Pergamon

Tetrahedron 58 (2002) 3667–3671

TETRAHEDRON

Nitrone cyclisations: the development of a semi-quantitative model from ab initio calculations

María A. Silva and Jonathan M. Goodman*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK

Received 18 December 2001; accepted 28 March 2002

Abstract—Ab initio and DFT calculations have been applied to the 1,3-dipolar cycloaddition of nitrones with olefins. The transition states for these structures were located and activation energies were calculated. These results were used to develop a semi-quantitative model, Simple Addition of Substituent Effects Model, which accounts for the experimentally observed regio- and stereoselectivity.

1. Introduction

1,3-Dipolar cycloaddition reactions of nitrones with alkenes have found general application in organic synthesis.[1] The isoxazolidines formed from these reactions are versatile intermediates in the synthesis of a multitude of natural compounds. Ab initio quantum mechanical calculations have been described in the literature to model the stereochemical outcome of reactions with nitrones and different dipolarophiles.[2,3] However, to date, they have not considered the effects of substitution of the nitrone moiety. In this paper we describe the results from a theoretical study in which the electronic effects of substitution of both the nitrone and dipolarophile are considered and a semi-quantitave model has been developed. The results agree, in general, with the stereoselectivity observed for the 1,3-dipolar cycloadditions of nitrones with olefins. Furthermore, the regioselectivity predicted by our model also agrees with the experimental results.

It is known that nitrones react with olefins bearing a strong electron-withdrawing group to give the C-4 substituted isoxazolidines, while the C-5 regioisomer is preferred when electron-donating and moderate electron-withdrawing substituted olefins are used. Nevertheless, there are some cases where the prediction of regioselectivity is not straight forward, especially when 1,2-disubstituted olefins are involved.[3c,4]

Reactions of substituted dipolarophiles with a simple nitrone have been studied computationally by Magnuson and Pranata.[2] Calculations at RHF level suggest that for substituted ethylene dipolarophiles with groups such as methyl or carboxaldehyde, the regioselectivity may be correlated with the ability of the substituent to donate or withdraw electrons. This result is expected from electronic considerations[5] and the same trend is observed experimentally.[6] However, the regioselectivity ratios calculated in Magnuson's paper[7] do not agree with the high regiochemical control exhibited for the addition of nitrones to different kind of dipolarophiles. We now wish to extend Magnuson and Pranata's study by looking at multiple substitutions.

2. Computational methods

Geometry optimisations of the transition structures and the reactants were carried out using ab initio methods at the restricted Hartree–Fock (RHF) level of theory with the 6-31G* basis sets. B3LYP/6-31G* single-point energy calculations were performed on the fully optimized RHF transition structures. Frequency calculations were used to confirm the nature of the stationary points. All transition state structures had only one imaginary harmonic vibrational frequency. Corrections for zero-point energies (ZPE) have not been included, because they were not expected to have a significant effect on the relative energies. Calculations were performed using Cadpac version 6.0[8] and run on Silicon Graphics Computers (IRIX 5.3 and 6.3).

3. Results and discussion

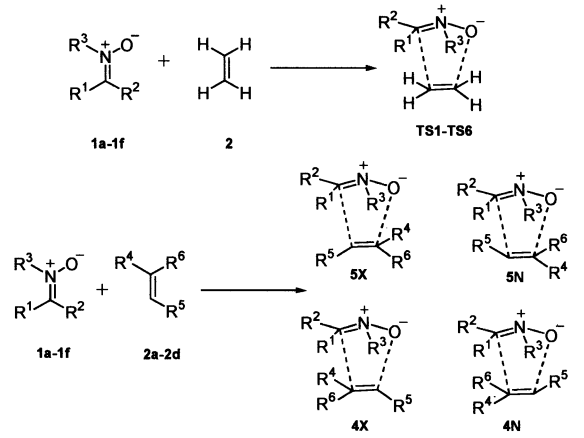
3.1. RHF/6-31G* calculations. Comparison to SASEM

We began our study with just one substituent in either nitrone or dipolarophile, to investigate the relative importance of electronic and steric effects in 1,3-dipolar cycloadditions. Scheme 1 shows all the possible modes of

Keywords: nitrones; 1,3 dipolar cycloadditions; ab initio calculations.

