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# Thermodynamic Control of the Electrocyclic Ring Opening of Cyclobutenes: C=X Substituents at C-3 Mask the Kinetic Torquoselectivity

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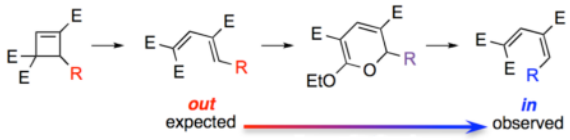
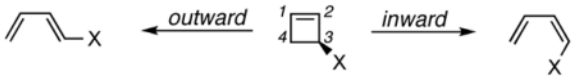
## Abstract

E = $CO_2$Et
R = Ph, Me




The thermal ring-opening reactions of 4-phenyl-1,3,3-triethoxycarbonylcyclobutene and 4-methyl-1,3,3-triethoxycarbonylcyclobutene yield dienes that result from an unexpected selectivity for “inward” rotation of the phenyl and methyl groups. With 1-ethoxycarbonyl-4-phenylcyclobutene, “outward” rotation of the phenyl group occurs exclusively. Density functional theory was used to investigate the role of the 3,3-geminal diester groups and the origin of torquoselectivity in these electrocyclic reactions. The rules of torquoselectivity still hold, with a calculated 6–8 kcal/mol preference for outward rotation of the methyl and phenyl substituents. However, cyclization of the “out” dienes to pyran intermediates allows for isomerization and thermodynamic control of stereoselectivity.

Cyclobutenes undergo conrotatory ring-opening reactions under thermal conditions to yield dienes.[1] Two conrotatory processes—clockwise or counter-clockwise rotation of all C-3 and C-4 substituents—are always possible, but one mode is preferred in asymmetric rings. This “torquoselectivity” is controlled by the electronic nature of the C-3 substituent: donors (X = $CH_3$, OR, halides) rotate outward, while strong acceptors (CHO, NO, $SiR_3$, $B(OR)_2$) rotate inward.[2] No violations of this fundamental stereochemical principle of electrocyclic reactions are known.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. Cartesian coordinates and energies of all reported structures and full authorship of reference [5]. This material is available free of charge via the Internet at http://pubs.acs.org.

However, one of our groups recently observed an unexpected *inward* rotation of donors in the ring-opening reactions of triester-substituted Cyclobutenes, **1a***–**b*** (Scheme 1).[3] The 3-phenyl Cyclobutenes exhibit normal *outward* rotation of the phenyl group; no previous examples of inward rotation of phenyl groups were known.[4] Because cyclobutene **1c*** opens in the expected outward fashion to give **3c***, it became clear that the geminal esters play a role in determining the final diene ratio. We now report a computational study that provides an explanation for the unexpected torquoselectivities of Cyclobutenes **la***–**b***.[5] All ethyl esters were modeled computationally by methyl esters; the experimental structures are designated by asterisks ("*").

In contrast to the experimental results in Scheme 1, all calculated activation enthalpies for inward (**TS1**) and outward (**TS2**) opening of Cyclobutenes **1a–c** show a high selectivity for outward rotation of $R_2$ (Table 1). Thus the rules of torquoselectivity are predicted to be preserved. **TS1b** and **TS2b** are shown in Figure 1.

This disagreement between theory and experiment is reconcilable if there is thermodynamic control of the experimental results. We explored the possibility that the terminal ester groups ($R_1$) may facilitate isomerization of "out" dienes **3***/**3′*** to the thermodynamically more stable "in" dienes **2***/**2′*** (Table 2). However, these isomerization barriers were calculated to be high (28–36 kcal/mol, entries 1–4). The lower barrier for **3b′** (entry 4) is presumably due to stabilizing C=O•••H interactions that are more pronounced compared to the other isomerization transition structures. (See Supporting Information). Diene **3c,** which does not bear the geminal esters, isomerizes to the "in" diene with a similar barrier (entries 5–6). These calculations were also performed with UB3LYP[6] and afforded the same results.

During the investigation of the isomerization of **3′a–b** to **2′a–b,** we located a low-energy (2H)-pyran intermediate **4** (Scheme 2). A similar cyclization was previously observed in the electrocyclic ring opening of 3-formyl-3-carboxymethyl-cyclobutene;[7] the resulting diene **5** cyclizes to (2H)-pyran **6**, which was observable by $^1$H-NMR but could not be isolated in pure form. Its structure was verified by Diels-Alder cycloaddition with tetracyanoethylene (TCNE) to yield **7**.

