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Lewis Acid Catalyzed [2σ+2σ] Cycloreversion Reaction of Strained Cage Ketones to Triquinane Skeletons: Kinetic Evidence for a Large Acceleration of the Reaction Owing to Stereoelectronic Requirement

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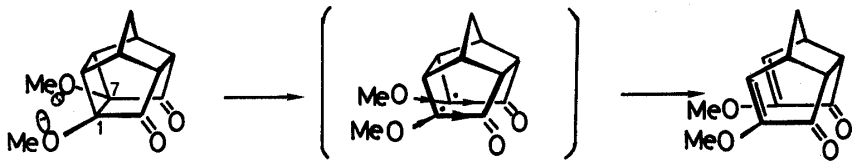
Cookson's pentacyclic cage diketones substituted with an electron-donating group (**1b—e**) underwent a remarkably fast [2σ+2σ] cycloreversion reaction under various Lewis acid catalyzed conditions. The high reactivity of these cage ketones is discussed in terms of push-pull type interactions on the basis of large substituent effects and kinetic measurements.

Keywords——cycloreversion reaction; Cookson's pentacyclic cage diketone; Lewis acid catalyst; electron-donating group; stereoelectronic effect

Strained cage molecules have been attracting a considerable attention in synthetic and physical organic chemistry,[1] since such compounds play important roles in natural product syntheses,[2] solar energy utilization,[3] and in understanding of many aspects of synthetic organic chemistry.[4] It is noteworthy that photochemical [2π+2π]cycloaddition followed by thermal [2σ+2σ]cycloreversion were skillfully applied to a synthesis of polyquinane antitumor agents such as coriolin and hirsutene.[2a-d] The thermal [2σ+2σ]cycloreversion is, however, symmetrically forbidden[5] and generally requires extremely high temperatures.[2e,3c]

In relation to the mode of reaction, we have previously reported that bond elongations caused by "enhanced through-bond interaction" of π-lone pairs and "synergetic capto-dative diradical stabilization" play a decisive role in the cycloreversion of the 1,7-dimethoxy-substituted Cookson's birdcage derivative **1a** under thermal conditions (Chart 1).[4d]



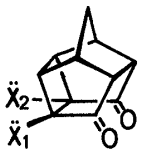
1a

Chart 1

In this paper, we report the Lewis acid catalyzed [2σ+2σ]cycloreversion of monosubstituted birdcage diketones with an electron-donating group (SR, OR, NR_2) at C(1), **1b—e**, where push-pull type interaction in the cage system plays an important role in increasing the reactivity.

Preparation of Cookson's Birdcage Derivatives 1

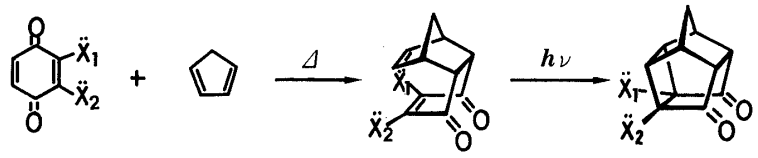
The 1-substituted derivatives were synthesized by the method previously reported (Chart 3).[2c,6] Monosubstituted *p*-benzoquinones were prepared by oxidation of the corresponding



	$\ddot{X}_1$	$\ddot{X}_2$
a	MeO	MeO
b	MeO	H
c	MeS	H
d	PhS	H
e	NHAc	H
f	H	H
g	Me	H

Chart 2

phenol or hydroquinone (see the Experimental section) and the yields of these reactions were generally high.



1a—h

Chart 3

TABLE I. Physical and Spectral Data for Diels–Alder Adducts of Cyclopentadiene and 2-Substituted *p*-Benzoquinones

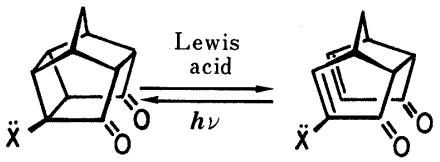
Quinone	Yield (%)	mp (°C)	^{1}H-NMR δ (in $CDCl_3$)	IR cm^{-1} (in $CHCl_3$)
2-OMe	88	97—99.5	1.32—1.58 (m, 2H), 3.20—3.36 (m, 2H), 3.40—3.68 (m, 2H), 3.72 (s, 3H), 5.90 (s, 1H), 6.04—6.20 (m, 2H)	1698, 1650, 1610
2-SMe	81	146—148	1.32—1.54 (m, 2H), 2.21 (s, 3H), 3.08—3.40 (m, 2H), 3.40—3.68 (m, 2H), 6.08 (br s, 2H), 6.25 (s, 1H)	1685, 1650, 1565
2-SPh	92	134.5—135	1.20—1.52 (m, 2H), 3.02—3.68 (m, 4H), 5.82 (s, 1H), 6.00—6.28 (m, 2H), 7.42 (br s, 5H)	1680, 1645, 1565
2-NHAc	Quant.	145.5—147 (dec.)	1.36—1.60 (m, 2H), 2.20 (s, 3H), 3.20—3.40 (m, 2H), 3.48—3.68 (m, 2H), 5.92—6.24 (m, 2H), 7.60 (s, 1H), 8.06 (br s, 1H)	1720, 1680, 1655, 1620

