Mechanistic Study on Thermal Isomerization of 1-Methylbenzocyclobutenol to 2-Methylacetophenone

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Received April 27, 1999

Heating 1-trideuteriomethylbenzocyclobutenol **7** in benzene-d_6 at 160 °C gave 2-monodeuteriomethyl- and 2-methylacetophenone **9** and **10** in a ratio of 96:4. Thermolysis of **7** in nonpolar solvents (hexane, toluene, mesitylene) gave similar results. On the contrary, heating **7** in polar solvents (ethanol, acetonitrile, chloroform) or in benzene-d_6 in the presence of proton source ($PhCO_2H$) gave **10** as the major product. However, heating a mixture of **7** and *N*-phenylmaleimide at 160 °C in benzene-d_6 or acetonitrile-d_3 gave adduct **12** of *N*-phenylmaleimide and the dienol generated by ring opening of **7** almost quantitatively. These results indicate that 1-methylbenzocyclobutenol undergoes selective thermal opening to the *E*-dienol. The resulting *E*-dienol isomerizes to 2-methylacetophenone by 1,5-sigmatropic shift of hydrogen from the methyl group in nonpolar solvent. In polar solvent, the *E*-dienol isomerizes to 2-methylacetophenone by both intra- and intermolecular processes. The k_H/k_D value for isomerization was 1.13. Since this relatively low value is a secondary kinetic effect, overall reaction is governed by the ring opening step. The selective opening to the *E*-dienol was supported by calculation.

Introduction

Aryl ketones with *o*-alkyl groups are known to undergo a highly efficient photoinduced enolization.[1] The triplet states of these ketones are transformed into triplet biradicals via γ-hydrogen abstraction, which decay to *Z*- and *E*-isomers of the dienol in the electronic ground state.[2] These enols have quite similar spectroscopic properties but are widely different in their kinetic behavior.[2] In nonpolar solvent, the *Z*-dienols undergo a rapid 1,5-sigmatroic hydrogen shift to regenerate the starting ketones ($>10^6$ s^{-1}).[2] On the contrary, the *E*-dienols are sufficiently long-lived to cyclize to benzocyclobutenols[3] or to react with various dienophiles such as olefins[4] and O_2.[5]

The dienol species can also be generated by thermal electrocyclic ring opening of benzocyclobutenols.[1a,6] The dienols thus generated are trapped with various dienophiles to give cycloadducts.[7] Sammes and co-workers reported that the benzocyclobutenols underwent selective ring opening of the cyclobutene ring to the *E*-dienol on the basis of trapping reactions.[6a] Heating 1-methyl-1,2-dihydrobenzocyclobuten-1-ol **1** with maleic anhydride (MA) in refluxing toluene gave the adduct **2** together with 2-methylacetophenone **3** in a ratio of 2:1 (Scheme 1), implying that at least 67% of the benzocyclobutenol **1** was converted to the *E*-dienol which reacted with maleic anhydride to give **2**.[6b] However, heating **1** alone gave cleanly 2-methylacetophenone **3**. Therefore, compound **3** can arise from both *Z*- and *E*-dienols. Although the *Z*-dienol is converted to **3** with a rapid 1,5-sigmatropic hydrogen shift from the OH group, the *E*-dienol can also afford **3** by a sigmatropic hydrogen shift from the methyl group followed by ketonization or as a result of intermolecular hydrogen transfers. Since 1-methoxy-1-methyl-1,2-dihydrobenzocyclobutene was smoothly and quantitatively converted into 2-methyl-α-methoxystyrene on heating via a 1,5-sigmatropic hydrogen shift from the *E*-diene,[6b] 2-methylacetophenone **3** from **1** was assumed to arise by an intramolecular process from the *E*-dienol. However, the mechanism for ketonization of the *E*-dienol in polar solvent has remained obscure, because the lifetime of *E*-dienols is shortened under acidic or basic conditions.[8]

We report here that 1-methylbenzocyclobutenol underwent highly selective opening to the *E*-dienol regardless of solvent polarity and that the resulting *E*-dienol isomerized to 2-methylacetophenone by intra- and intermolecular processes.

