

SYN-ANTI ISOMERISM IN THE 1,3-DIPOLAR CYCLOADDITION TO CIS-3,4-DISUBSTITUTED CYCLOBUTENES.

1. ROLE OF OUT-OF-PLANE DISTORTIONS.

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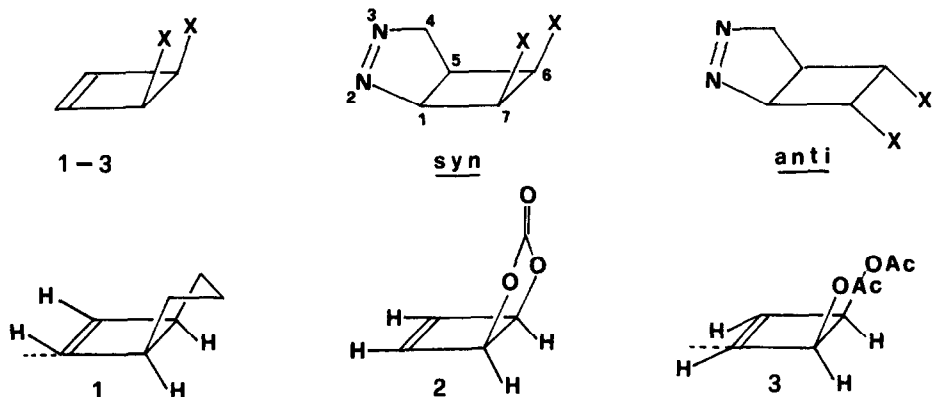
Summary: Cyclobutenes 1-3 react with diazomethane covering the complete range of facial selectivity. Non planarity of the double bond moiety and consequent energetic asymmetry of out-of-plane distortions, mainly due to $\pi/C-X$ and $\pi/C-H$ interactions, parallel the stereochemistry of cycloaddition.

The reactions of cis-3,4-disubstituted cyclobutenes with 1,3-dipoles, often characterized by non-intuitive contra-steric dominance of syn attack, have played an important role in the investigation of syn-anti selectivity in 1,3-dipolar cycloadditions.¹⁻⁵ Although several qualitative factors have been advanced to explain experimental findings, their quantitative control has been very limited and, actually, the facial selectivity observed has so far eluded a convincing theoretical rationalization.

In the light of great and growing interest recently accorded to facial selectivity in organic reactions, particularly in cycloadditions,⁶ we report here some theoretical results and new suitable experimental data, which allow us to start approaching this problem in a systematic way.

Diazomethane reacted with bicyclo [3.2.0] hept-6-ene 1, cis-3,4-carbonyldioxcyclobutene 2, and cis-3,4-diacetoxy cyclobutene 3 to give the sole anti adduct, a mixture of anti and syn adducts (64:36) and the sole syn adduct, respectively.⁷ Owing to the low dipole moment of diazomethane and its small steric requirement, the observed selectivity can be ascribed, confidently, to an "intrinsic" propensity of the partner dipolarophile to suffer syn or/and anti attack on its diastereotopic faces. Covering the complete range of selectivity, 1-3 lend themselves as good models to challenge the factors governing that stereoselectivity.

The simple hypothesis that the favoured attack should be assisted by the less expensive out-of-plane bending of the olefinic hydrogens is quite appealing in that it explores a contribution which is independent of the partner reagent, of the reaction mechanism and of the orbital control.⁸ As a consequence of this distortion the π -type AO 's⁹ take new hybrid characters and directions, and modify their intramolecular overlaps; furthermore, if the assumption is made that the 1,3-dipole reaction centers approach their partners along the directions of the π -type hybrids, the in-



termolecular repulsive interactions are efficiently reduced, mainly for syn attack.

