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A Theoretical Study of Acetylene, Ethylene, and Cyclopropene Additions to Benzo[b]- and Benzo[c]-fused Heterocycles

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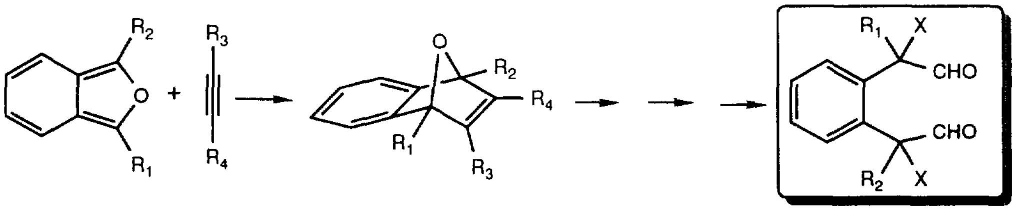
Summary: The reactivity of benzo[b]- and benzo[c]-fused heterocycles as dienes for Diels-Alder reactions were evaluated on the basis of Frontier Molecular Orbital (FMO) energy gaps between reactants, necessary FMO changes for the transformation of reactants into transition state structures, uniformity of bond orders of heterocyclic rings, and uniformity of bond orders of the six-membered cyclic transition state structures All of these values were obtained with AM1 semiempirical methods. The selectivity of the cycloaddition reaction was also judged with Secondary Orbital Interactions (SOI) between two reactant moieties in isomeric transition state structures. For every possible reaction pathway, AM1 and B3LYP/AM1 energies were evaluated. The relative reactivity and selectivity obtained by computing activation barriers for these reactions were in full agreement with our qualitative studies as well as with experimental results. The usefulness of the FMO and bond order uniformity approach for the study of the Diels-Alder reaction was discussed. © 1997 Elsevier Science Ltd.

Introduction

Benzene fused five-membered heterocyclic compounds are, from an experimental point of view, an ideal starting material for the preparation of complex organic compounds that contain a 1,2-disubstituted benzene ring. One possible transformation begins with benzene[c]-fused heterocycles through a Diels-Alder reaction with acetylene derivatives. The formed cycloadduct can be ozonized and the furan ring can be easily opened generating the desirably functionalized 1,2-disubstituted benzene (Scheme 1). Some theoretical studies pertaining to the reactivity of benzo-fused heterocycles in cycloaddition reactions was published previously.[1] While benzo[b] heterocyclic compounds are stable compounds, benzo[c] heterocycles are very reactive species which are usually difficult to isolate in pure form.[2] For instance, the existence of benzo[c]furan was unequivocally proven by Fieser and Haddadin.[3] There are many methods for preparing benzo[c]furan but it is quite difficult to obtain in a pure form.[4] Some of the methods which produce relatively pure compounds were published in 1972. These include the pyrolysis of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene at 650°C and 0.1 torr.[5] We have studied the reactivity of benzo-fused heterocycles through B3LYP/6-31G(d) evaluations of relative energies. Here we would like to present our evaluation of their reactivities by exploring the uniformity of the rings' bond orders and Frontier Molecular Orbital (FMO) energies.



Scheme 1. A possible transformation of benzo-fused heterocycles into 1,2-functionalized benzene derivatives

Computational Methods

All semiempirical calculations were performed on a DEC 7620 computer. Chem-3D Plus on a Macintosh IIfx was used as a graphical interface for drawing and visualizing all structures and for preparing input files for MOPAC.[6] In AM1, bond order is defined as the sum of the squares of the density matrix elements containing any two atoms. For instance, the C-C bond orders for ethane, ethylene, and acetylene are, by definition, 1, 2, and 3, respectively.[6] The transition state structures were localized, optimized, and verified as explained in our previous work.[7] All Density Functional Theory (DFT) computational studies were performed with B3LYP[8] and the 6-31G(d)[9] basis set as incorporated into the GAUSSIAN[10] computational package.