Results and Discussion

Preparation of 1-Methyl- and 1-Trideuteriomethyl-1,2-dihydrobenzocyclobutenols. The benzo-

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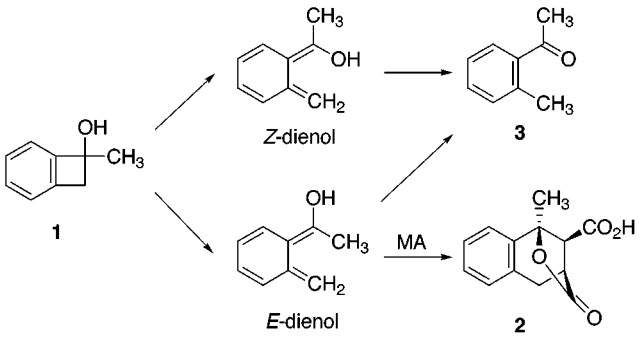
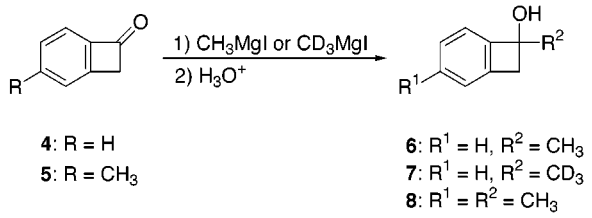
10.1021/jo990705n CCC: $18.00
Published on Web 09/10/1999

Scheme 1



Scheme 2



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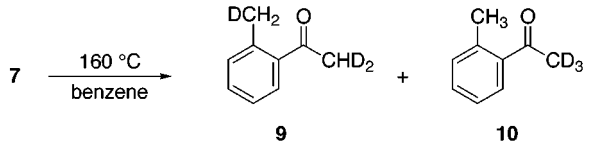

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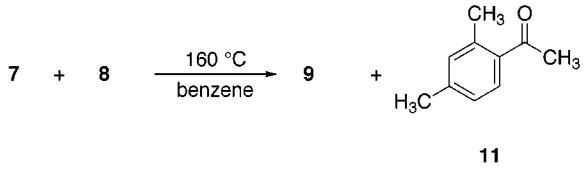

Scheme 5

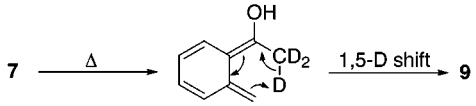

Table 1. Thermal Isomerization of Benzocyclobutenol 7

			product ratio[b]	
solvent	temp (°C)	time (h)[a]	**9**	**10**
C_6D_6	160	5	96	4
C_6D_6	140	12	95	5
C_6H_6	80	36	no reaction	
hexane	160	5	97	3
toluene	160	5	92	8
mesitylene	165	4	>99	trace
none	160	5	39	61
EtOH	160	5	36	64
CD_3CN	160	7	31	69
CD_3CN + 1% H_2O	160	7	20	80
$CHCl_3$	160	5	8	92

[a] Over 90% of benzocyclobutenol disappeared. [b] Product ratios were determined by ^{1}H NMR spectroscopy directly in the reaction mixture after evaporation of the solvent.

cyclobutenols **6**, **7**, and **8** were synthesized by the reaction of the corresponding benzocyclobutenones **4** and **5** with methyl- and trideuteriomethylmagnesium iodides,[6b] where **4** and **5** were prepared by the photochemical cyclization of 2,2,4-trimethyl-1-(*o*-tolyl)pentane-1,3-diones followed by the thermal retroaldol cleavage of the resulting benzocyclobutenols (Scheme 2).[9]

