Activation energy and NBO interaction approaches to torquoselectivity and its dependence on the conformational profile of the substituent

Veejendra K. Yadav*

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India

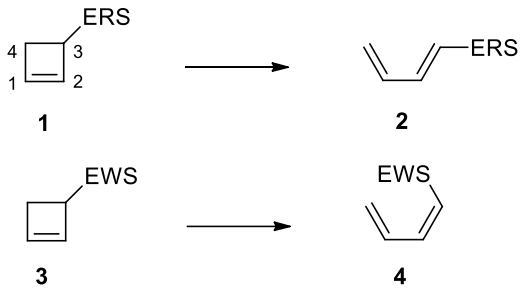
vijendra@iitk.ac.in

Abstract: The torquoselectivity of ring opening of 3-fluoromethylcyclobutenes, 2-fluoromethyl-3-oxetenes and perfluoro-3-methyl-cyclobutene have been studied at the MP2/cc-pVTZ level of theory and the results analysed by using the activation energy approach and also the NBO interactions of the breaking ring bond with the substituent bond. The outward or inward opening that has lower activation energy in the activation energy approach or larger interaction in the NBO approach constitutes the preferred mode. The CHF_2 and CH_2F substituents on cyclobutene and oxetene can adopt three distinct conformations with respect to the cleaving ring bond. It has been discovered that each conformer exhibits a distinct level of torquoselectivity and some higher lying conformer may even significantly contribute to the overall selectivity. The conformational profile of the substituent, therefore, is recommended for taking into consideration in any serious treatment of the subject. The experimental selectivity, if otherwise, is likely to be a consequence of secondary reactions such as the reaction equilibration, which honours the relative thermodynamic stabilities of the ring opened products.

Keywords: torquoselectivity, 3-fluoromethylcyclobutenes, 2-fluoromethyl-3-oxetenes, perfluoro-3-methylcyclobutene, activation energy, NBO interaction, conformational effects

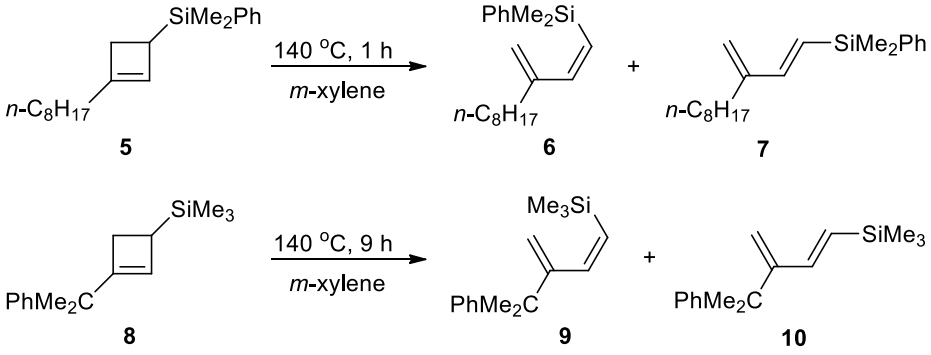
Introduction

The ring opening of cyclobutene proceeds in conrotatory fashion under thermal conditions to form 1,3-butadiene.[1] The predominant outward (**1** → **2**) and inward (**3** → **4**) rotations of, respectively, electron-rich and electron-deficient substituents are controlled by the phenomenon called torquoselectivity. It has typically been predicted by estimating the activation barriers and the lower barrier pathway constitutes the preferred mode of opening.[2]



ERS = Electron-Rich Substituent
EWS = Electron-Withdrawing Substituent

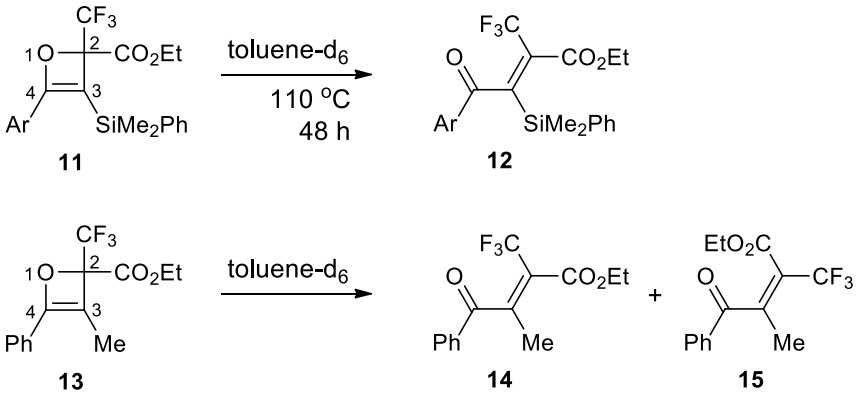
In 2001, Murakami and co-workers observed 83:17 kinetic distribution of the inward and outward opened products on heating 1-octyl-3-dimethylphenylsilylcyclobutene **5** at 140 °C in *m*-xylene for 1 hour.[3] Likewise, the reaction of 1-dimethylphenylmethy-3-trimethysilylcyclobutene **8** at 140 °C in *m*-xylene for 9 hours generated a 69:31 mixture of the inward and outward opened products, respectively. The preference for inward rotation of the silyl substituent was ascribed to a favorable overlap of the low lying σ* orbital of the silyl substituent with the occupied σ_{C3C4} orbital of the breaking bond in the corresponding transition state (TS) structure. The activation energy approach predicts the inward opening of 3-trimethylsilylcyclobutene favored over outward opening by 2.0 kcal/mol at M06-2X/6-31G(d) level of theory.[4] The inward and outward opening reactions of 3-trimethylsilylcyclobutene are exergonic by, respectively, 6.7 and 9.2 kcal/mol. The interaction $\sigma_{C3C4} \rightarrow \sigma^*_{C\text{-}Si}$ was estimated at 11.3 kcal/mol in the inward TS structure as against only 5.0 kcal/mol in the outward TS structure.



