Diels–Alder Reactions of D-Glucose-Derived Dienophiles with Cyclopentadiene: A Computational Study

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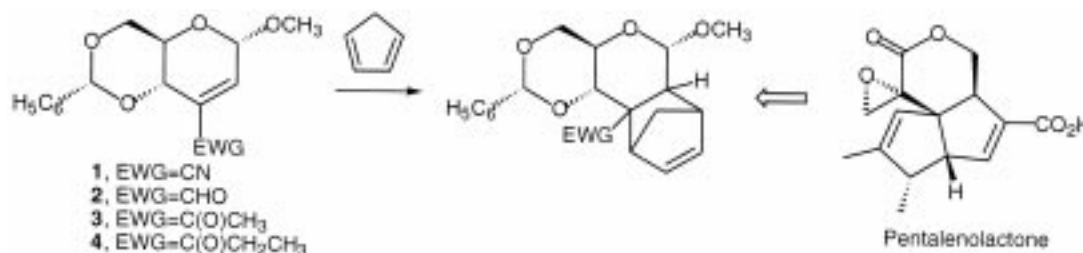
Abstract—AM1 and B3LYP calculations were performed for the Diels–Alder reactions of a series of D-glucose-derived dienophiles with cyclopentadiene. The preferred β vs. α diastereofacial addition and *exo* vs. *endo* selectivities are explained on the basis of products and transition states stabilities. Computed *exo*/*endo* ratios change in the correct direction although they do not agree quantitatively with available experimental data. The relative reactivity of the dienophiles bearing a carbonyl group can be interpreted in terms of FMO theory as well as of repulsive interactions in the corresponding transition states. The calculations fail to explain the observed lack of reactivity for the dienophile bearing a cyano group. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

One of the most efficient methodologies leading to oxygenated cyclohexanes and cyclopentanes involves the use of carbohydrate derivatives in Diels–Alder reactions.[1–3] We have previously reported the synthesis of a series of D-glucose-derived enantiomerically pure dienophiles (**1–4**) bearing different exocyclic electron withdrawing groups (EWG) (Scheme 1). We have also investigated the outcome of their Diels–Alder reactions with cyclopentadiene.[4,5] These cycloadditions allow the stereoselective generation of the quaternary carbon center present in a broad family of natural products with diverse carbocyclic skeletons.[6–9]

This synthetic strategy has been successfully applied to the construction of the basic framework of pentalenolactone, a natural sesquiterpenoid with important biological properties and interesting structural features.[10]

The experimental results of these Diels–Alder reactions are summarized in Table 1. The nature of the electron withdrawing group influences the outcome of the cycloaddition both in terms of reactivity as well as stereoselectivity. α,β-Unsaturated nitrile **1** showed an unexpected lack of reactivity. For α,β-unsaturated carbonyl compounds **2–4**, a decrease in dienophilicity and stereoselectivity is observed as the length of the side chain increases. In addition, these

1, EWG=CN
2, EWG=CHO
3, EWG=C(O)CH₃
4, EWG=C(O)CH₂CH₃

Pentalenolactone

Scheme 1.

Table 1.

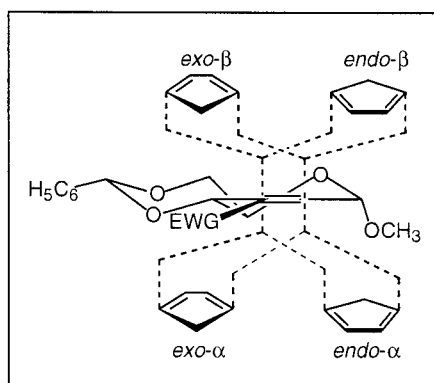| Dienophile	Products (%)				Starting material recovery (%)
	endo-α	*exo-α*	*endo-β*	*exo-β*	
1, EWG=CN	–	–	–	–	Quantitative
2, EWG=CHO	–	–	–	85	–
3, EWG=C(O)CH$_3$	–	–	3.75	8.25	75
4, EWG=C(O)CH$_2$CH$_3$	–	–	–	–	Quantitative

Figure 1.

processes have an intrinsic preference for *exo-β* approach of cyclopentadiene (Fig. 1), violating Alder's rule which predicted the generation of *endo* adducts.

