Interplay of Theory and Experiment: Reversal of the Torquoselectivity of the Electrocyclic Ring Opening of 3-Acetylcyclobutene by a Lewis Acid

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Theoretical predictions, accompanied by firm experimental verification, are presented on the "torquoselectivity" of the thermal ring opening of 3-acetylcyclobutene (**1**). 3-Acetylcyclobutene was synthesized from commercially available 1,1-cyclobutanedicarboxylic acid. Thermolysis of 3-acetylcyclobutene resulted in a mixture of *E*- and *Z*-dienes with a slight preference for the *E*-diene. This preference was reversed by the Lewis acid, ZnI_2, as predicted from theoretical calculations.

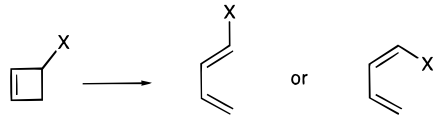
Introduction

Cyclobutenes undergo thermally allowed conrotatory electrocyclic ring opening to afford *E*-dienes or *Z*-dienes by outward or inward rotation, respectively (Scheme 1). The twisting mode is dependent upon the electronic properties of the substituent, X. Previously, Houk et al. rationalized this selectivity and termed it "torquoselectivity".[1ab] As a general tendency, electron donors and mild electron acceptors rotate outward to form the *E*-diene, and only powerful π-electron acceptors rotate inward to form the *Z*-diene. This selectivity has been explained based on electronic effects which develop from the interaction between molecular orbitals of the substituents (π orbitals) and the breaking C−C bond during the electrocyclic process as in Scheme 2.[1a,b] Qualitatively, donor groups, such as alkyl (Taft $\sigma_R° = -0.11$ for CH_3)[4] and hydroxyl (Taft $\sigma_R° = -0.43$), attached to the breaking bond will maximize the stabilizing two-electron interaction, or minimize the destabilizing four-electron interaction, with the orbital attached to the substituent in the transition state during outward rotation. Most substituents prefer outward rotations due to either of these two electronic effects. When the substituent is an electron acceptor, inward rotation can be favorable because this motion permits a vacant π^* orbital of the substituent to overlap with the remote terminus of the breaking σ bond. This stabilizing interaction overwhelms the steric repulsions which occur upon inward rotation only with the most powerful π-acceptors, such as formyl (Taft $\sigma_R° = 0.24$) and dialkylboryl groups.[1,2,4]

According to this theory, it should be possible to control the torquoselectivity of the ring opening of 3-substituted cyclobutenes by changing the electron-withdrawing or -donating character of the substituents. Earlier, using ab initio calculations, it was predicted that substituents that rotate outward could be enticed to rotate inward by coordination with Lewis acids, since inward rotation is favored only with very strong electron acceptors according to predictions described above.[5]

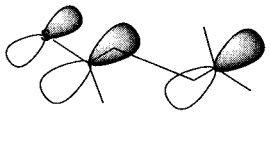
Acetyl group is a mild electron-withdrawing group (Taft $\sigma_R° = 0.16$) and expected to be on the borderline

Scheme 1

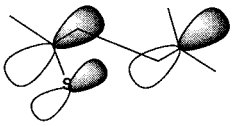


Scheme 2

Orbital interaction of the substituent(S) p orbital with σ or σ* bond in the transition state of ring opening of 3-substituted cyclobutene[1a,b]

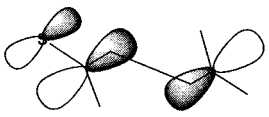


Interaction of p orbital of the substituent with σ* bond in outward rotation

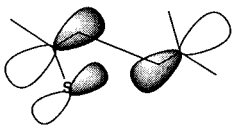


Interaction of p orbital of the substituent with σ* bond in inward rotation

Stabilizing two-electron interaction for high-lying filled π orbitals



Interaction of p orbital of the substituent with σ bond in outward rotation



Interaction of p orbital of the substituent with σ bond in inward rotation

Stabilizing two-electron interaction for low-lying vacant π orbitals*

Destabilizing four-electron interaction for high-lying filled π orbitals

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(1) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106,* 7989. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099.

(2) Rudolf, K.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 3708.

(3) Buda, A. B.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 2264.

(4) Houk and Niwayama et al.[4a] recently examined that inherent torques calculated for 3-substituted cyclobutenes show a remarkable correlation with the Taft $\sigma_R°$ value,[4b] which is an experimentally determined measure of the resonance contribution to the net electron-donating or -withdrawing character of the substituents. (a) Niwayama, S.; Kallel, E. A.; Sheu, C.; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* Manuscript submitted for publication. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(5) Niwayama, S.; Houk, K. N. *Tetrahedron Lett.* **1993**, *34*, 1251.

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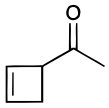
between outward and inward rotational selectivity. Therefore the subtle torquoselective behavior of 3-acetylcyclobutene is extremely intriguing from both experimental and theoretical points of view.



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Herein the full details of the interplay of theory and experiment for the electrocyclic ring opening of 3-acetylcyclobutene (**1**) will be described.