In 2003, Houk observed that the filled orbital of a donor substituent experienced closed-shell repulsion with the filled orbital of the breaking ring bond upon inward rotation and, thus, it preferred to rotate outward. In contrast, a vacant acceptor orbital on the substituent was predicted for inward rotation to maximize orbital interaction between the filled orbital of the breaking bond and the vacant orbital

of the substituent in the TS structure.[5] The orbital interaction was therefore concluded to control the TS structure.

In application of the activation energy approach, calculations at B3LYP/6-31G(d) level predicted the outward openings of 3-CF_3-, 3-CHF_2- and 3-CH_2F-cyclobutenes favored over the corresponding inward openings by, respectively, 2.3, 0.3 and 2.0 kcal/mol.[5] In partial contrast, the activation energies calculated at M06-2X/6-311+G(2d,p) level by Barquera-Lozada favored inward opening of 3-CHF_2-cyclobutene by 1.5 kcal/mol.[6] Dolbier and co-workers have experimentally discovered 3-CF_3-cyclobutene to open predominantly outward.[7] However, the relative concentration of the inward product was found to rise with raise in the reaction temperature. For instance, the outward:inward ratio was discovered to change from 43.5:1 at 56.5 °C to 13.2:1 at 188.5 °C. The outward product was estimated to be more stable than the inward product with standard enthalpy difference of 2.5 ± 0.4 kcal/mol. The transformation of the outward product to the corresponding inward variant on rise in reaction temperature requires explanation as it is not likely to be due to double bond isomerization for the requirement of a generally high activation energy. *A priori*, it appears to be an instance of reaction equilibration that allows accumulation of the more stable outward product (vide infra).

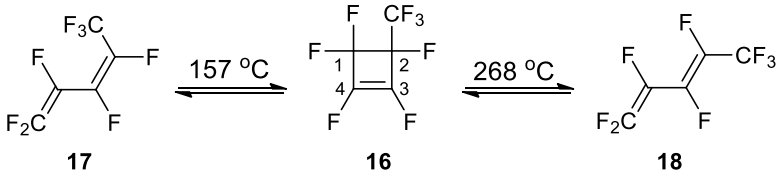


In 2011, Mikami studied the ring opening of 2-CO_2Et-2-CF_3-3-dimethylphenylsilyl-4-aryloxetene **11** under thermal conditions (toluene-d_6, 110 °C, 48 h) and observed its quantitative transformation to **12** with the exclusive inward rotation of CF_3.[8] He also observed predominance of inward rotation of CF_3 on ring opening of the closely related 2-CO_2Et-2-CF_3-3-methyl-4-phenyloxetene **13** by a margin of 81:19 at 70 °C and 77:23 at 100 °C.[9] The rise in concentration of the outward product on rise in reaction temperature must be noted. The results were explained by the $\sigma_{C2\text{-}O1} \rightarrow \sigma_{C\text{-}F}^*$ interaction that was larger in the TS for inward rotation of CF_3 than outward rotation. Going by the activation energy approach, CF_3 group appears more electron-deficient than CO_2Et. It will therefore be interesting to

investigate 2-CF_3-3-oxetene alone to assess the otherwise unperturbed electronic effects of CF_3 in regard to the activation barrier and also NBO interaction.

In 2015, Houk and Mikami concluded from M06-2X/6-31+G(d,p) level calculations that the torquoselectivies of a series of mono-, di-, and trifluoromethylcyclobutenes and also oxetenes resulted from the interplay of favorable orbital interactions and closed-shell repulsions.[10] The authors articulated that there was a favorable $\sigma_{C\text{-}O} \rightarrow \sigma^*_{C\text{-}F}$ interaction when the substituent rotated inward in fluoromethyloxetenes. Also, the preference for inward rotation of the fluoromethyl group decreased because the closed-shell repulsion n_F–$\sigma_{C\text{-}O}$ competed with the $\sigma_{C\text{-}O} \rightarrow \sigma_{C\text{-}F}^*$ interaction. The closed-shell repulsion arose when the distance between oxygen and fluorine was less than the sum of their van der Waals radii. An attempt to first amalgamate the activation barrier with NBO interaction to lend additional support to the former and then turning completely to NBO interaction alone is apparent.