* Corresponding author. Tel.: +44-1223-336-434; fax: +44-1223-763-076; e-mail: jmg11@cam.ac.uk

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00349-6



Scheme 1.

Table 1. TS activation energies (kJ/mol) of the 1,3-dipolar cycloaddition of nitrones **1a**–**1f** to ethylene (**2**) at RHF/6-31G* (B3LYP/6-31G*// HF/6-31G*, in parentheses) and relative energies to **TS1** at RHF/6-31G*

	Nitrone	R1	R2	R3	$\Delta E^{\ddagger}$ (kJ/mol)	E_{rel}
TS1	**1a**	H	H	H	116.20 (47.51)	0
TS2	**1b**	Me	H	H	110.04 (43.24)	−6.17
TS3	**1c**	H	Me	H	132.22 (62.95)	16.02
TS4	**1d**	H	H	Me	120.17 (39.74)	3.97
TS5	**1e**	CHO (*s-cis*)	H	H	128.20 (51.92)	12.10
TS6	**1f**	H	CHO (*s-cis*)	H	117.20 (56.44)	1.00

addition for each reaction. For the systems with substituted olefins there are four possible isomers (4-/5-isomers and *exo*/*endo*-isomers). The results are summarized in Tables 1 and 2.

We see that, in general, electron-donating and withdrawing substituents at the dipolarophile have opposite effects on the regioselectivity, although steric hindrance may also be important in some cases.[4b,c] While with electron-donating groups, the favoured regiochemistry results from substitution at the oxygen end of the dipole, the other regioisomer becomes more important as the electron-withdrawing ability of the substitutent increased. The Boltzmann factors were calculated at room temperature in order to predict the degree of regioselectivity for each system, which gave high regiochemical control (Table 3).[9]

The first calculations were carried out for the transition state structures with the nitrones **1a**–**1f** and ethylene. C-substitution of the nitrone gave an interesting result, suggesting that both electronic and steric effects influence the stability of the transition states and play an important role in the course of the cycloaddition (Table 1). In the case of **TS2** with a *C*-methyl nitrone, we found lower energy for the transition state, 6.17 kJ/mol, than the unsubstituted one, **TS1**. The **TS2** is also 22.19 kJ/mol lower in energy than **TS3**. This suggests that E-alkyl-substituted nitrones should be more reactive than Z-alkyl-substituted nitrones, as has been reported.[10] The transition states with carbonyl C-substituted nitrones were calculated to be higher in energy than the unsubstituted transition state, **TS1**.

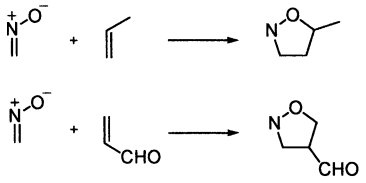
Table 2. TS activation energies (kJ/mol) of the 1,3-dipolar cycloaddition of nitrones to different alkenes at RHF/6-31G* (B3LYP/6-31G*// HF/6-31G*, in parentheses)

Entry	Nitrone	Alkene	R4	R5	R6	$\Delta E^{\ddagger}$ (kJ/mol)			
Mono alkene-substitution									
						5X	**5N**	**4X**	**4N**
1	**1a**	**2a**	Me	H	H	115.24 (48.49)	118.69 (51.84)	132.27 (61.46)	133.08 (61.81)
2	**1a**	**2b**	CHO (*s-cis*)	H	H	110.84 (34.78)	94.58 (12.87)	89.85 (39.16)	77.46 (27.04)
3	**1a**	**2b**	CHO (*s-trans*)	H	H	117.41 (44.36)	115.42 (38.97)	96.71 (38.50)	94.46 (36.26)
Double substitution									
4	**1a**	**2c**	CHO (*s-cis*)	Me	H	128.61 (50.53)	111.34 (27.77)	96.05 (47.38)	79.80 (30.74)
5	**1a**	**2d**	CHO (*s-cis*)	H	Me	118.12 (44.31)	98.13 (19.22)	111.14 (47.38)	100.31 (43.77)
6	**1b**	**2a**	Me	H	H	108.95 (44.36)	112.21 (47.31)	126.40 (56.87)	128.69 (58.82)
7	**1b**	**2b**	CHO (*s-cis*)	H	H	105.26 (31.39)	89.25 (9.09)	70.85 (35.12)	56.38 (18.53)
8	**1d**	**2b**	CHO (*s-cis*)	H	H	113.87 (31.39)	113.74 (20.28)	91.18 (32.92)	84.31 (26.79)
9	**1e**	**2a**	Me	H	H	127.77 (52.90)	131.35 (56.45)	143.45 (64.11)	146.55 (66.26)
10	**1f**	**2a**	Me	H	H	116.06 (56.64)	120.49 (61.14)	143.15 (76.74)	133.63 (69.42)

