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Diels-Alder cycloadditions of 1,3-cyclohexadien-4,5-diones (*o*-benzoquinones) with norbornadiene. Part II. A high level computational study of their stereospecificities.

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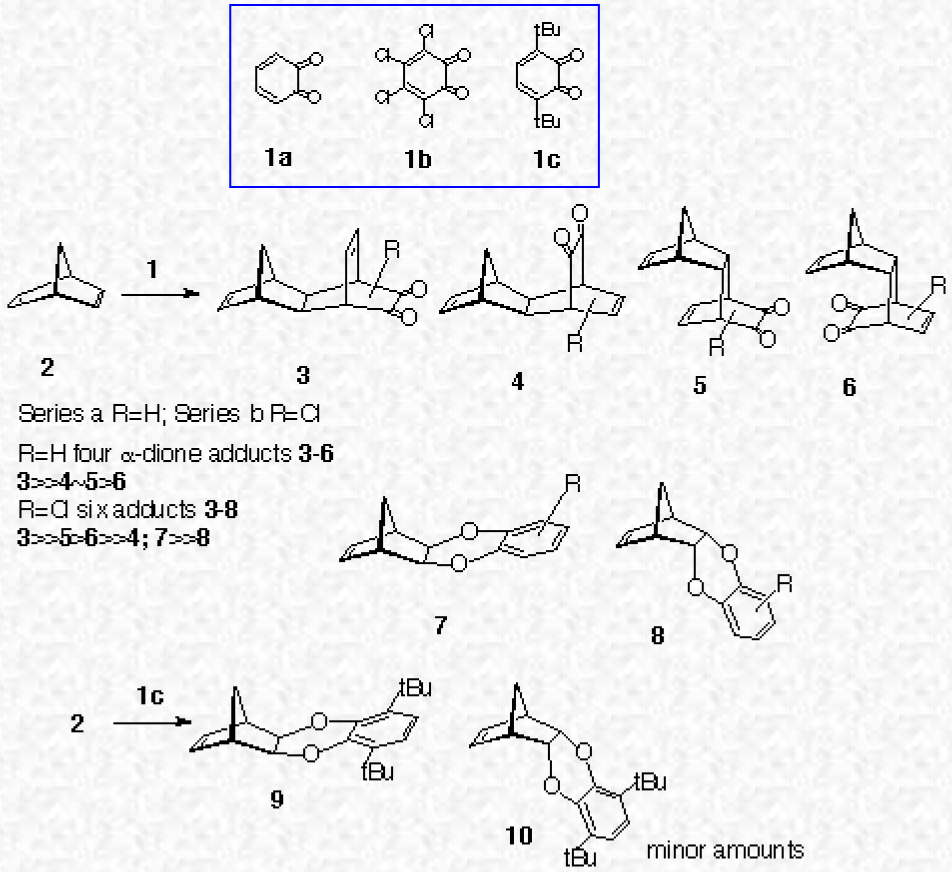
Abstract: *Ab initio* and DFT quantum chemical calculations have been applied to a study of Diels-Alder reactions of *o*-benzoquinone as diene and norbornadiene as dienophile. Transition states for these reactions are located and activation energies estimated. The prefered *exo*-¶- facial selectivities and *exo,endo*- stereospecificities exhibited in these cycloadditions are readily predicted using RHF/3-21G or higher levels of calculations. Differences between experimentally observed results and calculations may be explained by the postulation of a second, nonconcerted biradical mechanism leading to formation of hetero Diels-Alder products.

Introduction. Diels-Alder methodology has been used by ourselves[1] and others[2] to produce rigid polyalicyclic structures. The overall shape of such systems depends on the specificity of the reactions used in each step of the construction. With a knowledge of stereospecificity, for example, it is possible to introduce a bend in the framework or to extend the structure linearly.

In the previous paper (**Part I**) we have described synthetic methods for preparation of *o*-benzoquinone, *o*-chloranil and 2,5-di-(*t*-bu)-benzoquinone adducts with norbornadiene.[3,4] Here, we will present the results of the computational study of these reactions using high level quantum mechanical calculations. We have found that *o*-benzoquinone **1a** generated *in situ* gives four a-dione adducts **3-6** (Scheme 1) with adduct **3** being the dominant product and adducts **4** and **5** are found in smaller amounts and **6** only spectroscopically detected. In contrast to this reaction, *o*-chloranil **1b** gives six adducts **3-8**, while 2,5-di-(*t*-bu)-benzoquinone **1c** gave only adducts **9** and in minor amounts **10**.