Like the interaction $\sigma_{C\text{-}O} \rightarrow \sigma_{C\text{-}F}^*$ in oxetenes, the interaction $\sigma_{C\text{-}C} \rightarrow \sigma_{C\text{-}F}^*$ may also be expected in 3-fluoroalkyl-cyclobutenes such as 3-CF_3-, 3-CHF_2- and 3-CH_2F-cyclobutenes. An investigation into this and also whether or not the findings differed from those for the corresponding oxetenes was, therefore, felt necessary. It also provides an opportunity to study, for the first time, the effects of conformational changes in CHF_2 and CH_2F relative to the breaking ring bond on torquoselectivity. The orbital interaction is the greatest when the bonds are antiperiplanar.[11] The effect of conformational change in the substituent on torquoselectivity has not been investigated prior to this report.



17 **16** **18**

In 1986, Dolbier reported that perfluoro-3-methylcyclobutene **16** furnished only **17**, the product of inward rotation of CF_3, on conducting the reaction at 157 °C. However, the product profile changed to exclusively **18**, the product of outward rotation of CF_3, on raising the reaction temperature to 268 °C.[12] The switch over from (*Z*)-**17** at lower temperature to (*E*)-**18** at higher temperature also requires an explanation.

Computational Methodology: We have carried out quantum chemical calculations at MP2/cc-pVTZ level of theory to elucidate the electronic control of the substituents on the torquoselectivities of 3-fluoromethylcyclobutenes and 2-fluoromethyl-3-oxetenes using Gaussian 09[13]. Since the frequency calculations and, thus, the estimation of the Gibbs free energies for the reactions of 3-trimethtlsilylcyclobutene and perfluoro-3-methylcyclobutene were not possible at MP2/cc-pVTZ level of theory, M06-2X/6-31+G(d) level was

used instead. Optimized structures were verified as minima or first order saddle points by harmonic vibrational frequency analyses. All the energies reported are Gibbs' Free Energies (Sum of electronic and thermal Free Energies). See the Supporting Information (SI) for the geometrical coordinates of the ground and TS structures.

Results and Discussion

The activation energies for the ring openings in 3-CF_3-, 3-CHF_2- and 3-CH_2F-cyclobuetenes are collected in Table 1. For the substituents CF_2H and CH_2F, three different conformers were considered. The torsion angle of $\sigma_{C\text{-}H}$ bond in CHF_2 with $\sigma_{C3\text{-}C4}$ bond of cyclobutene was varied to have three distinct conformers. All these conformers are within 0.9 kcal/mol and, hence, abundantly available at 298.15 K. Likewise, the torsion angle of $\sigma_{C\text{-}F}$ bond in CH_2F with $\sigma_{C3\text{-}C4}$ bond of cyclobutene was varied to arrive at the three distinct conformers, all within 0.6 kcal/mol and, hence, abundantly available at 298.15 K for the reaction. The torsion angles are given in the footnote to the Table. This exercise was taken to study the conformational effects on torquoselectivity. Some of the higher lying conformers are likely to be closer to the transition state structure to react faster than the lower lying conformers. Further, since the NBO interactions in the TS structures for different conformers are expected to be different in reference to stereoelectronic effects[11], the torquoselectivity may alter completely or, in the least, the level may be affected.

Table 1. Gibbs free energy of activation ($\Delta G^{\ddagger}$), kcal/mol, obtained at 298.15 K and 1 atm pressure for ring openings in 3-fluoromethylcyclobutenes. The Gibbs free energy changes ($\Delta G_{product}$ - $\Delta G_{reactant}$) are given in the parentheses. $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{outward} - \Delta G^{\ddagger}_{inward}$

Entry	Substituent	$\Delta G^{\ddagger}_{outward}$	$\Delta G^{\ddagger}_{inward}$	$\Delta\Delta G^{\ddagger}$
1	**CF_3**	33.2 (-5.6)	36.3 (-1.8)	-3.1
2	**CHF_2** [a]	32.8 (-5.4)	33.2 (-5.0)	-0.4
3	**CHF_2** [b]	32.9 (-6.2)	36.1 (-2.8)	-3.2
4	**CHF_2** [c]	31.9 (-6.3)	35.4 (-2.0)	-3.5
5	**CH_2F** [d]	31.4 (-7.1)	34.5 (-5.7)	-3.1
6	**CH_2F** [e]	31.3 (-7.2)	32.9 (-6.3)	-1.6
7	**CH_2F** [f]	30.6 (-7.6)	36.5 (-3.5)	-5.9

[a] Torsion angle C4-C3-C-H = -47.0. [b] Torsion angle C4-C3-C-H = 70.7. [c] Torsion angle C4-C3-C-H = -169.0.
[d] Torsion angle C4-C3-C-F = 72.6. [e] Torsion angle C4-C3-C-F = -167.6. [f] Torsion angle C4-C3-C-F = -49.4

A bird's eye view of the activation energy data demonstrates that all the three substrates must open predominantly outwards. Two entries, however, need special mention. First, the most stable of the three conformers, Entry 2, shows the lowest level of selectivity with approximately 2:1 kinetic distribution of the products in favor of outward opening. The other two conformers, entries 3 and 4, must exclusively form the outward product for > 3.0 kcal/mol difference in the activation energies.

