# Regioselectivity on Electroreductive Transannular Reaction of 7-Methylenebicyclo[3.3.1]nonan-3-one

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A competitive transannular reaction occurred to give 7-methyltricyclo[3.3.1.$0^{3,7}$]nonan-3-ol (**5**) and 1-adamantanol (**6**) in the non-mediated electroreduction of 7-methylenebicyclo[3.3.1]nonan-3-one (**1**) in *N*,*N*-dimethylformamide. The apparent temperature dependence of the regioselectivity of the reaction may be attributed to the competitive operation of both kinetic and thermodynamic controls in the cyclization of the ketyl radical anion. The differences in the parameter of activation between the 5-exo- and 6-endocyclizations of $\mathbf{1}^{\bullet-}$, $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ and $\Delta\Delta S^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$, were evaluated to be –3.1 kcal mol$^{-1}$ and –11 cal mol$^{-1}$ K$^{-1}$, respectively. Semiempirical PM3 (RHF and UHF) calculations were also carried out to elucidate the reaction mechanism.

Electroreduction of $\delta,\varepsilon$-unsaturated ketones has attracted a great deal of interest as a useful synthetic method of *trans*-methylcyclopentyl alcohols.[1] Regioselectivity of the cyclization of $\delta,\varepsilon$-unsaturated ketyl radicals was derived from the kinetic preference of the 5-exocyclization of 5-hexenyl radicals (Baldwin's rules).[2] The stereoselectivity was controlled by the steric and the electrostatic repulsion between the eclipsed methylene terminal carbon having an odd electron and the negatively charged oxygen atom.[1]

7-Methylenebicyclo[3.3.1]nonan-3-one, (**1**), containing a $\delta,\varepsilon$-unsaturated carbonyl unit in itself, exists in the double-chair conformation in which both π-electron moieties are on the same plane of symmetry and face each other. The intramolecular through-space interaction between two π-orbitals of **1** which was revealed in the carbon-13 NMR chemical shifts[3] affords characteristic reactivities in some reactions, such as the catalytic hydrogenation,[4] the chemical reduction,[5] and the photoreaction.[6] It is quite interesting to examine the effect of such an intramolecular through-space interaction on the electrochemical reduction of **1**. Since the bicyclic structure of $\mathbf{1}^{\bullet-}$ derived from one electron reduction of **1** prevents itself from having a staggered conformation between the methylene terminal carbon and the negatively charged oxygen atom, it would be expected that decrease in the efficiency of 5-exocyclization of $\mathbf{1}^{\bullet-}$ may enhance some alterative behavior such as 6-endocyclization and/or simple reduction of $\mathbf{1}^{\bullet-}$. We present here a study of the electroreduction of 7-methylenebicyclo[3.3.1]-nonan-3-one. Effects of temperature and some additives on the electrolysis and the parameter of activation of the reaction will be discussed from the experimental and the quantum-mechanical approaches.

## Experimental

**General.** $^{13}$C NMR and $^{1}$H NMR spectra were obtained with a JEOL JNM α-400 instrument in the pulse Fourier mode. Infrared spectra were obtained with a Hitachi 270-50 spectrophotometer.

**Materials.** The solvent, *N*,*N*-dimethylformamide, dried over Molecular Sieves was vacuum distilled before use. All other chemicals used were reagent grade and were recrystallized or distilled if necessary.

**7-Methylenebicyclo[3.3.1]nonan-3-one (1);** 7-Methylenebicyclo[3.3.1]nonan-3-one (**1**) was prepared according to the procedure of Momose and Muraoka from adamantane.[7] Bromination of adamantane (43 g, 0.32 mol) with bromine (500 g, 3.1 mol), boron tribromide (75 g, 0.30 mol), and anhydrous aluminium tribromide (1.0 g, 0.0037 mol) was carried out by refluxing for 4 h and gave 1,3-dibromoadamantane (79 g, 85%). Subsequent alkaline cleavage was carried out by heating of a 200-cm$^3$ autoclave containing the dibromide (10 g, 0.034 mol) in dioxane (80 cm$^3$) and 5 wt% aqueous sodium hydroxide (70 cm$^3$) to 175–180 °C for 18 h. The cooled reaction mixture was extracted with ether, and dried over anhydrous sodium sulfate. Isolation by column chromatography ($SiO_2$, hexane–ethyl acetate) and recrystallization from hexane afforded 3.6 g (70%) of the product. Mp 160–163 °C (lit.; 161–163 °C)[7]; $^{1}$H NMR ($CDCl_3$) $\delta$ 1.88–1.99 (m, 2H), 2.24–2.44 (m, 10H), 4.77 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 30.8 (C1 and C5), 32.1 (C9), 41.4 (C6 and C8), 47.4 (C2 and C4), 114.7 (C10), 141.8 (C7), 211.0 (C3); IR (0.20 M in $CCl_4$) $\nu_{C=O}$ 1716 cm$^{-1}$.