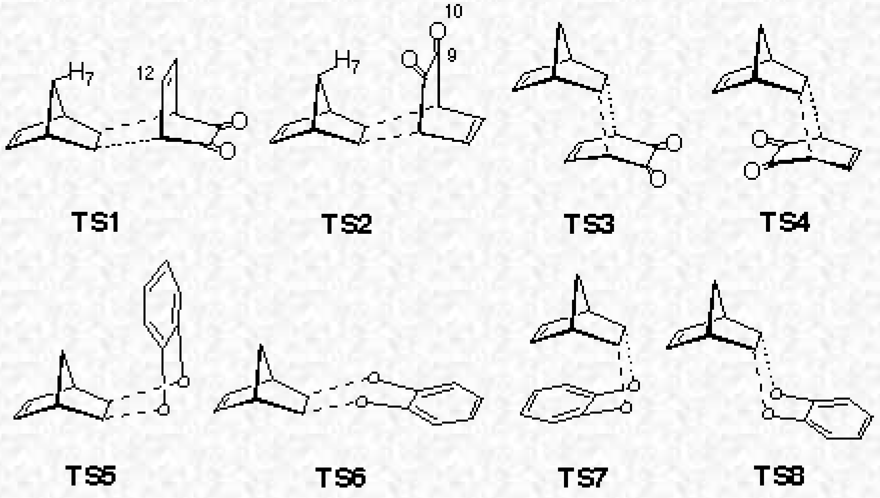
Scheme 1.

High levels *ab initio* [5] and B3LYP/6-31G* DFT methods[6] have proved to give excellent results for energy barrier estimation of pericyclic reactions. We have previously used *ab initio* and DFT calculations to successfully predict stereospecificities of different Diels-Alder reactions of cyclic dienes with cyclic dienophiles.[7]

In order to explain the experimentally observed stereospecificites, transition states for these reactions have been located and activation energies estimated at various levels of theory.

Computational methodology. All *ab initio* calculations were conducted using the SPARTAN program[8] on a Silicon Graphics Oxygen R5000 workstations. These geometries have been used as the initial geometries for DFT calculations with Gaussian98.[9] MP2 calculations were conducted using IBM SP2 supercomputer. Geometric optimizations were carried out without using symmetry or other structural restrictions. All calculations are performed at the restricted Hartree-Fock level[10] with 3-21G and 6-31G* basis sets[11]. Each transition structure was located using a standard routine within Gaussian 98.[12] For all structures the vibrational analysis was performed with the same basis set used for optimization. The activation energies were also estimated from 6-31G* and MP2/6-31G* single point calculations on the RHF/3-21G and RHF/6-31G* optimized geometries. Further optimizations were carried out with density functional theory (DFT) hybrid B3LYP (Becke's 3 parameter functional[13] with the non-local correlation provided by the expression of Lee *et al.*)[14]. Single point energy calculations were also estimated using DFT B3LYP method: B3LYP//3-21G[15] and B3LYP/6-31G*. In order to minimize computational efforts, all substituents (chlorine or *t*-Bu) were omitted and only the parent *o*-benzoquinone reaction was studied.

Results and discussion. The total energies of the calculated molecules and their associated transition states (Scheme 2) are collected in Table 1, while activation energies and relative energies are presented in Tables 2 and 3. B3LYP transition state structures are depicted in Figures 1-4. All located transition state structures correspond to the concerted, synchronous mechanism. The lenghts of the bonds undergoing first-order changes in these transition structures are commensurate with those expected for concerted cycloaddition reaction transition states.



Scheme 2.

FMO analysis has shown that norbornadiene HOMO and *o*-benzoquinone LUMO are the most important interacting orbitals, *i.e.* this represents an inverse electron-demand Diels-Alder reaction (norbornadiene HOMO -6.73 eV, LUMO 0.0 eV, *o*-benzoquinone HOMO -6.79 eV, LUMO -3.54 eV). Furthermore, quantum of charge transfer (qCT) from diene to dienophile for **TS1** - **4** are estimated to be -0.124, -0.108, -0.136 and -0.120 eV, respectievly, clearly indicating inverse mechanism.