We thus undertook a computational study of these Diels–Alder reactions in order to rationalize reactivity and stereoselectivity trends. We first carried out a comparative study of the reactivity of dienophiles **1**–**4** considering ground-state conformations and molecular orbitals levels. We also investigated the thermodynamics and kinetics of these cycloadditions to provide a rationale of the observed diastereofacial and *exo/endo* selectivities.
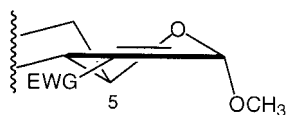

Figure 2.

Computational Methods

Semiempirical investigations were carried out at the Restricted Hartree–Fock (RHF) AM1[11] level of theory using the program AMPAC version 2.1. Initial geometries were built with Hyperchem and converted into AMPAC input. Geometry optimizations were performed using standard defaults. AM1 transition structures were fully optimized with Powell's method. Energy minimum structures had all real frequencies and transition structures had only one imaginary frequency. B3LYP[12] energies were estimated from RHF/6-31G* single point calculations on the AM1 optimized geometries using GAUSSIAN 98.[13]

Results and Discussion

The search of a simple method to rationalize reactivity trends led to the application of frontier molecular orbital theory (FMO) since the reactivity of dienophiles in normal Diels–Alder reactions can be correlated with their LUMO energies. This kind of treatment has been used in important qualitative studies about reactivity and regioselectivity of cycloaddition reactions,[14] including the investigation of dienophilic systems derived from carbohydrates.[15,16] We hence studied the geometric and electronic properties of the structures of dienophiles **1**–**4**. Molecular models inspection shows that the benzylidene acetal group imparts conformational rigidity to these bicyclic dienophiles forcing the pyranose rings to adopt $^O H_5$ half-chair conformations (Fig. 2).[17]

Consequently, the degrees of freedom of these systems are reduced and the search of conformational space is further simplified. Table 2 shows the AM1 results of such conformational analysis for dienophiles **1**–**4**, in which the dihedral angle indicated corresponds to the angle formed between the carbonyl group and the carbon–carbon double bond.

Table 2.

