



Classical and non-classical secondary orbital interactions and Coulombic attraction in the regiospecific dimerization of acrolein

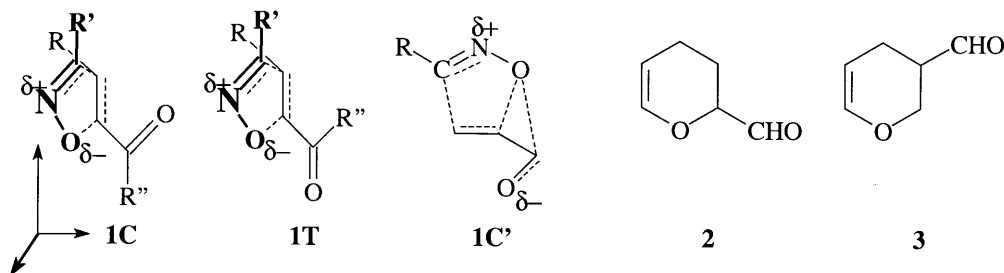
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Abstract—Non-classical (bridging) and classical (Woodward–Hoffmann) secondary orbital interactions as well as a favourable electrostatic interaction are involved in the stabilization of the two lowest transition passes of the acrolein dimerization. The heteroatoms provide anchimeric assistance to the hetero Diels–Alder reaction through a neighbouring-group mechanism. © 2001 Elsevier Science Ltd. All rights reserved.

The cycloadditions of nitrile oxides to cyclic α,β -unsaturated carbonyl compounds take place with high regioselection affording the 4-acyl heterocycles, while the related acyclic crotonoyl dipolarophiles display decreased regioselectivity.¹ The origin of the distressingly dissimilar behaviour of cyclic and acyclic α,β -unsaturated dipolarophiles could be related to the conformational flexibility of the acyclic derivatives and to a remarkable stabilization of the transition structure (TS) **1C** leading to the 5-acyl heterocycles and involving the *cisoid* conformation of the dipolarophiles.² At the B3LYP/6-31G* level the *cisoid* TS **1C** is stabilized with respect to the *transoid* TS **1T** because of an efficient secondary orbital interaction between the nucleophilic nitrile oxide oxygen and the carbonyl π^* orbital, as sketched in **1C'**.



The size of the effect is noteworthy and could be estimated at ~ 3 kcal/mol at the B3LYP/6-31G* level. Acrolein adopts the *s-trans* conformation in the ground state and the cost of the conformational switch (1.7

kcal/mol) is more than compensated in TS **1C** ($R=R'=R''=H$), which is 1.3 kcal/mol below TS **1T**. We wondered if an effect of this size could have a broader significance in organic reactivity other than in nitrile oxide regiochemistry. A related and intriguing case is the well-known dimerization of acrolein, which undergoes a regiospecific Diels–Alder (DA) cycloaddition to yield only the dimer **2** and not the electronically favoured regioisomeric adduct **3**.³

The regiospecific acrolein dimerization to dimer **2** is a text-book example of the validity of the frontier orbital (FO) approach to organic reactivity and regiochemical issues.⁴ However, FO interactions alone do not satisfactorily account for the exclusive formation of dimer **2** owing to the small differences in the coefficients of the

interacting orbitals and recourse is frequently made to the bond integrals of the forming bonds ($\beta_{C...C} > \beta_{C...O}$), which differ in size,^{4,5} or rather qualitatively to the classical secondary orbital interactions involved in the *endo* TSs⁶ or to stabilizing electrostatic interactions.⁷

We have located the eight possible TSs for the acrolein dimerization at the B3LYP/6-31G* level, which gives

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Table 1. Electronic activation energies relative to the reactants (kcal/mol), activation enthalpies, entropies (e.u.) and free energies, forming bond lengths (Å) and dipole moments μ (D) of the TSs of acrolein dimerization^{a,b}

TS	ΔE_c^\ddagger	ΔH^\ddagger	ΔS^\ddagger	ΔG^\ddagger	C...C	C...O	μ
2TX	23.82	25.42	−35.76	36.08	1.951	2.267	5.07
2TN	23.08	24.65	−36.46	35.52	1.983	2.263	5.05
2CX	20.86	22.66	−36.71	33.60	1.922	2.316	3.70
2CN	18.60	20.47	−36.51	31.35	1.885	2.490	2.70
3TX	23.90	25.63	−36.71	36.57	2.149	1.985	2.28
3TN	24.07	25.78	−36.68	36.71	2.139	1.973	1.71
3CX	23.74	25.56	−36.72	36.51	2.198	1.960	3.75
3CN	22.89	24.71	−37.02	35.75	2.227	1.916	2.66

^a Thermodynamic values at 298.15 K.