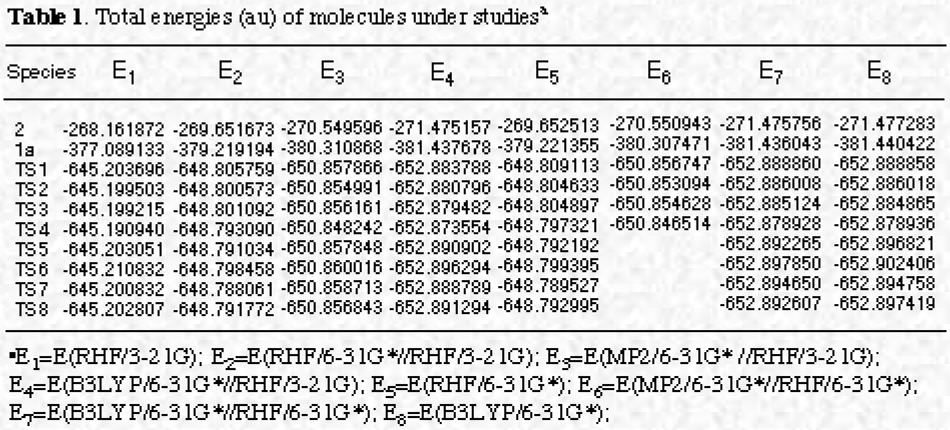


Table 1. Total energies (au) of molecules under studies[a]

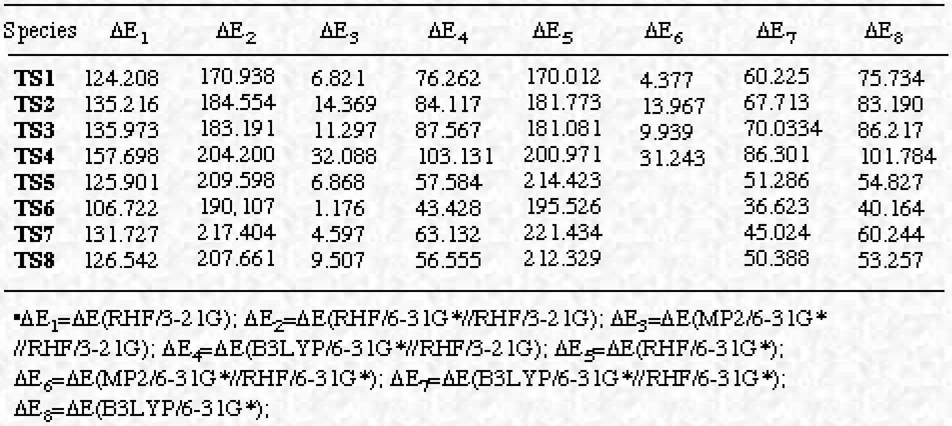
Species	E_1	E_2	E_3	E_4	E_5	E_6	E_7	E_8
2	-268.161872	-269.651673	-270.549596	-271.475157	-269.652513	-270.550943	-271.475756	-271.477283
1a	-377.089133	-379.219194	-380.310868	-381.437678	-379.221355	-380.307471	-381.436043	-381.440422
TS1	-645.203696	-648.805759	-650.857866	-652.883788	-648.809113	-650.856747	-652.888860	-652.888858
TS2	-645.199503	-648.800573	-650.854991	-652.880796	-648.804633	-650.853094	-652.886008	-652.886018
TS3	-645.199215	-648.801092	-650.856161	-652.879482	-648.804897	-650.854628	-652.885124	-652.884865
TS4	-645.190940	-648.793090	-650.848242	-652.873554	-648.797321	-650.846514	-652.878928	-652.878936
TS5	-645.203051	-648.791034	-650.857848	-652.890902	-648.792192		-652.892265	-652.896821
TS6	-645.210832	-648.798458	-650.860016	-652.896294	-648.799395		-652.897850	-652.902406
TS7	-645.200832	-648.788061	-650.858713	-652.888789	-648.789527		-652.894650	-652.894758
TS8	-645.202807	-648.791772	-650.856843	-652.891294	-648.792995		-652.892607	-652.897419