Thermal Reactions of 1-Methyl- and 1-Deuteriomethyl-1,2-dihydrobenzocyclobutenols. When a dilute solution of **7** in benzene-d_6 (1.9×10^{-1} mol/L) was heated at 160 °C in a NMR tube for 5 h, it disappeared over 90% with producing acetophenones **9** and **10** cleanly (Scheme 3). The two hydrogens of the 2-monodeuteriomethyl group and a hydrogen of dideuterioacetyl group in **9** appeared as a triplet and a quintet at δ 2.50 and 2.07, respectively, in the NMR spectrum of the mixture. The 2-methyl group in **10** appeared as a singlet at δ 2.52. On the basis of the integration of these peaks, it was estimated that **7** was converted into **9** and **10** in a ratio of 96:4, suggesting that **7** underwent selective ring opening to the *E*-dienol and that the resulting *E*-dienol rearranged to **9** by intramolecular process. The thermolysis of **7** in nonpolar solvents such as hexane, toluene, and mesitylene gave the similar results. However, the possibility that **9** is also formed by intermolecular process from the *E*-dienol cannot be ruled out from these results. To examine whether **9** was formed by intra- or intermolecular process, or by both processes, the thermolysis of a mixture of **7** and 1,4-dimethylbenzocyclobutenol **8** was carried out. Heating a 1:1 mixture of **7** and **8** in benzene-d_6 gave **9** and 2,4-dimethylacetophenone **11** (Scheme 4). Neither deuterated 2,4-dimethylacetophenone nor dideuterated 2-methylacetophenone could be detected. This indicates that **7** and **8** underwent isomerization to **9** and **11**, respectively, by an intramolecular process via the *E*-dienol. Houk reported that the ring opening of 3-substituted cyclobutenes with strong donors such as an alkoxy group preferred outward rotation to inward rotation of the substituent.[10] The benzocyclobutenols with donor substituent such as 1-methoxy or 1-acetoxy also underwent selective outward opening to the *E*-dienols on heating (Scheme 5).[11,12]

It has been shown by the thermal reaction of benzocyclobutenols in the presence of dienophiles that the process leading to *Z*-dienol formation is highly unfavorable.[6a] The result described above also supports the selective opening to the *E*-dienol. Therefore, the minor product **10** probably arose by intermolecular process. Interestingly, when **7** was heated at 160 °C in a glass tube without solvent, it was converted cleanly into **9** and **10** in a ratio of 39:61. This result suggested that **10** arose by an intermolecular process from the *E*-dienol because of the close contact of the initially formed *E*-dienol species. In sharp contrast to the reaction in nonpolar solvents, heating **7** in ethanol caused the preferential conversion into **10** rather than **9**, probably by external protonation of the *E*-dienol. Thermolysis of **7** in polar solvents such as acetonitrile and chloroform also gave **10** as the major product as shown in Table 1. The **10**/**9** ratio was higher in acetonitrile containing H_2O than in distilled acetonitrile. The **10**/**9** ratio was much higher in

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Scheme 6

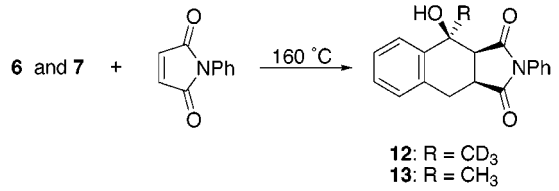


Table 2. Thermal Reaction of Benzocyclobutenol 7 in the Presence of Additives[a]

additive	9[b]	10[b]	12[b]
$PhCO_2H$[c]	33	67	
NPM[d] + $PhCO_2H$[c]		trace	>99

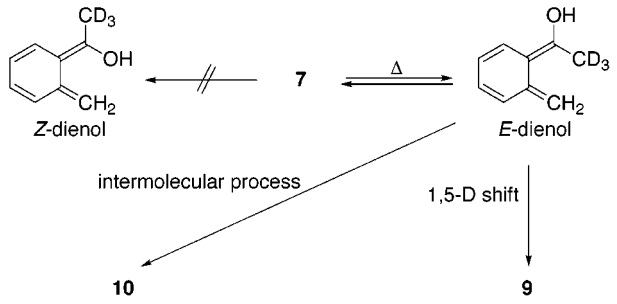
[a] The reaction was carried out in bezene-d_6. [b] Product ratios were determined by ^1H NMR. [c] 0.2 equiv to **7**. [d] 2 equiv of *N*-phenylmaleimide to **7**.