Results and Discussion

Recently we have proposed a new approach to determine the reactivity of aromatic compounds as dienes for Diels-Alder reactions.[11] The approach is based on a simple principle; if an unsaturated cyclic system has a uniform distribution of bond orders (π-bonds), it is very stable (aromatic[12]) and does not engage in chemical reactions easily. Let us first examine the aromatic character of the benzo[b]heterocycle (Table 1). It is very interesting to mention that little aromatic stability for benzene is lost by its fusing with furan, pyrrole, or thiophene to make benzo[b]heterocycles. Actually, the difference in bond order deviation in the benzene ring from the average bond order is very small. The closest resemblance with separated benzene is obtained for benzo[b]furan, which is the least aromatic compound of the three heterocycles (Table 1). The highest uniformity

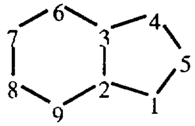


Table 1. Bond order uniformity in the heterocyclic and benzene ring of the benzo[b]heterocycle as computed with the AM1 semiempirical method

	Benzo[b]furan		Benzo[b]pyrrole		Benzo[b]thiophene	
bonds	BO	BOD	BO	BOD	BO	BOD
			Heterocyclic ring			
X(1)-C(2)	1.060	-0.194	1.123	-0.143	1.097	-0.180
C(2)-C(3)	1.297	0.043	1.274	0.006	1.316	0.039
C(3)-C(4)	1.102	-0.152	1.161	-0.107	1.140	-0.137
C(4)-C(5)	1.742	0.488	1.643	0.376	1.704	0.427
C(5)-X(1)	1.067	-0.186	1.136	-0.132	1.129	-0.148
S	6.267	1.063	6.337	0.764	6.387	0.932
ABO	1.253	0.213	1.267	0.153	1.277	0.186
			Benzene ring			
C(2)-C(3)	1.297	-0.080	1.274	-0.091	1.316	-0.059
C(3)-C(6)	1.342	-0.035	1.301	-0.063	1.296	-0.079
C(6)-C(7)	1.460	0.083	1.501	0.136	1.507	0.132
C(7)-C(8)	1.371	-0.006	1.327	-0.038	1.323	-0.052
C(8)-C(9)	1.452	0.075	1.502	0.137	1.505	0.130
C(9)-C(2)	1.340	-0.037	1.283	-0.082	1.305	-0.070
S	8.261	0.316	8.188	0.547	8.253	0.523
ABO	1.377	0.053	1.365	0.091	1.376	0.087
Total BOD		1.379		1.311		1.455

BO = bond order; BOD = bond order deviation from average bond order; S = sum of bond orders or sum bond order deviation from average bond order; ABO = average ring bond order for the heterocycles was observed for pyrrole. Overall, benzo[b]pyrrole should be the most aromatic, while benzo[b]furan should be the least aromatic of these three heterocycles.

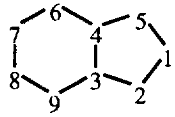


Table 2. Bond order uniformity in the heterocyclic and benzene ring of benzo[c]heterocycles as computed with the AM1 semiempirical method

	Benzo[c]furan		Benzo[c]pyrrole		Benzo[c]thiophene	
bonds	BO	BOD	BO	BOD	BO	BOD
			Heterocyclic ring			
X(1)-C(2)	1.133	-0.158	1.225	-0.065	1.240	-0.069
C(2)-C(3)	1.525	0.234	1.401	0.111	1.434	0.125
C(3)-C(4)	1.140	-0.152	1.199	-0.092	1.198	-0.111
C(4)-C(5)	1.525	0.234	1.401	0.111	1.434	0.125
C(5)-X(1)	1.133	-0.158	1.225	-0.065	1.240	-0.069
S	6.455	0.935	6.451	0.445	6.544	0.500
ABO	1.291	0.187	1.290	0.089	1.309	0.100
			Benzene ring			
C(3)-C(4)	1.140	-0.184	1.199	-0.138	1.198	-0.138
C(4)-C(6)	1.117	-0.206	1.161	-0.176	1.149	-0.186
C(6)-C(7)	1.710	0.387	1.655	0.318	1.669	0.334
C(7)-C(8)	1.146	-0.177	1.190	-0.147	1.178	-0.157
C(8)-C(9)	1.710	0.387	1.655	0.318	1.669	0.334
C(9)-C(3)	1.117	-0.206	1.161	-0.176	1.149	-0.186
S	7.939	1.547	8.021	1.273	8.013	1.335
ABO	1.323	0.258	1.337	0.212	1.335	0.223
Total BOD		2.482		1.718		1.835

BO = bond order; BOD = bond order deviation from average bond order; S = sum of bond orders or sum of bond order deviation from average bond order; ABO = average ring bond order