[a] E_1=E(RHF/3-21G); E_2=E(RHF/6-31G*//RHF/3-21G); E_3=E(MP2/6-31G*//RHF/3-21G); E_4=E(B3LYP/6-31G*//RHF/3-21G); E_5=E(RHF/6-31G*); E_6=E(MP2/6-31G*//RHF/6-31G*); E_7=E(B3LYP/6-31G*//RHF/6-31G*); E_8=E(B3LYP/6-31G*);

¶-facial selectivity. The exclusive *exo*- side preference in cycloaddition reactions on the norbornene double bond[16] however was not observed in the reactions with the *o*-benzoquinone presented here. The *o*-benzoquinone (**1a**) and *o*-chloranil (**1b**) alongside *exo,exo*- (**3**) and *exo,endo*- (**4**) adducts the reaction mixtures also contained detectable amounts of *endo,exo*- (**5**) and *endo,endo*- (**6**) adducts.

The analysis of results collected in Tables 1 - 3 shows that all methods employed, starting with RHF/3-21G gave a good prediction of *exo*- ¶-facial selectivity in norbornene system. Regardless of the computational level employed, *exo,exo*- adduct **3** (which is formed via **TS1**) was found to be the prefered by 7.5-13.6 kJ/mol over *exo,endo*- adduct **4**, what was observed experimentally. The largest difference (13.6 kJ/mol) was estimated at the 6-31G*//3-21G level. These results reinforce our previous findings that 6-31G*//3-21G and higher theoretical levels correctly model ¶-facial selectivity in cycloaddtion reactions with norbornenes.[7] As expected, estimated energy barriers vary with the computational level applied.[17] In contrast to these findings, there was found no significant difference was found between activation energies for the formation of *exo,endo*- **4** and *endo,exo*- **5** adducts. These predictions are less consistent, depending on the calculation level employed. While 3-21G full otimization, single point B3LYP/6-31G* energy estimations on the 3-21G and 6-31G* optimized structures and B3LYP/6-31G* calculations predict smaller activation energies for **TS2** than **TS3** (by 0.76, 3.5, 2.3 and 3.03 kJ/mol. respectively), the 6-31G*//3-21G, MP2/6-31G*//3-21G, 6-31G* and MP2/6-31G*//6-31G* calculations (Table 3) predict smaller activation energies for **TS3** over **TS2** (by 1.4, 3.1, 0.7 and 4.0 kJ/mol, respectively). However, we may conclude that, since **TS2** - **TS3** energy differences are relatively small, all calculations predict formation of similar amounts of products **4** and **5**. Furthermore, the large differences in activation energies between **TS1** and **TS4** (within a range of 25.3 and 33.5 kJ/mol, as estimated by MP2/6-31G*//3-21G and 3-31G methods, respectively, Table 3), clearly indicate that formation of product **6** is greatly disfavoured. This prediction is in accord with our experimental results as well as computational results obtained by Hehre *et al.* having recently shown that *ab initio* calculations using 3-21G model correctly predict the relative energies of the transition states for the two modes of attack to diastereotopic faces of a diene.[18]

Table 2. Calculated activation energies (kJ/mol) for the Diels-Alder reactions of 1,3-cyclohexadien-4,5-diones with norboradiene[a]