chloroform than in other polar solvents used, probably due to HCl contamination. The preferential formation of **10** rather than **9** in polar solvents would be attributed to the increased probability of intermolecular process from the *E*-dienol or to the favored formation of the *Z*-dienol which undergoes a rapid ketonization by 1,5-hydrogen shift from the OH group. To clarify the geometry of intermediary dienol leading to the acetophenone in polar solvents, thermolysis of **7** in the presence of dienophile in benzene-d_6 and acetonitrile-d_3 was investigated. Heating **7** in the presence of 2 equiv of *N*-phenylmaleimide (NPM) at 160 °C for 7 h gave a single isomer of [4 + 2] cycloadduct **12** of the dienol and NPM quantitatively regardless of solvent polarity (Scheme 6). Neither **9** nor **10** were detected. The compound **12** must be formed by the addition of NPM to the *E*-dienol because the *Z*-dienol undergoes rapid ketonization.[2] The thermal reaction of 1,2-dihydrobenzocyclobuten-1-ol in the presence of NPM affords the only adduct between the *E*-dienol and NPM.[6a] These facts provide unambiguous evidence for the exclusive opening of **7** to the *E*-dienol on heating regardless of solvent polarity.

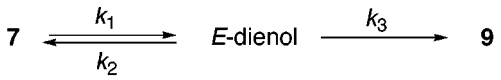
Thermal Isomerization of 1-Methylbenzocyclobutenol in the Presence of Proton Source. The benzocyclobutenol was converted into the *E*-dienol regardless of solvent polarity and the resulting *E*-dienol isomerized to the ketone by an intramolecular process in nonpolar solvents. However, the production of **10** in preference to **9** in the thermolysis of **7** in polar solvents suggested that the *E*-dienol also isomerizes to the ketone by an intermolecular process in polar solvents. To get information for the course of ketonization in polar solvents, influence of acid was examined because the protonation of the *E*-dienol would promote its ketonization. Heating **7** in the presence of 0.2 equiv of benzoic acid in benzene-d_6 gave **9** and **10** in a ratio of 33:67, implying that isomerization of the *E*-dienol to the ketone can be ascribed in part to an intermolecular process (Scheme 7, Table 2). However, heating a 1:2 mixture of **7** and *N*-phenylmaleimide in the presence of benzoic acid in benzene-d_6 afforded a [4 + 2] cycloadduct **12** quantitatively. These results indicate that the *E*-dienol reacts with *N*-phenylmaleimide faster than its ketonization via intermolecular protonation.[13] Thus, the thermally generated *E*-dienol from 1-methylbenzocyclobutenol isomerizes to 2-methylacetophenone by inter- and intramolecular processes.

Kinetics of Thermal Isomerization of 1-Methylbenzocyclobutenol to 2-Methylacetophenone. The

Scheme 7



Scheme 8



reaction rate for thermal isomerization of the benzocyclobutenol to the acetophenone was measured by monitoring the disappearance of the benzocyclobutenol in benzene-d_6 by ^1H NMR. The deuterated compound **7** disappeared with the first-order rate constant of 1.37×10^{-4} s^{-1} at 160 °C, whereas the nondeuterated compound **6** disappeared with that of 1.55×10^{-4} s^{-1} under the same conditions. The k_H/k_D value in benzene was 1.13.