Lewis Acid Catalyzed [$2\sigma+2\sigma$]Cycloreversion of 1b—e

It is well known that the Lewis acid catalyzed rearrangements of polycyclic systems give the thermodynamically most stable isomer.[7] We have found that the 1,7-dimethoxy-substituted cage diketone (**1a**) underwent cycloreversion even under reflux in benzene,[4d] whereas the 1-methoxy-substituted compound (**1b**) was quite stable under the same conditions. Surprisingly, however, the treatment of **1b** with various Lewis acids resulted in cycloreversion under mild reaction conditions (Chart 4 and Table III). Among the substituent examined, the compounds with an electron-donating group at C(1) (**1b—e**) were found to be extremely reactive with various Lewis acids. These reactions are strongly influenced by the Lewis acid and can be controlled by choosing an appropriate Lewis acid catalyst: $TiCl_4$ seems to be too strong, and $PdCl_2$ too weak. Stronger Lewis acids gave greater amounts of complex

TABLE II. Physical and Spectral Data for Cookson's Cage Ketones (Pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undeca-8,11-diones)

Substituent	Yield (%)	mp (°C)	^{1}H-NMR δ (in $CDCl_3$)	IR cm^{-1} (in $CHCl_3$)
1-OMe	93	72—74	1.88—2.13 (m, 2H), 2.62—2.78 (m, 2H), 2.79—3.32 (m, 5H), 3.46 (s, 3H)	1768, 1745
1-SMe	81	91—91.5	2.00 (m, 2H), 2.12 (s, 3H), 2.68—3.12 (m, 5H), 3.16—3.36 (m, 2H)	1765, 1750
1-SPh	90	99—101	1.98 (m, 2H), 2.52—3.38 (m, 6H), 7.33—7.37 (m, 5H)	1765, 1745
1-NHAc	Quant.	Oily	1.86—2.19 (m, 2H), 2.04 (s, 3H), 2.52—3.64 (m, 7H), 6.38 (br s, 1H)	3370, 1750, 1670



1b—e **2b—e**

Chart 4

TABLE III. Lewis Acid Catalyzed Cycloreversion of **1b—e**

Compd.	X_1	X_2	Lewis acid (eq)	Solvent	Temp. (°C)	Yield (%)
1a	OMe	OMe	None	C_6H_6	90	Quant.[a]
1b	OMe	H	$BF_3 \cdot Et_2O$ (1.0)	$CHCl_3$	−5	Quant.
			$BF_3 \cdot Et_2O$ (0.1)	C_6H_6	r.t.	Quant.
			$TiCl_4$ (1.0)	$CHCl_3$	−55	35
			$TiCl_4$ (0.1)	$CHCl_3$	−5	68
			$PdCl_2$ (0.1)	C_6H_6	r.t.	64
1c	SMe	H	$BF_3 \cdot Et_2O$ (1.0)	$CHCl_3$	−5	Quant.
			$BF_3 \cdot Et_2O$ (0.1)	$CHCl_3$	−5	Quant.
			$TiCl_4$ (1.0)	$CHCl_3$	−55	53
1d	SPh	H	$BF_3 \cdot Et_2O$ (1.0)	C_6H_6	r.t.	69
			$BF_3 \cdot Et_2O$ (0.1)	C_6H_6	r.t.	15
			$BF_3 \cdot Et_2O$ (0.1)	C_6H_6	Reflux.	18
			$TiCl_4$ (1.0)	$CHCl_3$	Reflux.	37
1e	NHAc	H	$BF_3 \cdot Et_2O$ (1.0)	C_6H_6	r.t.	[b]
			$BF_3 \cdot Et_2O$ (0.1)	$CHCl_3$	Reflux.	63

a) Ref. 4*d*. *b*) After 10 h, the reaction did not proceed.
r.t. = room temperature.

products.