^b *s-trans* Acrolein, −191.912049 hartrees, $\delta H=42.01$, $S=66.46$, $\mu=3.16$; dimer **2**, $\Delta E_c=-22.10$.

satisfactory geometries and reliable energies for pericyclic reactions.⁸ The TSs were labelled as usual: the numbers specify the position of the formyl group in the forming heterocyclic ring, T and C refer to the *transoid* or *cisoid* conformation of the dienophile and X or N refer to the *exo* or *endo* location of the formyl moiety.

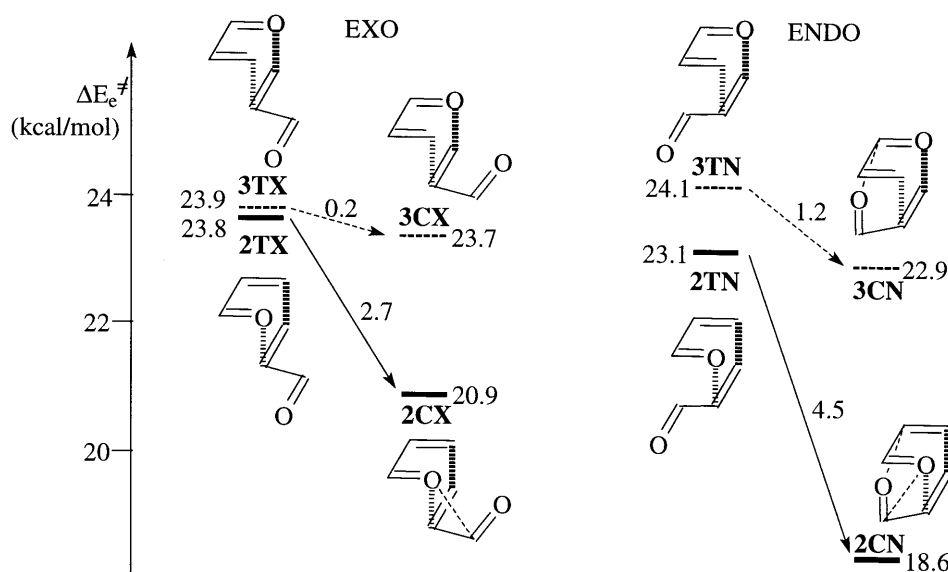
The electronic activation energies ΔE_c^\ddagger of the TSs relative to the reactants are given in Table 1 along with the activation enthalpies, entropies and free energies, as well as the forming bond lengths and the dipole moments. The electronic activation barriers are displayed in Fig. 1.

As shown in Fig. 1 the two *exo* TSs involving the *transoid* dienophiles, **2TX** and **3TX**, occur at relatively high and almost identical energies, while the corresponding *endo* TSs, **2TN** and **3TN**, are still high but more spaced (by 1.0 kcal/mol), well in keeping with the difficulties of the FO approach in accounting for the observed regioselectivity.

On going to the *cisoid* TSs, **3CX** remains essentially at the same energy of **3TX**, while **2CX** gratifyingly lowers by 2.7 kcal/mol with respect to **2TX**. In the case of the *endo* TSs, **3CN** is stabilized somewhat with respect to **3TN** (by 1.2 kcal/mol), while **2CN** drops remarkably (by 4.5 kcal/mol) and becomes the lowest TS.

All the TSs belong to the asynchronous concerted variety and the forming bond lengths are in the usual range reported for DA reactions involving acrolein as dienophile⁹ or diene.¹⁰ In all cases the forming bonds at the β carbon of the acrolein dienophile are more advanced than those at the α carbon (Table 1) and in the lowest TS **2CN** asynchronicity is significantly magnified.

