J|A|C|S COMMUNICATIONS

Published on Web 04/29/2009

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

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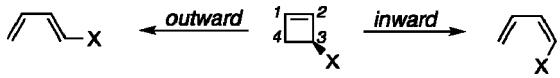
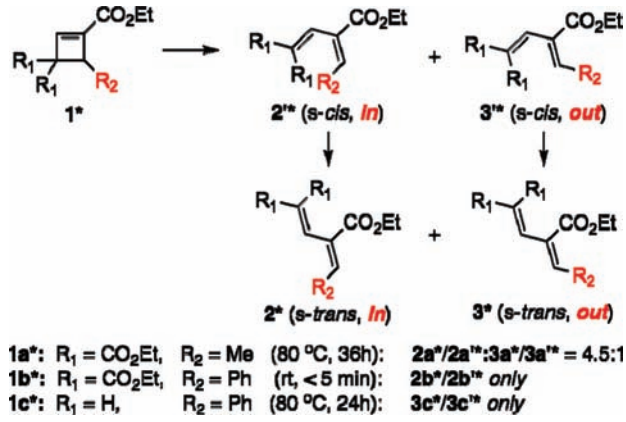
Cyclobutenes undergo conrotatory ring-opening reactions under thermal conditions to yield dienes.[1] Two conrotatory processes, clockwise or counterclockwise rotation of all C-3 and C-4 substituents, are always possible, but one mode is preferred in asymmetric rings. This "torquoselectivity" is controlled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



No violations of this fundamental stereochemical principle of electrocyclic reactions are known.

However, one of our groups recently observed an unexpected *inward* rotation of donors in the ring-opening reactions of the triester-substituted cyclobutenes **1a*** and **1b*** (Scheme 1).[3] The 3-phenylcyclobutenes 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 **1a*** and **1b***.[5] All of the ethyl esters were modeled computationally by methyl esters; the experimental structures are designated by asterisks (*).

Scheme 1



In contrast to the experimental results in Scheme 1, all of the 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.

Table 1. Calculated Ring-Opening Activation Enthalpies (kcal/mol) for **1a**−**c**

entry	cyclobutene	**TS1** (inward)	**TS2** (outward)	$\Delta\Delta H^{\ddagger}$ (**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

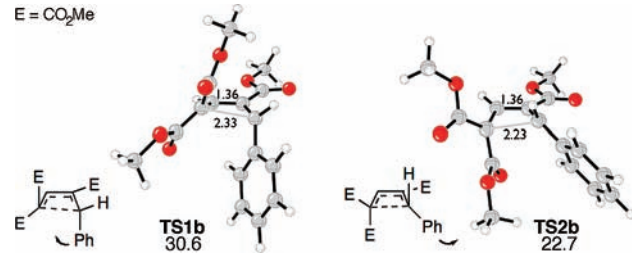


Figure 1. Ring-opening transition-state structures of 1,3,3-trimethoxycarbonyl-4-phenylcyclobutene (**1b**).

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 in **3b'** than in the other isomerization transition-state structures (see the 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 at the UB3LYP level,[6] and the same results were obtained.

Table 2. Activation Enthalpies for Isomerization of **3/3'** to **2/2'**

entry	H_{rel} of **3/3'** ("out" diene)	$\Delta H^{\ddagger}_{isomerization}$	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'**)

During the investigation of the isomerization of **3a'/3b'** to **2a'/2b'**, we located the low-energy (2*H*)-pyran intermediate **4** (Scheme 2). A similar cyclization was previously observed in the electrocyclic ring opening of 3-formyl-3-carboxymethylcyclobutene;[7] the resulting diene **5** cyclizes to (2*H*)-pyran **6**, which was observable by ^{1}H NMR but could not be isolated in pure form. Its structure was

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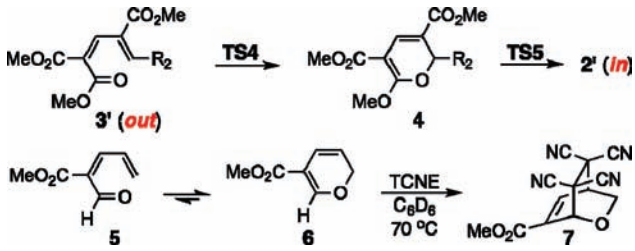
10.1021/ja9016446 CCC: $40.75

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



verified by Diels−Alder cycloaddition with tetracyanoethylene (TCNE) to yield **7**.