**Bicyclo[3.3.1]nonan-3-one (2);** Bicyclo[3.3.1]nonan-3-one, as a standard compound of **1**, was also prepared by modifying the procedure described by Momose and Muraoka.[7] The mixture of 2-cyclohexen-1-one (26.8 g, 0.28 mol), methyl acetoacetate (39.0 g, 0.33 mol), and sodium methoxide (17.9 g, 0.33 mol) in dry methanol (400 cm$^3$) was refluxed for 35 h to give methyl 5-hydroxy-3-oxobicyclo[3.3.1]nonan-2-carboxylate. The product was used for the next step without purification. Decarboxylation of the bicyclic product was carried out by refluxing with potassium hydroxide (33.0 g, 0.59 mol) in aqueous ethanol solution (500 cm$^3$) for 8 h to give 1-hydroxybicyclo[3.3.1]nonan-3-one (19.9 g, yield for 3 steps; 46%). Bromination of the hydroxy ketone (17.8 g, 0.12 mol) by phosphoryl bromide (17.5 g, 0.065 mol) in dry benzene (60

$cm^3$) at 3 °C for 5 h gave 5-bromobicyclo[3.3.1]nonan-3-one. The product was used for the next step without purification. Hydrogenation of the bromide (13.3 g) was carried out over Raney Ni (14.0 g) in dry diisopropylamine (270 $cm^3$) under ambient temperature until the hydrogen uptake ceased. Sublimation afforded bicyclo[3.3.1]nonan-3-one (1.7 g, yield for 2 steps; 11%). Mp 166–170 °C (lit.; 170–176 °C)[8]; $^1$H NMR ($CDCl_3$) $\delta$ 1.37–1.97 (m, 8H), 2.35–2.51 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.2 (C7), 30.9 (C1 and C5), 32.1 (C6 and C8), 32.8 (C9), 47.4 (C2 and C4), 213.5 (C3); IR (0.20 M in $CCl_4$) $\nu_{C=O}$ 1714 $cm^{-1}$.

**7-Methylenebicyclo[3.3.1]nonan-3-*endo*- and *exo*-ols** (**3** and **4**, respectively). The reduction of **1** by $NaBH_4$ gave a mixture of the *exo*- and *endo*-alcohols.[5]

**1-Adamantanol** (**6**) was purchased from Nacalai Tesque, INC.

**Cyclic Voltammetry.** Cyclic voltammetry was carried out using a four-necked 10-$cm^3$ cell system with a glassy carbon (as a working electrode), a platinum wire (a counter electrode), an SCE (a reference electrode), and an argon inlet tube. A Hokuto HA-310 potentiostat/galvanostat and a Hokuto HB-104 function generator controlled the potentials. Tetraethylammonium tetrafluoroborate ($TEA^+BF_4^-$; polarographic grade, 100 mM) was used as a supporting electrolyte without further purification. DMF solution of the substrate (10 mM) with or without a mediator (biphenyl, 2.0 mM) was bubbled by argon (15 min) before the measurement. The current-voltage curve from 0.00 to –3.10 V vs. SCE was recorded on a Rikadenki model RW-21 electric XY recorder with the scan rate of 50 mV $s^{-1}$ at 25.0 ± 0.5 °C.

**Potential Controlled Electrolysis of 1.** A preparative-scale non-mediated electrolysis was carried out in an H-style cell separated by glass filter at 0.0 ± 0.5 °C. The cathode compartment (100 $cm^3$) was attached to carbon rods (WE: diameter; 5 mm, length; 60 mm × 6), an SCE (RE: bridged with an agar containing saturated potassium chloride), an argon inlet tube, and a stirring rod. The anode compartment (50 $cm^3$) was attached to the carbon rod (CE). The reduction potential was controlled to be –3.00 V and the amount of charge passed was monitored by the coulometer (Hokuto Hf-201). In cathode compartment, 1.48 g (9.9 mmol) of **1** was added to 100 $cm^3$ of DMF containing 200 mM of $TEA^+BF_4^-$. After the argon bubbling for 15 min, the solution was electrolyzed until the amount of the electricity was 2.5 F/mol. Time dependence of the solution was monitored by gas chromatography for each 0.5 F/mol of electricity passed. Finally, the mother solution was extracted with chloroform, washed with saturated brine, dried over anhydrous sodium sulfate. Separation of the concentrated residue by column chromatography ($SiO_2$, hexane–ethyl acetate) and recrystallization afforded 7-methyltricyclo[3.3.1.0$^{3,7}$]nonan-3-ol (**5**, 163 mg, isolated yield; 13%) and 1-adamantanol (**6**, 226 mg isolated yield; 18%). Diminution of the isolated yield of **5** is due to the difficulty of separation from the starting material.

7-Methyltricyclo[3.3.1.0$^{3,7}$]nonan-3-ol (**5**); Mp 167–168 °C, (lit.169–170 °C)[9]; $^1$H NMR ($CDCl_3$) $\delta$ 0.97 (s, 3H), 1.39–1.63 (m. s, 7H), 1.76–1.83 (m., 4H), 2.14 (br. s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.4 ($CH_3$), 33.3 (C9), 35.0 (C1 and C5), 43.7 (C7), 50.7 (C6 and C8), 51.0 (C2 and C4), 83.2 (C-OH); IR (KBr) $\nu_{OH}$ 3320 $cm^{-1}$.

1-Adamantanol (**6**); $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (br. s., 4H) 1.50–1.80 (m., 12H), 2.15 (m., 3H)[10]; $^{13}$C NMR ($CDCl_3$) $\delta$ 30.8 (C3, C5, and C7), 36.2 (C4, C6, and C10), 45.4 (C2, C8, and C9), 68.1 (*C*–OH); IR (KBr) $\nu_{OH}$ 3250 $cm^{-1}$.[11]

Quantification was carried out as follows; cyclohexanol, as an internal standard, was added to each separated mother solution (3 $cm^3$), and the solution was extracted by three 10 $cm^3$ portions of hexane. The combined hexane layers were washed three times with saturated brine and dried over anhydrous sodium sulfate. Gpc analysis was performed on a Shimadzu model GC-8A with a Shimadzu fused silica capillary column CBP2-M25-0.25 (0.25 mm × 25 m) at an injection temperature of 250 °C and a column temperature of 150 °C. Retention time of each chemical was compared with that of the authentic sample. Finally, gpc analysis showed that 89% of **1** were consumed. The yields of **5** and **6** against the consumed **1** were 34 and 20%, respectively. The gpc analysis detected neither *exo*- nor *endo*-alcohol, **3** or **4**.