Benzo[c]-fused heterocycles (Table 2) possess the same interesting features. All of the heterocycles have a much more uniform ring bond order than their benzo[b] isomers. Here benzene bond order uniformity is considerably more disrupted by the presence of the five-membered heterocycle (Table 2). According to the rings' bond orders, the most uniform heterocycle is benzo[c]pyrrole with a total bond order deviation of 1.718. This difference in bond order deviations for benzo[c]pyrrole and benzo[c]thiophene suggest that they have comparable aromaticity. However, it is well known that the semiempirical AM1 method underestimates bond distances because of the presence of d-orbitals in sulfur. Therefore, benzo[c]thiophene could be found less reactive than benzo[c]pyrrole if a higher level of theory is applied, as we will demonstrate later. Nevertheless, from the presented results, it is obvious that benzo[b] heterocycles have a more even distribution of bond orders (delocalization), hence they are more aromatic in comparison to their benzo[c] isomers. Furthermore, the difference in the energy between these two groups of isomers should be very high for benzofuran, while benzopyrrole and benzothiophene should have a similar energy difference between their [b] and [c] isomers. Considering the fact that benzene is more aromatic than any of the heterocyclic aromatic compounds, the system that has a higher benzene bond order deviation is less stable and therefore more reactive. In our case, our results show bond order deviation as benzo[c]furan first, followed by benzo[c]thiophene and finally benzo[c]pyrrole.

To confirm this finding we have computed energy differences between these two series of isomers. In order to discuss the relative stability of these compounds, one can imagine fusing benzene with a five-membered heterocycle with the elimination of ethylene through an isodesmic reaction. The energy of this imaginary reaction might also suggest the relative stability of benzo-fused heterocycles. All calculations suggest that benzo[b]-fused heterocycles are more stable than benzo[c] heterocycles. This is in perfect agreement with the bond order deviation computed from ring uniformity (Table 1 and 2). The enthalpy for the imaginary reaction between the heterocycle and benzene, which produces a benzo-fused heterocycle and ethylene, is also a good measure of their stability. This reaction, as for all cases, is endothermic and the more endothermic the system is, the less stable it is. As mentioned previously, the fused benzene and heterocyclic system is less thermally favorable than the two separated aromatic systems. The least unfavorable fusion is for benzo[b]furan, while the most unfavorable fusion is for benzo[c]furan. Almost identical energies are obtained for the imaginary ring fusion between benzene and pyrrole on one side and benzene and thiophene on the opposite side (Table 3), indicating that they may possess similar aromatic properties. Therefore, the most favorable diene for the Diels-Alder reaction should be benzo[c]furan.

Table 3. Energy differences (kcal/mol) between the two isomers and energies for the imaginary reaction of benzene fusing with a five-membered heterocycle

Method of computing	Benzofuran			Benzopyrrole			Benzothiophene		
	ΔE_{I}	ΔE_{II}	ΔE_{III}	ΔE_{I}	ΔE_{II}	ΔE_{III}	ΔE_{I}	ΔE_{II}	ΔE_{III}
AM1	7.1	13.9	20.9	6.6	11.3	17.8	7.1	10.9	18.0
B3LYP/6-31G(d)//AM1	14.3	5.3	19.6	9.2	6.6	15.8	12.1	6.6	18.8

ΔE_{I} = energy difference between benzo[b]heterocycle and benzo[c]heterocycle; ΔE_{II} = imaginary enthalpy of reaction, benzene + heterocycle into benzo[b]heterocycle plus ethylene; ΔE_{III} = imaginary enthalpy of reaction, benzene + heterocycle into benzo[c]heterocycle plus ethylene

Let us now explore Frontier Molecular Orbital (FMO)[13] energies as a measure of the reactivities of benzo-fused heterocycles in reactions with acetylene, ethylene, and cyclopropene. According to this approach, the most reactive pair would be the one which has the smallest FMO gap between the two reactants. Selectivity can be determined through atomic orbital coefficients in the FMO's of the reactants (while considering maximal molecular orbital overlap). These simple tools have been used successfully by organic synthetic chemists to predict the reactivity of organic molecules. It has been successfully used to explain reactivities and reaction outcomes of pericyclic reactions.[14] FMO's and their energy gaps for Diels-Alder reactions with benzo-fused heterocycles are

Table 4. Frontier Molecular Orbital (FMO) energy (eV) changes going from reactants to transition state structures computed with the AM1 semiempirical method

	HOMO	LUMO	A	B	C	D	E	F
acetylene	-11.500	2.053						
ethylene	-10.551	1.438						
cyclopropene	-9.819	1.042						
benzo[b]furan	-9.010	-0.063	11.063	11.436	10.448	10.488	10.052	9.755
benzo[c]furan	-8.263	-0.396	10.316	11.104	9.701	10.156	9.305	9.423
benzo[b]pyrrole	-8.403	0.300	10.456	11.799	9.841	10.851	9.446	10.119
benzo[c]pyrrole	-7.796	0.142	9.849	11.641	9.234	10.693	8.838	9.960
benzo[b]thiophene	-8.430	-0.166	10.483	11.334	9.868	10.386	9.472	9.653
benzo[c]thiophene	-8.340	-0.592	10.393	10.908	9.778	9.960	9.382	9.227

