

## Syn–Anti Isomerism in the Reactions of *cis*-3,4-Disubstituted Cyclobutenes. Part 7.<sup>1</sup> HF/3-21G Transition Structures of the Reaction of Diazomethane with *cis*-3,4-Dichlorocyclobutene

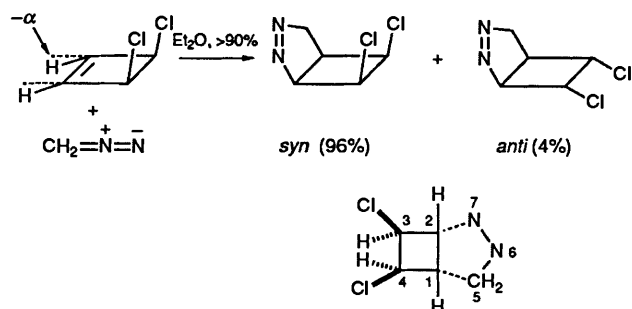
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Transition structures for the *syn* and *anti* attack of diazomethane on *cis*-3,4-dichlorocyclobutene have been obtained with the HF/3-21G model. These calculations correctly predict the dominance of *syn* attack. Analysis of the activation energy shows that the inherent facial bias of dichlorocyclobutene is reflected, at the transition state, in the deformation energy of both dichlorocyclobutene and diazomethane and in the interaction energy between them.

A very high *syn* selectivity is exhibited by the reaction of diazomethane with *cis*-3,4-disubstituted cyclobutenes bearing electron withdrawing substituents such as chloro, methoxy, mesyloxy, acetoxy *etc.*<sup>2</sup> A clear-cut dominance of *syn* attack has also been documented for the reaction of other 1,3-dipoles<sup>2b</sup> as well as of OsO<sub>4</sub><sup>1</sup> with the same cyclobutenes. These findings provide *bona fide* examples of contra-steric facial selectivity and can be quoted as experimental evidence for a relationship between pyramidalization<sup>3a</sup> and facial selectivity.<sup>3b</sup> In fact, *ab initio* calculations have shown that in these cyclobutenes the olefinic hydrogens are bent out-of-plane in the *anti* direction by 2–3°. <sup>2c,d</sup> Moreover, the energy required to bend these hydrogens in the *anti* direction by 20° (which was assumed to mimic the deformation present in the TS) is less, by *ca.* 1.2–2.9 kcal mol<sup>-1</sup>,<sup>†</sup> than that to bend them in the *syn* direction by the same amount.<sup>2c</sup> Consequently, the intrinsic facial bias of these cyclobutenes can be traced back to the *syn* pyramidalization of the double bond and related deformability effects. This simple and straightforward explanation is based on the properties of isolated reactants so that the question arises of whether the role of out-of-plane deformation is also apparent in a calculated transition structure. Given that facial selectivity plays a central role in modern organic chemistry we decided to calculate transition structures of the reaction of diazomethane with dichlorocyclobutene (Scheme 1) by *ab initio* methods.<sup>4</sup> The



Scheme 1

problem of facial selectivity in 1,3-dipolar cycloaddition has not previously been addressed at an *ab initio* level.<sup>5</sup> Thus, we also hoped to obtain evidence about the role of other effects such as Cieplak's effect.<sup>6</sup>

We used the HF/3-21G model<sup>4</sup> and gradient techniques with

optimization of all variables. Critical points were characterized by diagonalizing the Hessian matrices of the optimized structures; transition structures have only one negative eigenvalue (first-order saddle points), the corresponding eigenvectors involving the expected concerted formation of the two new bonds.

It is gratifying that these calculations correctly predict dominance of the *syn* attack ( $E_{a,syn} = 19.9$  and  $E_{a,anti} = 22.8$  kcal mol<sup>-1</sup>)<sup>‡</sup> in agreement with the experimental finding (*syn:anti* = 96:4).<sup>2d</sup> The relative stability of the TSs does not reflect the relative stability of the adducts [the *anti* adduct is predicted to be more stable than the *syn* by 3.2 kcal mol<sup>-1</sup>], *i.e.* the reaction is not under product development control.

As for the reliability of the model used, Hehre *et al.* have recently concluded<sup>7</sup> that the HF/3-21G model correctly predicts the relative energies of the TSs of the two attacks to diastereotopic faces of a diene.