**Current Controlled Electrolysis (Typical).** The cathode compartment (45 $cm^3$) was attached to a lead plate electrode (WE: 14 $cm^2$), an SCE (RE: bridged with agar containing saturated potassium chloride), an argon inlet tube, and a stirring rod. The anode compartment (5 $cm^3$) was attached to a platinum electrode (CE). In the cathode compartment, 338 mg (2.3 mmol) of **1** was added to 45 $cm^3$ of DMF containing a 200 mM of $TEA^+BF_4^-$. A constant current of 100 mA was passed until the amount of the electricity was 1.0 F/mol to determine the distribution of the chemicals during the early stages (up to 15%) of the reduction, except in cases in which the difference in reactivity was very large. Quantification of the chemicals was performed by the same method as the case of preparative electrolysis. The temperature effect on the product distribution was studied at –18, 0, 25, and 38 °C. Electrolysis of the cyclized product, (**5** or **6**; 136 mg, 0.89 mmol), was examined independently at 0 °C. It was proven that no mutual conversion occurred. The effect of additives such as water, methanol, ethanol, and 2-propanol on the electrolysis of **1** at 0 °C was also investigated under the same conditions.

**Quantum-Mechanical Calculations.**[12] Semiempirical PM3[13]/RHF method was used for the analysis of the neutral **1**. UHF method[14] was used for the calculation of each transition-state of the 5-exo- and 6-endocyclizations of $\mathbf{1}^{\bullet-}$. The transition state obtained was ascertained by "Force" calculation.

## Results and Discussion

Previously, Kariv–Miller reported that the reduction potential of 6-hepten-2-one, (**7**), showed a relatively more positive shift in the presence of homogeneous mediator such as biphenyl than in its absence.[15] Though the non-mediated electroreduction of **7** at –3.00 V vs. SCE gave only 6-hepten-2-ol, the mediated reduction of **7** (2.0 mM) with biphenyl (10 mM) at –2.725 V gave *cis*- and *trans*-1,2-dimethylcyclopentanols as exclusive products. Passage of 1 F/mol afforded 49% of the reactant conversion and 48% of 1,2-dimethylcyclopentanols in which the ratio of *cis* to *trans* was 4.0 (Fig. 1). The proposed mechanism involved reversible cyclization of the ketyl radical anion formed from reduction of the ketone. The cis- or trans-cyclized radical anions can be trapped by further reduction or by protonation to form the observed products.

**Cyclic Voltammetry.** Preliminary cyclic voltammetry measurement of **1** showed an irreversible wave and the reduction peak potential, $E_{red}$, was determined to be –2.88 V vs. SCE. Contrary to the case in 6-hepten-2-one, the $E_{red}$ of **1** shifted negatively to –2.96 V in the presence of biphenyl. Bicyclo[3.3.1]nonan-3-one, (**2**), bearing no methylene moiety, showed no reduction peak in the range from 0.00 to –3.10 V. Such a result suggests that the intramolecular through-space interaction exists in between two π-orbitals of **1**. Molecular orbital calculation revealed that the LUMO of **1** showed appreciable magnitude of eigenvectors on both π-orbitals (Fig. 4).

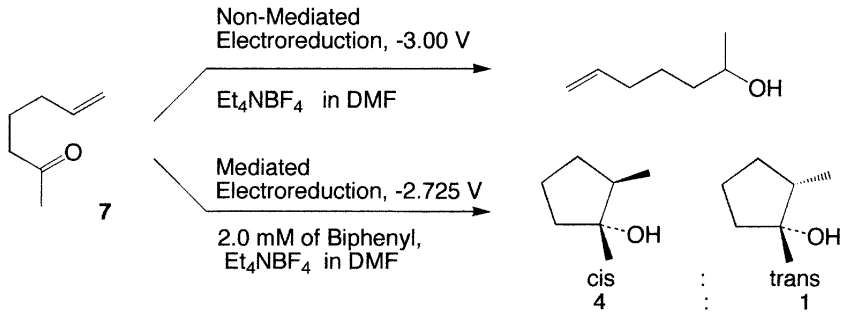



Fig. 1. Electroreduction of 6-hepten-2-one (**7**).[15]

The perturbation of $\pi^*_{C=O}$ with $\pi^*_{C=C}$ causes the lowering of the energy level of $\pi^*_{C=O}$ which lies essentially lower than $\pi^*_{C=C}$. Since the negative shift of $E_{red}$ of **1** in the presence of mediator was attributed to suppressing the intramolecular through-space interaction of **1**, we decided to examine the non-mediated electroreduction of **1**.

**Preparative-Scale Electrolysis of 1.** A quite interesting result was obtained by the potential controlled non-mediated reduction of **1**. In addition to the observation that neither 7-methylenebicyclo[3.3.1]nonan-3-*endo*- nor *exo*-ol, (**3**) or (**4**), was formed, competitive cyclization to give 7-methyltricyclo-[3.3.1.$0^{3,7}$]nonan-3-ol (**5**) and 1-adamantanol (**6**) was found (Fig. 2). It is noteworthy that the formation of **6**, derived from the 6-endocyclization, does not obey the Baldwin's rule. It is well known that the 5-exocyclization of $\delta,\varepsilon$-unsaturated radicals is kinetically preferred despite the thermodynamic preference for the 6-endo cyclization. Time dependent examination showed the slight enhancement of the product ratio, (**5/6**), from 1.3 to 1.6 (Table 1, entries 1a–1e). Increase in the product ratio seemed to be affected by decrease in the amount of electricity with the progress of the reaction. The controlled potential electrolysis afforded the low cyclization efficiency for the conversion of **1**. It was considered that the low cyclization efficiency originated from the low current efficiency of the carbon rods used as the cathode electrode. For the kinetic analysis of the competitive cyclization of **1**, the constant current electrolysis was examined by using a lead plate electrode of which the hydrogen overvoltage was higher than the graphite.