Background

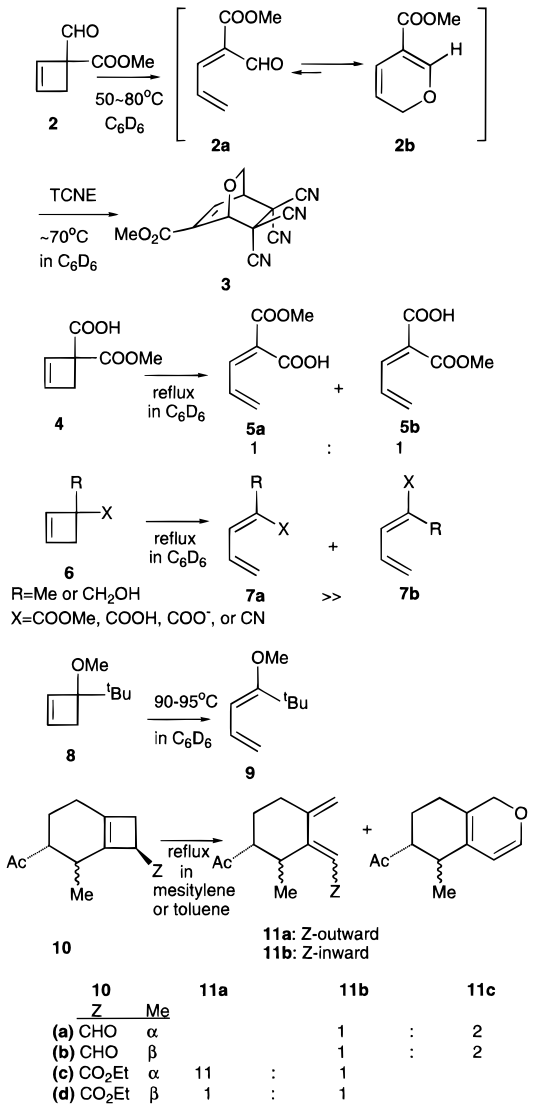
Although Houk's theory on the torquoselectivity offers reasonable predictions on rotational selectivity of 3-substituted cyclobutene electrocyclic ring openings, only a few clear experimental verifications have been reported. This is primarily because ring openings of cyclobutenes are usually conducted in complicated multifunctionalized systems, which can interfere with the substituent effects during the ring openings.

For a related system, Rudolf, Spellmeyer, and Houk reported that 3-formylcyclobutene opens with inward rotation of the formyl group, in accord with the quantum mechanical prediction.[2] Ab initio calculations (6-31G*//3-21G) predict a 4.6 kcal/mol lower activation energy for inward rotation than outward rotation.[2,4]

Similarly, Niwayama and Houk reported that thermal ring opening of methyl 3-formylcyclobutene-3-carboxylate (**2**) produces only inward rotation, with respect to the formyl group, to form the diene **2a** and cyclized **2b** (Scheme 3).[6a] This is a result of a clear-cut competition between two electron-acceptors that possess different degrees of torquoselectivity. They also observed that a series of 3,3-disubstituted cyclobutenes undergo thermal ring openings to afford dienes with regiochemistry consistent with ab initio calculations.[6b,c] Several of the results are opposite to expectations based upon the thermodynamic stability of the products. It should also be noted that electronic effect, rather than steric effect, clearly determines the torquoselectivity. Houk et al. demonstrated that 3-methoxy-3-*tert*-butylcyclobutene (**8**) produces only the *E*-diene **9** in which the *tert*-butyl group rotated inwardly upon thermolysis at 90−95 °C for 6.5 h in C_6D_6.[6d] Similar experimental studies were reported by Wallace et al. for ring openings of 3,4-disubstituted cyclobutenes.[7]

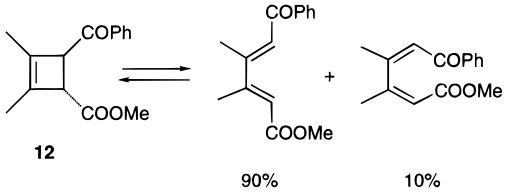
Piers *et al.* observed exclusive inward rotation of the formyl group and preferential outward rotation of carbethoxy group (Taft $\sigma_R° = 0.16$) on the thermolysis of substituted 7-formylbicyclo[4.2.0]oct-1-(6)-enes **10a**−**d**. These results are also compatible with Houk's theory, although steric repulsion between the β-methyl group and the outwardly rotated carbethoxy group decreased the selectivity for the carbethoxy group in **10d**.[8]

Scheme 3



10 Z	Me	11a		11b		11c
(a) CHO	α			1	:	2
(b) CHO	β			1	:	2
(c) CO_2Et	α	11	:	1		
(d) CO_2Et	β	1	:	1		

Scheme 4



Alkylketo (X = RCO, (Taft $\sigma_R° = 0.16$ for R = $-CH_3$)) groups are less powerful π-acceptors than a formyl group. Ab initio calculations predict a small preference toward outward rotation over inward rotation by 1.2 kcal/mol for an acetyl group as will be described later.[5] The thermolysis of keto ester **12** gave a 90:10 preference for outward rotation of the phenylketo groups, but this reaction is under thermodynamic control (Scheme 4).[9] This result is consistent with Niwayama's experimental observation of thermolysis of 3-acetylcyclobutene.[5]

It is predicted that this preference for outward rotation is reversed by powerful electron-withdrawing additives due to the increased π-electron-withdrawing character