The activation enthalpies for closing "out" diene **3′** to pyran **4** (**TS4**) was calculated to be only 12–13 kcal/mol (Table 3). The facile ring closure of 2,4-pentadienals has been attributed to the close proximity of the nucleophilic oxygen lone pairs with the C-5 terminus.[8] Pyran **4** re-opens to "in" diene **2′** (**TS5**) with higher barriers of 14–17 kcal/mol. The preferential *outward* rotation of donor $R_2$ (**TS4** vs. **TS5**) is consistent with the torquoselectivities of previously investigated 6π electrocyclic reactions.[9] The structures of **TS4b, 4b,** and **TS5b** are given in Figure 2.

Based on these results, the overall free energy profile for the ring-opening reactions of **1a** and **1b** is shown in Figure 3. The normal rules of outward torquoselectivity are followed, but cyclization of dienyl esters **3′a–b** to pyrans leads to isomerization and thermodynamic control of stereoselectivity. $^1$H-NMR studies support this mechanism. When either cyclobutene **1a*** or a 4.5:1 mixture of dienes **2a*:3a*** is heated in $d_6$-DMSO at 80 °C, a ratio of approximately 3:1 is established after 12 h.

Finally, because pyran **4** was not observed by $^1$H-NMR, we attempted to trap pyran intermediate **4a** via a Diels-Alder cycloaddition with TCNE. The product was not observable even at 140 °C, which was not surprising considering the steric and electronic nature of **4.** Calculations predict that the reaction of **4a** with TCNE is highly unfavored, with $\Delta G^{\ddagger}$ = 23.0 kcal/mol (**TS6**) and $\Delta G_{rxn}$ = 13.5 kcal/mol. In agreement with experimental results, the activation free energy for cycloaddition of simple pyran **6** with TCNE was calculated to be feasible, with $\Delta G^{\ddagger}$ = 20.9 kcal/mol (**TS7**) and $\Delta G_{rxn}$ = −6.2 kcal/mol.

In conclusion, we have shown that electronic control of the kinetic torquoselectivity in thermal ring-opening reactions of cyclobutenes consistently holds, even in highly substituted cases, but extended conjugation at C-3 allows for isomerization of products and thermodynamic control of the diene *in:out* ratio.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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3. For the syntheses of the cyclobutenes 1a* and 1c* see: Xu H, Zhang W, Shu D, Werness JB, Tang W. Angew Chem Int Ed 2008;47:8933–8936.8936The ring opening reactions described in this current manuscript are reported for the first time (see Supporting Information). Cyclobutene 1b* could not be isolated. When the precursor cyclopropane diazoacetate S1 is treated with 5 mol% AgOTf at room temperature, the proposed cyclobutene directly undergoes ring opening to form diene 2b*. The low ring-opening activation enthalpy of 1b* (Table 1, entry 2) supports these results.
4. For examples of outward 3-Ph rotation, see: (a)Murakami M, Miyamoto Y, Ito Y. J Am Chem Soc 2001;123:6441–6442.6442 [PubMed: 11427081](b)Shindo M, Sato Y, Yoshikawa T, Koretsune R, Shishido K. J Org Chem 2004;69:3912–3916.3916 (c) ref. 2h. [PubMed: 15153025]
5. All structures were optimized in the gas phase using density functional theory (B3LYP/6-31G(d)) as implemented in the Gaussian 03 suite of programs. (Frisch, M. J. et al. Gaussian, Inc., Wallingford CT, 2004). All stationary points were verified as minima or first-order saddle points by vibrational frequency analysis. Resulting thermal corrections were applied to single point energy calculations with M06/6-31+G(d) as implemented in Q-Chem 3.0.0.6 (Shao, Y. et al. Q-Chem, Inc., Pittsburgh PA, 2007). These energies are given in the text, tables, and figures. For the full references, see Supporting Information.
6. The “guess=(mix, always)” option was used.
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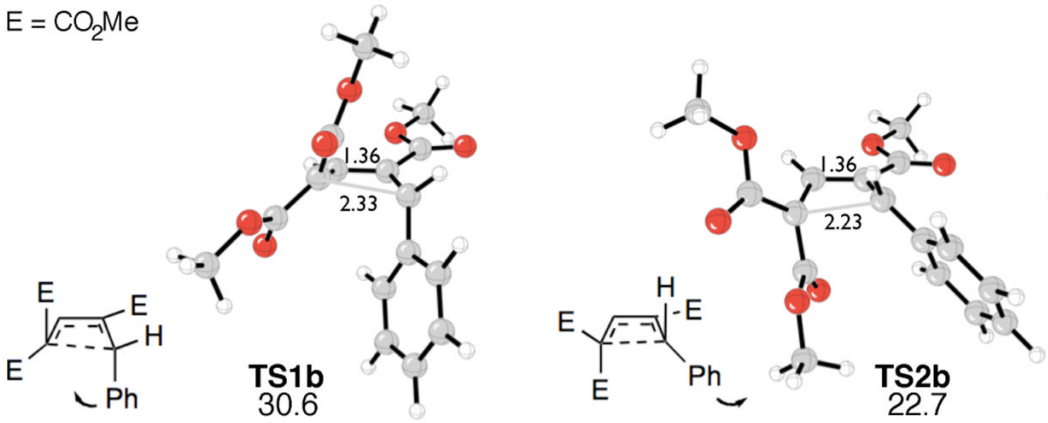



