadiene Aromatic. *J. Am. Chem. Soc.* **1999**, *121*, 6872−6875. (b) Schleyer, P. v. R.; Nyulászi, L.; Kárpáti, T. To What Extent Can Nine-Membered Monocycles Be Aromatic? *Eur. J. Org. Chem.* **2003**, *10*, 1923−1930. (c) Fernández, I.; Wu, J. I.; Schleyer, P. v. R. Substituent Effects on “Hyperconjugative” Aromaticity and Antiaromaticity in Planar Cyclopolyenes. *Org. Lett.* **2013**, *15*, 2990−2993. (d) Levandowski, B. J.; Zou, L.; Houk, K. N. Schleyer hyperconjugative aromaticity and Diels-Alder reactivity of 5-substituted cyclopentadienes. *J. Comput. Chem.* **2016**, *37*, 117−123.

(27) The electronegativities of nitrogen and oxygen are, respectively, 3.0 and 3.5 on the Pauling scale.

(28) (a) Fukuzumi, S.; Kochi, J. K. Electron transfer activation of the Diels-Alder reaction: Quantitative relationship to charge transfer excited states. *Tetrahedron* **1982**, *38*, 1035–1049. (b) Sustmann, R.; Korth, H.-G.; Nüchter, U.; Siangouri-Feulner, J.; Sicking, W. Are Charge-Transfer Complexes Intermediates in Diels-Alder Reactions? A Case Study of the Reaction of 1,2-Dimethylenecyclopentane with Tetracyanoethylene. *Eur. J. Inorg. Chem.* **1991**, *124*, 2811–2817. (c) Korchowiec, J. Role of charge-transfer effects in regioselectivity. *Int. J. Quantum Chem.* **2005**, *101*, 714–721. (d) Domingo, L. R.; Sáez, J. A. Understanding the mechanism of polar Diels–Alder

reactions. *Org. Biomol. Chem.* **2009**, *7*, 3576–3583. (e) Rosokha, S. V.; Korotchenko, V.; Stern, C. L.; Zaitsev, V.; Ritzert, J. T. Substituent-Induced Switch of the Role of Charge-Transfer Complexes in the Diels–Alder Reactions of *o*-Chloranil and Styrenes. *J. Org. Chem.* **2012**, *77*, 5971–5981. (f) Sexton, T.; Kraka, E.; Cremer, D. Extraordinary Mechanism of the Diels–Alder Reaction: Investigation of Stereochemistry, Charge Transfer, Charge Polarization, and Biradicaloid Formation. *J. Phys. Chem. A* **2016**, *120*, 1097–1111. (g) Shimizu, R.; Okada, Y.; Chiba, K. Stepwise radical cation Diels–Alder reaction via multiple pathways. *Beilstein J. Org. Chem.* **2018**, *14,* 704–708. (h) Levandowski, B. J.; Hamlin, T. A.; Helgeson, R. C.; Bickelhaupt, F. M.; Houk, K. N. Origins of the Endo and Exo Selectivities in Cyclopropenone, Iminocyclopropene, and Triafulvene Diels-Alder Cycloadditions. *J. Org. Chem.* **2018**, *83*, 3164–3170.

(29) (a) Westerhausen, M.; Stein, B.; Ossberger, M. W.; Görls, H.; Ruiz, J. C. G.; Nöth, H.; Mayer, P. Diels-Alder cycloaddition reaction of 1,1-dichloro-2,3,4,5-tetraethylgermole and 1-chloro-2,3,4,5-tetraethylphosphole with maleic acid anhydride and maleimide. ARKIVOC **2007**, Part (iii), 46–59. (b) Laporterie, A.; Manuel, G.; Dubac, J.; Mazerolles, P.; Iloughmane, H. *J. Organomet. Chem.* **1981**, *210,* C33–C36.

(30) Alder, K.; Stein, G. Untersuchungen über den Verlauf der Diensynthese. *Angew. Chem.* **1937**, *50*, 510–519.

(31) (a) Hoffmann, R.; Woodward, R. B. Orbital Symmetries and endo-exo-Relationships in Concerted Cycloaddition Reaction. *J. Am. Chem. Soc.* **1965**, *87*, 4388–4389. (b) Hoffmann, R.; Woodward, R. B. Orbital Symmetries and Orientational Effects in a Sigmatropic Reaction. *J. Am. Chem. Soc.* **1965**, *87*, 4389–4390.

(32) (a) Wassermann, A. The Mechanism of addition to double bonds. Part II. The steric course of two diene syntheses. *J. Chem. Soc.* **1935**, 1511–1514; (b) Williamson, K. L.; Hsu, Y. F. L. Stereochemistry of the Diels-Alder reaction. II. Lewis acid catalysis of syn-anti isomerism. *J. Am. Chem. Soc.* **1970**, *92*, 7385–7389. (c) Furukawa, J.; Kobuke, Y.; Fueno, T. Endo selectivities of some methyl-substituted dienophiles in Diels-Alder reactions with cyclopentadiene. *J. Am. Chem. Soc.* **1970**, *92*, 6548–6553. (d) Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. Role of attractive interactions in endo-exo stereoselectivities of Diels-Alder reactions. *J. Am. Chem. Soc.* **1972**, *94*, 3633–3635.