Among the conformers of the substrate bearing the CH_2F substituent, all but the conformer at Entry 6 are expected to exclusively open outwards. The conformer at Entry 6, which has $\sigma_{C3\text{-}C4}$ and $\sigma_{C\text{-}F}$ nearly antiperiplanar, is comparatively less selective as it can generate close to 10% of the inward product also. The conformational effect of the substituent on the resultant torquoselectivity is obvious.

We now switch to looking at the NBO interactions collected in Table 2. The interactions $\sigma_{C3C4} \rightarrow \sigma^*_{C\text{-}F/H}$ and $\sigma_{C\text{-}F/H} \rightarrow \sigma^*_{C3C4}$ are to be taken together because both weaken the σ_{C3C4} bond. The $\sigma_{C\text{-}F/H}$ refers to all the $\sigma_{C\text{-}H}$ and $\sigma_{C\text{-}F}$ bonds in the substituent group. On account of significantly higher interaction in the inward mode of opening compared to interactions in the corresponding outward opening, all the three substrates are predicted for inward opening, which clearly contradicts the prediction made above by the activation energy approach. The difference of interactions in the inward and outward openings of the least stable CH_2F conformer at the last entry is the least (only 2.3 kcal/mol), which may be expected to somewhat compromise the selectivity.

Table 2. NBO interactions (kcal/mol) in the TSs for ring opening of 3-fluoromethycyclobutenes. The values in the parentheses are for inward opening TSs.

Substrate	$\pi_{C1C2} \rightarrow \sigma^*_{C3C4}$	$\sigma_{C3C4} \rightarrow \pi^*_{C1C2}$	$\sigma_{C3C4} \rightarrow \sigma^*_{C\text{-}F/H}$	$\sigma_{C\text{-}F/H} \rightarrow \sigma^*_{C3C4}$
CF_3	64 (71)	78 (84)	11 (21)	1.9 (1.7)
CHF_2[a]	62 (64)	81 (83)	9 (25)	6.4 (2.8)
CHF_2[b]	63 (73)	77 (84)	10 (18)	2.5 (2.1)
CHF_2[c]	61 (69)	81 (85)	9 (16)	6.4 (4.7)
CH_2F[d]	55 (62)	78 (85)	7 (19)	9.5 (4.0)
CH_2F[e]	55 (64)	78 (81)	7 (23)	9.5 (3.2)
CH_2F[f]	61 (68)	80 (86)	7 (12)	10 (7.3)

[a] Torsion angle C4-C3-C-H = -47.0. [b] Torsion angle C4-C3-C-H = 70.7. [c] Torsion angle C4-C3-C-H = -169.0
[d] Torsion angle C4-C3-C-F = 72.6. [e] Torsion angle C4-C3-C-F = -167.6. [f] Torsion angle C4-C3-C-F = -49.4

Appropriate orbital interaction is more important than steric interaction, so much so that conformers facing severest of steric interactions are known to react in exclusive preference to the almost all relaxed (the most stable) conformer.[14] We, therefore, prefer the NBO interaction approach to activation energy approach for the prediction of torquoselectivity.

3-CF_3-cyclobutene has been reported to open exclusively outward on heating at 146-186 °C in the gas phase at 3−4 mm pressure in a sealed tube. The experimental results of ring openings in 3-CHF_2- and 3-CH_2F-cyclobutenes are not reported in the literature. Both the outward and inward openings of 3-CHF_2- and 3-CH_2F-cyclobutenes are estimated to be sufficiently exergonic to discourage reaction equilibration under mild conditions. In contrast, the inward opening of 3-CF_3-cyclobutene is only 1.8

kcal/mol exergonic in comparison to 5.6 kcal/mol for outward opening. This translates into 38.1 and 38.8 kcal/mol as activation energies for the ring closing reverse reactions of the inward and outward products, respectively. Since the barrier for ring closing reaction of the inward opened product is only 1.8 kcal/mol higher than the corresponding ring opening reaction, it is likely that the two processes compete under the high energy conditions of the reaction while the more stable outward product accumulates. In contrast, the ring closing reaction of the outward opened product is 5.6 kcal/mol more difficult than the corresponding ring opening reaction. The profiles of the reactions of 3-CF_3-cyclobutene are given in Figure 1(a).