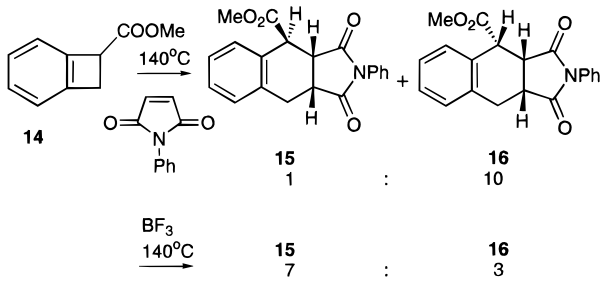
(6) (a) Niwayama, S.; Houk, K. N. *Tetrahedron Lett.* **1992**, *33*, 883. (b) Niwayama, S.; Houk, K. N.; Kusumi, T. *Tetrahedron Lett.* **1994**, *35*, 527. (c) Niwayama, S.; Wang, Y.; Houk, K. N. *Tetrahedron Lett.* **1995**, *36*, 6201. (d) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125.

(7) (a) Binns, F.; Hayes, R.; Ingham, S.; Saengchantara, S. T.; Turner, R. W.; Wallace, T. W. *Tetrahedron* **1992**, *48*, 515. (b) Hayes, R.; Ingham, S.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron Lett.* **1991**, *32*, 2953.

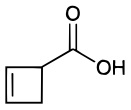
(8) (a) Piers, E.; Lu, Y.-F. *J. Org. Chem.* **1989**, *54*, 2268. (b) Piers, E.; Ellis, K. A. *Tetrahedron Lett.* **1993** *34*, 1875.

(9) Maier, G.; Wiessler, M. *Tetrahedron Lett.* **1969**, 4987.

Scheme 5



of the substituent. A theoretical study was carried out on the rotational selectivity of cyclobutene-3-carboxylic acid, **13**.[3] The carboxyl group is a similarly mild electron-



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withdrawing group (Taft $\sigma_R° = 0.14$): **13** is predicted to slightly prefer outward rotation by 1.5−2.3 kcal/mol. The electron-withdrawing power theoretically correlates nicely with the tendency for inward rotation. For example, protonation increases the electron-withdrawing character enormously, and inward rotation is calculated to be favored by 4.8−6.3 kcal/mol.[3]

In support of this calculation, Jefford and Houk et al.[10] found that thermolysis of methyl benzocyclobutene-7-carboxylate (**14**) with Lewis acid BF_3 in the presence of N-phenyl maleimide afforded a 7:3 mixture of **15** and **16**, favoring inward rotation (Scheme 5). Without BF_3, the formation ratio of **15** and **16** was 1:10. While this ring opening is an eight-electron process, it nonetheless provides good evidence for the reversal of rotational selectivity for four-electron cyclobutene ring opening since they both proceed via conrotatory mechanism. The extent of the reversal was disappointingly small, perhaps due to equilibration of *o*-xylylenes before trapping.

On the basis of this background, both theoretical and experimental studies on the torquoselectivity for 3-acetylcyclobutene was carried out in order to further study the reversal of torquoselectivity.

Theoretical Study

RHF ab initio calculations on the ring opening of 3-acetylcyclobutene, **1**, were performed employing the GAUSSIAN 90 series of programs.[11]

Four transition structures were located for the conversion of **1** to (*E*)- or (*Z*)-3,5-hexadien-2-one with the 3-21G basis set.[12] Transition structures were fully optimized and gave only one imaginary frequency in the harmonic frequency analysis. The energy values calculated were summarized in Table 1. The structures are as shown in Figure 1. Single point calculations were carried out with

Table 1. RHF/3-21G and RHF/6-31G*//3-21G Relative Energy Differences (kcal/mol) in the Transition Structures of the Ring Opening of 3-Acetylcyclobutene

structure	3-21G relative energy	6-31G*//3-21G relative energy
A (outward O-syn[a])	0.0	0.0
B (outward O-anti[b])	+1.6	+1.2
C (inward O-anti)	+1.5	+1.2
D (inward O-syn)	+2.5	+2.9

[a] Syn: carbonyl group directs toward the cyclobutene ring. [b] Anti: carbonyl group directs away from the cyclobutene ring.

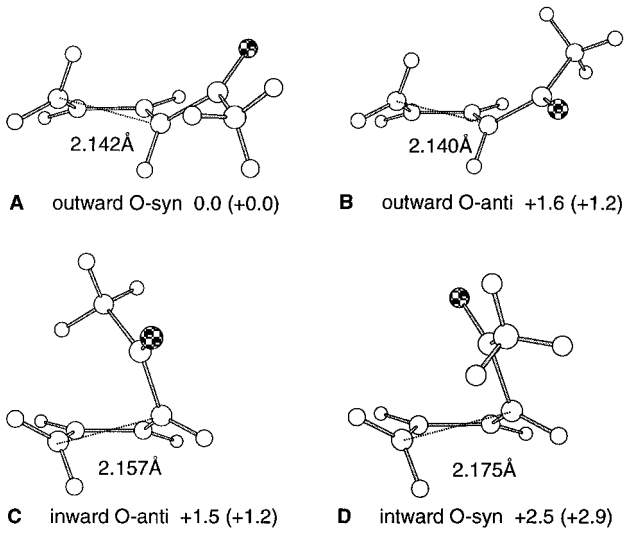


Figure 1. Transition structures of the 3-acetylcyclobutene electrocyclization. Relative energies at the RHF/3-21G and RHF/6-31G*//3-21G (parentheses) levels are shown (kcal/mol).

the 6-31G* basis set[13] on these optimized structures. In the lowest energy outward rotation structure (**A**), the carbonyl oxygen is pointed toward the opening cyclobutene ring, most likely to avoid steric repulsions between the methyl group and the cyclobutene ring, while it is pointed away from the cyclobutene ring in the more stable transition states for inward rotation (**C**). From the energy difference between these two structures, the activation energy difference between inward and outward rotation for 3-acetylcyclobutene was calculated to be 1.2 kcal/mol at the 6-31G*//3-21G level, with outward rotation preferred. This energy difference is calculated to give the product ratio of 85:15(*E*-diene:*Z*-diene) at 80 °C in the gas phase. As will be described later, this prediction proved to be quite close to the experimental result.