Table 3. Calculated Boltzmann ratios in percentage at 300 K

Entry	Nitrone+alkene	**5X**	**5N**	**4X**	**4N**
1	**1a**+**2a**	80	20	0	0
2	**1a**+**2b** (*s-cis*)	0	0	0	100
3	**1a**+**2b** (*s-trans*)	0	0	29	71
4	**1a**+**2c**	0	0	0	100
5	**1a**+**2d**	0	70	<0.5	30
6	**1b**+**2a**	78	22	0	0
7	**1b**+**2b**	0	0	0.3	99.7
8	**1d**+**2b**	0	0	6	94
9	**1e**+**2a**	81	19	<0.5	0
10	**1f**+**2a**	85	15	0	0

Next we explored the transitions states for the reaction between the parent nitrone and propene or acrolein (Table 2, entries 1–3). We observed that electron-donating groups, such as methyl, in the dipolarophile gave the 5-substituted isoxazolidine **5X**, entry 1, (115.24 kJ/mol) as preferred (Scheme 1), while for electron-withdrawing groups, like carbonyl, the 4-substituted isoxazolidine **4N**, entry 2, is favoured (77.46 kJ/mol) (Scheme 2). Furthermore, this result allows us to predict that electron-withdrawing groups should accelerate nitrone cycloadditions, which is consistent with the frontier orbital treatment of nitrone 1,3-dipolar cycloadditions.[5]



Scheme 2.

positive values found for the transition structures **4X** and **4N**, entry 7, (Table 4, Fig. 1), suggest that stabilizing effects, such as secondary orbital interactions (SOI) or Coulombic attractions between the nitrogen and carbonyl groups, may be present. Some authors have recently questioned the role, even the existence of SOI.[12] More recent calculations, however, on a simple model clearly give evidence that such interactions should be present, thereby accounting

Table 4. Estimated double-substitution TS activation energies in kJ/mol, as addition of substituent effects, SASEM (differences with the corresponding ab initio activation energies in Table 2, in parentheses)

Entry	Nitrone/alkene	5X	5N	4X	4N
4	**1a/2c**	127.71 (−0.90)	110.65 (−0.69)	92.34 (−3.70)	76.50 (−3.30)
5	**1a/2d**	113.33 (−4.79)	93.62 (−4.51)	106.73 (−4.41)	93.53 (−6.78)
6	**1b/2a**	109.07 (0.13)	112.53 (0.32)	126.10 (−0.29)	126.91 (−1.78)
7	**1b/2b**	104.67 (−0.58)	88.42 (−0.83)	83.69 (12.83)	71.30 (14.92)
8	**1d/2b**	114.80 (0.93)	98.55 (−15.20)	93.82 (−2.64)	81.43 (−2.89)
9	**1e/2a**	127.34 (−0.43)	130.79 (−0.56)	144.37 (0.92)	145.18 (−1.37)
10	**1f/2a**	116.24 (−0.17)	119.69 (−0.79)	133.27 (−9.88)	134.08 (−0.45)

TS1+$\sum\Delta E_i$, ΔE_i are the corresponding energy changes for the TSs in Tables 1 and 2 (entries 1–3), respect to **TS1**.