A = $LUMO_{acetylene}$ - $HOMO_{benzoheterocycle}$; B = $LUMO_{benzoheterocycle}$ - $HOMO_{acetylene}$; C = $LUMO_{ethylene}$ - $HOMO_{benzoheterocycle}$; D = $LUMO_{benzoheterocycle}$ - $HOMO_{ethylene}$; E = $LUMO_{cyclopropene}$ - $HOMO_{benzoheterocycle}$; F = $LUMO_{benzoheterocycle}$ - $HOMO_{cyclopropene}$

presented in Table 4. According to these calculations, benzo[c]heterocycles are much better dienes for Diels-Alder reactions than their benzo[b]isomers. In all cases of acetylene, ethylene, and cyclopropene additions to the benzo[c]heterocycle are HOMO diene controlled. Furthermore, all calculations agree that benzo[c]pyrrole is the most reactive diene for the Diels-Alder reaction due to its very high HOMO energy. This finding contradicts the results obtained from our bond uniformity studies. The imaginary benzene and heterocycle fusion reaction energy selects benzo[c]pyrrole as having at least the same stability, if not higher, as benzo[c]thiophene, but it is much more stable than benzo[c]furan. Thus benzo[c]furan must be the most reactive diene for the Diels-Alder reaction, not pyrrole.

Recently, we introduced a more reliable way to adjust the reactivity of various dienes for Diels-Alder reactions by estimating the FMO energy changes necessary to transfer reactants to transition state structures. In many cases, more than one isomer of the cycloaddition reaction can be formed for which FMO energy gaps between reactants cannot be used to assess the selectivity of the reaction. Our approach should allow us to determine energy preferences of one isomer over the other. The transition state structures, as well as their energies, for this study must be available.[16] The AM1 geometries of the transition state structures will be presented later. There are two changes of FMO energies in the transformation of reactants into transition state structures: a HOMO diene controlled (Σ_1) and a LUMO diene controlled (Σ_2) Diels-Alder reaction (Table 5).

Table 5. Frontier Molecular Orbital (FMO) energy (eV) changes going from reactants to transition state structures with cyclopropene as the dienophile computed with the AM1 semiempirical method

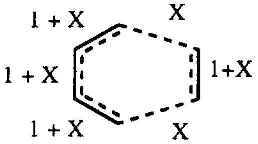
Type of addition	HOMO	LUMO	A	B	C	D	Σ_1	Σ_2
exo benzo[b]furan	-7.841	-0.725	1.169	-0.662	1.978	-1.767	2.936	2.640
endo benzo[b]furan	-7.013	-1.582	1.997	-1.519	2.806	-2.624	4.621	4.325
exo benzo[c]furan	-8.305	-0.228	-0.042	0.168	1.514	-1.270	1.312	1.682
endo benzo[c]furan	-8.311	-0.210	-0.048	0.186	1.508	-1.252	1.300	1.694
exo benzo[b]pyrrole	-7.564	-0.692	0.839	-0.992	2.255	-1.734	2.573	3.247
endo benzo[b]pyrrole	-6.920	-1.333	1.483	-1.633	2.899	-2.375	3.858	4.532
exo benzo[c]pyrrole	-8.150	0.066	-0.354	-0.076	1.669	-0.976	1.330	1.745
endo benzo[c]pyrrole	-8.142	0.061	-0.346	-0.081	1.677	-0.981	1.327	1.758
exo benzo[b]thiophene	-6.929	-1.611	1.501	-1.445	2.890	-2.653	4.154	4.335
endo benzo[b]thiophene	-7.027	-1.585	1.403	-1.419	2.792	-2.627	4.030	4.211
exo benzo[c]thiophene	-8.490	-0.390	-0.150	0.202	1.329	-1.432	1.582	1.531
endo-benzo[c]thiophene	-8.403	-0.424	-0.063	0.168	1.416	-1.466	1.529	1.584

A = $HOMO_{TS}$ - $HOMO_{diene}$; B = $LUMO_{TS}$ - $LUMO_{diene}$; C = $HOMO_{TS}$ - $HOMO_{cyclopropene}$; D = $LUMO_{TS}$ - $LUMO_{cyclopropene}$; $\Sigma_1 = |A| + |D|$; $\Sigma_2 = |B| + |C|$.