(33) (a) Sustmann, R.; Boehm, M.; Sauer, J. Effect of diene 1,4-distance on the reactivity in Diels-Alder reactions *Chem. Ber.* **1979**, *112*, 883−889. (b) Scharf, H. D.; Plum, H.; Fleischhauer, J.; Schleker, W. Diels-Alder reactivity of *s*-cis-fixed 1,3-dienes. *Chem. Ber.* **1979**, *112*, 862−882. (c) Vogel, P; Houk, K. N. in Organic Chemistry: Theory, Reactivity and Mechanisms in Modern Syntheses, Wiley-VCH, 2019, Chapter 5.3.12.

(34) (a) Wiberg; K. B.; Nakaji, D. Y.; Morgan, K. M. Heat of hydrogenation of a cis imine. An experimental and theoretical study. *J. Am. Chem. Soc*. **1993**, *115*, 3527−3532. (b) Wiberg, K. B.; Nakaji, D.; Breneman, C. M. Azines. A theoretical study of .pi.-electron delocalization. *J. Am. Chem. Soc.* **1989**, *111*, 4178−4190.

(35) Boger, D. L. Diels-Alder Reactions of Heterocyclic Azadienes: Scope and Applications. *Chem. Rev.* **1986**, *86*, 781−793.

(36) For theoretical calculations of the DA reactions of benzene and naphthalene, see: Kiselev, V. D.; Kashaeva, E. A.; Potapova, L. N.; Iskhakova, G. G. Diels-Alder reaction between naphthalene and *N*-phenylmaleimide under mild conditions. *Russ. Chem. Bull.* **2004**, *53*, 51–54. For DA reaction of naphthalene at elevated temperature and pressure, see: (a) Jones, W. H.; Mangold, D.; Plieninger, H. Diensynthesen under hohem druck. *Tetrahedron* **1962**, *18*, 267−272. (b) Klarner, F.-G.; Breitkopf, V. The Effect of Pressure on Retro Diels-Alder Reactions. *Eur. J. Org. Chem.* **1999**, 2757−2762. For DA reaction of naphthalene under co-encapsulated condition, see: Murase, T.; Horiuchi, S.; Fujita, M. Naphthalene Diels-Alder in a Self-Assembled Molecular Flask. *J. Am. Chem. Soc.* **2010**, *132*, 2866–2867.

(37) For temperature effect on the Diels-Alder reaction of furan with maleic anhydride and maleimide, see: Yadav, V. K.; Prasad, D. L. V. K.; Yadav, A.; Yadav, K. On the solvent and temperature driven stereoselectivity of the Diels-Alder cycloaddition reactions of furan with maleic anhydride and maleimide. *ChemRxiv. Preprint.* (**2019**) https://doi.org.10.26434/chemrxiv.11410059.v1

(38) Papaspyrou, A.; Spyropoulou, K.; Paraskevas, M. S.; Paraskevas, S. M. Synthesis and Electron Spin Resonance Studies of Cu(II) Complexes with Schiff Base Macroligands. *Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry* **2008**, *38*, 623–628. However, for a report on the formation of a single product, see: Leont'eva, S. V.; Manulik, O. S.; Evstigneeva, E. M.; Bobkova, E. N.; Flid, V. R. Unconventional catalytic allylation of 5-norbornene-2,3-dicarboxylic anhydrides: 7-oxa and 7-aza analogues. *Kinet.Catal.* **2006**, *47*, 384–388.

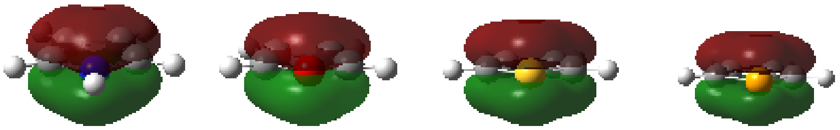
(39) Woodward, R. B.; Baer, H. The Reaction of Furan with Maleic Anhydride. *J. Am. Chem. Soc.* **1948**, *70*, 1161–1166.

Table of Contents

A computational study of the relative aromaticity of pyrrole, furan, thiophene and selenophene, and their stereoselectivities in Diels-Alder reactions

Veejendra K. Yadav*

The interaction energy of heteroatom lone pair with ring π bonds suggests the relative aromaticity order to be pyrrole >> furan > thiophene > selenophene. The activation energies of Diels-Alder reactions of thiophene and selenophene depend more on termini separation of the diene than their resonance energies unlike pyrrole and furan.



	pyrrole	furan	thiophene	selenophene
$lp\text{-}\pi^*_{C=C}$ (kcal/mol) ⇨	61.9	42.9	41.9	33.0