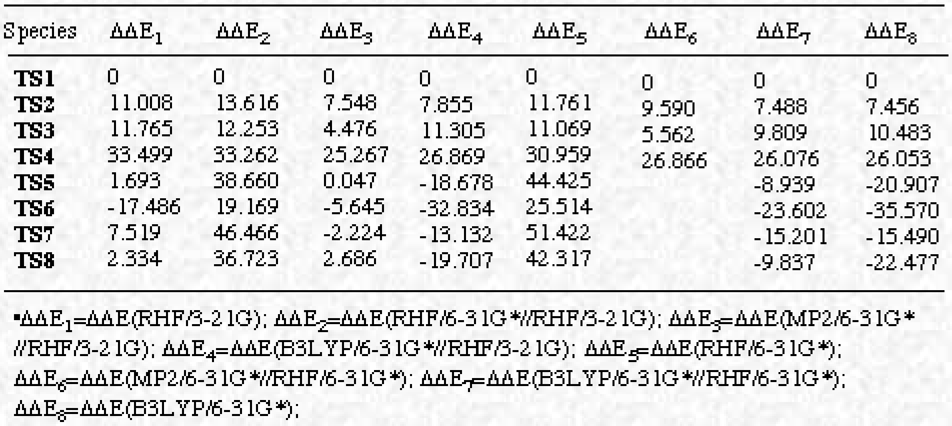
Species	ΔE_1	ΔE_2	ΔE_3	ΔE_4	ΔE_5	ΔE_6	ΔE_7	ΔE_8
TS1	124.208	170.938	6.821	76.262	170.012	4.377	60.225	75.734
TS2	135.216	184.554	14.369	84.117	181.773	13.967	67.713	83.190
TS3	135.973	183.191	11.297	87.567	181.081	9.939	70.0334	86.217
TS4	157.698	204.200	32.088	103.131	200.971	31.243	86.301	101.784
TS5	125.901	209.598	6.868	57.584	214.423		51.286	54.827
TS6	106.722	190, 107	1.176	43.428	195.526		36.623	40.164
TS7	131.727	217.404	4.597	63.132	221.434		45.024	60.244
TS8	126.542	207.661	9.507	56.555	212.329		50.388	53.257

[a] ΔE_1=ΔE(RHF/3-21G); ΔE_2=ΔE(RHF/6-31G*//RHF/3-21G); ΔE_3=ΔE(MP2/6-31G*//RHF/3-21G); ΔE_4=ΔE(B3LYP/6-31G*//RHF/3-21G); ΔE_5=ΔE(RHF/6-31G*); ΔE_6=ΔE(MP2/6-31G*//RHF/6-31G*); ΔE_7=ΔE(B3LYP/6-31G*//RHF/6-31G*); ΔE_8=ΔE(B3LYP/6-31G*);

The origin of stereospecifity may be rationalized using Mulliken population analysis, which gives a qualitative indicator of the amount of electron density shared by two atoms, and also provides some evidence for secondary orbital interaction between two reactantants. Such an analysis was employed succesfully by Houk *et al.* to explain the stereoselectivities of several Diels - Alder reactions.[19]

In **TS1** the methylene hydrogen - double bond carbon (H_7C_{12}) overlap density has a positive value of 0.0014, indicating an attractive interaction, while in **TS2** the methylene hydrogen - carbonyl carbon atom (H_7C_9) overlap population is repulsive with value of -0.003. Furthermore, the methylene carbon - carbonyl carbon (C_7C_9) overlap population is also repulsive with value of -0.002, and methylene carbon - carbonyl oxygen (C_7O_{10}) overlap population is repulsive with value of -0.005, indicating larger destabilizing secondary orbital interactions in **TS2**. However, the similar analysis of overlap densities employed on the **TS3** and **TS3** does not give such conclusive differences.

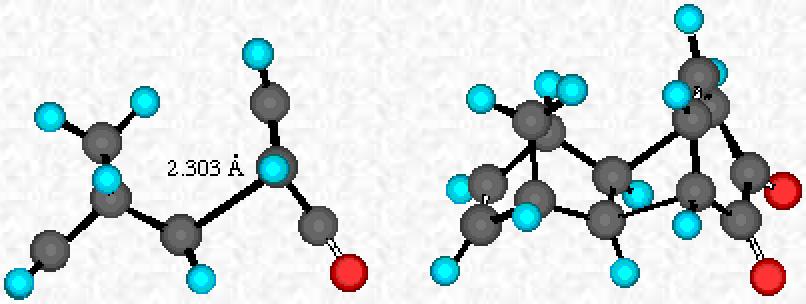
Table 3. Relative energies (kJ/mol) for the studied Diels-Alder reactions[a]