**Temperature Effect on the Product Ratio.** As a closely relevant cyclization reaction, Chen and his coworkers reported the temperature dependence examination of the trapping product ratio from 7-methylenebicyclo-[3.3.1]nonyl radical, (**8**$^{\bullet}$), with $CCl_4$ over the 75–126 °C range.[16] The ratio of 5-exocyclization product (chloro(3-noradamantyl)methane) to 6-endocyclization product (1-chloroadamantane) appeared to change very slowly (53.6 and 27.3, for 75 °C and 126 °C, respectively). The Arrhenius plot did not produce a credible result. They also evaluated the difference in the enthalpy of activation between the 5-exo- and 6-endocyclizations, $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$, at 25 °C to be –2.8 kcal mol$^{-1}$ by using molecular mechanics calculation (Table 2).

After establishing the absence of any mutual conversion of the products by the electoreduction of **5** or **6**, we examined the electroreduction of **1** at –18, 0, 25, and 38 °C. A constant current of 100 mA was passed until the amount of the electricity was 1.0 F/mol, to determine the distribution of the chemicals during the early stages (up to 15%) of the reduction. The ratio of **5** to **6** decreased moderately from 2.2 to 0.61 with increasing the reaction temperature from –18 to 38 °C (Table 1, entries 2a–2d). This indicates that the regioselectivity of the reaction is controlled by the competitive operation of both kinetic and thermodynamic factors in the cyclization of the rigid ketyl radical anion. We wish to propose the mechanism for the competitive cyclization on the electroreduction of **1** as depicted in the Scheme 1. Initially formed radical anion of **1** kinetically cyclizes to give **5**$^{\bullet-}$ which contains steric and electrostatic repulsion between the eclipsed methylene terminal carbon having an odd electron and the negatively charged oxygen atom. On the

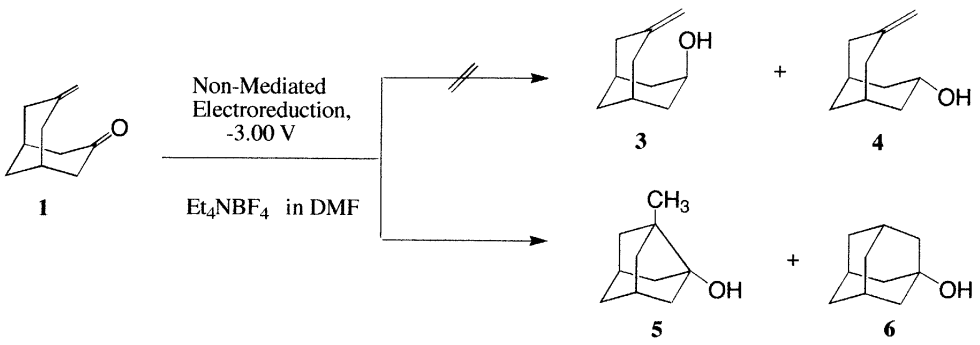



Fig. 2. Non-mediated electroreductive transannular reaction of **1**.

Table 1. Electroreductive Transannular Reaction of 7-Methylenebicyclo[3.3.1]nonan-3-one (**1**) in DMF[1)]

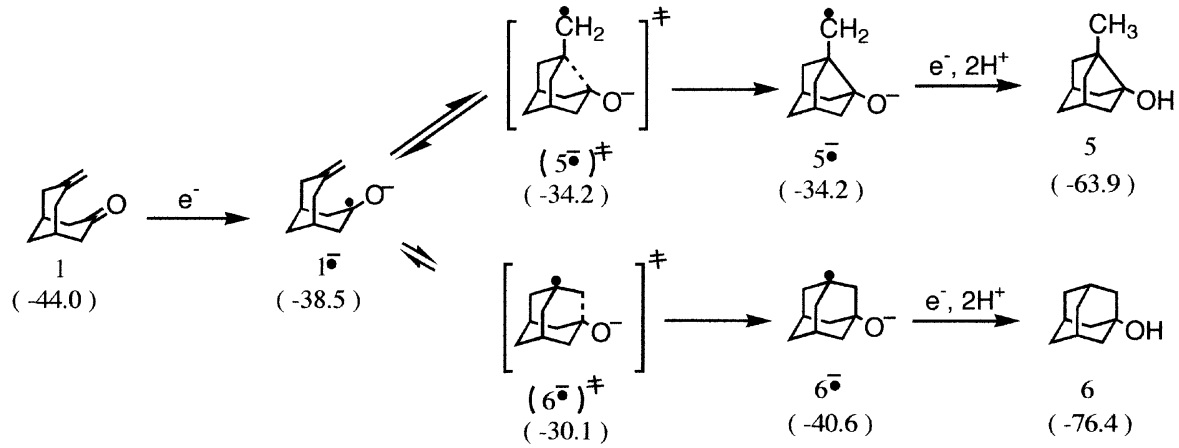
| Entry | Additive (concn/mM) | Temp. /°C | Amount of charge/F mol$^{-1}$ | Conv. of **1**/% | Product yield/% **5** | **6** | Ratio **5/6** |
|---|---|---|---|---|---|---|---|
| Potential controlled electrolysis[2)] | | | | | | | |
| 1a | non | 0 | 0.5 | 21 | 9.1 | 7.2 | 1.3 |
| 1b | non | 0 | 1.0 | 41 | 20 | 14 | 1.4 |
| 1c | non | 0 | 1.5 | 60 | 26 | 18 | 1.5 |
| 1d | non | 0 | 2.0 | 77 | 27 | 19 | 1.5 |
| 1e | non | 0 | 2.5 | 89 | 30(34[3)]) | 18(20[3)]) | 1.6 |
| Current controlled electrolysis[4)] | | | | | | | |
| 2a | non | −18 | 1.0 | 13 | 9.0 | 4.1 | 2.2 |
| 2b | non | 0 | 1.0 | 11 | 5.0 | 5.8 | 0.86 |
| 2c | non | 25 | 1.0 | 15 | 5.8 | 7.0 | 0.83 |
| 2d | non | 38 | 1.0 | 12 | 4.6 | 7.5 | 0.61 |
| 3a | $H_2O$ ( 10) | 0 | 1.0 | 15 | 8.5 | 6.4 | 1.3 |
| 3b | $H_2O$ ( 100) | 0 | 1.0 | 25 | 15 | 10 | 1.5 |
| 3c | $H_2O$[5)] ( 500) | 0 | 1.0 | 29 | 19 | 10 | 1.9 |
| 3d | $H_2O$ (1000) | 0 | 1.0 | 36 | 30 | 5.8 | 5.2 |
| 4 | MeOH[5)] (500) | 0 | 1.0 | 43 | 41 | 2.2 | 19 |
| 5 | EtOH[5)] (500) | 0 | 1.0 | 33 | 28 | 4.7 | 6.0 |
| 6 | 2-PrOH[5)] (500) | 0 | 1.0 | 37 | 27 | 9.1 | 3.0 |