Because cyclopropene is the most reactive dienophile studied here, we will only present a FMO study for the addition of cyclopropene to benzo-fused heterocycles. There are twelve possible transition state structures and a FMO change for each was computed. It is obvious that the reaction is HOMO diene controlled with the exception of the *endo* and *exo* cyclopropene additions to benzo[b]furan and the *exo* cyclopropene addition to benzo[c]thiophene (Table 5). Similarly, the conclusion obtained from FMO energy gaps between reactants (Table 4) is that in all cases benzo[c]heterocycles are much better dienes for Diels-Alder reactions than benzo[b]heterocycles. This is demonstrated by a lower FMO energy change if cyclopropene is coupled with the benzo[c]heterocycle than with the benzo[b]heterocycle as the diene (Table 5). A review of the computed FMO energy changes (Σ_1) shows the order of reactivity of benzo-fused heterocycles as benzo[c]furan, benzo[c]pyrrole, benzo[c]thiophene, benzo[b]pyrrole, benzo[b]furan, and finally benzo[b]thiophene. For the addition of cyclopropene to benzo[c]furan, the *exo* isomeric transition state structure is predicted to have a lower activation energy while for the reaction with benzo[c]pyrrole, an opposite reaction outcome is expected.

Now we would like to introduce transition state ring bond order uniformity (π-molecular orbital delocalization) as a measure of stability, and therefore selectivity, between two or more isomeric transition state structures. A view that transition state structures which can be classified as aromatic and antiaromatic is widely accepted in organic chemistry.[17] A stabilized aromatic transition state will lead to a lower activation energy barrier. Also, it can be said that a more uniform bond order transition state structure will have a lower activation barrier and will therefore be allowed. An ideal uniform bond order for a six-membered transition state is presented in Scheme 2. According to this definition, a six-electron transition state structure can be defined through a bond order distribution with an average bond order X. Therefore, less deviation from these ideally distributed bond orders should be associated with a more stable transition state structure. Therefore, it is energetically preferred over other transition state structures.

2X + 4(1+X) = sum of the **TS** ring's bond orders



Scheme 2. The distribution of bond orders in an ideal six-membered aromatic transition state structure

Let us now apply this bond order deviation from an ideal transition state structure to an example of cyclopropene added to a benzo-fused heterocycle. Before we examine bond order deviation from an ideal transition state structure, we need to take a look at the sums of the rings' bond orders in the transition state structures. To simplify this picture, we will focus only on the *exo* transition state structures between cyclopropene and benzo[c]heterocycles. Previously ,we mentioned that the Diels-Alder reaction with benzo[c]heterocycles as dienes is a HOMO controlled diene reaction and therefore, an electron rich (higher sum of bond order) transition state structure should be energetically preferred. If this is the case, the order of reactivity should be benzo[c]furan, benzo[c]thiophene, and then benzo[c]pyrrole, which is exactly the same order determined by the FMO energy change (Table 5).

The transition state structure with the highest Bond Order Deviation (BOD) also has a higher energy. From the example of the cyclopropene addition to benzo-fused furans, we can demonstrate this approach. BOD's for both *exo* and *endo* transition state structures of the cyclopropene addition to benzo[b]furan are higher than the BOD's for the addition to benzo[c]furan (Table 6). On the other hand, the transition state structure for the *exo*