These four structures have a narrow range in energy, which reflects that acetyl group possesses a mild electron-withdrawing character that dictates subtle twisting selectivity on the borderline between outward and inward rotations.

Both outward rotation transition structures, **A** and **B**, have shorter breaking bond lengths than the inward rotation transition structures, **C** and **D**, which implies that outward rotation has an earlier transition state.

This tendency, in which the carbonyl group points toward the cyclobutene ring was also found in cyclobutene-3-carboxylic acid (**13**).[3] In both outward and inward rotations, the optimized geometries of **13** have the carbonyl groups pointed towards the cyclobutene ring

(10) Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157.

(11) *GAUSSIAN 90*: Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1990.

(12) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(13) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

Table 2. RHF/3-21G Relative Energy Differences (kcal/mol) in the Transition Structures of the Ring Opening of 3-Acetylcyclobutene with BH_3 Coordination with 3-Acetylcyclobutene Frozen

structure	3-21G relative energy
A-a (outward O-syn B-syn[1])	+2.7
A-b (outward O-syn B-anti[2])	+6.3
B-a (outward O-anti B-syn)	+4.5
B-b (outward O-anti B-anti)	+3.5
C-a (inward O-anti B-syn)	+1.0
C-b (inward O-anti B-anti)	0.0
D-a (inward O-syn B-syn)	+3.0
D-b (inward O-syn B-anti)	+4.9

[a] B-syn: B coordinates from the same side as the methyl group. [b] B-anti: B coordinates from the other side of the methyl group.

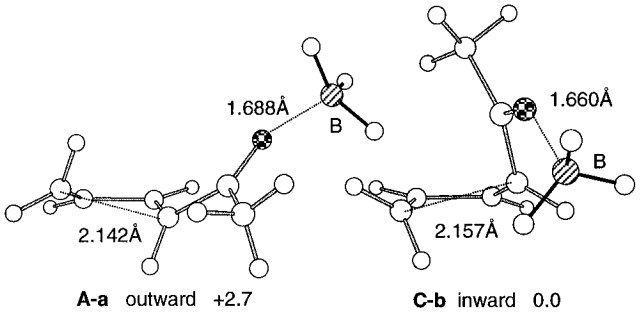


Figure 2. Transition structures for 3-acetylcyclobutene electrocyclization with BH_3 coordination. Relative energies are shown (kcal/mol).

in the lower energy structures. All four structures also have similar energies, probably because carbonyl and hydroxyl oxygens have similar steric and electrostatic interactions with the cyclobutene ring.

In the case of 3-formylcyclobutene, which has a large preference for inward rotation, the oxygen points away from the cyclobutene ring in both inward and outward rotations, presumably since steric interactions between the cyclobutene ring and hydrogen are smaller than for the cyclobutene ring and oxygen.[2,3]

In order to investigate the possibility of reversal of the torquoselectivity for 3-acetylcyclobutene qualitatively, the model calculations were performed using 3-21G basis set with the hypothetical Lewis acid, BH_3, added to the four transition state structures with the 3-acetylcyclobutene geometries frozen. The position and geometry of BH_3 was optimized in each structure. Since the carbonyl oxygen has two lone pairs for coordination of BH_3, eight structures were located altogether. The calculated results are summarized in Table 2. The two lowest structures from inward (**C-b**) and outward rotation (**A-a**)(underlined in Table 2) are shown in Figure 2. As expected, inward rotation is now favored by 2.7 kcal/mol. BH_3 is coordinated from the same side as the cyclobutene ring, while in outward rotation, BH_3 is coordinated from the other side of the carbonyl oxygen. The distances between B and O are slightly shorter by 0.02 Å for inward rotation than for outward rotation, showing that B−O coordination is tighter for inward rotation. Similarly, the structure of the complexation of boron Lewis acid, BH_3 and BF_3, to aldehydes and ketones were examined both theoretically and experimentally earlier. The anti complexations with respect to the bulkier group observed in these references were rationalized based on mostly steric arguments.[21] Here, this preference does not seem clear, presumably due to slightly loosened coordination between

Table 3. RHF/STO-3G* Relative Energy Differences (kcal/mol) in the Transition Structures of the Ring Opening of 3-Acetylcyclobutene with ZnH_2 Coordination with 3-Acetylcyclobutene Frozen

structure	STO-3G* relative energy
A-a′ (outward O-syn Zn-syn[a])	+1.8
A-b′ (outward O-syn Zn-anti[b])	+1.9
B-a′ (outward O-anti Zn-syn)	+2.1
B-b′ (outward O-anti Zn-anti)	+1.5
C-a′ (inward O-anti Zn-syn)	+2.1
C-b′ (inward O-anti Zn-anti)	+2.2
D-a′ (inward O-syn Zn-syn)	+3.5
D-b′ (inward O-syn Zn-anti)	0.0

[a] Zn-syn: Zn coordinates from the same side as the methyl group. [b] Zn-anti: Zn coordinates from the other side of the methyl group.