1) 200 mM of $TEA^+BF_4^-$ was contained. 2) Concentration of **1**; 100 mM. 3) Only the two values are yield to the consumed **1**. 4) Concentration of **1**; 50 mM. 5) Swains solvent polarity: $H_2O$; 2.0, MeOH; 1.25, EtOH; 1.11, 2-PrOH; 1.04. C. G. Swain, M. S. Swain, A. L. Powell, and S. Alunni, *J. Am. Chem. Soc.*, **105**, 502 (1983).

Table 2. Relative Heats of Formation at 298 K, in kcal mol$^{-1}$ to the Ketyl Radical Anions for the 5-Exocyclized and 6-Endocyclized Radical Anions and the Corresponding Transition States

| Reactant | (5-Exocyclized)$^{\bullet-}$ | [TS]$^{\ddagger}$ ⇌ | (Ketyl radical anion) | [TS]$^{\ddagger}$ ⇌ | (6-Endocyclized)$^{\bullet-}$ | $\Delta\Delta H^{\ddagger}$ ($TS_{5\text{-exo}} - TS_{6\text{-endo}}$) | $\Delta\Delta H$ (5-Exo – 6-endo) |
|---|---|---|---|---|---|---|---|
| **1** | ~4.3[1)] | 4.3 | 0.0[2)] | 8.4 | −2.1 | −4.1 (−3.1[3)]) | 6.4 |
| **7** | 3.6[4)] | 6.3[4)] | 0.0 | 9.7 | −1.4 | −3.4 | 5.0 |
| **8**$^{\bullet}$ | −9.0[5)] | 5.4[5)] | 0.0[5)] | 8.2[5)] | −20.0[5)] | −2.8[5)] | 11.0[5)] |

1) Optimized structure was not obtained. The value was obtained as the energy minimum of the reaction coordinate. 2) The value of $\mathbf{1}^{\bullet-}\mathbf{c_O c_C}$. 3) The value was obtained by the temperature dependent examination. 4) The approach of the two functional groups was assumed to be in staggered mode. 5) The values were for radicals and obtained by molecular mechanics calculation. A. M. Mueller and P. Chen, *J. Org. Chem.*, **63**, 4581 (1998).




Scheme 1. Non-mediated electroreductive transannular reaction of **1**. The values in parentheses are Heats of formation at 25 °C (kcal/mol) obtained by MO calculation.

other hand, even though the energy level of the transition state of 6-endocyclization is higher than that of 5-exocyclization, the formation of $\mathbf{6}^{\bullet-}$ is thermodynamically favored. As Kariv–Miller proposed, the cyclized radical anions can be trapped by further reduction or by protonation to form the final products. If one supposes that 5-exocyclization and 6-endocyclization process are rate-determining and if the rate constants are defined as $k_5$ and $k_6$, respectively, the following equation can be derived (Eq. 1).

$$\begin{aligned}\ln([\text{product } \mathbf{5}]/[\text{product } \mathbf{6}]) &= \ln(k_5/k_6) \\ &= -\{[\Delta H^{\ddagger}_{(5\text{-exo})} - \Delta H^{\ddagger}_{(6\text{-endo})}]/R\}(1/T) \\ &\quad +[\Delta S^{\ddagger}_{(5\text{-exo})} - \Delta S^{\ddagger}_{(6\text{-endo})}]/R \end{aligned} \quad (1)$$

The logarithmic plot of the product ratio against the reciprocal of temperature showed good Eyring correlation; the slope and intercept were $1.57 \times 10^3$ and –5.55 (r; 0.91), respectively. The difference in the parameter of activation between the 5-exo- and 6-endocyclizations was defined as follows.

$$\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})} = [\Delta H^{\ddagger}_{(5\text{-exo})} - \Delta H^{\ddagger}_{(6\text{-endo})}] = -1.57 \times 10^3 \cdot R \quad (2)$$

$$\Delta\Delta S^{\ddagger}_{(5\text{-exo}-6\text{-endo})} = [\Delta S^{\ddagger}_{(5\text{-exo})} - \Delta S^{\ddagger}_{(6\text{-endo})}] = -5.55 \cdot R \quad (3)$$

the values of $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ and $\Delta\Delta S^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ were evaluated to be –3.1 kcal mol$^{-1}$ and –11 cal mol$^{-1}$ K$^{-1}$, respectively. It suggests that the transition state of 5-exocyclization is kinetically preferred and that the structure is more rigid than that of 6-endocyclization. The negative values of both $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ and $\Delta\Delta S^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ suggest a relatively large magnitude of inter-orbital interaction of $\mathbf{1}^{\bullet-}$ in the manner of 5-exocyclization. More detailed consideration will be carried out later with the data of molecular orbital calculations. As the results, the difference in Gibbs function of activation at 0 °C, $\Delta\Delta G^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$, can be derived to be – 0.1 kcal mol$^{-1}$.