Both transition structures (Table 1) correspond to early transition states in terms of bond breaking and bond making. They are both asynchronous with the forming carbon–carbon bond shorter than the carbon–nitrogen bond. The most interesting geometry changes on going from educts to TSs take place in dihedral and bond angles. The out-of-plane bending of the olefinic hydrogens (as described by  $\alpha_1$  and  $\alpha_2$ , Table 1) is significantly higher in the *syn* transition structure (by 7.6° for  $\alpha_1$  and by 3.7° for  $\alpha_2$ ) than in its *anti* counterpart. Moreover, the olefinic hydrogen attached to the carbon atom involved in formation of the carbon–carbon bond experiences a much higher bending in both TSs ( $\alpha_1 = -37.0^\circ$  and  $+29.4^\circ$  for the *syn* and *anti* attack, respectively) than that attached to the carbon atom involved in formation of the carbon–nitrogen bond ( $\alpha_2 = -24.2^\circ$  and  $+20.5^\circ$ , respectively). The linear arrangement of the CNN atoms of diazomethane suffers a relevant bending both in the *syn* and in the *anti* attack but the former (30.7°) is smaller than the latter (34.0°). Finally, in the *anti* TS the cyclobutane ring is flat ( $\beta = -0.4^\circ$ ) whereas in the *syn* it is already substantially puckered ( $\beta = 6.2^\circ$ ).

Inspection of Fig. 1 clearly shows that (i) staggering between forming bonds and allylic bonds<sup>5a</sup> cannot be advanced as a factor which favours the *syn* attack; actually this staggering is similar in both TSs; (ii) there is no allylic bond which bears an antiperiplanar relationship to the forming bonds; consequently, hyperconjugative electron donation by *anti* allylic  $\sigma$  bonds to the  $\sigma^*$  orbital of the forming bonds (on which Cieplak's effect is

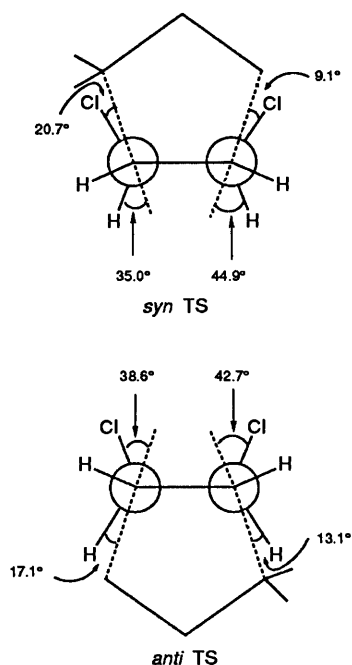
<sup>†</sup> 1 cal = 4.184 J.

<sup>‡</sup> In contrast AM1 calculations slightly favour the *anti* transition structure ( $E_{a,syn} = 20.6$  and  $E_{a,anti} = 20.4$  kcal mol<sup>-1</sup>).

**Table 1** Bond lengths (Å), bond and dihedral angles (°)<sup>a</sup> for the HF/3-21G-optimized geometries of educts, transition structures and products of the reaction of diazomethane with dichlorocyclobutene

	Educts	Transition structures		Adducts	
		<i>Syn</i>	<i>Anti</i>	<i>Syn</i>	<i>Anti</i>
C1-C2	1.33	1.38	1.38	1.56	1.56
C5-N6	1.28	1.33	1.33	1.51	1.52
N6-N7	1.13	1.13	1.13	1.23	1.23
C3-Cl	1.86	1.89	1.87	1.84	1.85
C4-Cl	1.86	1.88	1.86	1.85	1.84
C3-H	1.07	1.07	1.07	1.07	1.07
C4-H	1.07	1.07	1.07	1.07	1.08
C1-C5		2.19	2.21	1.53	1.52
C2-N7		2.32	2.25	1.50	1.50
C5-N6-N7	180.0	149.3	146.0	113.7	113.2
$\alpha_1 = \text{H1-C1-C2-C4}$	-1.9	-37.0	29.4	-62.6	63.3
$\alpha_2 = \text{H2-C2-C1-C3}$	-1.9	-24.2	20.5	-61.1	55.9
$\beta = \text{C4-C1-C2-C3}$	0.0	6.2	-0.4	8.7	11.2
$\gamma_1 = \text{C5-C1-C2-C4}$		-110.8	103.9	-117.9	113.8
$\gamma_2 = \text{N7-C2-C1-C3}$		108.7	-99.4	116.1	-110.1

<sup>a</sup>  $\alpha_1$  and  $\alpha_2$  give the out-of-plane bending of the olefinic hydrogens H1 and H2.  $\alpha_1$  ( $\alpha_2$ ) is the difference between 180° and the absolute value of the dihedral angle H1-C1-C2-C4 (H2-C2-C1-C3).  $\alpha_1$  ( $\alpha_2$ ) is given a positive sign when H1 (H2) is bent in the *syn* direction and a negative sign when H1 (H2) is bent in the *anti* direction with respect to the chlorine atoms.

**Fig. 1** Staggering between the forming bonds and the allylic bonds in the *syn* and *anti* TSs. Newman projections along the C1-C4 and C2-C3 bonds.

based) should be weak in either one of the two transition states. In agreement with this statement the anticipated (as a result of Cieplak's effect)<sup>8c</sup> bond lengthening of C-Cl bonds in the *anti* TS (C3-Cl = 1.87 Å and C4-Cl = 1.86 Å) as compared to the *syn* TS (C3-Cl = 1.89 Å and C4-Cl = 1.88 Å) is not observed. This observation also holds for the C-H bonds (C3-H = C4-H = 1.073 Å in both TSs). These findings strongly suggest that the facial selectivity of cyclobutene reactions cannot be controlled by the highly questioned<sup>6,8</sup> Cieplak's effect.