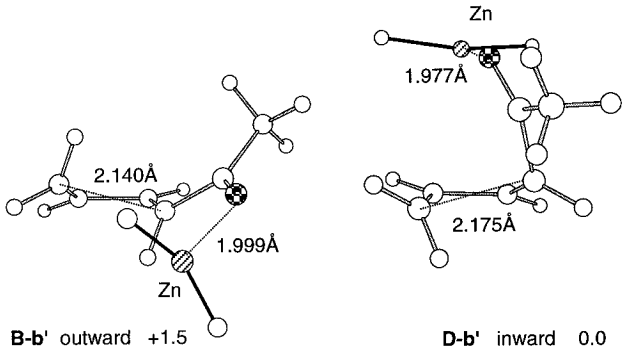


Figure 3. Transition structures for 3-acetylcyclobutene electrocyclization with ZnH_2 coordination. Relative energies are shown (kcal/mol).

O and B compared to aldehydes. For example, the coordination bond length of BH_3 to propanal was calculated to be ~1.704 Å with the 3-21G basis set.[21a] Previous studies also suggest that this structural preference is basis set dependent.

Since the experiments were carried out with zinc halides as catalysts (see later) the same calculations as for BH_3 coordination were also conducted for hypothetical zinc Lewis acids, ZnH_2, and ZnF_2 as model Lewis acids using the STO-3G* basis set,[14] which is the most economical basis set for qualitative analysis. The results are summarized in Table 3. As summarized in Figure 3, for ZnH_2, inward rotation (**D-b′**) is calculated to be favored over outward rotation (**B-b′**) by 1.5 kcal/mol. This energy difference corresponds to a ratio of outward/inward formation rates of 10/90 at 80 °C, which is quite consistent with the experimental result that will be described later. In both transition states, the carbonyl oxygen is pointed opposite to the direction calculated for BH_3. During inward rotation, oxygen is pointed toward the cyclobutene ring, and for outward rotation oxygen is directed away from the ring. In both transition structures, ZnH_2 is coordinated from the same side of the cyclobutene ring instead of the methyl group side. Additionally, ZnH_2 is coordinated in such a way that Zn−H bonds are directed almost perpendicular to C=O plane rather than parallel. This orientation could decrease steric repulsion between Zn−H and the cyclobutene ring.

Calculations for ZnF_2 coordination were also performed (Table 4). The two most stable structures of outward and

(14) (a) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657. (b) Collins, J. B.; Schleyer, P. v. R.; Binkley, J. S.; Pople, J. A. *J. Chem. Phys.* **1976**, *64*, 5142.

Table 4. RHF/STO-3G* Relative Energy Differences (kcal/mol) in the Transition Structures of the Ring Opening of 3-Acetylcyclobutene with ZnF_2 Coordination with 3-Acetylcyclobutene Frozen

structure	STO-3G* relative energy
A-a″ (outward O-syn Zn-syn[a])	+1.4
A-b″ (outward O-syn Zn-anti[b])	+0.7
B-a″ (outward O-anti Zn-syn)	+1.6
B-b″ (outward O-anti Zn-anti)	+1.0
C-a″ (inward O-anti Zn-syn)	+0.9
C-b″ (inward O-anti Zn-anti)	+1.4
D-a″ (inward O-syn Zn-syn)	+1.8
D-b″ (inward O-syn Zn-anti)	0.0

[a] Zn-syn: Zn coordinates from the same side as the methyl group. [b] Zn-anti: Zn coordinates from the other side of the methyl group.

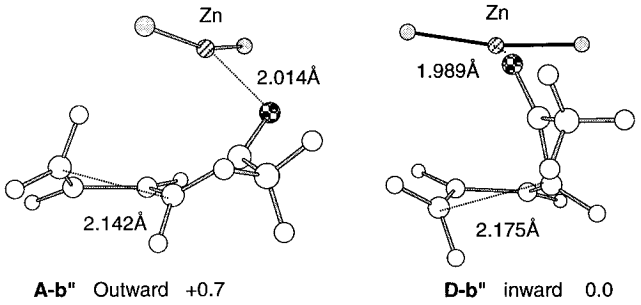


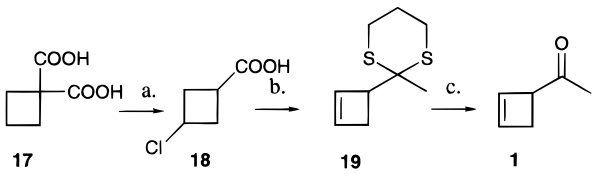
Figure 4. Transition structures for 3-acetylcyclobutene electrocyclization with ZnF_2 coordination. Relative energies are shown (kcal/mol).