The structures of the cycloreversion products **2b—e** were consistent with the spectral data (Table IV) and were further confirmed by the photocyclization back to **1b—e**. In contrast, **1f** ($X_1 = X_2 = H$) was quite stable under the some conditions. Quite recently, Mehta and his co-workers obtained the same result for **1b**, and they also emphasized the importance of the methoxy group on C(1).[8]

Anyways, considering the characteristic substituents such as oxygen, nitrogen, and sulfur, the cyclobutane ring-cleaving reaction seems to be strongly affected by an electron-

TABLE IV. Physical and Spectral Data for Triquinanes, **2b**–**e**

Compd.	mp (°C)	^{1}H-NMR[a] δ (in $CDCl_3$)	IR (cm^{-1}, in $CHCl_3$)
2b	102—103	1.85 (dt, J=14.7, 2.6 Hz, 1H), 2.31 (dt, J=14.7, 9.4 Hz, 1H), 3.20—3.60 (m, 4H), 3.63 (s, 3H), 5.89 (dd, J=6.0, 2.7 Hz, 1H), 6.16 (d, J=3.0 Hz, 1H), 7.50 (dd, J=6.0, 2.5 Hz, 1H)	1730, 1630
2c	118.5—120	1.89 (dt, J=14.5, 2.0 Hz, 1H), 2.27 (s, 3H), 2.30 (dt, J=14.5, 9.0 Hz, 1H), 3.12—3.67 (m, 4H), 5.94 (dd, J=5.5, 2.0 Hz, 1H), 6.73 (d, J=2.5 Hz, 1H), 7.45 (dd, J=5.5, 2.5 Hz, 1H)	1710, 1575
2d	Oily	0.95 (dt, J=14.0, 2.5 Hz, 1H), 1.34 (dt, J=14.0, 9.5 Hz, 1H), 2.49—2.96 (m, 4H), 5.72 (dd, J=6.0, 3.0 Hz, 1H), 6.20 (d, J=3.0 Hz, 1H), 6.52 (dd, J=6.0, 2.5 Hz, 1H), 6.93—7.40 (m, 5H)	1725, 1585
2e	176—178	0.80—1.40 (m, 2H), 1.52 (s, 3H), 2.56—2.96 (m, 4H), 5.61 (dd, J=5.5, 2.0 Hz, 1H), 6.72 (dd, J=5.5, 2.5 Hz, 1H), 7.20 (br s, 1H), 7.40 (d, J=2.5 Hz, 1H)	1735, 1710, 1640

a) Solvents: $CDCl_3$ for **2b** and **2c**, C_6D_6 for **2d**, $CDCl_3+C_6D_6$ for **2e**.

TABLE V. Rates of Rearrangement Catalyzed by $BF_3 \cdot Et_2O$

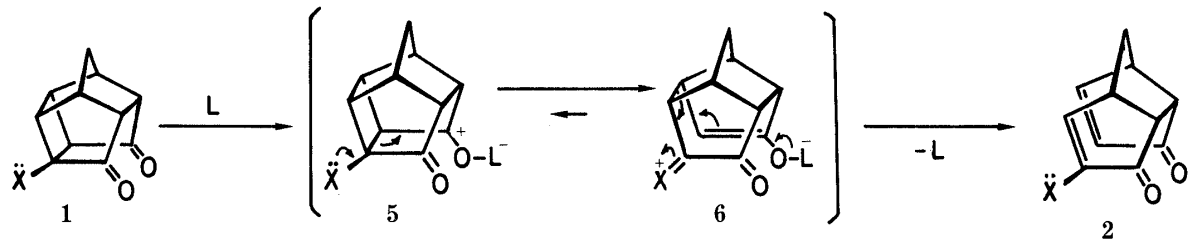
Compd.	X_1	10^2-[$BF_3 \cdot Et_2O$] (M)	Temp. (°C)	$10^5 \cdot k_1$ (s^{-1})	$10^3 \cdot k_2$ ($s^{-1} \cdot M^{-1}$)
1b	OMe	1.76	30.0	35.3	8.8
		1.23	30.0	16.0	
		0.70	30.0	5.7	
		0.35	30.0	2.3	
1c	SMe	3.09	30.0	1990	45
		2.16	30.0	1620	

donating group at C(1). In this connection, Yonemitsu *et al.*[9] reported a novel acid catalyzed cycloreversion reaction of a strained cage compound where a methyl group is essential to stabilize the cationic intermediate. Mehta *et al.*[10] showed that the methyl-bearing **1g** underwent 1,2-rearrangement.