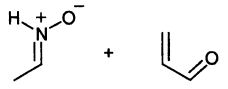


Figure 1.

When the dipolarophile is substituted with a carbonyl, we found that the *s-cis* conformation in the TS is preferred to the *s-trans*. Since acrolein itself is more stable in the *s-trans* conformation, this model predicts that there is a switch in the conformation of the dipolarophile from the ground state to the transition state. The conformational switch from *s-cis* to *s-trans* for acrolein is 34.26 kJ/mol (calculated at RHF/6-31G*), which is lower than the cycloaddition barrier (77.46 kJ/mol). This follows a precedent found by Houk et al.[11] for Diels–Alder reaction of butadiene with acrolein.

In order to explain the experimental results found for nitrone cycloadditons, we decided to investigate systems where both nitrone and dipolarophile were substituted. We have located the four possible transition structures for each (3+2) interaction between substituted nitrones (**1a–1f**) and propene, acrolein, *E*-crotonaldehyde and methacrolein. The results are listed in Table 2, entries 4–10.

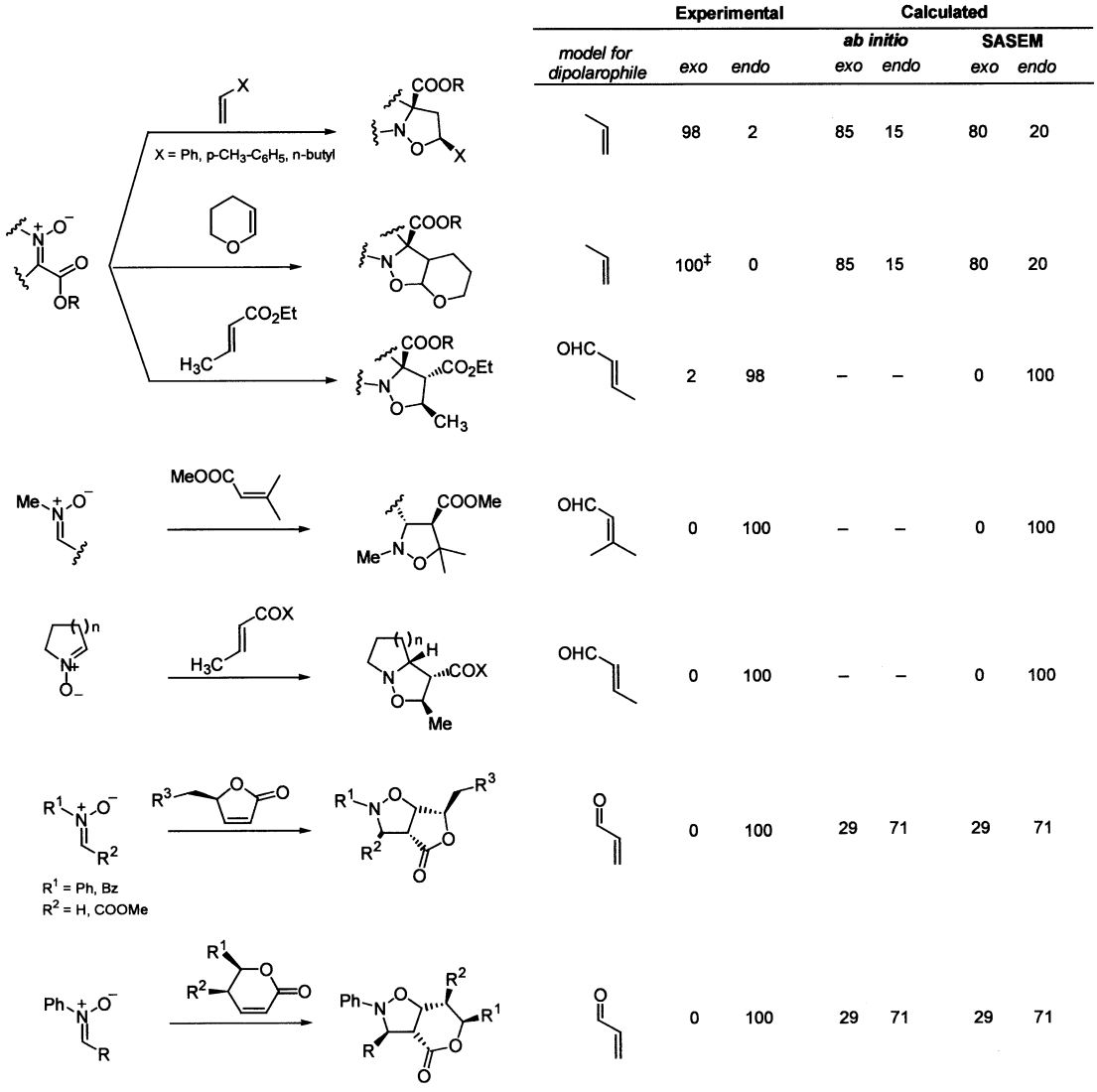
We confirmed that in cases where the effects of steric hindrance are expected to be minimal, the electronic effects of the substituents are additive. Table 4 shows the estimated energy barrier for the transition states with two substituents by adding the electronic effect of the substituents obtained from the ab initio calculations to **TS1**. The contribution of each substituent resulted from the difference in energy between **TS1** and each of the transition states with one substituent. We then compared the resulting energies obtained by this simple addition of substituent effects model (SASEM) with the ab initio energies. Since steric effects between substituents are not considered in these estimated energies, we expected all the difference of energies to be negative, as it is in most of the cases. However, the large, for experimental observations.[13] This result is consistent with the experimental findings for C-substituted nitrones and olefins with electron-withdrawing groups. It has been reported that substitution of the carbon of the nitrone functionality increases the tendency toward formation of the 4-regioisomer.[14]