The activation enthalpy for closing the "out" diene **3′** to give 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 to the C-5 terminus.[8] Pyran **4** reopens to the "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.

Table 3. Relative Enthalpies for Cyclization of **3′**

entry	R_2	$\Delta H^{\ddagger}_{\text{cyclization}}$ for **3′**	**4**	$\Delta H^{\ddagger}_{\text{ring-opening}}$ for **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′**.

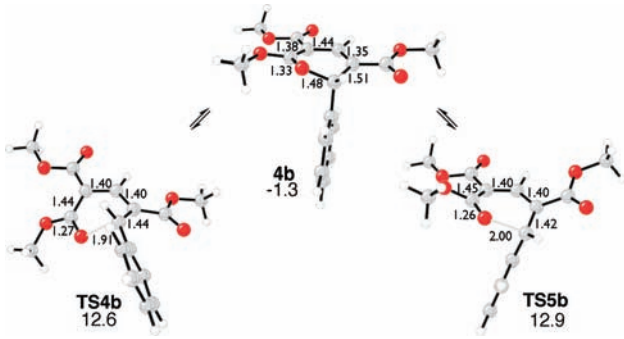


Figure 2. Ring closure of **3b′** and ring opening of pyran **4b**.

On the basis of 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 **3a′** and **3b′** 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*** and **3a*** is heated in DMSO-d_6 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 in view of 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 $\Delta G_{\text{rxn}} = 13.5$ kcal/mol. In agreement with experimental results, the cycloaddition of simple pyran **6** with TCNE was calculated to be feasible, with $\Delta G^{\ddagger} = 20.9$ kcal/mol (**TS7**) and $\Delta G_{\text{rxn}} = -6.2$ 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,

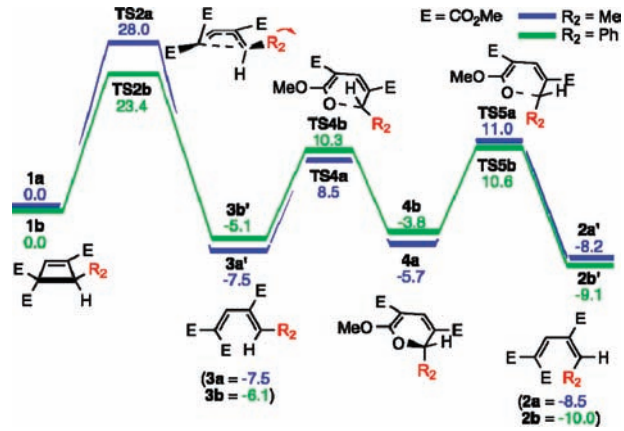


Figure 3. Free-energy profile for the overall reaction pathway (relative free energies in kcal/mol).

but extended conjugation at C-3 allows for isomerization of products and thermodynamic control of the in:out diene ratio.

Acknowledgment. We are grateful to the National Institute of General Medical Sciences, National Institutes of Health (GM 36700, K.N.H.) and University of Wisconsin (W.T.) for support of this work.

Supporting Information Available: Experimental procedures and spectral data for all new compounds, Cartesian coordinates and energies of all reported structures, and complete refs 5a and 5b. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For the syntheses of the cyclobutenes **1a*** and **1c***, see: Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 8933–8936. The ring-opening reactions described in the current manuscript are reported for the first time (see the 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. (b) Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912–3916. (c) ref 2h.
(5) (a) All of the 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 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004). All of the stationary points were verified as minima or first-order saddle points by vibrational frequency analysis. (b) Required thermal corrections were applied to the single-point energy calculations using M06/6-31+G(d), as implemented in Q-Chem (Shao, Y.; et al. *Q-Chem*, version 3.0.0.6; Q-Chem, Inc.: Pittsburgh, PA, 2007). These energies are given in the text, tables, and figures.
(6) The "guess=(mix, always)" option was used.
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JA9016446