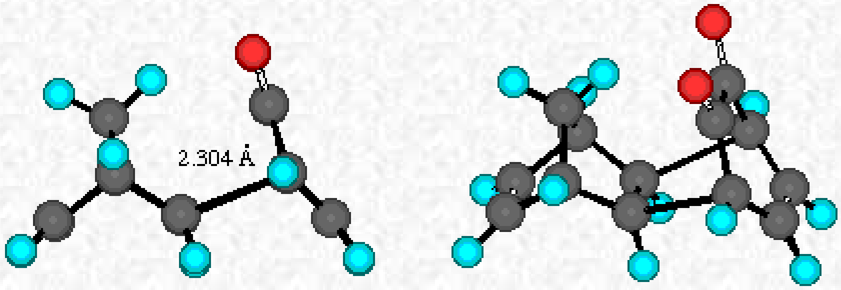
Species	$\Delta\Delta E_1$	$\Delta\Delta E_2$	$\Delta\Delta E_3$	$\Delta\Delta E_4$	$\Delta\Delta E_5$	$\Delta\Delta E_6$	$\Delta\Delta E_7$	$\Delta\Delta E_8$
TS1	0	0	0	0	0	0	0	0
TS2	11.008	13.616	7.548	7.855	11.761	9.590	7.488	7.456
TS3	11.765	12.253	4.476	11.305	11.069	5.562	9.809	10.483
TS4	33.499	33.262	25.267	26.869	30.959	26.866	26.076	26.053
TS5	1.693	38.660	0.047	-18.678	44.425		-8.939	-20.907
TS6	-17.486	19.169	-5.645	-32.834	25.514		-23.602	-35.570
TS7	7.519	46.466	-2.224	-13.132	51.422		-15.201	-15.490
TS8	2.334	36.723	2.686	-19.707	42.317		-9.837	-22.477

[a] $\Delta\Delta E_1$=$\Delta\Delta E$(RHF/3-21G); $\Delta\Delta E_2$=$\Delta\Delta E$(RHF/6-31G*//RHF/3-21G); $\Delta\Delta E_3$=$\Delta\Delta E$(MP2/6-31G*//RHF/3-21G); $\Delta\Delta E_4$=$\Delta\Delta E$(B3LYP/6-31G*//RHF/3-21G); $\Delta\Delta E_5$=$\Delta\Delta E$(RHF/6-31G*); $\Delta\Delta E_6$=$\Delta\Delta E$(MP2/6-31G*//RHF/6-31G*); $\Delta\Delta E_7$=$\Delta\Delta E$(B3LYP/6-31G*//RHF/6-31G*); $\Delta\Delta E_8$=$\Delta\Delta E$(B3LYP/6-31G*);

Formation of hetero Diels-Alder products. We have found that in the cycloaddition reactions *o*-chloranil **1b** and 2,5-di-(*t*-bu)-benzoquinone **1c** also serve as heterodienes. While **1b** gave a mixture of normal Diels-Alder adducts **3-6**, and smaller quantities of *exo*- and *endo*- adducts **7** and **8**, the quinone **1c** gave only hetero Diels-Alder adducts **9** (major product) and **10**. Similar behaviour of *o*-benzoqunione was observed previously by Kumar *et al.* [20]



TS1



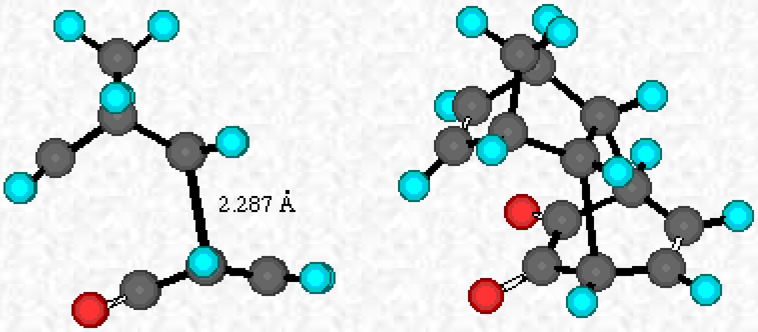
TS2

Figure 1. B3LYP/6-31G* structures of **TS1** and **TS2**

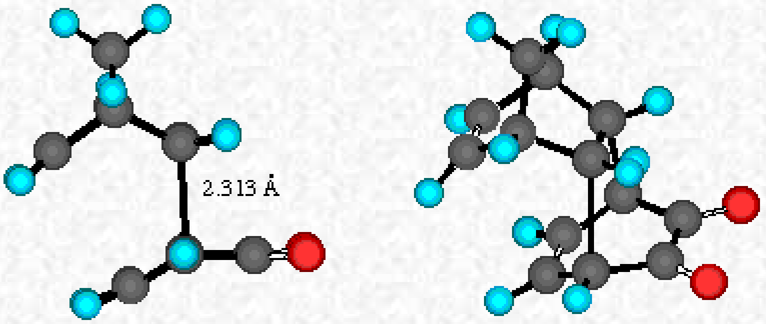
For each mode of attack to the ¶-system, we have located two transition structures: for *exo*- approach **TS5** (where aromatic ring is facing methylene bridge) and **TS6** (where aromatic ring lay in the plane of norbornene cyclohexene ring), and for the *endo*- addition **TS7** (where aromatic moiety is facing double bond) and **TS8** (where aromatic ring is outside norbornene moiety) (Scheme 2). While these structures possess some energy differences, we were unable to see discrete species using $_1$H-NMR, which suggest their rapid interconversion at room temperature.