3.2. B3LYP/6-31G* single point energies

Single-point electronic energies were computed to the B3LYP/6-31G* level on RHF/6-31G* geometries and the results were similar to the ab initio RHF ones, except for the case of *s-cis* acrolein as dipolarophile where DFT calculations do not seem to predict the reversal on the regiochemistry observed for olefin containing electron-withdrawing substituent.[6] At both levels of calculation, the frontier molecular orbital (FMO) analysis for the cycloaddition of nitrone **1a** and acrolein shows that the main interaction occurs between the HOMO of the nitrone (9.35 eV, RHF value and 6.10 eV, B3LYP value) and the LUMO of the acrolein (2.70 eV, RHF value and 1.49 eV, B3LYP value). The regioselectivity could then be rationalized in terms of more favorable FMO interactions between the largest coefficient centers of the dipole and dipolarophile. In the case of RHF, the favoured interaction leads to the regioisomers found by the study of the transition structures.[15] However, at B3LYP level, the ground state FMO prediction is reversed in the TS. The results obtained at RHF and B3LYP level of calculation agree with the experimental findings for olefins containing electron-donating groups. For electron-withdrawing groups, only the RHF transition state energies correlates with the experimentally observed regiochemistry.[6] For the nitrone and acrolein, MP2/6-31G*//RHF/6-31G* agrees with B3LYP/6-31G*//RHF/6-31G*.

3.3. Assessment of SASEM with experimental results

Our calculations predict that the effect of substitution of the olefin is additive for nitrone 1,3-dipolar cycloadditions, in



model for dipolarophile	Experimental exo	Experimental endo	Calculated ab initio exo	Calculated ab initio endo	Calculated SASEM exo	Calculated SASEM endo
	98	2	85	15	80	20
	100‡	0	85	15	80	20
OHC	2	98	–	–	0	100
OHC	0	100	–	–	0	100
OHC	0	100	–	–	0	100
O	0	100	29	71	29	71
O	0	100	29	71	29	71

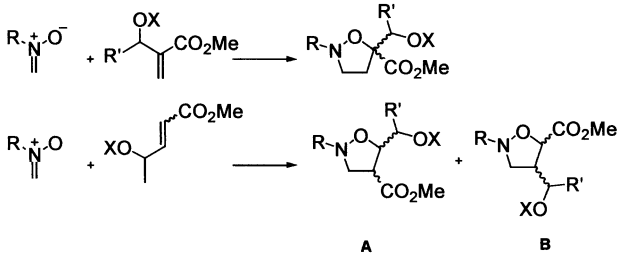
Scheme 3. Regioselectivity is always complete and always calculated correctly. No minor regioisomer reported.‡ Exo/endo assignment uncertain.

those cases where steric factors are less important. If this model is good, it would provide a semi-quantitative method for explaining the stereochemical outcome of these reactions and therefore at this point we wanted to check that experimental data was in agreement.

