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COMPETITION BETWEEN CARBOMETHOXY AND CARBOXYL IN ELECTROCYCLIC OPENING OF A 3,3-DISUBSTITUTED CYCLOBUTENE

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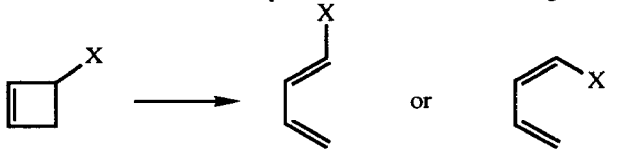
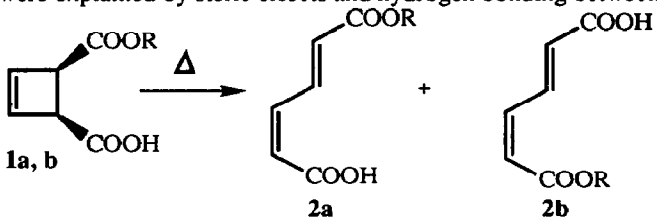
Summary: Thermolysis of 3-carbomethoxycyclobutene-3-carboxylic acid afforded two dienes in equal amounts, which is consistent with our prediction. The structures of the dienes were determined by $^3J_{CH}$ long range coupling constants between the carbonyls and β-olefinic protons by long range selective proton decoupling.

The 3-substituted cyclobutenes may undergo ring opening either by outward or inward rotation to afford E- or Z-dienes, depending on the electronic properties of the substituent, X.[1, 2] Torquoselectivity is the selectivity of this ring opening, named because the substituents dictate a specific twist of the breaking bond.



Using quantum mechanical calculations, we predicted that electron donors and weak electron acceptors induce outward rotation, and only very strong electron acceptors entice inward rotation. Furthermore, this torquoselectivity is predicted to be approximately additive in polysubstituted cyclobutenes.[1, 3] We have reported several experimental verifications of our predictions.[4-7]

Trost *et al.* reported experimental data on the thermolysis of 3-carboalkoxy-4-carboxylic acids, **1a** and **1b**, in several solvents.[8] Modest stereoselectivity was observed, with a slight preference for outward rotation of carboalkoxy groups. These selectivities were explained by steric effects and hydrogen bonding between the substituents.



a, R=n-Bu	75~50	:	25~50
b, R=$(CH_2)_2SiMe_3$	75~55	:	25~45

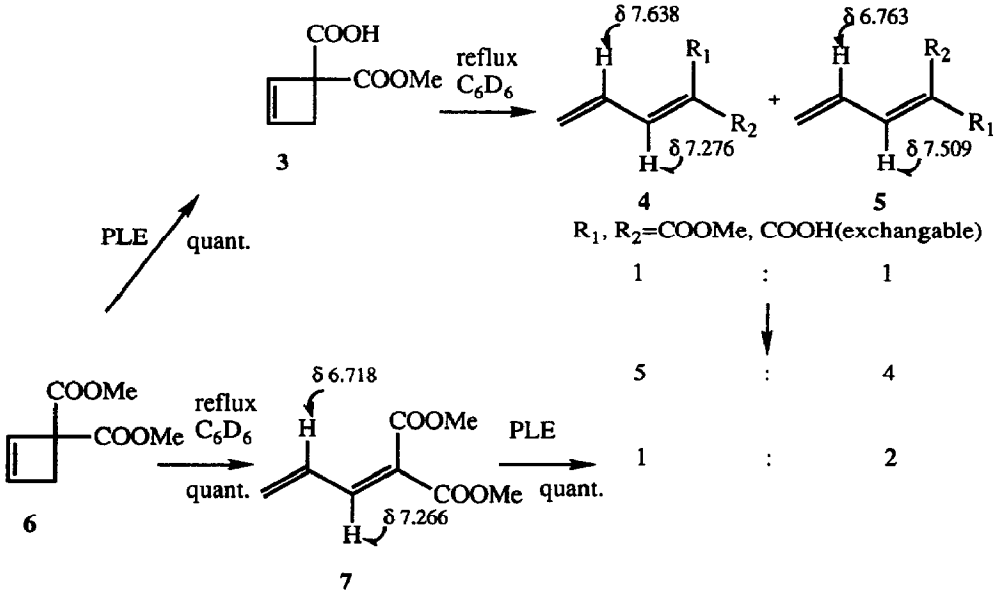
Wallace *et al.* systematically investigated cis-3,4-disubstituted cyclobutenes and proved that the ring opening is influenced by electronic effects of the substituents rather than steric effects.[9] Related studies were carried out by Piers.[10] These results are consistent with our predictions.

With this background, we designed 3-carbomethoxycyclobutene-3-carboxylic acid, **3**, which possesses two mild electron acceptors. Steric effects should not influence the ring opening transition states. The relative activation energies calculated by *ab initio* methods with the 3-21G basis set for COOMe and COOH are 1.7 and 1.5 kcal/mol respectively. Outward rotation is favored in both cases. From these values, **3** is expected to afford the two dienes in similar amounts, due to the predicted 0.2 kcal/mol difference in $\Delta G^{\neq}$, favoring outward rotation of the ester.

The carbomethoxy-carboxylic acid, **3**, was synthesized in four steps from commercially available cyclobutane-1,1-dicarboxylic acid using an efficient enzymatic hydrolysis as reported earlier.[5, 11] The thermal ring opening was followed in an NMR probe. The progress of the reaction was monitored in 5 minute intervals by ^{1}H-NMR.