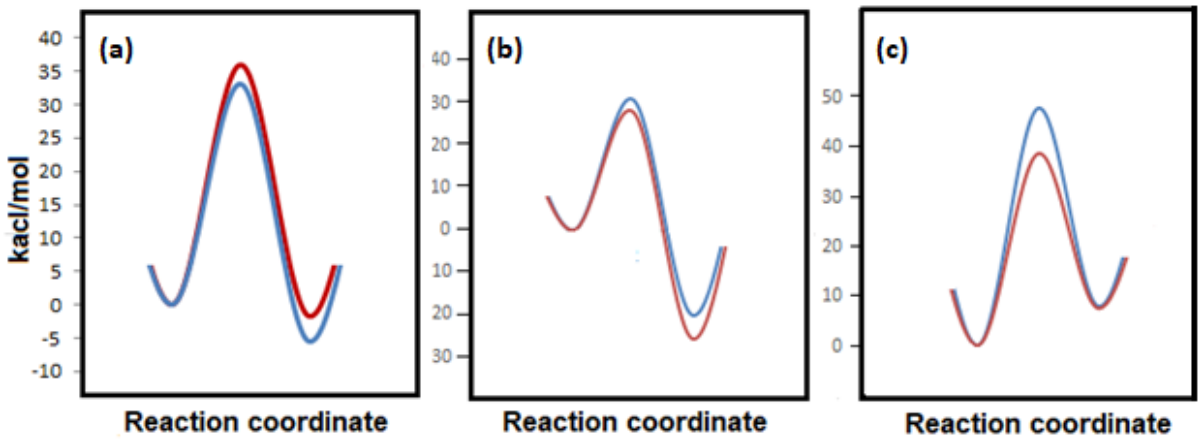


Figure 1. Reaction profile for inward (solid red line) and outward (solid blue line) ring openings in (a) 3-CF_3-cyclobutene, (b) 2-trifluoromethyl-3-oxetene, and (c) perfluoro-3-methylcyclobutene

The activation energies and free energy changes for the openings of 2-fluoromethyl-3-oxetenes are collected in Table 3. All the reactions are highly exergonic and, hence, equilibration is unlikely. Since the activation energy for outward opening is significantly lower than inward opening, exclusive outward opening is predicted. The conformer at Entry 2 deserves special comment. This conformer is most stable of the three conformers. The differential activation energy is only 0.7 kcal/mol and, hence, it will be expected to generate approximately 25% of the inward product also. It is important to note that all the three conformers of CHF_2- and CH_2F-substituted oxetenes are, respectively, within 2.4 and 1.1 kcal/mol and, hence, abundantly available at 298.15 K for the reaction. The reaction profiles for the outward and inward openings of 2-trifluoromethyl-3-oxetene are given in Figure 1(b).

In contrast, NBO interactions $\sigma_{C\text{-}O} \rightarrow \sigma^*_{C\text{-}F}$ and $\sigma_{C\text{-}F} \rightarrow \sigma^*_{C\text{-}O}$ support inward rotation of the CF_3 group because their sum is > 7.0 kcal/mol larger in the TS structure for inward over outward rotation. Though all the conformers of CHF_2 are favored for inward rotation, the differential interaction energy decreases from 5.3 to 4.9 to 2.0 kcal/mol as one descends the Table. This could be taken for overall

reduced torquoselectivity. The story with the CH_2F substituent is different. The differential interaction energy is small, but in support of outward opening for the first two conformers and a 1:1 mixture for the last one. Overall, 3-CH_2F-3-oxetene is predicted for largely outward opening, which is the same as that predicted by the differential activation energy. The NBO interactions are collected in Table 4.

Table 3. Gibbs free energy of activation ($\Delta G^{\ddagger}$), kcal/mol, obtained at 298.15 K and 1 atm pressure for the ring openings of 2-fluoromethyl-3-oxetenes. The Gibbs free energy changes ($\Delta G_{product}$ - $\Delta G_{reactant}$) are given in the parentheses. $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{outward} - \Delta G^{\ddagger}_{inward}$

Entry	Substituent	$\Delta G^{\ddagger}_{outward}$	$\Delta G^{\ddagger}_{inward}$	$\Delta\Delta G^{\ddagger}$
1	**CF_3**	28.0 (-25.7)	30.8 (-20.1)	-2.8
2	**CHF_2**[a]	28.5 (-24.3)	29.2 (-23.1)	-0.7
3	**CHF_2**[b]	27.2 (-25.5)	29.9 (-24.3)	-2.7
4	**CHF_2**[c]	26.5 (-26.6)	30.8 (-19.5)	-4.3
5	**CH_2F**[d]	24.7 (-24.3)	31.0 (-24.9)	-6.3
6	**CH_2F**[e]	24.2 (-24.8)	28.5 (-25.5)	-4.3
7	**CH_2F**[f]	24.2 (-26.7)	30.7 (-26.0)	-6.5

[a] Torsion angle O1-C2-C-H = -49.1. [b] Torsion angle O1-C2-C-H = 60.6. [c] Torsion angle O1-C2-C-H = -172.6
[d] Torsion angle O1-C2-C-F = 74.6. [e] Torsion angle O1-C2-C-F = -174.7. [f] Torsion angle O1-C2-C-F = -61.9

Table 4. NBO interactions (kcal/mol) in the TSs for the ring opening of 2-fluoromethyl-3-oxetenes. The values in the parentheses represent interactions in the inward opening TSs.