inward rotation (**A-b″** and **D-b″**) are in Figure 4. The basic tendency is almost the same as for ZnH_2. Inward rotation (**D-b″**) is favored by 0.71 kcal/mol over outward rotation (**A-b″**). The slightly smaller preference toward inward rotation might arise from the π electron-donating character of F atom rather than its inductive electron-withdrawing character.[4] In both structures, the carbonyl oxygen is pointed toward the cyclobutene ring and ZnF_2 is also coordinated from the same side of the cyclobutene ring. The coordination seems somewhat looser than for ZnH_2, judging from the coordination lengths between the Zn and O: the Zn−O distances are 2.01 (outward) and 1.99 Å (inward) for ZnF_2, while the corresponding distances are 2.00 (outward) and 1.98 (inward) for ZnH_2. As in the case of ZnH_2, Zn−F bonds are also directed almost perpendicular to the C=O plane, which should also minimize the steric interaction described above. For both the coordination of ZnH_2 and ZnF_2, all the structures resulted in narrower energy ranges as compared to the BH_3 coordination. This is suggestive of the weaker coordination of ZnH_2 and ZnF_2, than that of BH_3. In both cases, the Zn−O distances are slightly shorter by ~0.02 Å for inward rotation than outward rotation, which implies these coordinations are tighter in inward rotation than outward rotation, as was the case for BH_3.

Experimental Study

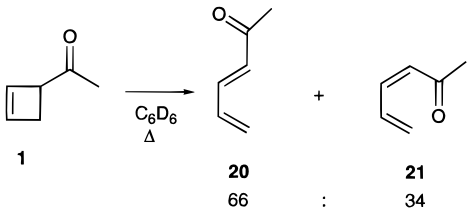
3-Acetylcyclobutene was synthesized as shown in Scheme 6. The commercially available cyclobutane-1,1-dicarboxylic acid (**17**) was monochlorinated selectively at the 3-position, followed by decarboxylation to afford 3-chlorocyclobutanecarboxylic acid (**18**) as a mixture of stereoisomers in 46% yield.[15] Treatment of this acid with 2 equiv of methyllithium gave the methyl ketone (22% yield). This methyl ketone was protected with 1,3-propanedithiol and dehydrochlorinated (~40%, for two steps) to afford the olefinic thioketal **19**. The deprotection of this olefin was performed with methyl iodide in aqueous acetonitrile in the presence of Na_2CO_3 to produce **1** in 27% yield.

Scheme 6



a. (1)SO_2Cl_2 / $(PhCO)_2O_2$, (2)~CO_2, 46%, 2steps
b. (1)2eq. MeLi, ~22%, (2)1,3-propanedithiol / $BF_3.OEt_2$, ~quant. (3)t-BuOK/DMSO, ~70%
c. MeI / aq.CH_3CN / Na_2CO_3, ~27%

Scheme 7

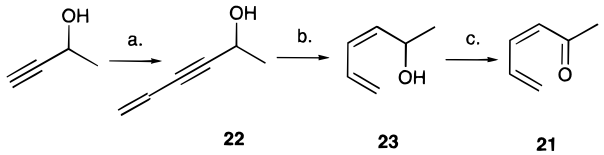


When acetylcyclobutene (**1**) was heated in benzene-d_6 in a sealed NMR tube at the reflux temperature overnight, it gave (*E*)-3,5-hexadien-2-one (**20**) almost exclusively. This diene **20** has a ^{1}H-NMR spectrum identical to the reported data.[16] However, this result does not necessarily signify a kinetic preference of the ring opening of **1** due to the expected ease of isomerization of the (*Z*)-3,5-hexadien-2-one (**21**). In order to examine whether the *Z*-diene **21** was formed but lost by equilibration, the thermolysis experiments were carried out by heating a benzene-d_6 solution of 3-acetylcyclobutene in a sealed NMR tube in an NMR probe. ^{1}H-NMR spectra of this reaction mixture were recorded periodically (every three minutes) at variable temperatures during very early stages of the ring openings. The determination of the product ratio was made on the basis of the integration of the singlet signal of the acetyl group in ^{1}H-NMR spectra.

Upon heating **1** at reflux temperature in benzene-d_6 (80 °C), it was observed that the product ratio of the two dienes **20** and **21** is 66:34 (±5)(*E*-diene:*Z*-diene) throughout the first ~100 min period, namely the beginning stage of this reaction (Scheme 7). This result should reflect the kinetic result, that is, the outward rotation is slightly preferred over the inward rotation by 1.2 kcal/mol. This kinetic result of the product ratio seems fairly consistent with the theoretical prediction: **20** and **21** should be formed in a ratio of ~85:15 at 80 °C (see above). This product ratio was observed from the first spectrum in which the ring opening started and remained unchanged throughout the first 100 min.[23] Considering the fact that this ring opening is a first-order reaction, this product ratio should correspond to the kinetic results. With further heating for several hours, until **1** is consumed, this product ratio gradually changed to ~95:5(±5)(*E*-

(15) Nevill, W. A.; Frank, D. S.; Trepka, R. J. *J. Org. Chem* **1962**, *27*, 422.
(16) Gavrishova, T. N.; Shastin, A. V.; Balenkova, E. S.; Novikov, N. A. *Zh. Org. Khim.* **1987**, *23(6)*, 1322.