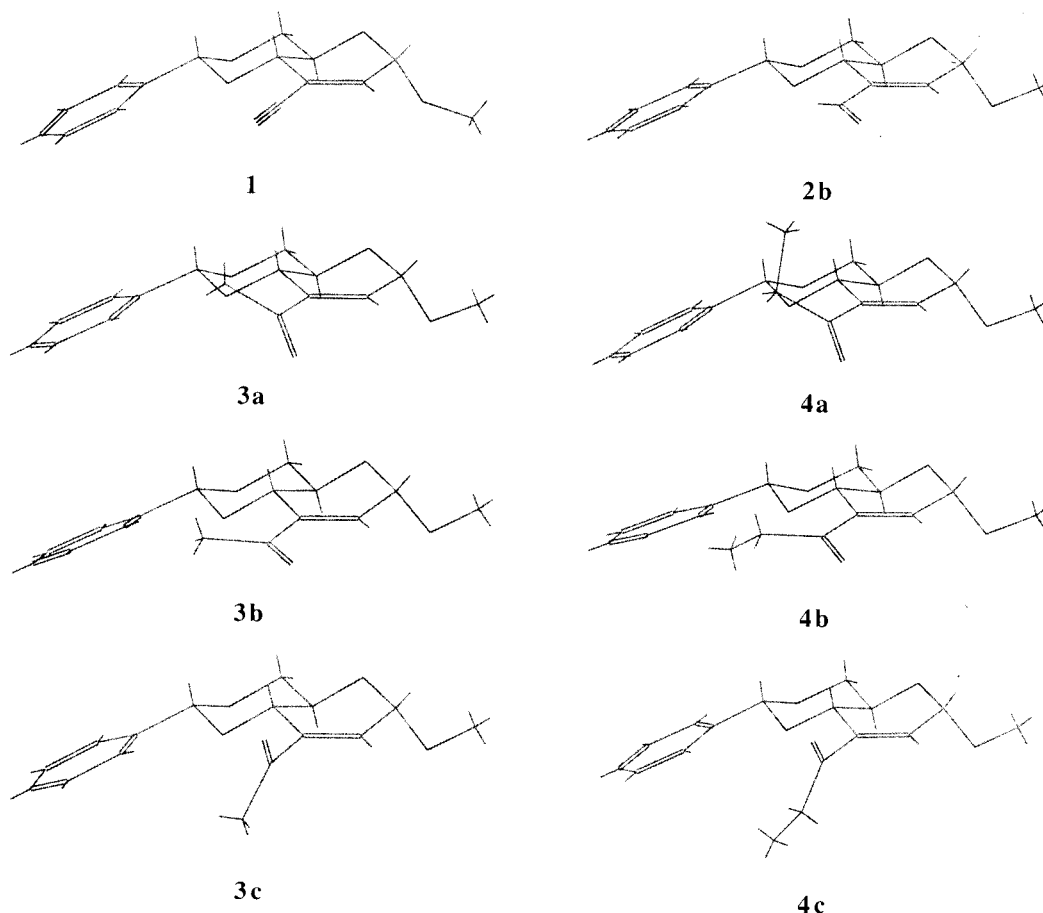| Dienophile	Conformer	Dihedral angle (°)	ΔH_f (kcal/mol)	LUMO (eV)	HOMO (eV)
1	**1**	–	−88.3	−0.43	−9.61
2	**2a**	−10	−151.9	−0.44	−9.69
	2b	0	−152.1	−0.45	−9.69
	2c	12	−152.2	−0.43	−9.70
3	**3a**	−40	−156.9	−0.19	−9.68
	3b	−7	−157.2	−0.34	−9.72
	3c	75	−157.6	0.13	−9.69
4	**4a**	−39	−162.5	−0.19	−9.67
	4b	−15	−163.1	−0.30	−9.71
	4c	76	−163.6	0.15	−9.69

Figure 3.

The linearity of cyano group leads to the localization of a single energy minimum for α,β-unsaturated nitrile **1**. We then explored the coordinate for the rotation of the carbonyl group for α,β-unsaturated carbonyl substrates. The investigation of these coordinates played a fundamental role in the study of the reactivities of α,β-unsaturated carbonyl dienophiles **2–4**. The inspection of the energy profile for the carbonyl rotation of α,β-unsaturated aldehyde **2** allowed the optimization of three local minima (**2a–c**) corresponding to structures with cisoid α,β-unsaturated carbonyl systems. For methyl α,β-unsaturated ketone **3**, three conformers corresponding to C2–C3–C=O dihedral angles of −40° (**3a**), −7° (**3b**) and 75° (**3c**) were located. The application of the same procedure for the ethyl α,β-unsaturated ketone **4** permitted the identification of three energy minima similar to that corresponding to the methyl α,β-unsaturated ketone **3**, that is, with C2–C3–C=O dihedral angles of −39° (**4a**), −15° (**4b**) and 76° (**4c**). Representative conformers are depicted in Fig. 3. Although calculated energy differences between minima **a–c** do not rule out any conformer, they do suggest favored ground-state conformations for dienophiles **2–4**.

At the same time, a single energy minima was found by AM1 for cyclopentadiene with a heat of formation of 37.1 kcal/mol and orbital energies of −9.08 and 0.48 eV for the HOMO and the LUMO, respectively. The same energy ordering of LUMOs and HOMOs of diene and dienophiles was obtained with B3LYP.