Upon thermolysis of **3** in refluxing benzene-d_6, two signals of the methoxy singlet appeared in a 1:1 ratio by integration. This was clearly observed throughout the first ~30 minute stage, which means that the dienes formed in equal amounts. This observation shows that the "torquoselectivities" of both the substituents are approximately equal, in accord with our prediction. However, with the passing of time, this ratio changed slightly and eventually became about 5:4, accompanied by some complicated by-products.

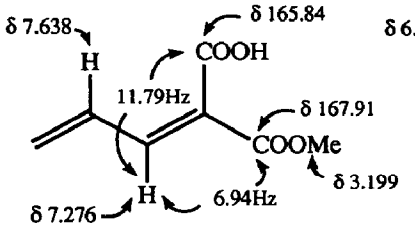
The chemical shifts of γ- (and β-) protons in the dienes **4** and **5** are significantly different, which is a quite unique tendency as compared to similar dienes of this type.[12] Therefore, we set out to assign the stereochemistries of the dienes, **4** and **5**.



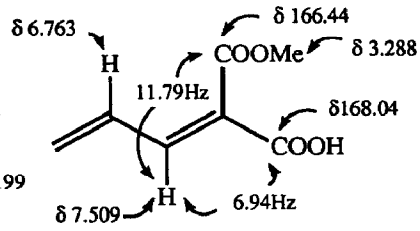
The dienes, **4** and **5**, were generated along with minor complex components. For further analysis, the mixtures of the pure dienes, **4** and **5**, were obtained by the monohydrolysis of the diester, **7**, with pig liver esterase. This gave **4** and **5** in 1:2 ratio.[13, 14] This unequal ratio enabled us to assign the olefinic protons and OMe signals for one of the two dienes. Although we could make a tentative assignment of the protons from the chemical shifts of **7** and the relative bulkiness of the substituents, unequivocal assignments are impossible on this basis. NOE experiments did not reveal the proximity of the COOMe and γ-proton.

Therefore, we measured the $^3J_{CH}$ coupling constant between the carbonyls of COOMe or COOH and the β-protons to assign the olefinic stereochemistry of the dienes. The assignments were made by a long-range selective proton decoupling (LSPD) experiment. Long-range carbon-proton (^{13}C-^{1}H) coupling constants, particularly $^3J_{CH}$, are sometimes used to elucidate connectivities in highly unsaturated compounds. General trends in the magnitudes of

^{13}C-^{1}H coupling constants have been observed.[15] The vicinal C-H coupling across the olefin are larger than terminal geminal ones, and the trans couplings are larger than the cis couplings, just as for geometrically equivalent ^{1}H-^{1}H couplings.[15] However, without the aid of computer simulation, the determination of stereochemistry from $^{3}J_{CH}$ value has hardly been reported[16] due to LSPD's sensitivity to the steric effect of the sample compounds, the measurement conditions and several technical problems. However, in our case, the $^{3}J_{CH}$ values decisively determine the alkene stereochemistries. The OMe groups in the mixture resonate close enough (3.288 and 3.199 ppm) to be irradiated simultaneously. The four signals in the ^{13}C-NMR spectra for the four carbonyls were assigned by matching them to the methoxy singlets and the β-protons in the 2D long-range C-H COSY NMR spectrum. Irradiation of the two methoxy singlets at the same time changed the carbonyls of the COOMe groups, which were multiplets in the gated decoupled ^{13}C NMR spectrum, to sharp doublets with coupling constants of 11.79 and 6.94Hz. From the other $^{3}J_{CH}$ values of the COOH carbonyls with the β-protons, the structures of these two dienes, **4** and **5**, were confirmed as shown below.

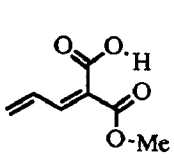


4

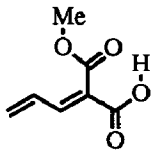


5

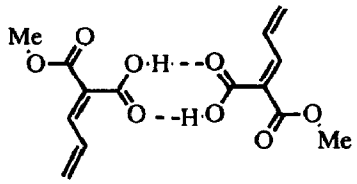
The origin of the large ^{1}H-NMR chemical shift difference between the two γ-protons could not be established unequivocally, since the mixture of the dienes **4** and **5** could not be separated. We propose a reason for this chemical shift difference qualitatively based on a few observations carried out on the mixture of **4** and **5**. Upon a ~5 fold dilution of the C_6D_6 solution, a ~0.2 ppm downfield shift of the γ-protons was observed. Furthermore, in CD3CN, the chemical shift difference between the γ-protons decreased to ~0.5 ppm, and the β–protons of **4** and **5** become almost equivalent. These results suggest that there is an equilibrium between intra-and intermolecular hydrogen-bonded forms of the dienes.



4I



5I



4D

In a non-hydrogen bonding solvent, C_6D_6, the intramolecular hydrogen bonding depicted in **4I** and **5I**, is likely. This causes one side of the diene, especially the γ-H, to be in the deshielding zone of the carbonyl group (**4I**) or shielding region of the alkoxy oxygen (**5I**). The intermolecular hydrogen-bonded forms, as shown for **4** (**4D**) will cause a very large difference in chemical shifts as well. The weak hydrogen-bonding acceptor, acetonitrile, could dissociate this intramolecular hydrogen bonded to some extent,[17] which could cause the attenuation of the chemical shift difference of the γ–protons.

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