The reaction rate for isomerization is governed by either ring opening to the *E*-dienol, k_1, or hydrogen shift from the resulting *E*-dienol, k_3 (Scheme 8). The relatively low k_H/k_D value must be a secondary isotope kinetic effect, indicating that the 1,5-sigmatropic hydrogen shift from the *E*-dienol is not rate-determining. The ring opening step governs the overall rate of reaction. Thus, the *E*-dienol underwent isomerization to 2-methylacetophenone faster than its closure to revert to the starting benzocyclobutenol; hence the relative rate for each step would be in the order $k_3 > k_2 > k_1$. Sammes and co-workers found that the thermally generated *E*-dienol from the benzocyclobutenol isomerized to the ketone faster than reversion to the starting benzocyclobutenol by thermolysis of the optically active benzocyclobutenol.[6a]

From an Eyring plot over the temperature range of 140−170 °C, the activation enthalpy $\Delta H^{\ddagger}$ and entropy $\Delta S^{\ddagger}$ were obtained for the opening of the deuterated compound **7** in benzene-d_6. The free energy of activation $\Delta G^{\ddagger}$ calculated at 160 °C from these values was appreciably lower than that for the opening of benzocyclobutene itself[14] and slightly lower than that for 1,1-dimethoxybenzocyclobutene.[15] An electron-donating group such as hydroxy or methoxy lowered the bond dissociation energy. A similar substituent effect was observed in the Cope rearrangement of 2-vinylbicyclo[2.2.2]oct-5-en-2-ol.[16]

Quantum Chemical Calculations. To assess why the benzocyclobutenol undergoes selective opening to the *E*-dienol, quantum chemical calculations were performed on benzocyclobuten-1-ol **14**. All calculations were performed with the B3-LYP/6-31G* level. Figure 1 shows a Gibbs energy profile corresponding to the ring opening of **14**. The energy barrier corresponding to the transition

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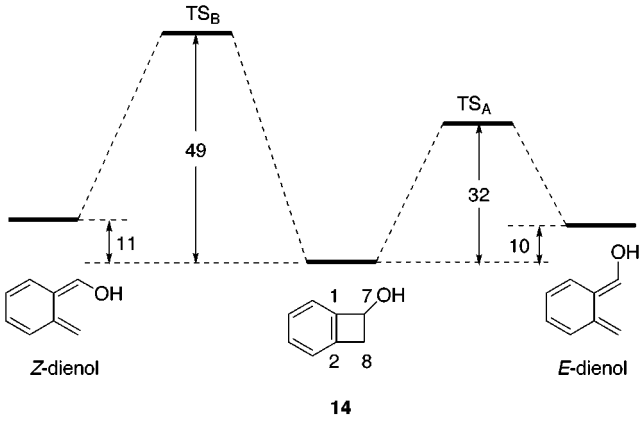
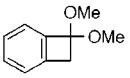
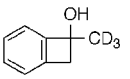


Figure 1. Schematic Gibbs energy (kcal mol^{-1}) profile.

Table 3. Activation Energies for Ring Opening Step of Benzocyclobutenes

	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})[a]
	38.9[b]	4.7[b]	37.9
	32.8[c]	-4.3[c]	34.7
	28.7	-10.8	33.4

[a] Calculated values at 160 °C. [b] Values from ref 14. [c] Values from ref 15.

Table 4. Selected Bond Lengths (Å) and Torsion Angles (deg) of 14 and Transition States (TS_A and TS_B) Calculated by B3-LYP/6-31G*

structure	C_7-C_8	$C_1-C_7-C_2-C_8$
14	1.590	3.32
TS_A	2.288	23.35
TS_B	2.401	27.01

state (TS_A) leading to the *E*-dienol is 17 kcal/mol lower than that (TS_B) leading to the *Z*-dienol. The energy difference (32 kcal/mol) between TS_A and **14** is approximately the same as the $\Delta G^{\ddagger}$ value for **7** obtained by the Eyring equation (Table 3). The deviation of the C_7-C_8 bond length and torsion angle between C_1-C_7 and C_2-C_8 from the starting **14** is larger in TS_B than in TS_A. The C_7-C_8 distances of TS_B, TS_A, and **14** are 2.401, 2.288, and 1.590 Å (Table 4). The benzocyclobutenol **14** has an almost planar structure. However, TS_B and TS_A have twisted structures with dihedral angles between C_1-C_7 and C_2-C_8 of 27.01° and 23.35°, respectively. The larger angle in TS_B than in TS_A causes more deformation of the benzene ring in TS_B than in TS_A. The lower activation energy in TS_A than in TS_B and the more deformed conformation of TS_B than that of TS_A are consistent with the selective opening of **7** to the *E*-dienol. The steric and/or the electronic effect would be responsible for the difference of ring opening modes. It has been reported that 3-hydroxycyclobutene and 3-methylcyclobutene open the ring with outward rotation of the substituents in 16.4 and 6.9 kcal/mol, respectively, lower in energy than with inward rotation, implying that the electronic effect is more responsible than the steric effect.[10]