Reaction Kinetics

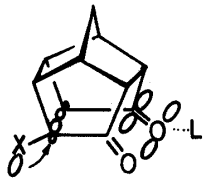
Kinetic data were collected by following the increase of absorption at 260 nm (for **1b**) or 300 nm (for **1c**) due to the enone moiety of the product **2** (Table V). The rates of the reaction are roughly proportional to the concentration of catalyst, $BF_3 \cdot Et_2O$. As can be seen in Table V, **1c** reacted about 5 times faster than **1b**. This cycloreversion reaction presumably occurred through the pathway depicted in Chart 5. Among the substituents examined, the reactivity toward $BF_3 \cdot Et_2O$ could be roughly estimated to be in the order **1c** > **1b** > **1d** ≫ **1e** (Table V). The above results seem to reflect the order of relative electron donating ability of the lone pair.

As shown in Chart 6, the interaction between the lone-pair of the hetero atom and the C(1)–C(7) bond and also between the C(1)–C(7) bond and the carbonyl with assistance from the Lewis acid might cause the selective cleavage of the bond. This interaction is an example of



L : Lewis acid

Chart 5



L : Lewis acid

Chart 6

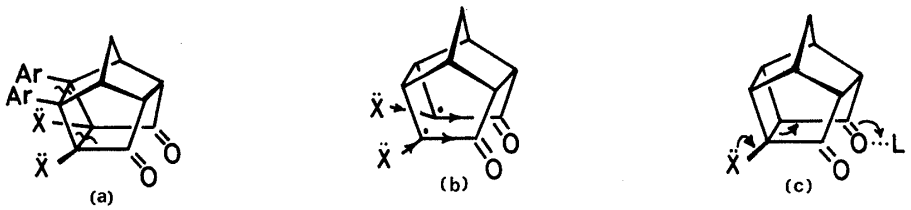


Fig. 1. Schematic Illustration of Factors Participated Affecting the Cycloreversion Reaction of Cookson's Cage Ketones

(a) through-bond interaction, (b) capto-dative radical stabilization, (c) stereoelectronic effect.

the well-known stereoelectronic effect,[11,12] where a lone-pair plays an important role in bond scission. In the case of **1d** ($X_1 = SPh$, $X_2 = H$), the lone-pair of the sulfur atom should be delocalized on the phenyl ring to decrease the reactivity. Furthermore, the lower reactivity of **1e** reflects a neighboring effect of the electron-withdrawing acetyl substituent.

It is supposed that in the case of Cookson's diketone **1**, the primarily cleaved C(1)–C(7) bond is rigidly fixed in parallel to C(8) carbonyl π-orbital and the C(1) lone pair can orient anti-periplanar to C(1)–C(7) as shown in Chart 6 to cause the preferential cleavage of this bond.[13] Thus, the intermediate **6** will undergo C(2)–C(6) bond scission to give the thermodynamically stable bis-enone **2**.

In conclusion, we propose that there are three controlling factors in the cycloreversion reaction of Cookson's cage diketone derivatives; the first one is bond-weakening by an "enhanced through-bond interaction" involving the lone pair or phenyl π-orbitals (Fig. 1(a));[4c,d] the second is the synergetic capto-dative stabilization of the diradical intermediate in the thermally induced reaction (Fig. 1(b));[4d] the third is the anti-periplanar orientation of push-pull functional groups (Fig. 1(c)), especially under catalytic conditions.

Experimental

The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. The

proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a JEOL PS-100 spectrometer with Me_4Si as an internal standard; chemical shifts are expressed in δ values. The infrared (IR) spectra were determined with a JASCO IRA-1 infrared spectrometer. All new products gave reasonable elemental analyses. A Hitachi EPS-3T spectrophotometer was used to measure the rates of cycloreversion. Column chromatography was done by using E. Merck Kieselgel 60 (70—200 mesh) as the stationary phase.

Preparation of Monosubstituted *p*-Benzoquinones——(1) 2-Methoxy-*p*-benzoquinone and 2-acetamido-*p*-benzoquinone were prepared by oxidation of the corresponding phenols with Fremy's salt[15] as described below.