As far as deformability effects on facial selectivity are concerned we carried out an analysis of activation energies according to a recent procedure suggested by Morokuma *et al.* and applied successfully to explain *exo* hydroboration of norbornene.<sup>9</sup> In this analysis (Table 2) deformation energies are provided by the energies of the isolated reactants deformed to the geometries they adopt in the transition state. The

**Table 2** Deformation and interaction energy contributions to activation energy (kcal mol<sup>-1</sup>) of *syn* and *anti* transition structures (HF/3-21G//HF/3-21G)<sup>a</sup>

	<i>Syn</i>	<i>Anti</i>	<i>Syn-Anti</i>
Deformation energy (cyclobutene)	12.1	9.2	2.9
Deformation energy (diazomethane)	17.0	20.8	-3.8
$\Sigma$ Deformation energies	29.2	30.0	-0.8
Out-of-plane bending (olefinic hydrogens)	7.1	7.1	0.0
Bending (diazomethane)	10.8	13.3	-2.5
Interaction energy	-9.3	-7.2	-2.1
Activation energy <sup>b,c</sup>	19.9	22.8	-2.9
Heat of reaction (adducts)	-45.8	-49.0	3.2

<sup>a</sup> The total energies of diazomethane and dichlorocyclobutene are the following: -146.995 820 and -1067.462 186 hartree, respectively. <sup>b</sup> 21.8 and 24.6 kcal mol<sup>-1</sup>, respectively, after zero point energy correction. <sup>c</sup>  $-T\Delta S^\ddagger$  (at 298 K) = 13.2 and 13.0 kcal mol<sup>-1</sup>, for the *syn* and *anti* TS, respectively.

contribution of out-of-plane bending of the olefinic hydrogens is given by the difference between the energy of the deformed (to TS geometry) dipolarophile and that of a dipolarophile in which all the geometrical parameters are those of the TS with the exception of olefinic hydrogen bending angles. These latter were assumed to be those of the dipolarophile equilibrium geometry (*i.e.* -1.9°). Likewise the bending of the three heavy atoms of diazomethane from the linear ground state geometry to the transition state angle allowed us to evaluate the role played by this deformation. The difference between the activation energy and the whole deformation energy gives the interaction energy which reflects steric and electrostatic interactions as well as stabilization due to incipient bond formation and, in general, to electron delocalization between the deformed reaction partners.

As a whole deformation energy slightly favours the *syn* attack over its *anti* counterpart but this is the result of two contrasting effects. In fact, the deformation energy of diazomethane (much higher than that of cyclobutene) is significantly less in the *syn* TS than in the *anti* one. Almost all of this difference is accounted for by the bending of the three heavy atoms of the 1,3-dipole. On the other hand the deformation energy of the dipolarophile as a whole clearly favours the *anti* attack. However, the out-of-plane deformation energy of the olefinic hydrogens is the same in the two diastereotopic TSs notwithstanding the higher out-of-plane deformation of these hydrogens in the *syn* attack. This

observation can be related to the *syn* pyramidalization of the dichlorocyclobutene ground state.

The *syn* TS is also favoured by interaction energy. Given that repulsive steric (notice how  $\gamma_1$  and  $\gamma_2$  are higher in the *syn* than in the *anti* transition structure) and electrostatic interactions are higher in the *syn* than in the *anti* TS, electron delocalization must be much more stabilizing in the former than in the latter TS.

The conclusion one can draw from these results is that simple and straightforward explanations of *syn/anti* selectivity based on the features of isolated dipolarophiles are untenable. The implicit assumption of strictly similar *syn* and *anti* TSs is disproved by calculations reported in this paper and, in particular, by the finding that the dipolarophile undergoes different deformations in the two diastereotopic TSs and that differential deformation energies of diazomethane are surprisingly important.

On the other hand, the very same results offer good suggestions for a new proposal. In particular, if we put in the foreground the observation that stabilizing electron delocalizations must be much higher in the *syn* approach (see the above discussion) and the finding that *syn* approach is characterized (Fig. 1) by presumably strong synperiplanar vicinal delocalizations between the incipient bonds and the C-Cl bonds, we can tentatively assume that these interactions are the driving force for *syn* selectivity in our example. Indeed, they are increased by large *anti* bendings of the olefinic hydrogens (high *syn* pyramidalization, see  $\alpha_1$  and  $\alpha_2$ ) which, in turn, cause both an inclined approach (see  $\gamma_1$  and  $\gamma_2$ ) of the 1,3-dipole (with a resultant lessening of short range steric interactions) and orientations of the new bonds which are compatible with a lower CNN bending.

Work is in progress to check these indications in the framework of a recent procedure for the analysis of intramolecular interactions.<sup>10</sup>

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