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THE TORQUOSELECTIVITY OF ELECTROCYCLIC REACTIONS OF 3-DONOR-3-ACCEPTOR-SUBSTITUTED CYCLOBUTENES

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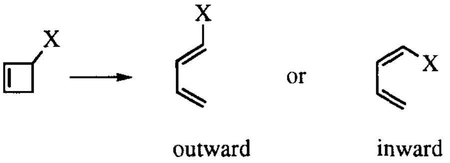
Abstract: Theory predicts that electron donors have larger outward rotation preferences than acceptors in thermal ring openings of cyclobutenes. Experimental verifications are presented for several 3,3-disubstituted cyclobutenes.

Cyclobutenes undergo thermal conrotatory ring openings to afford butadienes. As shown in Scheme 1, substituents on the 3-position may induce either outward rotation or inward rotation depending on the electronic properties of the substituent, X. We have made qualitative and quantitative predictions about this twisting preference (torquoselectivity) by quantum mechanical calculations.[1-3]

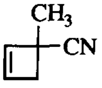
Scheme 1



The tendency for outward rotation increases with better π-electron donor substituents, while only very strong electron-withdrawing groups such as CHO or BH_2 cause inward rotation. When a low-lying vacant orbital of a substituent overlaps with the remote terminus of the breaking sigma bond, a two-electron stabilizing interaction overwhelms steric repulsion. This occurs only with very strong electron-withdrawing groups. We have reported several experimental verifications of these predictions for the thermal ring openings of 3-monosubstituted and 3,3-disubstituted cyclobutenes.[3-5]

Are these substituent effects additive? Some experimental results have been reported for 3,4-disubstituted cyclobutenes.[6,7] Wallace *et al.* found that ring openings of a variety of 3,4-disubstituted cyclobutenes are controlled by the electronic effects of the substituents.[6] Trost *et al.* reported that the thermolysis of 3,4-monoester-monoacids in several solvents shows negligible selectivity. The 3,4-disubstituted systems can be complicated due to the interaction between the two substituents during ring opening.[8]

Here, we report experimental studies of thermal ring openings of several types of 3,3-disubstituted cyclobutenes with one donor and one acceptor substituent. The 3,3-disubstituted systems have no significant steric repulsion changes between the two substituents during the ring openings. Therefore, the calculated substituent effects that arise from the interaction of substituent π-orbital and HOMO or LUMO of the cyclobutene are expected to be approximately additive. The 3,3-disubstituted cyclobutenes used in this study are **1-5**. The methyl esters **6** and **7** were previously reported,[3b, d] and the results are given here for comparison.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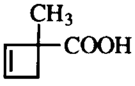
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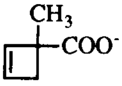
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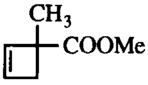
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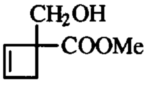
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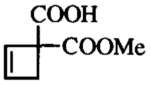
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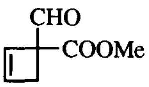
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The methyl-substituted derivatives, **1-4**, were synthesized starting from the [2+2] cycloadditions of allene and 2-substituted propenes as shown in Scheme 2. The cyanide, **1**, was prepared from the [2+2] cycloaddition of allene and methacrylonitrile.[9] Ozonolysis of this cycloadduct, **8**, and reduction with sodium borohydride afforded the alcohol, **10** (86%). Mesylation and treatment with t-BuOK in DMSO gave the desired olefin, **1**. The carboxylic acid, **2**, was prepared in almost the same manner, starting from the [2+2] cycloaddition of allene and methyl methacrylate at 200°C(20%), then ozonolysis and reduction with $NaBH_4$, followed by chlorination of the resulting alcohol with PPh_3/CCl_4. The resulting chloride was dehydrochlorinated with NaH/DMSO(78%) to produce the carboxylic acid, **2**. The methyl ester, **4**, was prepared by treating **2** with diazomethane. The alcohol **5**[10] was obtained by reduction of the formyl group of **7**, which was prepared by enzymatic hydrolysis of the mesomeric dimethyl ester as described before.[3b,d]

Scheme 2

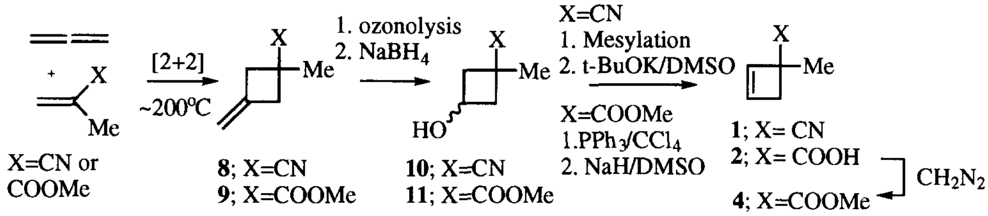


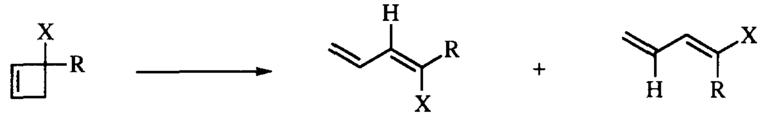
Table 1 summarizes calculated activation energy differences between inward and outward rotation for all the substituents described here. From these values, the torquoselectivities of those compounds, **1-5**, may be estimated by subtracting the relative energy difference between inward and outward rotation (ΔΔEact(rel)) for each substituent.