As the $HOMO_{diene}$–$LUMO_{dienophile}$ energy gaps for dienophiles **1–4** were lower than the corresponding $HOMO_{dienophile}$–$LUMO_{diene}$ ones, it was shown that the frontier orbitals involved in these cycloadditions were the HOMO of the diene and the LUMOs of the dienophiles. In other words, it was confirmed that, although these are highly oxygenated dienophiles, the processes under investigation corresponded to normal Diels–Alder reactions. A quick inspection of the LUMO energies reveals that it is not possible to explain the lack of reactivity of the α,β-unsaturated nitrile **1** by FMO theory since these calculated values may lead to the conclusion that its reactivity should be similar to that of aldehyde **2**. This could be attributed to electronic differences between cyano and carbonyl groups that make difficult to observe a linear relationship between calculated LUMO energies and dienophile reactivities. On the other hand, a comparative analysis of the results obtained for α,β-unsaturated carbonyl dienophiles **2–4** demonstrates that, as the length of the side chain increases, the existence of non coplanar structures is favored and the LUMO energies increase. As a consequence of this LUMO energies increase, the $HOMO_{diene}$–$LUMO_{dienophile}$ energy gaps increase, leading to lower reaction rates. This fact is in agreement with experimental dienophilicities and provides a rationale to reactivity trends for α,β-unsaturated carbonyl dienophiles.

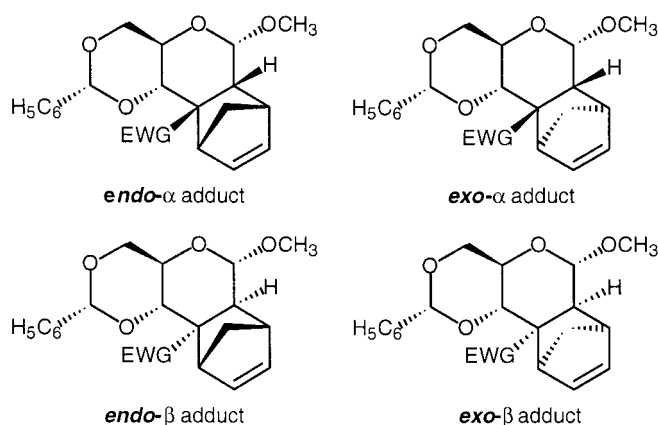It is worth remarking the substantial increase of LUMO energies observed for non coplanar structures. Calculated

Figure 4.

Table 3. Diastereomers' heats of formation relative to *exo*-β compounds (kcal/mol)

EWG	Adduct	*endo*-α		*exo*-α		*endo*-β	
		AM1	B3LYP/6-31G*//AM1	AM1	B3LYP/6-31G*//AM1	AM1	B3LYP/6-31G*//AM1
CN	**5**	2.94	2.71	4.74	1.74	−0.40	−0.10
CHO	**6**	3.72	2.98	5.13	1.65	0.02	−0.15
C(O)CH$_3$	**7**	5.80	5.64	6.57	4.82	0.42	1.18
C(O)CH$_2$CH$_3$	**8**	5.87	5.75	4.00	2.55	0.44	0.97

LUMO coefficients at the carbonyl atoms clearly show that as the conjugated system deviates from coplanarity there is a weaker interaction between the carbon–carbon double bond and the carbonyl π systems. Spectroscopic data support the existence of non coplanar structures for α,β-unsaturated ketones **3** and **4**. In particular, IR carbonyl stretching frequencies demonstrate the loss of conjugation as the length of the side chain increases, which results in a lower activation of dienophiles **3** and **4**.[18]

In the next stage we focused on interpreting the observed stereoselectivitites and thus undertook a theoretical investigation of the thermodynamics and kinetics of these processes. In order to establish any relationship between product stability and stereoselectivity, we calculated the heat of formation for each of the four possible diastereoisomeric products resulting from the reactions of dienophiles **1**–**4** with cyclopentadiene (Fig. 4).

