STRUCTURAL AND SUBSTITUENT EFFECTS ON THE SOLVOLYSIS REACTIVITY OF BRIDGEHEAD COMPOUNDS

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Contents

Preface

The carbocation has been the most intensely studied reactive intermediate in organic chemistry. The history of carbocation chemistry began in 1902 with the study on the triphenylmethyl cation and can be classified into two streams. One is the study on stable carbocations. Hückel predicted in 1931 the existence of stable carbocations having [4n + 2] electrons in cyclic π-conjugated systems. In 1954, Doering synthesized cycloheptatrienyl (tropylium) bromide as a Hückeloid carbocation salt. Since then, many Hückeloid carbocations have been synthesized, and the study on the stable carbocation has led to hydrocarbon salts. The other is the study on unstable carbocations. In the 1920s, the directly non-observable, short-lived, and low concentration carbocation was proposed as a reaction intermediate. In 1935, Hughes and Ingold established the S_N1 mechanism, ever since, many organic reactions were explained in terms of carbocation intermediate pathways. Moreover, σ-bridged carbocations with two electron-three center bonds were proposed as a transient intermediate. This nonclassical ion concept has been widely applied to understanding of reaction mechanisms. However, there has been a great deal of controversy about the nonclassical ion problem of the 2-norbornyl cation, which is probably the most intensely investigated carbocation in history. The presence of carbocation as a reaction intermediate was proposed not based on the direct observation, but based on the detailed kinetic study or stereochemical study of products. Since the 1960s, the development of superacid and NMR spectroscopy has enabled the direct observation of unstable carbocations, and recent progress in theoretical calculations has allowed the prediction of reaction intermediates.

The stability of carbocation is sensibly influenced by the electronic and

steric effects of substituents. Quantitative treatment of such electronic and steric effects on the reactivity has been one of major problems in physical organic chemistry. The quantitative treatment of electronic effects on the reactivity was first demonstrated by Hammett. In 1933, Hammett showed that a plot of log K for benzoic acid ionization against log k for alkaline ester hydrolysis of various *meta* and *para* substituents is linear. This relation is generalized to Eq.1, which is known as Hammett equation.

$$\log (k_X/k_H) = \rho \log (K_X/K_H) = \rho\, \sigma \qquad\qquad (Eq.1)$$

This relation means that the changes in the structure produce proportional changes in the activation energy ($\Delta G^{\ne}$) for the reaction. Therefore, it is known as Linear Free Energy Relationship (LFER), and Hammett equation is the best–known of LFER. In 1962, the first successful separation of steric effect from electronic effect was made by Taft, who proposed the steric parameter Es, following a suggestion by Ingold. On the assumption that the ground state energy level of a series is essentially constant, various LFER of Hammett type equation and substituent parameters have been proposed and given successful explanation of reactivities based on the electronic (Yukawa–Tsuno equation), steric (Taft–Ingold equation) and solvent (Winstein–Grunwald equation) effects.

With such background, the present thesis focuses on quantitative treatment of the ground state destabilizing effect of the substituents on the vicinal position of a reaction center. The thesis consists of six chapters in which the first chapter deals with synthetic studies and the following five chapters are related to the mechanistic studies. The outline is briefly described below.

In Chapter 1 is described the synthesis of 1–chlorobicyclo[2.2.2]oct–2–yl

benzoate and 1–halo–2–adamantyl benzoates via acylative ring expansion reaction of bicyclo[2.2.1]heptane–1–carbaldehyde and noradamantane–3–carbaldehyde, respectively. These benzoates have readily been reduced with $LiAlH_4$ to give 1–halo–2–ols which are useful starting materials leading to vicinal bifunctional, bicyclic or tricyclic compounds.

In Chapters 2 and 3 is described that solvolysis is applied to the evaluation of π–conjugative stabilization of 2–methylene and α–carbonyl carbocations. The cyano and carbonyl groups are strongly electron withdrawing (–I and –M effects). However, in the past decade considerable experimental and theoretical efforts have been made in evaluating the π–conjugative electron donating (+M) effect of these substituents toward cationic carbon (Schemes 1 and 2). This concept of the π–

Scheme 1

Scheme 2
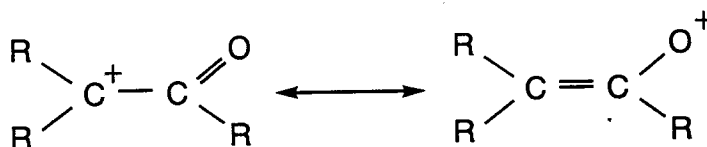
conjugative effect was based on the unexpectedly fast rates of solvolysis of α–cyano and α–carbonyl substrates. Recently, however, the interpretation of the rate data of α–cyano substrates has been questioned, and the importance of the geminal group interaction to destabilize the ground state has been proposed. On the other

hand, the π–conjugative stabilizing effect of a carbonyl group is still an open question. In these chapters, π–conjugative stabilization effect of α–keto cation is examined in solvolysis approach.