The inspection of results collected in Tables 2-4 reveals nonconsistent results for activation energies for **TS5-8** at all employed theoretical levels. For most transition structures, activation energies are smaller, or very similar to the one for the **TS1-4**, which is opposite to experimental results. For instance, the B3LYP/6-31G* method, which gives excellent results for cycloaddition reactions, predicts **TS6** to have the smallest energy followed by **TS5**, **TS7** and **TS8**, while activation energies for **TS1-4** are significantly greater, suggesting the exclusive formation of products **3-6**. However, these adducts have not been experimentaly detected. In this case, only the RHF/6-31G* method gave the correct predictions, *i.e.* exclusive formation of products **3-5**, while hetero Diels-Alder products have much bigger activation energies.

The lengths of the bonds undergoing first-order changes in these transtition structures are those expected for concerted cycloaddition transition states (Figures 3 and 4). However, harmonic frequency calculations identified these structures as second-order saddle points. Efforts to locate concerted, synchronous transition structures for hetero Diels-Alder reaction using various spin-restricted wave functions resulted in each case, in the location of a single stationary point possessing more than one negative mode of vibration. Despite an extensive search of the singlet-state energy surface using resticted levels of *ab initio* and DFT theory, we were unable to locate genuine transition structures for either synchronous or a nonsynchronous concerted cycloaddition process. The same finding was experienced using various spin-restricted wave functions (either 3-21G, 6-31G* or B3LYP methods).