Scheme 8



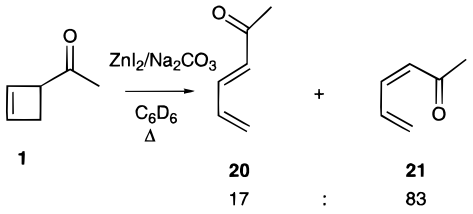
a. vinyl bromide/CuI-$(Ph_3P)_2PdCl_2$ / Et_2NH or $^iPr_2NH$ 25°C. (23%)
b. Zn(Cu/Ag), MeOH-H_2O, 25°C. (~73%)
c. activated MnO_2,25°C. (~quant.)

diene:*Z*-diene) to increase the proportion of the more stable *E*-diene **20**. This ratio is the result of thermodynamic equilibration of the initial kinetically determined ratio. After about 6 h, the *E*-diene **20** was the only detectable product. The similar thermodynamic control of stereochemistry was described before for the phenyl ketone **12**.[9]

An authentic sample of the minor product, (*Z*)-3,5-hexadien-2-one, **21**, was prepared for comparison in a separate experiment as shown in Scheme 8.[17−19] Although the procedure for preparation of the *Z*-diene **21** has already been reported,[20] an easier method was developed. The 3-butyn-2-ol was coupled with vinyl bromide catalyzed by copper(I), according to Sonogashira's procedure.[17,18] The resultant enyne **22** was submitted to stereoselective reduction of the triple bond,[19] followed by oxidation of the resultant allylic alcohol **23** as depicted in Scheme 8. This ^{1}H-NMR spectrum of **21** was identical to the reported ^{1}H-NMR data.[20]

The influence of Lewis acids on the stereochemistry of the ring opening was also studied. The Lewis acid $BF_3{\cdot}OEt_2$, which is soluble in organic solvents, gave only the *E*-diene smoothly at room temperature on completion of the reaction after 6 h. However, this ring opening is easily influenced by acid isomerization to afford more stable *E*-diene **20**. In fact, in a separate experiment, rapid isomerization of *Z*-diene **21** to *E*-diene **20** was observed at room temperature upon addition of $BF_3{\cdot}OEt_2$ to **21** in C_6D_6 solution. Therefore two-phase reaction with 1 equiv of a solid Lewis acid, ZnI_2, was performed in the presence of a slight molar excess of Na_2CO_3 in deuterated benzene. A thermolysis experiment was carried out in the same manner as the thermolysis of 3-acetylcyclobutene. Upon heating this mixture for 30 min at 80 °C in an NMR probe, a reversal of torquoselectivity was observed. The product ratio was 17:83(±5) throughout this period in favor of the *Z*-diene **21** (Scheme 9).[22] Therefore for the same reason stated above, the kinetic ratio is concluded to be 17:83 (*E*-diene:*Z*-diene).[23] Without Na_2CO_3, rapid isomerization to the *E*-diene **20** occurs

Scheme 9



and the solution turned brown, presumably due to the formation of HI and I_2.

The influence of other Lewis acids was also investigated. Aluminum trichloride and trimethylsilyl triflate immediately afforded complex mixtures upon heating. In contrast, catalysis with tin(II) triflate gave exclusively the *E*-diene while zinc chloride or silica gel did not affect the product ratio. Finally treatment with zinc bromide increased the ratio of stereoisomers to approximately 1:1. Hence experimentally, zinc iodide turned out to be the most effective Lewis acid at reversing the torquoselectivity.[24]

As pointed out earlier, these results are most easily interpreted in light of the practical difficulty in detecting the thermodynamically less stable *Z*-diene **21** which isomerizes to the *E*-diene **20** quite rapidly with a catalytic amount of acid, which is inevitable even at room temperature.

Conclusion

The rotational selectivity on the thermal ring opening of 3-acetylcyclobutene (**1**) was predicted by ab initio calculations. Calculations correctly predicted that Lewis acids can reverse the selectivity. All of these predictions were verified by the experiments. This is the first unambiguous experimental evidence that Lewis acid, ZnI_2, reverses the rotational selectivity ("torquoselectivity") from outward rotation to inward rotation, during the electrocyclic ring opening of a substituted cyclobutene.

Experimental Section

General. ^{1}H-NMR spectra were recorded on Bruker AM360, AM500, or AF200 instruments. The residual proton peak of the deuterated solvent was used as the chemical shift standard. Mass spectra were obtained on an Associated Electrical Industries Double Focusing Mass Spectrometer Model MS-902.

All the thermolyses were carried out by variable temperature NMR in sealed tubes in an NMR probe in benzene-d_6 (dried over 3 Å molecular sieves). The NMR tubes were washed with 10% aqueous ammonium, dried in an oven, and sealed under a nitrogen atmosphere prior to thermolyses. The product ratios were determined directly by integration of the singlet signals from the acetyl protons of the resulting *E*-diene **20** and *Z*-diene **21** in the ^{1}H-NMR spectra of the reaction mixtures. The dienes **20** and **21** were identified on the basis of the reported ^{1}H-NMR spectrum data.[16,20] Thermolyses were conducted in duplicate, and the results were observed to be reproducible.