**Figure 1.**
Ring-opening transition structures of 1,3,3-trimethoxycarbonyl-4-phenyl-cyclobutene **(1b)**

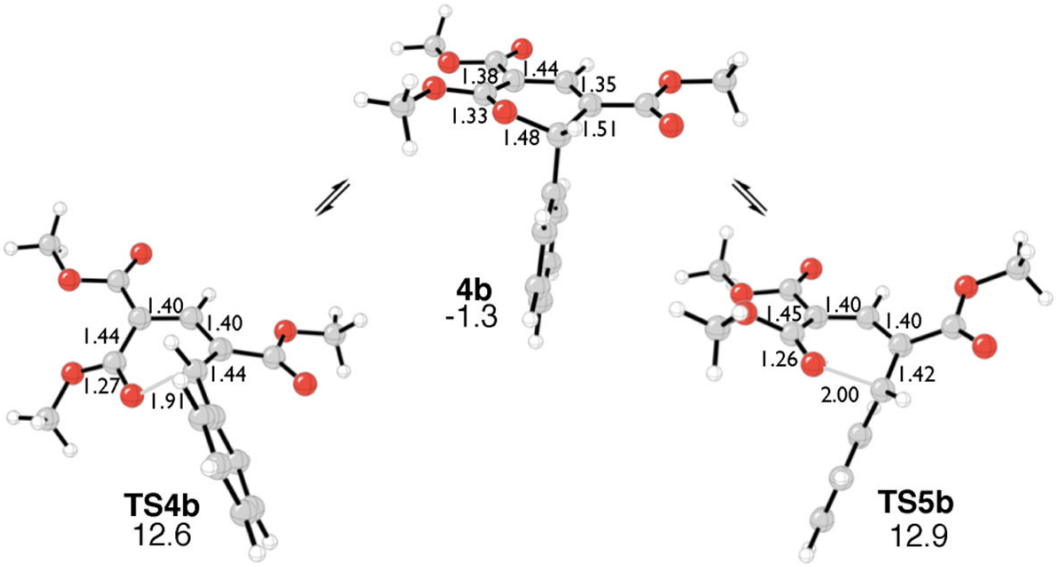