We have predicted regio- and stereoselectivities assuming Boltzmann distribution at room temperature for different 1,3-dipolar cycloadditions of nitrone found in the literature.[6a–i]

Scheme 3 shows the stereoselectivity ratios calculated using SASEM with the parent nitrone and the illustrated alkene, as models for the 1,3-dipolar cycloadditions. We also include the ratios from ab initio energies in those cases where we had computed a similar system. In all the cases, the experimental results showed total regioselectivity and the ratios calculated were in complete agreement with the regioselectivity found in the literature. The stereoselectivities were also consistent with the experimental findings.

In all the examples collected in Scheme 3 with electron-withdrawing substituents, the oxygen attacks away from the substituent. There are, however, examples in the literature[16] where the favoured regiochemistry, in contrast to expectations, leads to the regioisomer where the substituent in the olefin is oriented to the oxygen end of the dipole cycloadducts for these kinds of dipolarophiles. In a paper by Annunziata et al.,[16] β-alkoxy and γ-alkoxy-α,β-unsaturated esters were studied in their 1,3-dipolar cycloaddition with nitrones (Scheme 4).



Scheme 4. Surprising selectivities on cycloadditions, see Ref. 16. Regioselectivity is complete in the first case and 1:1–1:4 in the second.

For the β-alkoxy class of dipolarophiles, applying our SASEM, we get a prediction of 1:1 regioselectivity for these systems. This is closer to experiment than prediction by analogy to Diels–Alder reactions, for which a carbonyl group will have a much greater effect than a methyl. In the case of γ-alkoxy-α,β- unsaturated esters, our calculations do not predict the poor regiocontrol that is observed, but rather the formation of the regioisomer **A** only (Scheme 4). Since the regiochemical outcome of the cycloaddition for this type of olefin is unexpected when we consider the effect of the electron-withdrawing substituent, it is likely that the γ-alkoxy group is important in determining the regioselectivity and the methyl group might not be a good model for it.

4. Conclusion

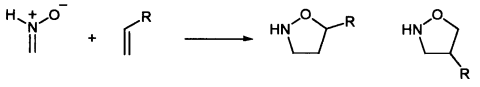
The ab initio calculation at RHF/6-31G* level for the 1,3-dipolar cycloaddition of substituted nitrones and olefins explain the experimental results observed in most cases. With these calculations, we could quantify the electronic and steric effect of the substituents for these reactions and this become a useful semi-quantitative method for predicting the stereochemical outcome of nitrone additions.

Acknowledgements

We thank the Royal Society, the Cambridge Centre for Molecular Recognition, and the European Community for a Marie Curie Fellowship (RG31637).