Substrate	$\pi_{C3C4}\rightarrow\sigma^*_{C\text{-}O}$	$\sigma_{C\text{-}O}\rightarrow\pi^*_{C3C4}$	$\sigma_{C\text{-}O}\rightarrow\sigma^*_{C\text{-}F/H}$	$\sigma_{C\text{-}F/H}\rightarrow\sigma^*_{C\text{-}O}$
CF_3	72 (80)	53 (61)	2.4 (10)	3.0 (2.6)
CHF_2[a]	70 (76)	54 (63)	1.8 (12)	7.9 (3.0)
CHF_2[b]	70 (79)	54 (60)	1.8 (10)	7.9 (4.6)
CHF_2[c]	74 (78)	57 (63)	1.8 (8.0)	12.4 (8.2)
CH_2F[d]	66 (76)	62 (72)	1.5 (7.7)	18 (10)
CH_2F[e]	66 (71)	62 (59)	1.5 (12)	18 (4.9)
CH_2F[f]	68 (73)	56 (64)	1.5 (6.6)	19 (14)

[a] Torsion angle O1-C2-C-H = -49.1. [b] Torsion angle O1-C2-C-H = 60.6. [c] Torsion angle O1-C2-C-H = -172.6
[d] Torsion angle O1-C2-C-F = 74.6. [e] Torsion angle O1-C2-C-F = -174.7. [f] Torsion angle O1-C2-C-F = -61.9

Finally, we return to perfluoro-3-methylcyclobutene **16**, which is reported to furnish only the (*Z*)-olefin **18** from the inward rotation of CF_3 on conducting the reaction at 157 °C and (*E*)-olefin **19** from the outward rotation of CF_3 at 268 °C.[12] The activation energies for ring openings entailing inward and outward rotations of CF_3 are, respectively, 38.9 and 48.1 kcal/mol. Thus, the inward rotation is favored over outward rotation by 9.2 kcal/mol. Both the reactions are endergonic, the free energy change being 7.5 and 7.9 kcal/mol, respectively, and hence reversible. The activation energies for the

corresponding ring closing reactions, therefore, are 31.4 and 40.3 kcal/mol, respectively. The activation energies are collected in Table 5.

Table 5. Gibbs free energies of activation ($\Delta G^{\ddagger}$), kcal/mol, obtained at 298.15 K and 1 atm pressure for ring openings in perfluoro-3-methylcyclobutene **16**. The Gibbs free energy change ($\Delta G_{product} - \Delta G_{reactant}$) is given in parentheses. $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{outward} - \Delta G^{\ddagger}_{inward}$

Substrate	$\Delta G^{\ddagger}_{outward}$	$\Delta G^{\ddagger}_{inward}$	$\Delta\Delta G^{\ddagger}$
16	48.1 (7.5)	38.9 (7.9)	9.2

At the lower end of the reaction temperature (157 °C), only the lower energy inward opening leading to (*Z*)-olefin and the associated ring closing reactions predominate, and we observe only the (*Z*)-olefin **17**. At the higher end of the reaction temperature (268 °C), outward ring opening pathway requiring higher activation energy also becomes active and the consequent (*E*)-olefin **18** predominates for its relatively lower reversibility due to larger thermodynamic stability. The reaction profiles are shown in Figure 1(c).

Table 6. NBO interactions (kcal/mol) in the TS structures for ring opening in perfluoro-3-methylcyclobutene **16**. The values in the parentheses are for the inward opening TS structures

$\pi_{C1C2}\rightarrow\sigma^*_{C3C4}$	$\pi_{C1C4}\rightarrow\pi^*_{C2C3}$	$\pi_{C2C3}\rightarrow\pi^*_{C1C4}$	$\sigma_{C3C4}\rightarrow\sigma^*_{C\text{-}F}$	$lp_F\rightarrow\pi^*_{C1C4/C2C3}$
0 (0)	65 (62)	60 (60)	0 (0)[a]	76 (77)[b]

[a]The $\sigma_{C\text{-}F}$ in the interaction $\sigma_{C3C4}\rightarrow\sigma^*_{C\text{-}F}$ refers to the CF_3 group. [b]$lp_F\rightarrow\pi^*_{C1C4/C2C3}$ refers to the interactions of the lone pairs of electrons of fluorine atoms directly attached to C3 and C4.