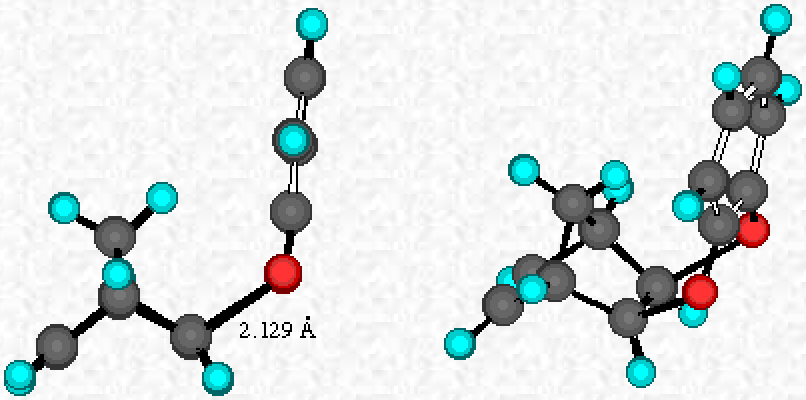
TS3



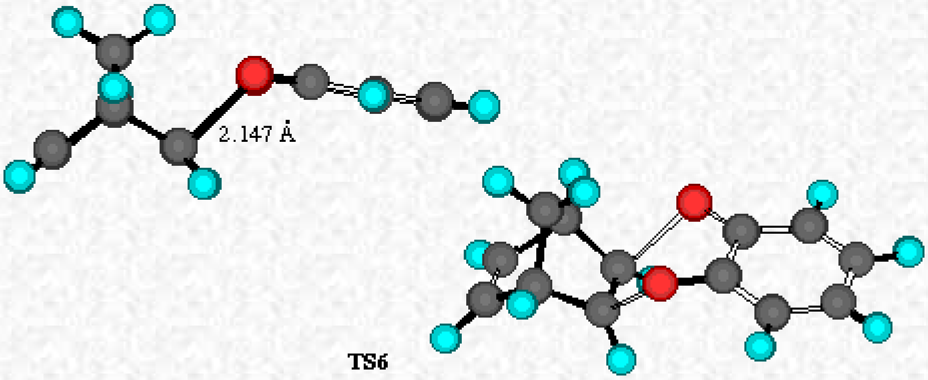
TS4

Figure 2. B3LYP/6-31G* structures of **TS3** and **TS4**

The discrepancies between the experimentally observed results and the theoretical analysis may be explained by the postulation of a second, nonconcerted biradical mechanism leading to formation of hetero Diels-Alder products **5-10**. Given our failure to locate concerted transition strucutre for the *o*-benzoquinone hetero Diels-Alder cycloaddition, our attention is now focused on calculations of nonconcerted reactions. The calculations employing unrestricted *ab initio* and B3LYP calculations are currently being undertaken and these results will be reported in due course.



TS5



TS6

Figure 3. B3LYP/6-31G* structures of **TS5** and **TS6**

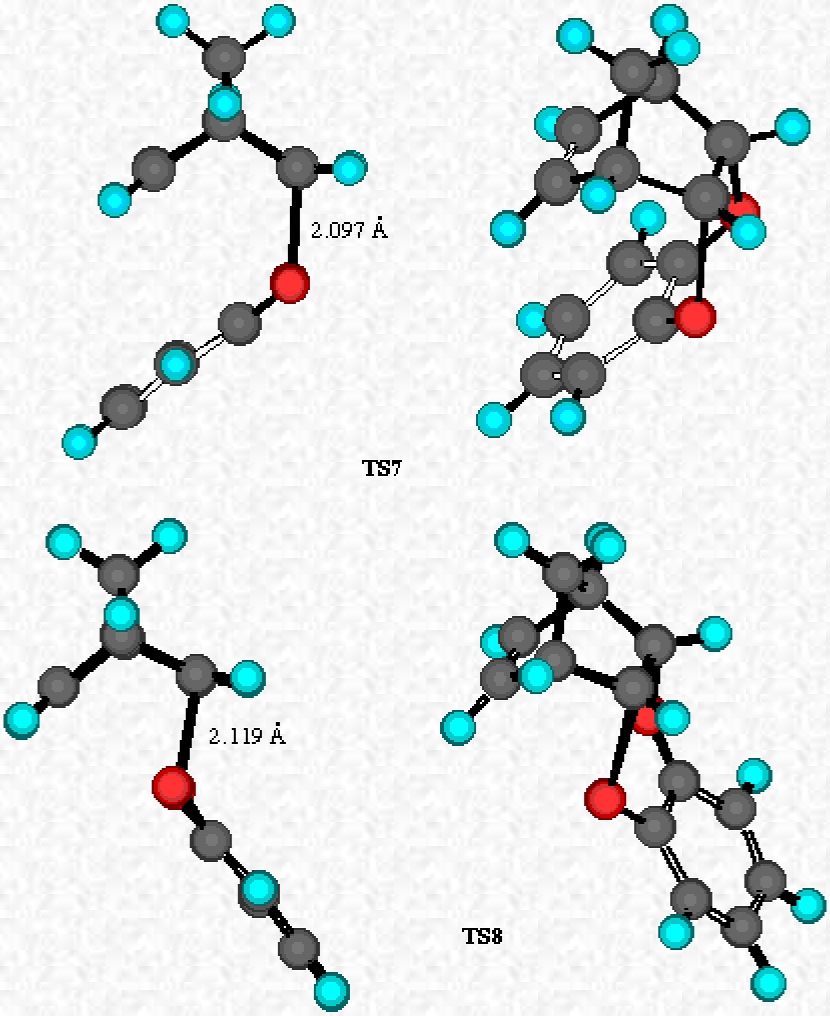


Figure 4. B3LYP/6-31G* structures of **TS7** and **TS8**

Conclusion. The present results demonstrate the ability of *ab initio* calculations to accurately predict relative reactivities and stereospecificities for inverse electron-demand Diels - Alder reactions in alicyclic systems with cyclic 1,3-dienes. Transition states were located and activation barriers estimated at different levels of theory, by Hartree-Fock, post- Hartree-Fock and DFT methods. The high *exo*-¶-facial selectivity exhibited in these cycloadditions are readily predicted using RHF/3-21G or higher *ab initio* levels. In the case of hetero Diels-Alder products, all quantum chemical levels employed failed to correctly predict energy barriers, which suggests that second, nonconcerted biradical mechanism may be operating.

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