**Figure 2.**
Ring closure of **3b′** and ring opening of pyran **4b**.

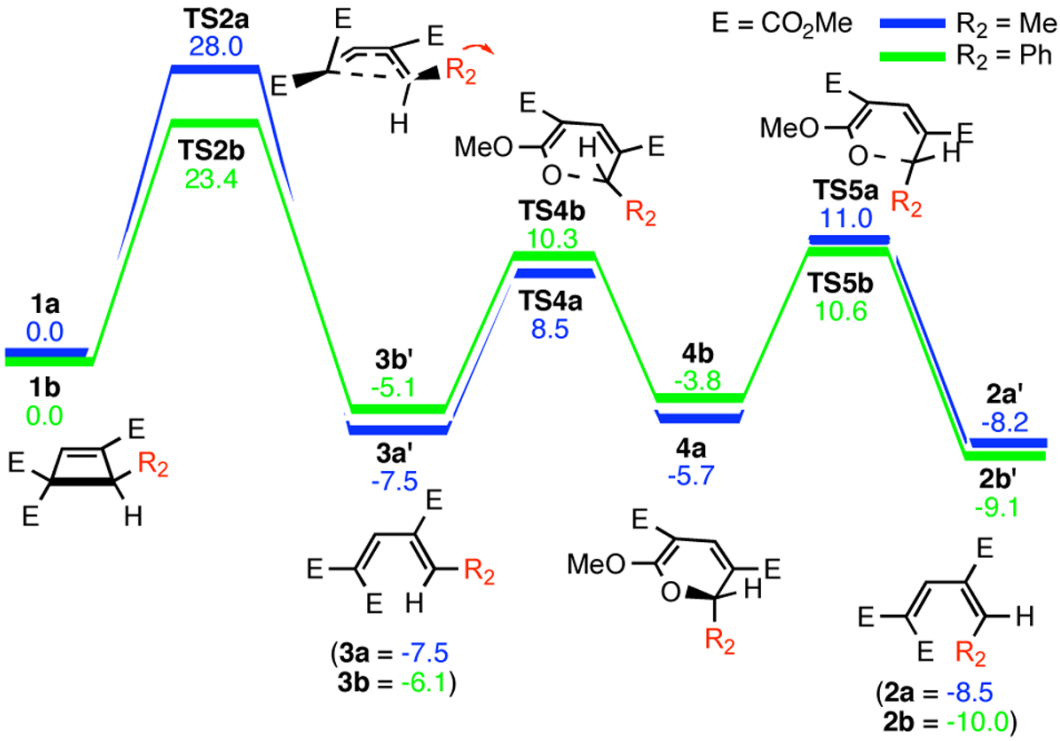
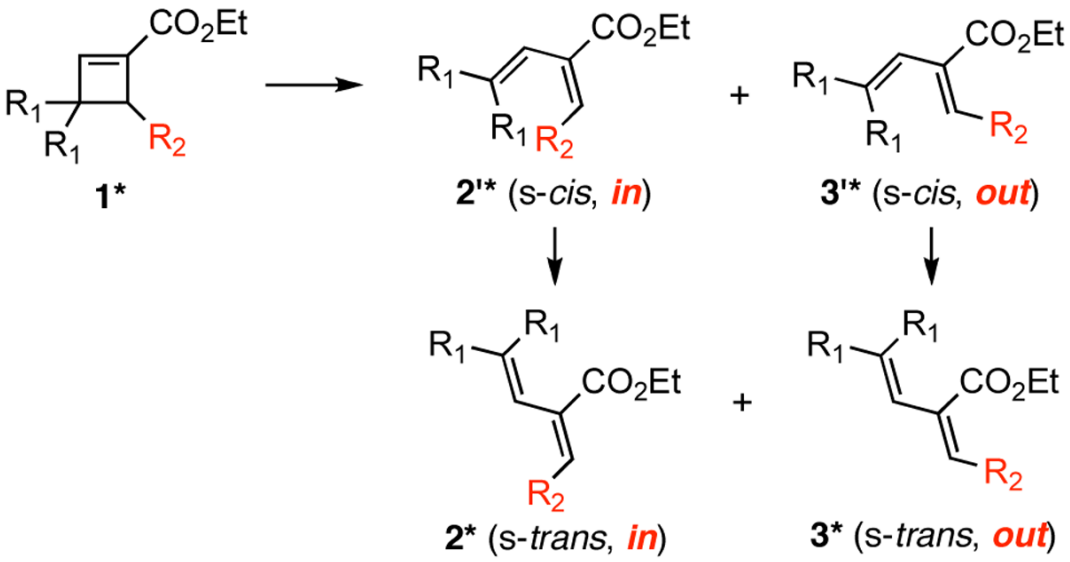