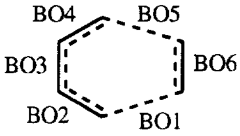
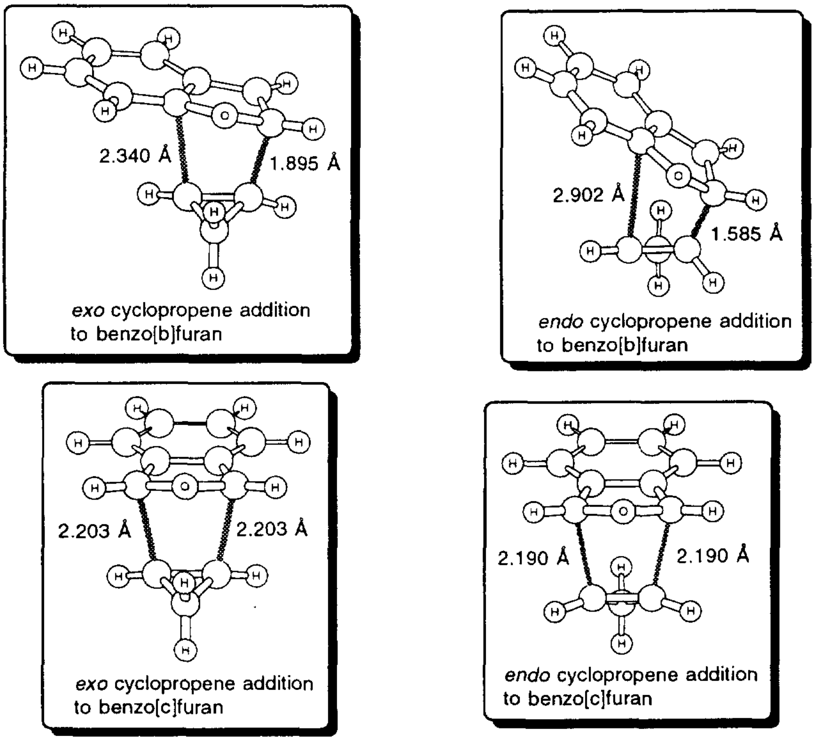


Table 6. Bond orders for the transition state ring computed with the AM1 semiempirical method using cyclopropene as the dienophile

Type of addition	BO1	BO2	BO3	BO4	BO5	BO6	BO7	BO8	SBO	X	BOD
exo benzo[b]furan	0.256	1.194	1.394	1.273	0.467	1.439	0.004		6.023	0.337	0.577
endo benzo[b]furan	0.151	1.219	1.316	1.129	0.744	1.219	0.000	0.045	5.778	0.296	0.934
exo benzo[c]furan	0.323	1.233	1.262	1.233	0.323	1.542	0.004		5.916	0.319	0.460
endo benzo[c]furan	0.342	1.232	1.262	1.232	0.342	1.519	0.002	0.002	5.929	0.322	0.477
exo benzo[b]pyrrole	0.256	1.175	1.438	1.222	0.512	1.396	0.003		5.999	0.333	0.693
endo benzo[b]pyrrole	0.190	1.199	1.384	1.120	0.739	1.217	0.000	0.035	5.849	0.308	1.013
exo benzo[c]pyrrole	0.376	1.159	1.282	1.159	0.376	1.470	0.003		5.822	0.304	0.622
endo benzo[c]pyrrole	0.388	1.169	1.280	1.169	0.388	1.457	0.002	0.002	5.851	0.309	0.615
exo benzo[b]thiophene	0.087	1.202	1.422	1.124	0.751	1.223	0.023		5.809	0.302	1.141
endo benzo[b]thiophene	0.180	1.227	1.357	1.140	0.764	1.209	0.000	0.039	5.877	0.313	0.991
exo benzo[c]thiophene	0.385	1.181	1.288	1.181	0.385	1.464	0.018		5.884	0.314	0.584
endo-benzo[c]thiophene	0.385	1.210	1.281	1.210	0.385	1.465	0.003	0.003	5.936	0.323	0.534

SBO = BO1 + BO2 + BO3 + BO4 + BO5 + BO6; X is the ideal bond order delocalization computed from the formula presented in Scheme 2; BOD = bond order deviation from uniform bond order distribution in the transition state structure cyclopropene addition to benzo[c]furan has a slightly more uniform bond order transition state structure than for the *endo* transition state structure. Therefore, according to the AM1 computational study, it is the *exo* cycloadduct product between cyclopropene and benzo[c]furan which has the most stable transition state structure. The *exo* selectivity in the cyclopropene addition to benzo[c]furan can be explained by the stabilization effect of Secondary Orbital Interactions (SOI) in the transition state structure between the lone pair of electrons on the oxygen of furan and the methylene hydrogen of cyclopropene. There are also SOI in the *endo* transition state structure between the methylene hydrogen of cyclopropene and π-orbitals on the newly forming double bond. The n-H SOI are stronger in comparison to the π-H SOI and formation of an *exo* isomer is preferred, as in the case of the cyclopropene addition to isolated furan.[18] If we consider only bond order uniformity in the six-membered transition state structures, the *endo* addition of cyclopropene to both benzo[c]pyrrole and benzo[c]thiophene should be preferred over the *exo* addition. This might not be necessarily true, if we take into account that, for instance, the n-H SOI in the *exo* transition state structure with benzothiophene is extremely strong. Therefore, we can assume that the formation of an *exo* cycloadduct, as in case of the cyclopropene addition to both benzo[c]pyrrole and benzo[c]thiophene, might also be slightly preferred over the *endo* cycloaddition. Later, we will support these observations with computations of the activation energies for all possible reaction pathways.