The relevant NBO interactions are collected in Table 6. The absence of $\pi_{C1C2} \rightarrow \sigma^*_{C3C4}$ interaction and also the presence of $\pi_{C1C4} \rightarrow \pi^*_{C2C3}$ and $\pi_{C2C3} \rightarrow \pi^*_{C1C4}$ interactions clearly demonstrate that the TS structures are heavily advanced and product-like in both the modes of ring opening. The σ_{C3C4} bond is completely broken in the TS structure and, hence, its interaction with $\sigma^*_{C\text{-}F}$ is absent. F atoms directly bonded to the ring appear to play a role through the interactions of their lone pairs with the largely developed π bonds between C1 and C4, and C2 and C3. The differential interaction, however, is marginal and in favor of inward rotation by only 1.0 kcal/mol. The NBO interaction approach therefore predicts an approximately 1:1 mixture of the (*Z*)- and (*E*)-olefins.

Conclusions. The torquoselectivity of ring opening in substituted cyclobutenes and oxetenes is a consequence of NBO interactions of the breaking ring bond with substituent orbitals. The ring opening (outward or inward) that has larger interaction constitutes the preferred pathway. The experimental torquoselectivity, if otherwise, is a likely consequence of secondary reactions, specifically the reactant

⇌ product equilibration, while honouring the relative stabilities of the ring opened products. The more stable ring opened product predominates.

The conformational profile of the substituent relative to the cleaving bond impacts the torquoselectivity and, hence, it must be taken into consideration in any comprehensive treatment of the subject.[15] Conformational issues arise because the effective NBO interactions are largely antiperiplanar interactions and, hence, the relative orientation of the cleaving ring bond with the substituent bond is important. The higher lying conformers react with lower activation energies and also result in enhanced torquoselectivity.

ASSOCIATED CONTENT

Supporting Information

Supporting Information (SI) available: Cartesian coordinates of the optimized substrates and TS structures, Gibbs' free energies of the ground and TS structures, Imaginary Frequencies of the TS structures (34 pages)

Conflict of Interest

There is no conflict of interest.

ORCID

Veejendra K. Yadav: 0000-0001-8294-0677

ACKNOWLEDGEMENTS

The author acknowledges allocation of time on HPC series of supercomputers by the Computer Centre, Indian Institute of Technology Kanpur, and Dr. Dasari L. V. K. Prasad for fruitful discussions.

REFERENCES

1. R. B. Woodward, R. Hoffmann, Stereochemistry of Electrocyclic Reactions, *J. Am. Chem. Soc.* **1965**, *87*, 395−397.
2. (a) W. Kirmse, N. G. Rondan, K. N Houk, Stereoselective substituent effects on conrotatory electrocyclic reactions of cyclobutenes, *J. Am. Chem. Soc.* **1984**, *106*, 7989−7991. (b) N. G. Rondan, K. N. Houk, Theory of stereoselection in conrotatory electrocyclic reactions of substituted cyclobutenes, *J. Am. Chem. Soc.* **1985**, *107*, 2099−2111. (c) K. Rudolf, D. C. Spellmeyer, K. N. Houk, Prediction and experimental verification of the stereoselective electrocyclization of 3-formylcyclobutene, *J. Org. Chem.* **1987**, *52*, 3708−3710. (d) K. N. Houk, D. C. Spellmeyer, C. W. Jefford, C. G. Rimbault, Y. Wang, R. D. Miller,

Electronic control of the stereoselectivities of electrocyclic reactions of cyclobutenes against incredible steric odds, *J. Org. Chem.* **1988**, *53*, 2125−2127. (e) C. W. Jefford, G. Bernardinelli, Y. Wang, D. C. Spellmeyer, A. Buda, K. N. Houk, Torquoselectivity in the electrocyclic conversion of benzocyclobutenes to o-xylylenes, *J. Am. Chem. Soc.* **1992**, *114*, 1157−1165. (f) S. Niwayama, K. N. Houk, Lewis acid reversal of the torquoselectivity of the electrocyclic ring opening of 3-acetylcyclobutene, *Tetrahedron Lett.* **1993**, *34*, 1251−1254. (g) K. Nakamura, K. N. Houk, Substituent Effects on Torquoselectivity. Computational Investigations of the Thermal Ring Openings of Cyclobutenes Fused to Substituted Cyclohexenes, *J. Org. Chem.* **1995**, *60*, 686−691. (h) S. Niwayama, Y. Wang, K. N. Houk, The torquoselectivity of electrocyclic reactions of 3-donor-3-acceptor-substituted cyclobutenes, *Tetrahedron Lett.* **1995**, *36*, 6201−6204. (i) S. Niwayama, A. K. Kallel, D. C. Spellmeyer, C. Sheu, K. N. Houk, Substituent Effects on Rates and Stereoselectivities of Conrotatory Electrocyclic Reactions of Cyclobutenes. A Theoretical Study, *J. Org. Chem.* **1996**, *61*, 2813−2825.