References

1. (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909. (b) Frederickson, M. *Tetrahedron* **1997**, *53*, 403–424. (c) Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp 83–168 Chapter 9. (d) Paquette, L. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5 Chapter 3.
2. Magnuson, E. C.; Pranata, J. *J. Comput. Chem.* **1998**, *19*, 1795–1804.
3. (a) Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737–6746. (b) Carda, M.; Portolés, R.; Murga, J.; Uriel, S.; Marco, J. A.; Domingo, L. R.; Zaragozá, R. J.; Röper, H. *J. Org. Chem.* **2000**, *65*, 7000–7009. (c) Herrera, R.; Nagarajan, A.; Morales, M. A.; Méndez, F.; Jiménez-Vázquez, H. A.; Zepeda, L. G.; Tamariz, J. *J. Org. Chem.* **2001**, *66*, 1252–1263. (d) Valentin, C. D.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 6112–6120. (e) Tanaka, J.; Kanemasa, S. *Tetrahedron* **2001**, *57*, 899–905. (f) Domingo, L. R.; Eur *J. Org. Chem.* **2000**, 2265–2272. (g) Pascal, Y. L.; Chanet-Ray, J.; Vessiere, R.; Zeroual, A. *Tetrahedron* **1992**, *48*, 7197–7208.
4. (a) Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *J. Org. Chem* **1987**, *52*, 3909–3917. (b) Alibés, R.; Busqué, F.; March, P. D.; Figueredo, M.; Font, J.; Parella, T. *Tetrahedron* **1998**, *54*, 10857–10878. (c) Ishar, M. P. S.; Singh, G.; Kumar, K.; Singh, R. *Tetrahedron* **2000**, *56*, 7817–7828.
5. (a) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301–7315. (b) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361–369.
6. (a) Bernotas, R. C.; Sabol, J. S.; Sing, L.; Friedrich, D. *Synlett* **1999**, *5*, 653–655. (b) Murahashi, S.-I.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett* **1993**, *6*, 395–396. (c) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098–3108. (d) Xian, Y.; Schinazi, R. F.; Zhao, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1475–1478. (e) Panfil, I.; Chmielewski, M. *Tetrahedron* **1985**, *41*, 4173–4716. (f) Alonso-Perarnau, D.; March, P. d.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron* **1993**, *49*, 4267–4274. (g) Yu, Y.; Ohno, M.; Eguchi, S.; Kawai, T.; Terada, Y. *Tetrahedron* **1997**, *53*, 5413–5422. (h) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R. *Tetrahedron* **1984**, *40*, 2283–2296. (i) Ondrus, V.; Orság, M.; Fisera, L.; Prónayová, N. *Tetrahedron* **1999**, *55*, 10425–10436. (j) Ali, S. A.; Senaratne, P. A.; Illig, C. R.; Meckler, H.; Tufariello, J. J. *Tetrahedron Lett.* **1979**, *43*, 4167–4170.
7. Ratios from the paper of Magnuson and Pranata (Ref. 2), given here with fewer significant figures:



R	RHF/6-31G*	B3LYP/6-31G*
NH_2	70 : 30	70 : 30
Me	50 : 50	60 : 40
CHO (*cis*)	40 : 60	60 : 40
CHO (*trans*)	40 : 60	50 : 50
CN	40 : 60	50 : 50

8. CADPAC: The Cambridge Analytic Derivatives Package Issue 6, Cambridge, 1995. A suite of quantum chemistry programs developed by R. D. Amos with contributions from I. L. Alberts, J. S. Andrews, S. M. Colwell, N. C. Handy, D. Jayatilaka, P. J. Knowles, R. Kobayashi, K. E. Laidig, G. Laming, A. M. Lee, P. E. Maslen, C. W. Murray, J. E. Rice, E. D. Simandiras, A. J. Stone, M.-D. Su, D. J. Tozer.
9. Although this is the same qualitative conclusion as Magnuson and Pranata, they do not give the procedure they used for calculating ratios from their energies. At room temperature the regioselectivites given seem inconsistent with the energies calculated.
10. (a) Jennings, W. B.; Boyd, D. R.; Waring, L. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 610–613. (b) Bjørgo, J.; Boyd, D. R.; Neil, D. C. *J. Chem. Soc., Chem. Commun.* **1974**, 478–479.
11. Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127–4133.
12. García, J. I.; Mayoral, J. A.; Salvatella, L. *Acc. Chem. Res.* **2000**, *33*, 658–664.
13. Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **2001**, *66*, 6178–6180.
14. Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, 5798–5800.
15. The coefficients of the frontier orbitals at RHF and B3LYP levels were very similar. The nitrone showed 0.49 and 0.51 (RHF and B3LYP, respectively) for the oxygen and −0.34 and −0.39 for the carbon. The values for the acrolein where 0.31 and 0.37 (C1, terminal carbon), and −0.21 and −0.22 (C2, carbon attached to the carbonyl group).
16. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Eur *J. Org. Chem.* **1998**, *9*, 1823–1840.