Our qualitative computational studies were confirmed by computing activation barriers with both AM1 semiempirical and B3LYP density functional theory methods. The transition state structures for different combinations of benzo-fused heterocycles with various dienophiles are very similar and therefore only transition state structures between benzo-fused furans and cyclopropene will be presented (Figure 1). The transition state



exo cyclopropene addition to benzo[b]furan

endo cyclopropene addition to benzo[b]furan

exo cyclopropene addition to benzo[c]furan

endo cyclopropene addition to benzo[c]furan

Figure 1. Four possible transition state structures for cyclopropene addition to benzo[b] and benzo[c]furan computed with AM1 semiempirical method

structures for the cyclopropene addition to benzo[b]furan are for an asynchronous, concerted mechanism. Higher asynchronicity is observed in *endo* isomers. We are assigning the lower asynchronchricity in *exo* isomers to a strong n-H SOI between the two reactant moieties of the transition state structure. On the other hand, the two transition state structures for the cyclopropene addition to benzo[c]furan have a plane of symmetry indicating the synchronous formation of both C-C bonds. If we apply the Hammond postulate,[20] we also have to determine which of the two isomeric transition state structures will have a lower energy. According to the Hammond postulate, the transition state structure which is closer in geometry to the reactants should also be

Table 7. The AM1 and B3LYP/6-31G(d) computed activation barriers for selected Diels-Alder cycloaddition reactions with benzofuran, benzopyrrole, and benzothiophene as dienes

reactant or reaction	HOF	E	ΔE_I	ΔE_{II}
acetylene	54.8	-77.325410		
ethylene	16.5	-78.587018		
cyclopropene	74.8	-116.617544		
benzo[b]furan	20.8	-383.670547		
benzo[b]pyrrole	55.2	-363.813914		
benzo[b]thiophene	42.4	-706.648776		
benzo[c]furan	27.9	-383.647816		
benzo[c]pyrrole	61.7	-363.799285		
benzo[c]thiophene	49.4	-706.629492		
acetylene + benzo[b]furan	120.8	-460.928333	45.2	42.4
acetylene + benzo[b]pyrrole	159.7	-441.065949	49.7	46.0
acetylene + benzo[b]thiophene	154.0	-783.912465	56.8	38.7
acetylene + benzo[c]furan	110.8	-460.942991	28.1	18.9
acetylene + benzo[c]pyrrole	150.9	-441.087810	34.4	23.1
acetylene + benzo[c]thiophene	147.9	-783.892088	43.7	39.4
ethylene + benzo[b]furan	75.7	-462.208252	38.4	30.9
ethylene + benzo[b]pyrrole	115.3	-442.328909	43.6	45.2
ethylene + benzo[b]thiophene	110.8	-785.160020	51.9	47.5
ethylene + benzo[c]furan	64.5	-462.208252	20.1	16.7
ethylene + benzo[c]pyrrole	104.8	-442.350109	26.6	22.7
ethylene + benzo[c]thiophene	102.4	-785.177698	36.5	24.4
exo cyclopropene + benzo[b]furan	131.1	-500.242907	35.5	28.4
exo cyclopropene + benzo[b]pyrrole	169.3	-480.379182	39.3	32.8
exo cyclopropene + benzo[b]thiophene	162.7	-823.203175	45.5	39.6
endo cyclopropene + benzo[b]furan	129.6	-500.238488	34.0	31.1
endo cyclopropene + benzo[b]pyrrole	168.1	-480.375076	38.1	35.4
endo cyclopropene + benzo[b]thiophene	161.2	-823.207174	44.0	37.1
exo cyclopropene + benzo[c]furan	121.9	-500.250434	19.2	9.4
exo cyclopropene + benzo[c]pyrrole	160.7	-480.395742	24.2	13.2
exo cyclopropene + benzo[c]thiophene	157.7	-823.221607	33.5	16.0
endo cyclopropene + benzo[c]furan	123.7	-500.247997	21.0	10.9
endo cyclopropene + benzo[c]pyrrole	162.9	-480.391950	26.4	15.6
endo cyclopropene + benzo[c]thiophene	159.6	-823.220062	35.4	16.9

HOF = heat of formation computed with AM1; E = total energy (a.u.) computed with B3LYP/6-31G(d)/AM1; ΔE_I = activation barrier (kcal/mol) computed with AM1; ΔE_{II} = activation barrier (kcal/mol) computed with B3LYP/6-31G(d)/AM1 closer in the energy. Therefore, this transition state should have a lower energy. If we consider only C-C bond distances in *exo* and *endo* transition state structures for the cyclopropene addition to benzo[c]furan then the *exo* transition state structure with the longer C-C bond distance is closer to the reactants, and is thus more stable. This conclusion is in full agreement with minimal bond order deviation from an ideal transition state structure (Table 5). This study also select this structure as the one with the lowest activation barrier.