**Conformation Analysis of 1 and $\mathbf{1}^{\bullet-}$ by MO Calculation.** Assuming that the difference in the heats of formation could be regarded as the difference in the free energies, we evaluated the ratio of the conformers of **1** or $\mathbf{1}^{\bullet-}$ (Fig. 3). PM3/RHF calculation reproduces well the result that the most stable conformation of the neutral **1** exists in a chair-chair form ($\mathbf{1c_Oc_C}$, 95.5%). As depicted in Fig. 4, the LUMO of $\mathbf{1c_Oc_C}$ shows significant magnitude of the eigenvectors on both the functional groups and the coincidence of the symmetry of the orbitals. It suggests that an incorporation of an electron to the LUMO should afford an inter-orbital interaction. On the other hand, PM3/UHF calculation shows that the corresponding conformer of the anion radical ($\mathbf{1^{\bullet-}c_Oc_C}$) is minor (12.5%) and the most stable conformation of $\mathbf{1}^{\bullet-}$ has the boat form of the methylenecyclohexane ring ($\mathbf{1^{\bullet-}c_Ob_C}$, 85.2%). For the ring inversion from $\mathbf{1^{\bullet-}c_Oc_C}$ to $\mathbf{1^{\bullet-}c_Ob_C}$, the enthalpy of activation, $\Delta H^{\ddagger}_{\text{calcd}}$, was calculated to be 0.6 kcal mol$^{-1}$. Since $\Delta H^{\ddagger}_{\text{calcd}}$ of the ring inversion is smaller

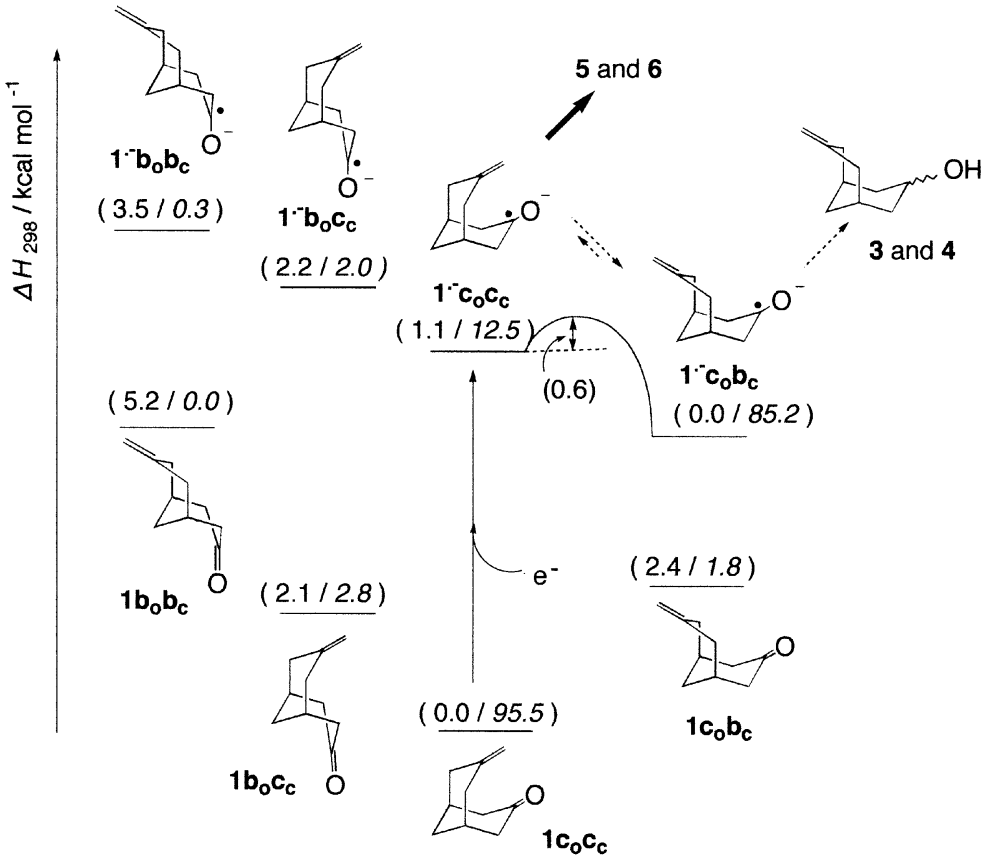



Fig. 3. The difference in the heats of formation ($\Delta H_{298}$) of **1** and $\mathbf{1}^{\bullet-}$ obtained by MO calculation. The values in parentheses are $\Delta H_{298}$ (kcal/mol) and *percent of existence*, respectively. The difference in $\Delta H_{298}$ between $\mathbf{1c_Oc_C}$ and $\mathbf{1^{\bullet-}c_Oc_C}$ is 4.4 kcal mol$^{-1}$.