3. M. Murakami, T. Miyamoto, Y. Ito, A Silyl Substituent Can Dictate a Concerted Electrocyclic Pathway: Inward Torquoselectivity in the Ring Opening of 3-Silyl-1-cyclobutene, *Angew. Chem., Int. Ed.* **2001**, *40*, 189−190.
4. The frequency calculation for the TS structures could not be achieved at the MP2/cc-pVTZ level and, hence, the calculations were performed at M06-2X/6-31+G(d) level to allow us estimate the Gibbs free energies. Similar was the case with perfluoro-3-methylcyclobutene.
5. P. S. Lee, X. Zhang, K. N. Houk, Origins of Inward Torquoselectivity by Silyl Groups and Other σ-Acceptors in Electrocyclic Reactions of Cyclobutenes, *J. Am. Chem. Soc.* **2003**, *125*, 5072−5079.
6. J. E. Barquera-Lozada, Torquoselectivity in Cyclobutene Ring Openings and the Interatomic Interactions That Control Them, *J. Phys. Chem. A* **2016**, *120*, 8450−8460.
7. (a) W. R. Dolbier, Jr, T. A. Gray, J. J. Keaffaber, L. Celewicz, H. Koroniak, Kinetic and Thermodynamic Effects in the Thermal Electrocyclic Ring-Openings of 3-Fluorocyclobutene, 3,3-Difluorocyclobutene, and 3-(Trifluoromethyl)cyclobutene, *J. Am. Chem. Soc.* **1990**, *112*, 363−367. (b) W. R. Dolbier, Jr, H. Koroniak, K. N. Houk, C. Sheu, Electronic Control of Stereoselectivities of Electrocyclic Reactions of Cyclobutenes: A Triumph of Theory in the Prediction of Organic Reactions, *Acc. Chem. Res.*, **1996**, *29*, 471−477.
8. K. Aikawa, Y. Hioki, N. Shimizu, K. Mikami, Catalytic Asymmetric Synthesis of Stable Oxetenes via Lewis Acid-Promoted [2 + 2] Cycloaddition, *J. Am. Chem. Soc.* **2011**, *133*, 20092–20095.
9. K. Aikawa, N. Shimizu, K. Honda, Y. Hioki, K. Mikami, Effect of the trifluoromethyl group on torquoselectivity in the 4π ring-opening reaction of oxetenes: stereoselective synthesis of tetrasubstituted olefins, *Chem. Sci.* **2014**, *5*, 410−415.
10. K. Honda, S. A. Lopez, K. N. Houk, K. Mikami, Mono-, Di-, and Trifluoroalkyl Substituent Effects on the Torquoselectivities of Cyclobutene and Oxetene Electrocyclic Ring Openings, *J. Org. Chem.* **2015**, *80*, 11768−11772. The publication concludes, “The torquoselectivities are thus controlled by a competition of $\sigma_{CO} \rightarrow \sigma_{CF}^*$ effect and unfavorable closed-shell repulsions. Our calculations suggest that 2-

difluoromethyloxetenes prefer inward rotation because the favorable $\sigma_{CO} \rightarrow \sigma_{CF}^*$ orbital effect outweighs closed-shell repulsions in the transition state."

11. (a) P. Deslongchamps, Stereoelectronic Effects in Organic Chemistry, Pergamon Press, 1983. (b) V. K. Yadav, Steric and Stereoelectronic Effects in Organic Chemistry, Springer, 2016.
12. (a) W. R. Dolbier, H. Koroniak, D. J. Burton, P. Heinze, The electrocyclic interconversion of perfluoro-3-methylcyclubutene with *Z*- and *E*-perfluro-1,3-pentadiene, *Tetrahedron Lett.* **1986**, *27*, 4387−4390. (b) W. R. Dolbier, H. Koroniak, D. J. Burton, A. R. Bailey, G. S. Shaw, S. W. Hansen, Remarkable, Contrasteric, Electrocyclic Ring Opening of a Cyclobutene, *J. Am. Chem. Soc.* **1984**, *106*, 1871-1872. These references do not specify anything about whether or not the reaction of perfluoro-3-methylcyclobutene was carried in a solvent. This prohibited us from studying solvent effects.
13. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, revision C.01, Gaussian, Inc., Wallingford, CT 2009.
14. J. A. Berson, The overlap component of the stereoelectronic factor. Remote control of stereogenicity transfer through the anisotropic influence of a ring, *Acc. Chem. Res.* **1991**, *24*, 215−222.
15. For a brief mention of conformational effect arising from geminal ethyl versus methyl groups, see: E. A., Kallel, Y. Wang, D. C. Spellmeyer, K. N. Houk, Electrocyclic ring openings of dialkylcyclobutenes: anomalies explained, *J. Am. Chem. Soc.* **1990**, *112*, 6759-6763. The inward rotation of the ethyl group was considered to give rise to more favorable gauche interactions than the methyl group.

For Table of Contents

The conformational profile of the substituent relative to the cleaving bond impacts torquoselectivity. The ring opening that has larger NBO interaction in the TS structure constitutes the preferred pathway.