The AM1 and B3LYP difference in heats of formation between the different adducts and the *exo*-β compounds are presented in Table 3.

The difference in calculated heats of formation showed the higher stability of β-adducts indicating the importance of this factor in determing π-facial preference. On the other hand, the lower energy differences between β adducts do not account for the experimental *endo/exo* selectivities. The observed *endo/exo* ratios do not result from a thermodynamical equilibrium. Instead, they should be determined by the energy gap between both transition states, through a kinetically controlled process.

We examined reaction surfaces in order to locate transition states structures for these cycloadditions. We found asynchronous concerted transition states for all reactions.[19] The comparison of activation energies would lead to a complete rationalization of reactivities and stereoselectivities trends. This investigation should also help assessing the relative importance of the different structural factors involved in determining the anomalous stereochemical outcome of these Diels–Alder reactions.

As in other addition reactions to sugar derivatives,[20,21] the β approach of cyclopentadiene could be assumed to be the result of an unfavorable interaction between the diene and the anomeric methoxy group of dienophiles in the α transition states. This fact is clearly shown by the transition states stabilities calculated and presented in Table 4. As can be seen from Tables 3 and 4, both products and transition states stabilities proved the unfavorable α approach of cyclopentadiene.

The calculated activation energy for *endo* and *exo*-β approaches for dienophiles **1**–**4** and the resulting activation energy difference are summarized in Table 5. Computed *exo/endo* ratios were also calculated and compared to those obtained experimentally. Since the enthalpic origin of *exo/endo* stereoselectivity has been demonstrated for other Diels–Alder reactions,[22,23] activation entropies were assumed to be equal. Product ratios were computed as usual.[24]

Table 4. AM1 heat of formation of transition states (kcal/mol)

EWG	TS	*endo*-α	*exo*-α	*endo*-β	*exo*-β
CN	**9**	−12.27	−12.72	−15.10	−15.37
CHO	**10**	−74.94	−76.99	−78.85	−80.62
C(O)CH$_3$	**11**	−76.03	−75.82	−81.99	−83.51
C(O)CH$_2$CH$_3$	**12**	−81.67	−86.99	−86.43	−87.58

Table 5.

EWG	TS	E_a (kcal/mol)	ΔE_a (exo−endo), kcal/mol		Ratio$_{comp}$ (exo/endo)		Ratio$_{exp}$ (exo/endo)
			AM1	B3LYP/6-31G*//AM1	AM1	B3LYP/6-31G*//AM1	
CN	**9**endo-β	36.08	−0.44	−2.23			–
	9exo-β	35.64					
CHO	**10**endo-β	36.15	−1.80	−2.82	95:5	99:1	100:0
	10exo-β	34.35					
C(O)CH$_3$	**11**endo-β	38.11	−1.52	−2.22	93:7	97:3	70:30
	11exo-β	36.59					
C(O)CH$_2$CH$_3$	**12**endo-β	39.57	−1.15	−3.61			–
	12exo-β	38.42					

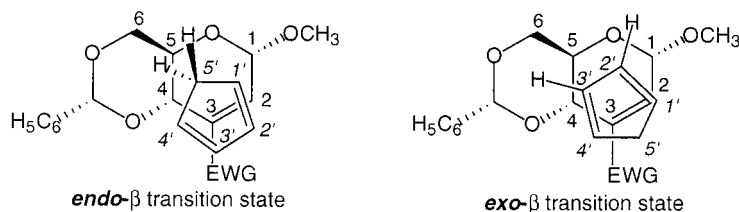**Figure 5.**

Except for α,β-unsaturated nitrile **1**, experimental results can be nicely explained by these kinetic calculations. The theoretical results take no account of the lack of dienophilicity of **1** as the activation energies for β additions of cyclopentadiene to **1** are of the same order of magnitude as those corresponding to **2** and **3**. This result as well as the FMO analysis indicate that these calculations are not adequate to correlate compounds belonging to different functional group families. On the other hand, this investigation agreed qualitatively with experimental reactivity and stereoselectivity trends for α,β-unsaturated carbonyl dienophiles **2**–**4**. Calculated energies show that transition states resulting from exo-β addition of cyclopentadiene are more stable than those leading to endo-β cycloadducts. The method correctly predicts the preferred mode of addition and, although computed exo/endo ratios do not agree quantitatively with available experimental data, they change in the correct direction.