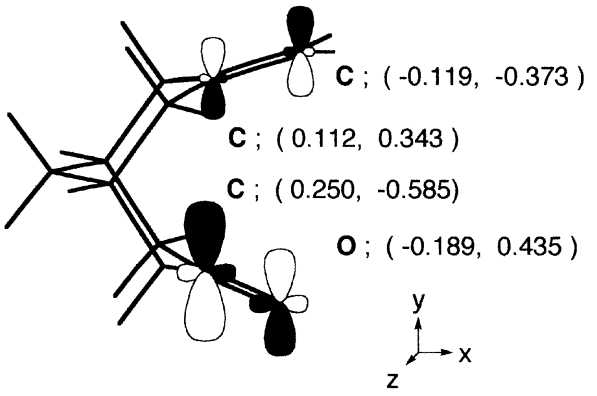


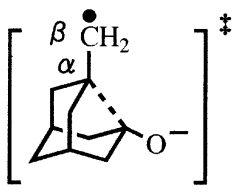

Fig. 4. LUMO of **1**. The values in parentheses are significant eigenvectors of 2px and 2py, respectively.

than those of 5-exo- and 6-endocyclizations ($\Delta H^{\ddagger}_{calcd}$; 4.3, 8.4 kcal mol$^{-1}$, respectively, shown in Table 2), $\mathbf{1}^{\bullet-}\mathbf{c_O c_C}$ could be changed to $\mathbf{1}^{\bullet-}\mathbf{c_O b_C}$ that should afford $\delta,\varepsilon$-unsaturated alcohols. The fact that no simple alcohol was formed on the electrolysis suggested that the adsorption of **1** on the electrode prevented any conformational exchange from $\mathbf{1}^{\bullet-}\mathbf{c_O c_C}$ to $\mathbf{1}^{\bullet-}\mathbf{c_O b_C}$.

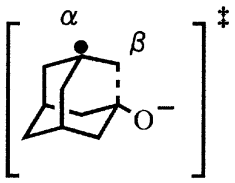
**Evaluation of the Parameter of Activation by MO Calculation.** As a standard reaction, we examined the electroreduction of **7**.[15] In order to search for the transition state of 5-exocyclization of $\mathbf{7}^{\bullet-}$, we postulated that the approach of the two functional groups took place in a staggered mode that, in fact, gave *cis*-1,2-dimethylcyclopentanol, as a major product. The assumed 6-endocyclizatin of $\mathbf{7}^{\bullet-}$ was not generated actually. Table 2 lists the relative values of the heat of formation to that of $\mathbf{7}^{\bullet-}$ to be 0.00. The value of $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ for $\mathbf{7}^{\bullet-}$ was evaluated to be –3.4 kcal mol$^{-1}$. It is well reproduced that the 5-exocyclization is the kinetically preferential process. Thermodynamic preference of 6-endocyclized intermediate was revealed by the difference in relative heats of formation of the two cyclized intermediates ($\Delta\Delta H_{(5\text{-exo}-6\text{-endo})}$; 5.0 kcal mol$^{-1}$). Calculation of the cyclization of $\mathbf{1}^{\bullet-}$ gave the unique character ascribed to the rigidity of $\mathbf{1}^{\bullet-}$. The reaction coordinate for the 5-exocyclization did not give the optimized structure as the stable intermediate of $\mathbf{5}^{\bullet-}$, and it barely gave the transition state as an inflection point, whereas the reaction coordinate for the 6-endocyclization showed clear maximum and minimum corresponding to the transition state and the stable intermediate of $\mathbf{6}^{\bullet-}$. It was also proven that the energy of the transition state for the 5-exocyclization was by far lower than that of the transition state for the 6-endocyclization. The evaluated difference in $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ was –4.1 kcal mol$^{-1}$ (Table 2). The calculated value was slightly more negative than that of experimental result. The characteristic parameters of the transition states from $\mathbf{1}^{\bullet-}$ are summarized in Table 3. The transition state of 5-exocyclization shows the effective bond order between the ketyl carbon and the inner methylene carbon as to be 0.218 at the distance of 235.6 pm. The transition state of 6-endocyclization shows the effective bond order between the ketyl carbon and the terminal methylene carbon as to be 0.116 at the distance of 249.1 pm. It suggests that the effective orbital interaction in manner of 5-exocyclization should occur in the rigid $\mathbf{1}^{\bullet-}$.

Though the difference of enthalpies of activation ($\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$) among $\mathbf{1}^{\bullet-}$, $\mathbf{7}^{\bullet-}$, and $\mathbf{8}^{\bullet}$ was similar (Table 2), the fact was that only $\mathbf{1}^{\bullet-}$ afforded the competitive 6-endocyclization as well as 5-exocyclization. Moderate temperature dependence in the competitive cyclization of $\mathbf{1}^{\bullet-}$ should be ascribed to the difference of entropies of activation. In cases of

Table 3. Characteristic Parameters of the Transition States of 5-Exo- and 6-Endocyclization of $\mathbf{1}^{\bullet-}$ Obtained by PM3/UHF Calculation




$(5^{\bullet-})^{\ddagger}$




$(6^{\bullet-})^{\ddagger}$

| Atom | Spin Density (Formal Charge) | Atom | Spin Density (Formal Charge) |
|---|---|---|---|
| $C_K$[1)] | 0.262 (+0.153) | $C_K$[1)] | 0.525 (−0.042) |
| O | 0.223 (−0.525) | O | 0.270 (−0.595) |
| $C_\alpha$ | −0.182 (−0.219) | $C_\alpha$ | 0.478 (−0.258) |
| $C_\beta$ | 0.718 (−0.333) | $C_\beta$ | −0.339 (−0.093) |
| Bond | Bond Order (Interatomic Distance/pm) | Bond | Bond Order (Interatomic Distance/pm) |
| $C_K$–O | 1.533 (125.3) | $C_K$–O | 1.390 (127.2) |
| $C_\alpha$–$C_\beta$ | 1.415 (137.8) | $C_\alpha$–$C_\beta$ | 1.658 (135.6) |
| $C_K$–$C_\alpha$ | 0.218 (235.6) | $C_K$–$C_\alpha$ | 0.016 (274.2) |
| $C_K$–$C_\beta$ | 0.019 (306.5) | $C_K$–$C_\beta$ | 0.116 (249.1) |
| O–$C_\alpha$ | 0.050 (303.4) | O–$C_\alpha$ | 0.000 (372.6) |
| O–$C_\beta$ | 0.001 (321.5) | O–$C_\beta$ | 0.020 (304.5) |

1) The carbon, $C_K$, was originally derived from ketyl radical center.