General Procedure: A phenol (1 mmol) was dissolved in $CHCl_3$ (20 ml) and potassium nitrosodisulfonate (Fremy's salt, 0.6 g) in H_2O (70 ml) containing sodium acetate (0.4 g) was added dropwise at 0 °C during 1—2 h. The reaction mixture was stirred at 0 °C for 1 h. The organic layer was separated and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography. 2-Methoxy-*p*-benzoquinone: yield 90%, mp 134—139 °C (lit.[15] 139—140 °C). ^{1}H-NMR ($CDCl_3$) 3.84 (s, 3H), 5.97 (br s, 1H), 6.72 (d, J=1.0 Hz, 2H). IR (Nujol) 1685, 1652 cm^{-1}. 2-Acetamido-*p*-benzoquinone: yield 89%, mp 143—145 °C. ^{1}H-NMR ($CDCl_3$) 2.20 (s, 3H), 6.77 (br s, 2H), 7.60 (br s, 1H). IR (Nujol) 1725, 1645 cm^{-1}.

(2) 2-Phenylthio-*p*-benzoquinone: 2-Phenylthio-*p*-benzoquinone was prepared by the following method. Thiophenol (5.2 ml, 50 mmol) in ether (*ca.* 20 ml) was added dropwise to a solution of *p*-benzoquinone (5.4 g, 50 ml) in $CHCl_3$ at 0 °C during 30 min. The reaction mixture was stirred at 0 °C until the materials were consumed, then extracted with 5% NaOH (50 ml × 2). The aqueous layer was neutralized with conc. HCl, and extracted with $CHCl_3$ (50 ml × 4). The chloroform layer was separated and dried over $MgSO_4$. After the solvent had been removed under reduced pressure, the residue was purified by silica gel column chromatography to give 2-phenylthiohydroquinone as a red oil. A mixture of 2-phenylthiohydroquinone (2.19 g, 10 mmol) and phenyliodine bis(trifluoroacetate)[16] (4.3 g, 10 mmol) in 15 ml acetone was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give 2-phenylthio-*p*-benzoquinone; yield 43% (from *p*-benzoquinone), mp 107—110 °C. ^{1}H-NMR ($CDCl_3$) 5.91 (d, J=2.0 Hz, 1H), 6.72—6.79 (m, 2H), 7.51 (s, 5H). IR (Nujol) 1670, 1640 cm^{-1}.

(3) 2-Methylthio-*p*-benzoquinone: The corresponding phenol was synthesized by following the reported method.[17] Oxidation of the phenol was done as described previously:[18] yield 98%, mp 146—149 °C. ^{1}H-NMR ($CDCl_3$) 2.34 (s, 3H), 6.37 (s, 1H), 6.79 (br s, 2H). IR (Nujol) 1670, 1647 cm^{-1}.

General Procedure for the Preparation of Diels–Alder Adducts of *p*-Benzoquinone Derivatives with Cyclopentadiene——A suspension of a *p*-benzoquinone derivative (1 mmol) and an excess of cyclopentadiene (3 eq) in dry benzene was stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography. The yield and spectral properties are listed in Table I.

Photocyclization of the [4+2]Adduct——A solution of the [4+2]cycloadduct (5×10^{-3} mol) in dry benzene was irradiated with a 400 W high-pressure mercury lamp under argon at room temperature. Consumption of the starting material was confirmed by thin-layer chromatography (TLC), and the solution was evaporated *in vacuo*. The residue was chromatographed on silica gel to give the pure photoproduct **1**. The spectral properties are summarized in Table II.

Lewis Acid Catalyzed Cycloreversion of Cage Compounds (1b—e)——General Procedure: A Cookson's diketone **1b—e** (1 mmol) was dissolved in 3 ml of $CHCl_3$ or dry benzene, and the Lewis acid was added dropwise with stirring under the condition listed in Table III. In the case of reaction with $BF_3 \cdot Et_2O$ or $TiCl_4$, the reaction mixture was quenched with MeOH. After filtration, the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel. Physical and spectral properties of the product are listed in Tables III and IV, respectively.

Kinetics of Acid Catalyzed Cycloreversion of Cage Compounds 1b and 1c——A chloroform solution of **1b** (7.2×10^{-5} M) or **1c** (12.5×10^{-5} M) was prepared. Various concentrations of the catalyst, $BF_3 \cdot Et_2O$, were also prepared. The rates of the acid-catalyzed cycloreversion of **1** were determined in thermostated 10 × 10 mm quartz cells by following the increase in the absorption at 260 nm (for **1b**) or 300 nm (for **1c**) due to the enone moiety. The first-order rate constants k_1 were calculated by the least-squares method. The second-order rate constants were calculated from the slope. The results are summarized in Table V.

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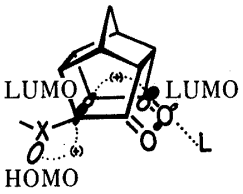

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