In conclusion, the 1-methylbenzocyclobutenol undergoes thermal ring opening unambiguously to the *E*-dienol. The generated *E*-dienol isomerizes to 2-methylacetophenone by 1,5-sigmatropic shift of hydrogen from the methyl group predominantly in nonpolar solvent. In polar solvent, the *E*-dienol isomerizes to 2-methylacetophenone by intra- and intermolecular processes. The ring opening step determines the overall reaction rate for isomerization.

Experimental Section

General Procedure. All solvents used in the reactions were purified by distillation. Melting points were uncorrected, and boiling points were measured from the oven temperatures in Kugelrohr distillation. ^{1}H NMR spectra were recorded at 200 or 400 MHz using tetramethylsilane as an internal standard with $CDCl_3$, C_6D_6, or CD_3CN as solvent. ^{13}C NMR spectra were recorded at 50 or 100 MHz with $CDCl_3$ as solvent. IR spectra were recorded for solution in CCl_4 or $CHCl_3$.

Preparation of Benzocyclobuten-1-ols 6, 7, and 8. To 157 mg (6.5 mmol) of magnesium in dry ether was added slowly at 0 °C 0.4 mL (6.6 mmol) of CH_3I or CD_3I. After magnesium had been dissolved completely, 510 mg (4.3 mmol) of benzocyclobuten-1(2*H*)-one or 570 mg (4.3 mmol) of 4-methylbenzocyclobuten-1(2*H*)-one was added at −20 °C. After stirring for 3 h, the reaction mixture was treated with a saturated aqueous NH_4Cl solution and extracted with ether. The organic layer was dried over $MgSO_4$ and filtered. Removal of the solvent afforded **6**, **7**, or **8** quantitatively.

1-Methyl-1,2-dihydrobenzocyclobuten-1-ol (6): colorless crystals; mp 63 °C (from hexane); IR ($CHCl_3$) 3600 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.64 (3H, s), 2.49 (1H, br), 3.20 (1H) and 3.33 (1H) (AB-system, J = 14 Hz), 7.10−7.30 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 25.6 (q), 48.2 (t), 78.2 (s), 120.4 (d), 124.0 (d), 127.2 (d), 129.3 (d), 141.1 (s), and 151.0 (s). Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.68; H, 7.62.

1-Trideuteriomethyl-1,2-dihydrobenzocyclobuten-1-ol (7): colorless crystals; mp 79 °C (from hexane); IR ($CHCl_3$) 3596 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.46 (1H, br), 3.19 (1H) and 3.33 (1H) (AB-system, J = 14 Hz), and 7.10−7.30 (4H, m); ^{1}H NMR (400 MHz; C_6D_6) δ 2.01 (1H, s), 2.95 (1H) and 3.06 (1H) (AB-system, J = 14 Hz), and 6.97−7.10 (4H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 24.7, 48.2 (t), 78.1 (s), 120.4 (d), 124.0 (d), 127.2 (d), 129.2 (d), 141.1 (s), and 151.0 (s).

1,4-Dimethyl-1,2-dihydrobenzocyclobuten-1-ol (8): colorless fine crystals; mp 41 °C (from hexane); IR (CCl_4) 3340 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.63 (3H, s), 2.34 (3H, s), 2.39 (1H, br), 3.16 (1H) and 3.30 (1H) (AB-system, J = 14 Hz), and 6.95−7.25 (3H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 22.1 (q), 25.7 (q), 48.0 (t), 77.9 (s), 120.2 (d), 124.6 (d), 128.0 (d), 139.2 (s), 141.1 (s), and 158.0 (s).