Preparation of 3-Acetylcyclobutene (1). 2-(3-cyclobutenyl)-2-methyl-1,3-dithiane (19). 3-chlorocyclobutanecarboxylic acid (**18**) was prepared as a mixture of two stereoiso-

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(18) Mushegyan, A. V.; Kinoyan, F. S. *Arm. Khim. Zh.* **1972**, *25(1)*, 3.
(19) Avignon-Tropics, M.; Pougny, J. R. *Tetrahedron Lett.* **1989**, *30*, 4951.
(20) Wolfhugel, J.; Maujean, A.; Chuche, J. *Tetrahedron Lett.* **1973**, *18*, 1635.
(21) (a) LePage, T. J.; Wiberg, K. B. *J. Am Chem. Soc.* **1988**, *110*, 6642. (b) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am Chem. Soc.* **1986**, *108*, 2405.
(22) During this period of reaction, remarkable reaction rate acceleration was not observed.
(23) These product ratios were determined on the basis of the relative intensities of the singlet signals from the proton of acetyl groups of *E*-diene **20** and *Z*-diene **21** at regular time intervals. The plot of the ratios of **20** to **21** versus reaction time gave nearly flat lines for both uncatalyzed and catalyzed thermolyses during the initial stage of the ring openings. The kinetic ratios were determined by extrapolating these plots to time zero.
(24) Considering the fact that only zinc Lewis acids induced inward rotation effectively, alternative interpretation might be possible on the basis of the "softness" of these acids. ZnI_2, $ZnBr_2$, and BH_3 are all classified as soft Lewis acids.[25] However, this argument would require more systematic theoretical study.
(25) Pearson, R. G. *Struct. Bonding (Berlin)* **1993**, *80*, 1.

mers by the reported procedure[2] from commercially available cyclobutane-1,1-dicarboxylic acid (**17**).

This carboxylic acid **18** (1.68 g, 12.52 mmol) was dissolved in 5 mL of anhydrous Et_2O in a 1000 mL round bottomed flask equipped with a reflux condenser and a spin bar. A solution of 1.4 M methyllithium in diethyl ether (20.6 mL, 28.84 mmol, 2.3 equiv) was added dropwise at such a rate as to maintain steady reflux, during which period suitable precautions were taken to vent the methane formed. The consumption of carboxylic acid **18** was monitored by TLC. Saturated aqueous NH_4Cl was added dropwise to the reaction mixture with vigorous stirring to destroy excess methyllithium. The ether layer was separated, washed with saturated NH_4Cl solution and water, and dried over anhydrous magnesium sulfate. The ether was removed in vacuo, and the residue was chromatographed on silica gel to afford a mixture of two stereoisomers of the corresponding methyl ketone (365 mg) in 22% yield from **18**. This methyl ketone (365 mg, 2.76 mmol) was dissolved in 15 mL of CH_2Cl_2. 1,3-Propanedithol (446 mg, 4.13 mmol, 1.5 equiv) and 0.1 mL of $BF_3{\cdot}OEt_2$ was added to this solution under a nitrogen atmosphere at room temperature. After 13 h, 5 mL of 5% aqueous NaOH was added. The organic layer was separated, washed with water, brine, and dried over anhydrous $MgSO_4$. Evaporation and subsequent silica gel column chromatography afforded corresponding thioketal as a mixture of two stereoisomers in quantitative yield. This thioketal (613 mg, 2.76 mmol) and t-BuOK (616 mg, 5.50 mmol), which was dried previously at 70 °C at 0.1 mmHg for 24 h, were stirred in freshly distilled DMSO (4.5 mL) under a nitrogen atmosphere at 40−50 °C for 19 h. The reaction mixture was poured into 50 mL of ice−water, extracted with Et_2O (×3), washed with water (×2) and brine, and dried over anhydrous $MgSO_4$. Silica gel column chromatography afforded 358 mg of **19** as a colorless oil (70% yield.). ^{1}H-MNR ($CDCl_3$, 200 MHz): 1.59 (3H, s), 1.94 (2H, m), 2.53 (2H, m), 2.83 (4H, m), 3.51 (1H, m), 6.03 (1H, br. d), 6.16 (1H, br. d). ^{13}C-NMR ($CDCl_3$, 50 MHz): 24.11, 25.29, 26.28, 31.14, 32.95, 51.44, 53.42, 137.07, 137.12. HRMS: calcd for $C_9H_{14}S_2$ 186.0537, found 186.0539 (M^+).

3-Acetylcyclobutene (1). The thioketal **19** (471 mg, 2.53 mmol) was dissolved in 6.1 mL of CH_3CN containing 1.2 mL of H_2O and 3.6 g of Na_2CO_3. This mixture was treated with 2.5 mL of MeI at room temperature; the flask was covered with aluminum foil to protect from light. After 3 days, ether and H_2O were added, and the mixture was extracted with ether (×3), washed with aqueous $Na_2S_2O_3$ and brine, and dried with anhydrous $MgSO_4$. The ether was removed under reduced pressure (20 mmHg) at 5 °C to afford 65 mg of **1** as a volatile, colorless oil (27% yield). ^{1}H-NMR (C_6D_6, 360 MHz): 1.75 (3H, s), 2.41 (1H, ddd, J = 13.8, 1.0, 2.0), 2.52 (1H, ddd, J = 13.8, 0.9, 5.4), 3.37 (1H, m), 5.85 (1H, m), 5.93 (1H, m). ^{13}C-NMR (C_6D_6, 50 MHz): 26.93 (q), 33.92 (t), 54.56 (d), 135.77 (d), 139.16 (d), 208.90 (s). HRMS: calcd for C_6H_8O 96.0575, found 96.0575 (M^+).

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Supporting Information Available: Total energies and geometries for the transition structures A-D, Aa-Db, Aa′-Db′, and Aa″-Db″ are in Tables A-D, Aa-Db, Aa′-Db′, and Aa″-Db″. Copies of NMR spectra of compounds **1** and **19** are also available (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS; see any current masthead page for ordering information.

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