Molecular geometry optimization¹⁰ of 1-3 reveals that the plane of CH bonds is significantly syn-bent in 1 ($\phi = 5.1^\circ$), anti-bent in 3 ($\phi = -3.2^\circ$), and nearly coplanar with the cyclobutene ring in 2 ($\phi = 0.6^\circ$). This behaviour parallels the experimental stereoselectivity, and offers a first indication that syn(anti) bending in the isolated dipolarophile may be one driving force for anti(syn) stereoselectivity, so that no significant bending (e.g. in 2) is bound to lack of selectivity.

When comparing equal ($\Delta = \pm 20^\circ$) syn and anti distortions in the STO-3G approximation, one finds that syn-bending is energetically favoured with 4.17 kcal/mole in 1; the opposite occurs in 3 (-2.70 Kcal/mole), whereas in 2 syn bending is only slightly favoured (0.56 Kcal/mole). The results are collected in the Table.

Once again the calculated trend appears to fit the experiment. It is interesting to observe that even the explanation of anti attack on 1 need not invoke the "intuitive" steric effects. The results strongly suggest that intramolecular interactions, responsible for non-planarity in the free molecule, are also responsible for the energetic asymmetry of out-of-plane distortions and, in turn, for the occurrence of stereoselectivity.

The analysis of intramolecular interactions needs to resort to the current conceptual structure of chemistry, recently termed as the Current Molecular Model (CMM),¹¹ the basic concepts of which are hybridization, localization and delocalization, π orbitals, lone pairs, through-space non-bonded interactions (TSI) and through-bond interactions (TBI). Even if arguments and conclusions have a qualitative value, the actual evaluation of terms requires some well defined choices, first of all the procedure for obtaining hybrid atomic orbitals (HAO).

Hybridization has been performed according to the Maximum Localization Criterion (MLC);¹² the MLC procedure is the choice of the unitary transformation of the Slater AO basis "best suited" for assigning HAO's to specific σ bonds, π -system or lone pairs. MO calculations are invariant to such a transformation, but now the off-diagonal elements of the energy matrix can be read as specific interactions defined in the molecular context. Elimination of selected ele-

Table. Theoretical results. Energies in Kcal/mole

Calculation	Bicycloheptene			Carbonyldioxycyclobutene			Diacetoxycyclobutene		
	Planar	ϕ opt	$5.15^\circ \Delta \pm 20^\circ$	Planar	ϕ opt	$0.65^\circ \Delta \pm 20^\circ$	Planar	ϕ opt	$-3.20^\circ \Delta \pm 20^\circ$
STO-3G	0.27	REF	4.17	0.00	REF	0.56	0.11	REF	-2.70
CNDO/2	0.36	REF	5.06	-0.00	REF	0.05	0.10	REF	-2.70
s%	0.00	0.09	1.29	0.00	0.00	1.27	0.00	0.03	1.25
Localization	-0.60	238.04	0.33	-0.05	550.92	0.35	-0.27	879.47	-0.35
Delocalization:									
1. TBI+TSI	0.60	-238.04	4.73	0.00	-550.92	-0.30	0.27	-879.47	-3.05
2. TSI	0.55	-59.47	4.74	0.00	-238.78	-0.21	0.24	-431.40	-2.93
3. π/σ	0.35	-34.44	5.12	0.00	-37.13	-0.08	0.14	-40.16	-2.80
3. $\pi/C-X$	0.02	-17.25	3.15	-0.02	-21.29	-1.41	0.19	-19.27	-3.62
5. $\pi/C-H$	-0.23	-12.16	1.16	0.02	-14.89	0.91	-0.14	-19.80	0.26
6. 4.+5.	0.15	-28.65	4.37	-0.00	-35.81	-0.46	0.15	-39.41	-3.37
Experiment									
<u>anti:syn</u>		100:0			64:36			0:100	

REF: reference energy (optimized out-of-plane distortion); planar: energy difference from the optimized distortion; $\Delta \pm 20^\circ$: difference of total energies of $\pm 20^\circ$ bent molecules ($E_{-20^\circ} - E_{+20^\circ}$); s% hybrid character of π -type AO.