Table 1 3-21G Relative Activation Energies (kcal / mol) of Ring Openings of 3-Substituted Cyclobutenes[1,2,3e]

Substituent	ΔE_{act}(rel)		$\Delta\Delta E_{act}$(rel)
	in	out	in - out
H	0.0	0.0	0.0
Me	5.7	-1.2	6.9
CO_2^-	0.7	-4.4	5.1
CN	2.3	-2.3	4.6
CO_2H	-1.6	-3.1	1.5
COOMe	-1.3	-3.0	1.7
CHO	-6.9	-2.4	-4.5
OH	7.1	-9.6	16.7

The thermolysis experiments were conducted in an NMR probe in benzene-d_6 or D_2O. In the case of the carboxylate, **3**, reactions were carried out in 15% NaOD, or the potassium salt of **3** was submitted to the same thermolysis in C_6D_6 in the presence of 18-crown-6. The first 30 minutes of each ring opening reaction was monitored at 5 minute intervals by ^{1}H-NMR. Scheme 3 shows the products formed by this thermolysis of the cyclobutenes **1**-**5**. The structures of the product dienes were determined by NOE experiments by irradiating methyl protons for the diene **12**-**18**[5] or methylene protons for **19**. Table 2 summarizes the product ratios of the dienes obtained in these experiments.

Scheme 3



1; R=CH_3, X=CN	**12**; R=CH_3, X=CN	**13**; R=CH_3, X=CN
2; R=CH_3, X=COOH	**14**; R=CH_3, X=COOH	**15**; R=CH_3, X=COOH
3; R=CH_3, X=COO^-	**16**; R=CH_3, X=COO^-	**17**; R=CH_3, X=COO^-
4; R=CH_3, X=COOMe	**18**; R=CH_3, X=COOMe	
5; R=CH_2OH, X=COOMe	**19**; R=CH_2OH, X=COOMe	

Table 2. The Predicted Activation Energy Differences(kcal/mol)[a] for the Two Ring-Opening Modes and Product Ratios from the Thermolysis of the Compounds **1**-**7**.

Rxn.	Substrate	$\Delta(\Delta\Delta E_{act(rel)})^a$	Solvent	Conditions	Products
1.	**1** (Me, CN)	2.3	C_6D_6	reflux	**12**:**13**=4:1
2.	**2** (Me, CO_2H)	5.4	C_6D_6	reflux	**14**
3.	**3** (Me, CO_2^-)	1.8	15% NaOD	reflux	**16**
4.	**3** (Me, CO_2^-)	1.8	18-crown-6/C_6D_6	reflux	**16**:**17**=10:1
5.	**4** (Me, CO_2Me)	5.2	C_6D_6	reflux	**18**
6.	**5** (CH_2OH, CO_2Me)	5.2[b]	C_6D_6	reflux	**20**
7.	**6** (CO_2H, CO_2Me)	0.2[c]	C_6D_6	reflux	1:1[3d]
8.	**7** (CO_2Me, CHO)	6.2[d]	C_6D_6	50~80°C	CHO inward only[3b]

a. Predicted $\Delta\Delta E_{act(rel)}$ for R - $\Delta\Delta E_{act(rel)}$ for X; using values from Table 1.

b. $\Delta\Delta E_{act(rel)}$ for CH_3 - $\Delta\Delta E_{act(rel)}$ for COOMe

c. $\Delta E(CO_2Me-CO_2H)$

d. $\Delta E(CO_2Me-CHO)$

From these experiments, it can be concluded that the product ratios are consistent with the predictions. The product ratios in Table 2 are all kinetic results which were observed during the first 30 minutes of the reactions. It is notable that in the reactions where the torquoselectivity differences between electron donors and acceptors are greater than 5 kcal/mol, only one diene was detected. In some reactions, a change of the product ratio was observed upon further heating. For example, in reaction 2, a small amount of the isomeric diene **15** was detected upon continuation of the heating for more than 1 hour. In reaction 7, the proportion of the two dienes changed slightly to ~5:4 after approximately 30 minutes of heating, as reported previously[3d].

In the case of 3-hydroxymethylcyclobutene, **5**, the 3-hydroxymethyl group should be similar to methyl group. The experiment showed that only **19**, in which the hydroxymethyl group rotated outward, was observed. The structure was determined by a NOE experiment (11.7% NOE between the methylene protons of hydroxymethyl group and β-proton) after assigning all the diene proton chemical shifts.[11]

For carboxylate **3**, our prediction is that outward rotation for methyl group is preferred over COO$^-$ by 1.8 kcal/mol. Only the diene **16** in which methyl group rotated outward was detected in 15% NaOD solution at the reflux temperature in reaction 3. In reaction 4, a small proportion of the isomer **17** was observed in benzene-d$_6$ with 18-crown-6.

In conclusion, we have shown additional experimental examples of torquoselectivity for 3,3-disubstituted cyclobutene ring openings. These results are in accord with theoretical predictions.

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(10) **5**;^{1}H-NMR(360MHz, C_6D_6);δ6.22(1H, m); 6.05(1H, m); 4.2(1H, br.); 3.74(2H, m); 3.62(3H, s); 2.74(1H, d, J=14.4); 2.34(1H, d, J=14.4): 13C-NMR(90MHz, CDCl3); δ168.5, 137.2, 139.6, 67.0, 57.0, 52.2, 37.7: MS;(142(M^+), 124(M^+-H_2O))

(11) **19**; ^{1}H-NMR (360MHz, C_6D_6); δ7.61(1H, ddd, J=11.3, 10.3, 16.5), 6.42(1H, d, J=11.3), 5.19(1H, br. d, J=16.5), 5.18(1H, br. d, J=10.3), 4.11(2H, br. s), 3.26(3H, s), 3.21(1H, br.): ^{13}C-NMR (90MHz, C_6D_6); 166.7(s), 140.2(d), 133.9(d), 126.2(s), 124.9(t), 63.7(t), 51.1(q): MS;(142(M^+), 124(M^+-H_2O))

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