General Procedure for Thermolysis of Benzocyclobutenol 7. Benzocyclobutenol **7** (15 mg, 0.11 mmol) and *p*-dimethoxybenzene (13 mg, 0.096 mmol) as an internal standard in 0.4 mL of solvent were placed in an 8 mm ϕ Pyrex tube (5 mm ϕ NMR tube was used for benzene-d_6 or acetonitrile-d_3 as solvent) and degassed by freeze−pump−thaw cycles. The tube was sealed and heated (see Table 1). The solvent was removed, and the residue was analyzed by ^{1}H NMR to reveal that **7** was converted cleanly into **9** and **10**. ^{1}H NMR (400 MHz) peaks of **9** and **10** in benzene-d_6 are as follows: **9**, δ 2.07 (1H, quint, J = 2 Hz), 2.50 (2H, t, J = 2 Hz), and 6.90−7.27 (4H, m); **10**, δ 2.52 (3H, s) and 7.10−7.30 (4 H, m).

Thermolysis of a Mixture of Benzocyclobutenols 7 and 8. Benzocyclobutenols **7** (13.5 mg, 0.1 mmol) and **8** (14.6 mg, 0.1 mmol) in 0.8 mL of benzene were placed in an 8 mm ϕ Pyrex tube and degassed by freeze−pump−thaw cycles. The tube was sealed and heated at 160 °C for 24 h. The solvent was removed, and the residue was analyzed by ^{1}H NMR and MS to reveal the formation of only **9** (M^+: 137) and **11** (M^+: 147).

Reaction of Benzocyclobutenol 7 with *N*-Phenylmaleimide. Benzocyclobutenol **7** (10 mg, 0.075 mmol), *N*-phenylmaleimide (26 mg, 0.15 mmol), and *p*-dimethoxybenzene (11 mg, 0.080 mmol) as an internal standard in benzene-d_6 or

acetonitrile-d_3 were placed in a 5 mm ϕ NMR tube and degassed by freeze−pump−thaw cycles. The tube was sealed and heated at 160 °C for 5.5 h. The ^{1}H NMR spectrum of the reaction mixture showed the complete disappearance of starting benzocyclobutenol **7** and the quantitative formation of adduct **12**. Heating a mixture of nondeuterated benzocyclobutenol **6** (16 mg, 0.12 mmol) and *N*-phenylmaleimide (20 mg, 0.12 mmol) in benzene gave the similar but nondeuterated adduct **13**: IR ($CHCl_3$) 1704 and 3460 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.69 (3H, s), 3.23 (2H, d, J = 6 Hz), 3.29 (1H, d, J = 9 Hz), 3.45 (1H, dt, J = 9 and 6 Hz), 4.56 (1H, s), and 6.90−7.70 (9H, m); ^{13}C NMR (100 MHz; $CDCl_3$) δ 27.0 (q), 29.6 (t), 38.9 (d), 49.8 (d), 72.2 (s), 123.7 (d), 126.3 (2d), 127.7 (d), 128.3 (2d), 128.8 (d), 129.1 (2d), 131.2 (s), 132.2 (s), 142.1 (s) and 178.6 (2s). Anal. Calcd for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.22; H, 5.55; N, 4.52.

Determination of Reaction Rate. Benzocyclobutenol **7** and *p*-dimethoxybenzene as an internal standard in benzene-d_6 were placed in an NMR tube and degassed by freeze−pump−thaw cycles. The tube was sealed and heated at 140, 150, 160, and 170 °C. The progress of reaction was followed by ^{1}H NMR, monitoring the decrease of peak intensity at δ 2.95 assignable to methylene protons. Benzocyclobutenol **7** disappeared with a first-order rate constant of 2.45×10^{-5}, 6.46×10^{-5}, 1.37×10^{-4}, and 2.83×10^{-4} at 140, 150, 160, and 170 °C, respectively.

JO990705N