$7^{\bullet-}$ and $8^{\bullet}$, both the cyclizations were derived substantially from the 2-centered interaction. In case of $1^{\bullet-}$, though 6-endocyclization was derived from the same 2-centered interaction as in the case of $7^{\bullet-}$ and $8^{\bullet}$, 5-exocyclization was initially derived from 4-centered interaction forced by the unavoidable rigidity. Preference in the entropy term of 6-endocyclization of $1^{\bullet-}$ was evidenced by the experimental result ($\Delta\Delta S^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$; $-11$ cal mol$^{-1}$ K$^{-1}$).

**Effect of the Additives on the Regioselectivity.** Finally, we examined the effect of additives such as water, methanol, ethanol, and 2-propanol on the regioselectivity of the electrolysis. On increasing the concentration of water from 0 to 1000 mM (1 M = 1 mol dm$^{-3}$), the ratio of **5** to **6** increased from 0.86 to 5.2 (Table 1, entries 2b, 3a–3d). Particularly, increasing the solvent polarity of alcohol (entries 4, 5, and 6) enhanced not only the conversion of **1** but also the regioselectivity of **5**. The fact that the addition of proton source caused the enhancement of both the reaction efficiency and the product ratio (**5**/**6**) must be attributed to stabilizing the electrostatic repulsion in $5^{\bullet-}$ formation further than that in $6^{\bullet-}$ formation.

## Conclusion

Contrary to the non-mediated electroreduction of the acyclic 6-hepten-2-one which gave only the $\delta,\varepsilon$-unsaturated alcohol, the corresponding reaction of the bicyclic **1** showed competitive transannular reaction. The intramolecular through-space interaction in the LUMO of **1** is responsible for the occurrence of the reactivity even in the non-mediated reduction. The appearance of 6-endocyclization is ascribed to the unavoidable electrostatic repulsion between the eclipsed methylene terminal carbon and the oxygen atom in the 5-exocyclization. The differences in parameters of activation between the 5-exo- and 6-endocyclizations of $1^{\bullet-}$, $\Delta\Delta H^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$ and $\Delta\Delta S^{\ddagger}_{(5\text{-exo}-6\text{-endo})}$, were experimentally evaluated to be $-3.1$ kcal mol$^{-1}$ and $-11$ cal mol$^{-1}$ K$^{-1}$, respectively. Semiempirical PM3 calculation also supported the proposed reaction mechanism. The addition of a proton source caused the enhancement of both the reaction efficiency and the product ratio (**5**/**6**).

## References


1 T. Shono and Y. Matsumura, "Electron transfer processes in organic chemistry," Nippon-Kagakukai, Gakkai-Shuppan center (1988), Chapt. 5, p. 71; T. Shono and M. Mitani, *J. Am. Chem. Soc.*, **93**, 5284 (1971); T. Shono, I. Nishiguchi, H. Ohmizu, and M. Mitani, *J. Am. Chem. Soc.*, **100**, 545 (1978); T. Shono, N. Kise, T. Suzumoto, and T. Morimoto, *J. Am. Chem. Soc.*, **108**, 4676 (1986).

2 J. E. Baldwin, *J. Chem. Soc., Chem. Comm.*, **1976**, 734.

3 Y. Senda, J.-I. Ishiyama, and S. Imaizumi, *J. Chem. Soc., Perkin Trans. 2*, **1981**, 90.

4 J.-I. Ishiyama, Y. Senda, and S. Imaizumi, *Chem. Lett.*, **1983**, 771.

5 C. A. Grob and H. Katayama, *Helv. Chim. Acta*, **60**, 1890 (1977).

6 T. Mori, K. H. Yang, K. Kimoto, and H. Nozaki, *Tetrahedron Lett.*, **1970**, 2419.

7 T. Momose and O. Muraoka, *Chem. Pharm. Bull.*, **26**, 288 (1978).

8 J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

9 M. Eakin, J. Martin, and W. Parker, *J. Chem. Soc., Chem. Comm.*, **1965**, 206.

10 C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra," Aldrich Chemical Co., Inc. (1974), **1**, p.120 C.

11 C. J. Pouchert, "The Aldrich Library of Infrared Spectra," Aldrich Chemical Co., Inc. (1970), p. 86 F.

12 Molecular orbital calculations were carried out by using a program of "CAChe MOPAC ver. 94" for power Machintosh with the permission by SONY Tektronix.

13 J. J. P. Stewart, *J. Comput. Chem.*, **10**, 209 (1989).

14 For the UHF calculation, see especially Chap. 9 of "Bunshi-kidoho MOPAC guide book (2nd ed)," ed by T. Hirano and K. Tanabe, Kaibundo Shuppan, Tokyo (1994).

15 J. E. Swartz, E. Kariv-Miller, and S. J. Harrold, *J. Am. Chem. Soc.*, **111**, 1211 (1989); F. Lombardo, R. A. Newmark, and E. Kariv-Miller, *J. Org. Chem.*, **56**, 2422 (1991).

16 A. M. Mueller and P. Chen, *J. Org. Chem.*, **63**, 4581 (1998).