The Chapter 2 describes that the rates of the solvolysis of 2–methylene bicyclic and tricyclic compounds relative to the corresponding parent compounds $[k(X = CH_2)/k(X = H_2)]$ markedly increase with the increase in the structural flexibility. These rate studies and molecular mechanics calculations (MM2) and semiempirical molecular orbital calculations (AM1) suggest the usefulness of the methodology to examine the conjugative ability of a group adjacent to the carbocationic center. In Chapter 3, this methodology is applied to the evaluation of π–conjugative ability of an α–keto carbocation. The $k(X = O)/k(X = H_2)$ rate ratios are sensibly constant, which suggests that the π–conjugative stabilization of α–carbonyl group is unimportant, at least in tertiary carbocations. The most important factor of unexpectedly fast rate of solvolysis of α–keto compounds would be geminal group interaction.

The preceding chapters mainly described about the electronic substituent effects. Molecular mechanics and semiempirical molecular orbital calculations supported the rate data. In Chapters 4, 5, and 6 is dealt with the ground state destabilization arising from steric substituent effect. In these chapters, the first typical examples are described on the solvolysis rate enhancements ascribed to the relief of ground state F–strain between an alkyl group and the leaving group atom directly attached to the reaction center. Molecular mechanics and semiempirical molecular orbital calculations supported the rate data. Chapter 4 reports the solvolysis of (Z)– and (E)–2–ethylidenebicyclo[2.2.2]non–1–yl triflates and (Z)– and (E)–2–ethylidene–1–adamantyl derivatives having OMs, F, Cl, Br, or I as a leaving group. The significant increases in the Z/E rate ratios of 2–ethylidene–1–

adamantyl series with the increase in the atomic size of halogen are explained in terms of the presence of F–strain in the Z substrates and its essential absence in the E substrates. Linear correlations are found in a plot of 1.36 × log $[k_Z/k_E]$ against the MM2 steric energy difference between the Z and E isomers (slope 1.0) and against Hansch's Es, demonstrating the significance of the F–strain effect in the enhanced rates of the (Z)–2–ethylidene–1–adamantyl system. On the other hand, more flexible (Z)–2–ethylidenebicyclo[3.2.2]non–1–yl mesylate solvolyzes 3.4 times slower than the E isomer (Chapter 5). This striking contrast suggests the importance of a rigid structure and coplanar arrangement of the Z–methyl group and the reaction center for exerting the F–strain. The Chapter 6 describes further supporting evidence for the F–strain effect in the solvolysis of (Z)–2–ethylidene–1–adamantyl derivatives. The rates of solvolysis are studied for the mesylates and iodides of the (Z)– and (E)–[*methyl–d_3*]–2–ethylidene–1–adamantyl and the corresponding *methyl–d_0* systems. The results for the iodides provide the first example in which the kinetic isotope effect has been observed in the F–strain effect in solvolysis.

The studies described in this thesis can be summarized that the ground state energy level of a neutral molecule is not only sterically but also electronically variable by introducing a substituent. This concept should be taken into account in any kind of reaction as well as solvolysis reactions. Generally, when the reactivity of organic compounds is to be interpreted in terms of the electronic or steric substituent effect, the energy level of transition state or intermediate is discussed. However, it is important to give much attention to the ground state potential energy of neutral molecules, and experimental evidence has just started to appear.

Acknowledgments

List of Publications

(1) Takeuchi, K.; Yoshida, M.; Ohga, Y.; Tsugeno, A.; Kitagawa, T. *J. Org. Chem.* **1990**, *55*, 6063–6065. (Chapter 3)

(2) Takeuchi, K.; Ohga, Y.; Kitagawa, T. *J. Org. Chem.* **1991**, *56*, 5007–5008. (Chapters 4 and 5)

(3) Takeuchi, K.; Ohga, Y.; Munakata, M.; Kitagawa, T. *Chem. Lett.* **1991**, 2209–2212. (Chapter 4)