The AM1 and B3LYP/6-31G(d) activation barriers for the Diels-Alder reactions with benzo-fused heterocycles are presented in Table 7. We have demonstrated that AM1 computed activation barriers for Diels-Alder reactions are too high in general, while B3LYP/6-31G(d) energies are very close to the experimental and full B3LYP/6-31G(d) estimated activation barriers.[21] These energies are in perfect agreement with the qualitative observations presented above. Regardless of the dienophile selected, the activation energies for its addition to the benzo[b]heterocycle is substantially higher than for its addition to the benzo[c]heterocycle. As expected, on the basis of FMO energy analyses, Diels-Alder reactions with acetylene as the dienophile are the least feasible of all cycloaddition reactions studied here. Estimated activation energies for additions to benzo[b]heterocycles are around 40 kcal/mol, which are too high to be achieved under normal reaction conditions. The acetylene addition to benzo[c]furan is computed to have an activation energy of only 18.9 kcal/mol and should be feasible experimentally (Table 1). In general, activation barriers with ethylene are lower than with acetylene as a dienophile, and with cyclopropene even lower (Table 7). For instance, the addition of ethylene to all benzo[c]-fused heterocycles should be experimentally feasible, with a higher activation barrier of 24.4 kcal/mol for the ethylene addition to benzo[c]thiophene. Of course, for the addition of cyclopropene, even lower activation barriers are computed. Thus 16.9 kcal/mol is the highest activation barrier for the *endo* cyclopropene addition to benzo[c]thiophene. Even for such a reactive dienophile as cyclopropene, the addition to benzo[b]heterocycles is predicted to be impractical experimentally, with the possible exception of the *exo* cyclopropene addition to benzo[b]furan for which a 28.4 kcal/mol reaction barrier is estimated (Table 7).

Let us now evaluate *exo-endo* selectivity in cyclopropene additions to benzo[c]heterocycles. On the basis of bond order analyses, the *exo* addition of cyclopropene to benzo[c]furan was selected over the *endo* addition. However, in the case of benzo[c]pyrrole and benzo[c]thiophene, it was suggested that SOI might be responsible for formation of an *exo* cycloadduct product. The computed activation energies for the cyclopropene addition to the benzo[c]-fused heterocycle clearly favors the formation of the *exo* cycloadduct. The activation barrier with benzo[c]furan is predicted to be a mere 9.4 kcal/mol, while the least reactive *exo* cyclopropene addition to benzo[c]thiophene is 16.0 kcal/mol. Therefore, our bond order uniformity, as well as SOI studies, are in agreement with the computed activation barriers for these cycloaddition reactions.

The experimental results fully support our computational studies. Benzo[b]furan, benzo[b]pyrrole, and benzo[b]thiophene do not take part in Diels-Alder reactions. The benzo[c]-fused heterocycles function as highly reactive dienes in [4+2] cycloaddition reactions. Thus benzo[c]furan, isoindole (benzo[c]pyrrole), and benzo[c]thiophene each yield Diels-Alder adducts with reactive dienophiles such as maleic anhydride.[22]

Conclusion

We have demonstrated that we can effectively determine the reactivities of benzo-fused heterocycles as dienes for Diels-Alder reactions through the following computational approaches: AM1 qualitative analyses based on FMO energy gaps between reactants, FMO energy changes caused by the transformations of reactants to transition state structures, and the determination of bond order uniformity in starting materials and in transition state structures. Due to their high π-bond delocalization, indicated through bond order uniformity, benzo[b]-fused heterocycles are not effective dienes for Diels-Alder reactions. On the other hand, in benzo[c]-fused heterocycles, bond order uniformity (for both benzene and heterocycles) is severely disrupted. Thus, a higher reactivity is seen. In regard to the transition state structures, ones with benzo[b]-fused heterocycles have a diminished bond order uniformity in contrast to those of the benzo[c]-fused heterocycles (which have a higher bond order uniformity and, hence, lower activation barriers). In conclusion, the computed activation barriers are in agreement with qualitative observations and our overall computational studies are in accordance with experimental results.

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