**Figure 3.**
Overall pathway (relative free energies).

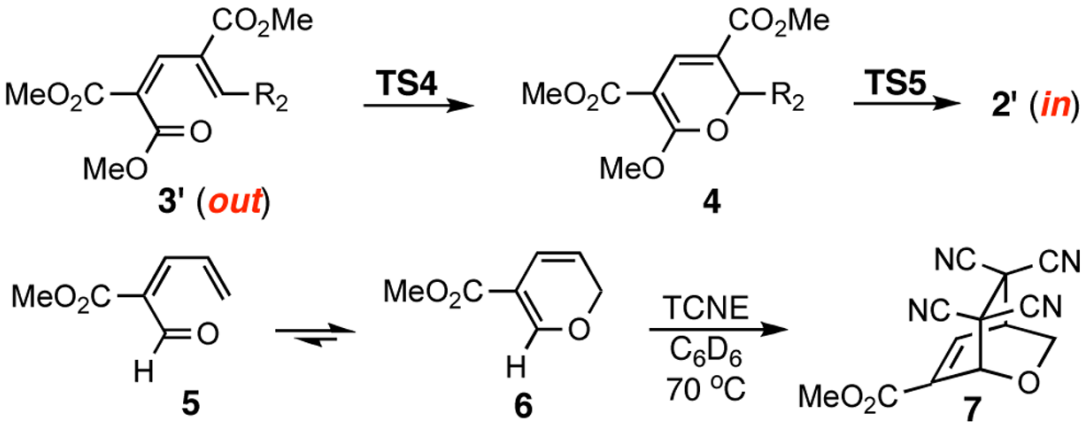



**Scheme 1.**

**1a***: $R_1$ = $CO_2Et$, $R_2$ = Me (80 °C, 36h): **2a***/**2a′***:**3a***/**3a′*** = 4.5:1

**1b***: $R_1$ = $CO_2Et$, $R_2$ = Ph (rt, < 5 min): **2b***/**2b′*** only

**1c***: $R_1$ = H, $R_2$ = Ph (80 °C, 24h): **3c***/**3c′*** only




**Scheme 2.**
Cyclization of dienes **3′** and **5** to (2H)-pyrans **4** and **6**

**Table 1**

Calculated ring-opening activation enthalpies of 1a–c[a]

| entry | cyclobutene | TS1 (*in*) | TS2 (*out*) | $\Delta\Delta H^{\ddagger}$ (TS1-TS2) |
|---|---|---|---|---|
| 1 | **1a** | 34.1 **(TS1a)** | 28.1 **(TS2a)** | 6.0 |
| 2 | **1b** | 30.6 **(TS1b)** | 22.7 **(TS2b)** | 7.9 |
| 3 | **1c** | 35.4 **(TS1c)** | 28.5 **(TS2c)** | 6.9 |

**Table 2**

Activation enthalpies for isomerization of **3**/**3′** to **2**/**2′**

| entry | $H_{rel}$ of 3/3′ (“out” diene) | $\Delta H^{\ddagger}$ of isomerization | $H_{rel}$ of 2/2′ (“in” diene) |
|---|---|---|---|
| 1 | 0.0 (**3a**) | 36.4 (**TS3a**) | −0.9 (**2a**) |
| 2 | 1.4(**3a′**) | 33.1 (**TS3a′**) | −0.5 (**2a′**) |
| 3 | 0.0 (**3b**) | 32.2 (**TS3b**) | −4.0 (**2b**) |
| 4 | 2.0 (**3b′**) | 27.6 (**TS3b′**) | −2.3 (**2b′**) |
| 5 | 0.0 (**3c**) | 35.2 (**TS3c**) | −0.9 (**2c**) |
| 6 | 3.0 (**3c′**) | 33.3 (**TS3c′**) | 0.2 (**2c′**) |

**Table 3**

Relative enthalpies for cyclization of **3′**

| entry | $R_2$ | cyclization $\Delta H^{\ddagger}$ of 3′ | 4 | ring opening $\Delta H^{\ddagger}$ of 4 |
|---|---|---|---|---|
| 1[a] | Me | 12.3 (**TS4a**) | −1.8(**4a**) | 14.7 (**TS5a**) |
| 2[b] | Ph | 12.6 (**TS4b**) | −1.3 (**4b**) | 12.9 (**TS5b**) |

[a] with respect to **3a′**.

[b] with respect to **3b′**.