(4) Takeuchi, K.; Kitagawa, T.; Ohga, Y.; Yoshida, M.; Akiyama, F.; Tsugeno, A. *J. Org. Chem.* **1992**, *57*, 280–291. (Chapter 2)

(5) Takeuchi, K.; Ohga, Y.; Kitagawa, T. *J. Chim. Phys.* **1992**, *89*, 1631–1637. (Chapters 4 and 5)

(6) Takeuchi, K.; Ohga, Y.; Munakata, M.; Kitagawa, T.; Kinoshita, T. *Tetrahedron Lett.* **1992**, *33*, 3335–3338. (Chapter 4)

(7) Ohga, Y.; Takeuchi, K. *J. Phys. Org. Chem.* **1993**, *6*, 293–301. (Chapter 6)

(8) Ohga, Y.; Munakata, M.; Kitagawa, T.; Kinoshita, T.; Takeuchi, K.; Oishi, Y.; Fujimoto, H. *J. Org. Chem.* **1994**, *59*, 4056–4067. (Chapters 1 and 4)

The following publications are not included in this thesis.

The Reactivity of 1–Chloro–3,3–dimethylbicyclo[2.2.2]octan–
2–one in the Radical Mechanism of Nucleophilic Substitution,
Santiago, A. N.; Takeuchi, K.; Ohga, Y.; Nishida, M.; Rossi, R. A.
J. Org. Chem. **1991**, *56*, 1581–1584.

Selective Oxidation of Tertiary–secondary *vic*–Diols to
α–Hydroxy Ketones by Dioxiranes,
Curci, R.; Accolti, L. D.; Detomaso, A.; Fuso, C.; Takeuchi, K.; Ohga, Y.;
Eaton, P. E.; Yip, Y. C. *Tetrahedron Lett.* **1993**, *34*, 4559–4562.

Chapter 1

Synthesis of 1–Halo–2–substituted Bicyclo[2.2.2]octyl and Adamantyl Compounds

Abstract

A new route for the synthesis of 1–halo–2–substituted bicyclic or tricyclic compounds was developed. The acylative ring expansion of 7,7–dimethylbicyclo-[2.2.1]heptane–1–carbaldehyde by using benzoyl chloride and aluminum chloride in carbon disulfide at 0 °C afforded 1–chloro–3,3–dimethylbicyclo[2.2.2]oct–2–yl benzoate. Treatment of noradamantane–3–carbaldehyde with benzoyl trifluoro-methanesulfonate (triflate) in CH_2Cl_2 followed by addition of a tetra–n–butylam-monium halide (n–Bu_4NX, X = Cl, Br, I) or lithium fluoride gave 1–halo–2–adamantyl benzoates. These benzoates were readily reduced with lithium alumi-num hydride to 1–halo–2–adamantanols, which were oxidized by using pyridini-um chlorochromate (PCC) to give the corresponding 1–halo–2–oxo compounds.

1–1. Introduction

Bicyclic or tricyclic bridgehead compounds are free from neighboring group participation or nucleophilic solvent assistance from the rear side of the bridgehead position. In addition, the steric circumstances around the reaction center are kept essentially unchanged in the various bicyclic or tricyclic compounds. Previously,

it has been reported from this laboratory that the acylative ring expansion of various bridgehead aldehydes with benzoyl trifluoromethanesulfonate (triflate) and trifluoromethanesulfonic acid (triflic acid) gives 1,2–diol monobenzoates which can be converted to the corresponding ketols (Scheme 1.1).[1] These ketols are useful starting materials leading to various bifunctional bicyclic or tricyclic compounds.

Scheme 1.1
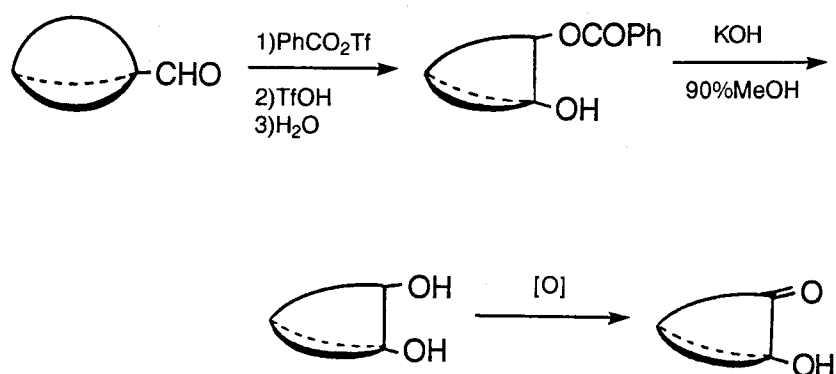
For the examination of structural and electronic effects of substituent on homolytic[2] and heterolytic[3] reactions, the halogen atom is preferable to the carboxylate or the sulfonate leaving group as the leaving group of bicyclic or tricyclic bridgehead compounds, because it is possible to rule out side reactions such as sulfur–oxygen cleavage reaction of a sulfonate leaving group. Tabushi and his coworkers obtained 1–fluoro–2–adamantanone[4a] and 1–bromo–2–adamantanone[4b] by direct fluorination and bromination of 2–adamantanone. Hirsl–Starevic and Majerski[4c] synthesized 1–chloro–2–adamantanone starting from 4–protoadamantanone. But, these synthetic methods are not appropriate for preparative purpose. This Chapter describes a new route for synthesis of 1–halo–2–benzoates via acyla-