Once we confirmed that the sense of stereoselectivity was reproduced by this method, we then inspected the structural features of transition states in order to better understand the origin of anomalous preference for exo additions (Fig. 5).

It is noticeable that transition states located for α,β-unsaturated carbonyl dienophiles **2**–**4** showed dihedral angles between C-2 and carbonyl oxygen (C2–C3–C=O) near to zero. This indicates that reactive conformations correspond to s-cis structures and validates the relevance of our FMO studies. The calculated distances (in Å) between atoms not directly involved in sigma bond making remain almost constant for any transition state. Among them, the most relevant C2–C3; C1'–C2'; C2'–C3' and C3'–C4'≅1.41 Å. The distance of the forming bonds are shown in Table 6. The differences between these lengths are approximately 0.22 and 0.34 Å for endo and exo transition states respectively.

We next turned our attention to detect the structural effects responsible for exo preferences. In contrast to exo transition states where two sp^2 carbons of cyclopentadiene (C-2' and C-3') lie over the pyranose ring of the dienophiles, in endo additions such position is replaced by a more sterically demanding sp^3 carbon of the diene (C-5'). Consequently, the distances between the hydrogens of cyclopentadiene and those attached to the rigid dienophilic system are lower. We inspected endo transition structures and found that the distances between C-5' H-α and C-4 H varied in the narrow range from 2.02 to 2.06 Å. Considering that the hydrogen van der Waals radius is 1.20 Å, computed distances should give rise to an important unfavorable steric interaction between these two hydrogens. This fact explains the lower stability of endo transition states. The C3–C4' distances were slightly higher for exo transition states. Another structural feature of endo transition states answered this question. The distances between the hydrogens attached to C-1' and C-1 were also low, ranging from 2.10 to 2.14 Å. This additional van der Waals repulsion justifies the more synchronous nature of endo transition states and further rationalizing their lower stabilities compared to exo transition structures.

Finally, we investigated the origin of the decrease of stereoselectivity with the increase of the length of the side chain for α,β-unsaturated carbonyl dienophiles **2**–**4**. When the

Table 6.

EWG	TS	endo-β		exo-β	
		(C2–C1')	(C3–C4')	(C2–C1')	(C3–C4')
CN	**9**	2.05	2.24	2.02	2.28
CHO	**10**	2.03	2.25	2.00	2.31
C(O)CH$_3$	**11**	2.03	2.26	1.99	2.33
C(O)CH$_2$CH$_3$	**12**	2.04	2.24	1.99	2.33

hydrogen atom of the formyl group in *exo* transition state **10***exo*-β was replaced with a larger alkyl group such as methyl or ethyl in transition structures **11***exo*-β and **12***exo*-β (Fig. 5), the hydrogen attached to C-4′ of cyclopentadiene experienced an additional weak unfavorable interaction with the hydrogens α to the carbonyl group. This steric hindrance diminished the relative stability of *exo* transition states and can be postulated as the basis for the predicted lower stereoselectivities of cyclopentadiene additions to ketones **3** and **4**.