ments from the energy matrix should correspond to the suppression of the related interactions, and the MO calculation should disclose their effects on the molecular properties. So, for example, elimination of all non-bonded interactions (TSI+TBI) produces a fully localized description (MO are bond orbitals or lone pairs, the density matrix has non-zero off-diagonal elements only for bonds) whose electronic energy, orbital energies, net-charges etc. are somewhat different from those of the complete calculation, where the full delocalization due to TSI and TBI is allowed. The mere suppression of TSI does not produce localization; however, as the off-diagonal blocks of the density matrix acquire fairly well localized structures, the calculation is significant for singling out the effects of the delocalization due to those interactions. Also, one can try to single out the role of subsets of TSI, e.g. π/σ interactions or interactions between orbitals involved in non-contiguous bonds, supposed to be relevant for the problem in study; a necessary requisite for the significance of the procedure is the coherent blanking of the corresponding elements of the density matrix.¹³

MO calculations have been done in the CNDO/2 approximation; in spite of the documented failure of NDO methods in reproducing the ground state endo-bending of the syn-sesquiorbornene ring system,¹⁴ it does appear that in our cases the syn and anti ground state distortions found by STO-3G optimizations are fairly well reproduced by CNDO/2 ($\phi=5.5^\circ$, 0.3° and -3.0° for 1,2,3 respectively); furthermore, the differences between the $\pm 20^\circ$ distorted molecules show the same trend as in STO-3G calculations.

The results of the analysis are collected in the Table. As expected, full localization introduces large destabilization energies (columns 3,6,9), favours planar conformations (columns 2,5,8) and suppresses the asymmetry of out-of-plane distortions (columns 4,7,10). Inversely, delocalization due to TSI + TBI is responsible for both distorted ground state conformations and distortion asymmetries. Separately considered, TSI display only a part (from 25 to 40%) of the stabilization due to delocalization, whereas they contribute the totality of the asymmetry ($\Delta \pm 20^\circ$). Among TSI, π/σ interactions account for the whole distortion asymmetry. Fairly large contributions to the bending

asymmetry appear to be due to $\pi/C-X$ and $\pi/C-H$, i.e. the interactions between the π -type HO and the orbitals involved in the C-X and C-H bonds of the atoms C_3 and C_4 : these contributions add up in **1**, thus accounting for the preferred syn bending (anti attack), counterbalance in **2** (mixture of syn and anti attack), whereas in **3** the negative contribution of $\pi/C-X$ (anti bending, syn attack) is largely prevalent.

By comparing calculations 4. and 5. with 6. (Table), the deviation from additivity can be checked (columns 3,6,9) and found quite reasonable for $\Delta \pm 20^\circ$, but too large to rely on the small differences of columns 2,5 and 8.

Investigations on other factors (charge-transfer stabilization, electrostatic and steric interactions), which are supposed to be more relevant with 1,3-dipoles other than diazomethane, are in progress.

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- The reaction of diazomethane with **1**, **2**, **3** were carried out in ether at room temperature. TLC, 1H NMR and ^{13}C NMR analysis of the crude product from reaction of **1** (70%; oil) and **3** (29%; m.p. 65-67°) showed the presence of only one adduct. The ratio between anti (53%; m.p. 122-123°) and syn (29%; m.p. 124-125°) adducts from **2** was evaluated by column chromatography. $J_{1,7}$ and $J_{5,6}$ are ≤ 3.0 Hz (indicative of a stereochemical trans relationship) in the anti adducts and ≥ 6.0 Hz in the syn adducts; the exo and endo hydrogens at position 4 in the anti adducts absorbed at the same field both in $CDCl_3$ and in C_6D_6 solutions. In contrast, the corresponding hydrogens in the syn adducts give rise to two signals separated by more than 0.30 ppm and 0.60 ppm in $CDCl_3$ and C_6D_6 solutions, respectively. Further details will be given in the extended paper.
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- π -Type AO stands for quasi-p π AO with some s character bound to enter quasi- π systems in non planar molecules.
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