tive ring expansion in good yields.[3b,d,e] The conversion to the corresponding 1–halo–2–oxo compounds is also described.
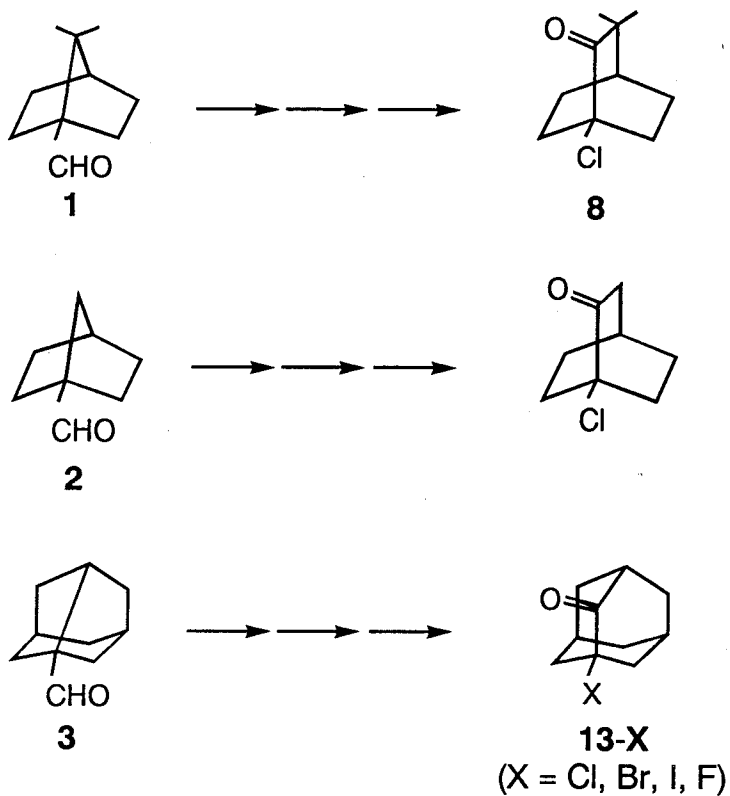
1–2. Results and Discussion

Acylative Ring Expansion of 7,7–Dimethylbicyclo[2.2.1]heptane–1–carbaldehyde (1) and Bicyclo[2.2.1]heptane–1–carbaldehyde (2). In the beginning, the most common reagents for the preparation of alkyl chlorides from alcohols

such as $SOCl_2$, PCl_3, and PCl_5 were attempted on 1–hydroxy–3,3–dimethylbicy-clo[2.2.2]oct–2–yl benzoate and 1–hydroxy–3,3–dimethylbicyclo[2.2.2]octan–2-one. But, these bridgehead alcohols were not converted to the corresponding chlorides because of their low reactivity. Therefore, a new route was developed.

Acylative ring expansion of 7,7–dimethylbicyclo[2.2.1]heptane–1–carbaldehyde 1 by using 1.2 equivalent of benzoyl chloride (PhCOCl) and 3.4 equivalent of aluminum chloride ($AlCl_3$) in carbon disulfide (CS_2) at 0 °C under N_2 afforded 1–chloro–3,3–dimethylbicyclo[2.2.2]oct–2–yl benzoate (6). The benzoate 6 was reduced with lithium aluminum hydride ($LiAlH_4$) to 1–chloro–3,3–dimethylbicyclo[2.2.2]octan–2–ol (7), which was then converted to 1–chloro–3,3–dimethylbicyclo[2.2.2]octan–2–one (8) by oxidation with pyridinium chlorochromate (PCC) in an overall yield of 46 % based on 1 (Scheme 1.2).