Conclusion

In the present investigation, the semiempirical AM1 method was used to study the course of the Diels–Alder reactions of a series of D-glucose-derived dienophiles with cyclopentadiene. The general trends obtained with AM1 were verified by B3LYP RHF/6-31G* single point calculations on the AM1 optimized geometries. The calculations reproduced qualitatively the direction and the general trends of experimental results. Particularly, they were successful in predicting the variation of reactivity and stereoselectivity for α,β-unsaturated carbonyl dienophiles **2**–**4**. FMO calculations led to a good correlation between reactivity with calculated LUMO energies for this series of compounds. Observed reactivities and stereoselectivities were also interpreted on the basis of transition state energies. Finally, the anomalous preference of these compounds to undergo stereoselective *exo* cycloadditions was rationalized. The destabilization of *endo* transition states was mainly attributed to steric effects caused by the methylene group of the diene. These results are an example of the rationalization of an abnormal addition mode, since the factors affecting the outcome of a cycloaddition process with a synthetically useful and complex molecular system, can hardly ever be established beyond an intuitive speculation.

References

1. Giuliano, R. M. *Cycloaddition Reactions in Carbohydrate Chemistry*, American Chemical Society: Washington, DC, 1992.
2. Primeau, J.; Anderson, R.; Fraser-Reid, B. J. *J. Chem. Soc., Chem. Commun.* **1980**, 6–8.
3. Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, 93, 2779–2831.
4. Pellegrinet, S. C.; Spanevello, R. A. *Tetrahedron: Asymmetry* **1997**, 8, 1983–1986.
5. Pellegrinet, S. C.; Spanevello, R. A. *Org. Lett.* **2000**, 2, 1073–1076.
6. Paquette, L. A.; Doherty, A. M. *Recent Synthetic Developments in Poliquinane Chemistry*; Springer-Verlag: New York, 1987.
7. Fu, X.; Cooks, J. M. *Aldrichim. Acta* **1992**, 25, 43–54.
8. Paquette, L. A. *Aldrichim. Acta* **1984**, 17, 43–51.
9. Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, 97, 671–719.
10. Pellegrinet, S. C.; Spanevello, R. A. *Tetrahedron Lett.* **1997**, 50, 8623–8626.
11. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, 107, 3902–3903.
12. (a) Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785.
13. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. GAUSSIAN 98 (Revision A.7); Gaussian: Pittsburgh PA, 1998.
14. Houk, K. N. *J. Am. Chem. Soc.* **1974**, 95, 4092–4094.
15. Fraser-Reid, B.; Underwood, R.; Osterhout, M.; Grossman, J. A.; Liotta, D. *J. Org. Chem.* **1986**, 51, 2152–2155.
16. Dauben, W. G.; Kowalczyk, B. A.; Lichtenthaler, F. W. *J. Org. Chem.* **1990**, 55, 2391–2398.
17. Schwarz, J. C. P. *J. Chem. Soc., Chem. Commun.* **1973**, 505–508.
18. The IR data confirmed the loss of conjugation of the α,β-unsaturated ketones, specially in the case of the ethyl ketone **4**. On the other hand, the IR spectrum of nitrile **1** shows an absorbance peak (for the carbon–nitrogen stretching vibrations) within the range for conjugated nitrile groups as it was expected for a group with linear geometry. IR absorbance [observed (theoretical)] in [cm^{-1}]: nitrile **1**: 2227 (*2240–2215*); aldehyde **2**: 1690 (*1695–1660*); methyl ketone **3**: 1696 (*1675*); ethyl ketone **4**: 1702 (*1675*).
19. Silvero, G.; Lucero, M. J.; Winterfeldt, E.; Houk, K. N. *Tetrahedron* **1998**, 54, 7293–7300.
20. López, J. C.; Lameignere, E.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1988**, 706–707.
21. Giuliano, R. M.; Buzby, J. H.; Marcopulos, N. *J. Org. Chem.* **1990**, 55, 3555–3562.
22. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, 19, 779–807 (and references cited therein).
23. Fotiadu, F.; Michel, F.; Buono, G. *Tetrahedron Lett.* **1990**, 34, 4863–4866.
24. Product ratios were computed from the equation: $k_1/k_2 = e^{-\Delta E_a/RT}$, where ΔE_a is the difference between the calculated activation energies for the two processes, $T = 298.15$ K and $R = 1.9872$ cal K^{-1} mol^{-1}.