The geometric features of the two lowest TSs **2CX** and **2CN** are shown in Fig. 2. In TS **2CX** the diene oxygen lies on an excellent Bürgi–Dunitz trajectory¹¹ to the dienophile carbonyl, with one of the oxygen sp^2 lone pairs¹² pointing resolutely toward the p_z carbonyl carbon. This interaction is similar to that described in the

**Figure 1.** Transition structures for the acrolein dimerization. Full levels refer to TSs leading to the isolated dimer **2**, while dashed levels refer to the regioisomer **3**. The arrows point out the energy changes which accompany the conformational switch of the acrolein dipolarophile.

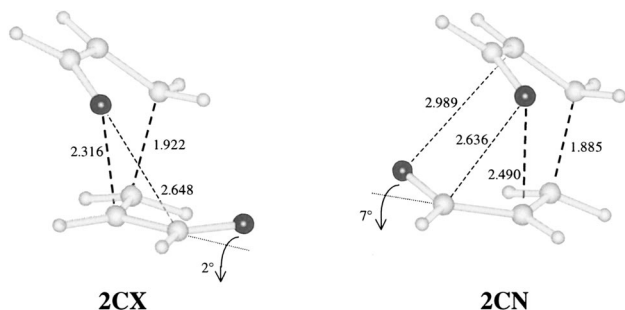
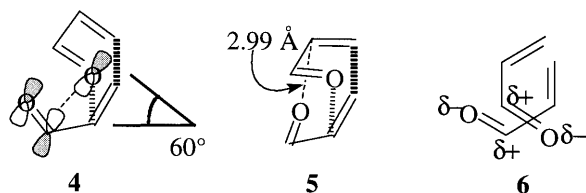


Figure 2. Geometric features of the *cisoid* TSs **2CX** and **2CN**. The curved arrows specify the rotation of the aldehyde oxygen out of the plane of the acrolein carbons in the direction shown.

nitrile oxide case **1C'** but it is more efficient here despite the slightly longer $\text{O}\cdots\text{C}=\text{O}$ distance (2.65 versus 2.58 Å). The interaction is sketched as bridging in the formulas of Fig. 1.

The extraordinary stabilization of TS **2CN** may be in part attributed to bridging. The diene oxygen still rests on an excellent trajectory with an $\text{O}\cdots\text{C}=\text{O}$ distance of 2.64 Å. Some overlap is possible between the $p\pi$ orbital of oxygen and the π^* carbonyl because of the inclined plane approach sketched in **4**. In addition the classical Woodward–Hoffmann secondary orbital interaction,^{6c} shown in **5**, is clearly manifest. The $\text{O}\cdots\text{C}\alpha$ bond distance is 2.99 Å and the Mulliken overlap population, a useful indicator of secondary interactions,^{9b,13} is positive (0.021). A similar secondary orbital interaction was discerned in the *endo cis* TS for the DA reaction of butadiene to Lewis Acid (LA) complexed acrolein and is believed to be responsible of the high *endo cisoid* preference in the LA catalyzed DA cycloadditions.⁹ Further stabilization of TS **2CN** derives from the very favourable electrostatic interactions between the carbonyl moieties of the addends as exemplified in **6**. The Mulliken charges of TS **2CN** correspond to a Coulomb attraction of 1.9 kcal/mol between the addends, in fair agreement with the Salem perturbational prevision.⁷



In summary, FO interactions promote the concerted hetero DA dimerization of acrolein and the two heteroatoms involved play a decisive role in facilitating the otherwise energetically demanding cycloaddition and in determining the regioselectivity. The two heteroatoms provide anchimeric assistance to the cycloaddition through a mechanism of neighbouring-group participation, which remarkably stabilizes the bridged TS **2CX** and even more the coiled TS **2CN**. Lastly, we have to

mention the amazing fit between the calculated and the experimental activation energy ($E_a = 19.6$ kcal/mol in heptane)¹⁴ of the acrolein dimerization. The dimerization is slightly slowed down in polar solvents owing to the solvation of the more polar reactants.

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