Scheme 1.2
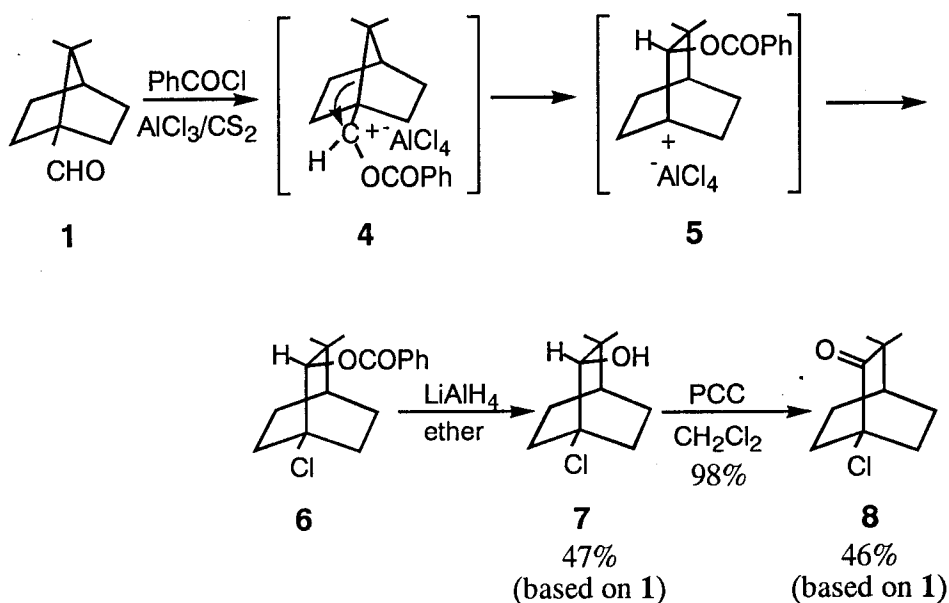
Similarly, 1–chlorobicyclo[2.2.2]oct–2–yl benzoate was obtained by acylative ring expansion of bicyclo[2.2.1]heptane–1–carbaldehyde (**2**) with PhCOCl and AlCl$_3$. Reduction with LiAlH$_4$ followed by oxidation with PCC gave 1–chlorobicyclo[2.2.2]octan–2–one in an overall yield of 48% based on **2**.

The formation of 1–halo–2–benzoates can be explained by following the aforementioned acylative ring expansion mechanism (Scheme 1.1). The reaction probably proceeds following Scheme 1.2 via the nucleophilic attack of the aldehyde oxygen to benzoyl chloride giving **4**. The rapid Wagner–Meerwein rearrangement of **4** gives **5**, which is captured by Cl⁻ to give **6**.

Acylative Ring Expansion of Noradamantane–3–carbaldehyde (3) in the Presence of tetra–n–Butylammonium Halides (n–Bu$_4$NX, X = Cl, Br, I). Similar attempts to carry out acylative ring expansion of **3** in the presence of PhCOI and AlI$_3$ in CS$_2$ failed. The major product was benzoate–iodide **9–I** (Scheme 1.3).

Scheme 1.3
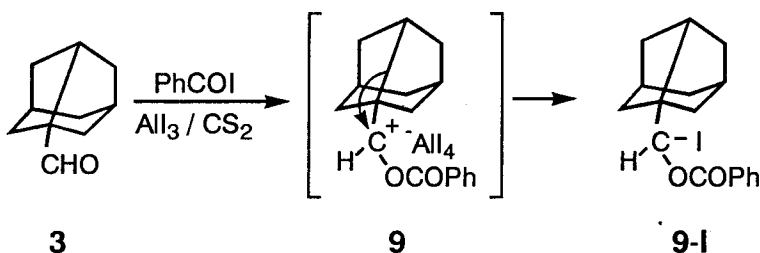
Obviously, it was required to add the iodide ion after **9** has rearranged to **10**. Acylative ring expansion of **3** with 1.2 equivalent of benzoyl trifluoromethanesulfonate (triflate) (PhCOOTf) in CH$_2$Cl$_2$ at 0 °C followed by treatment with 1.5

equivalent of n–Bu$_4$NX (X = Cl, Br, I) gave 1–halo–2–adamantyl benzoates (**11–X**). The benzoates were reduced with LiAlH$_4$ in ether and then oxidized by PCC to give 2–oxo–1–haloadamantanes (**13–X**) (Scheme 1.4, Tables 1.1, 1.2, and 1.3).

Scheme 1.4
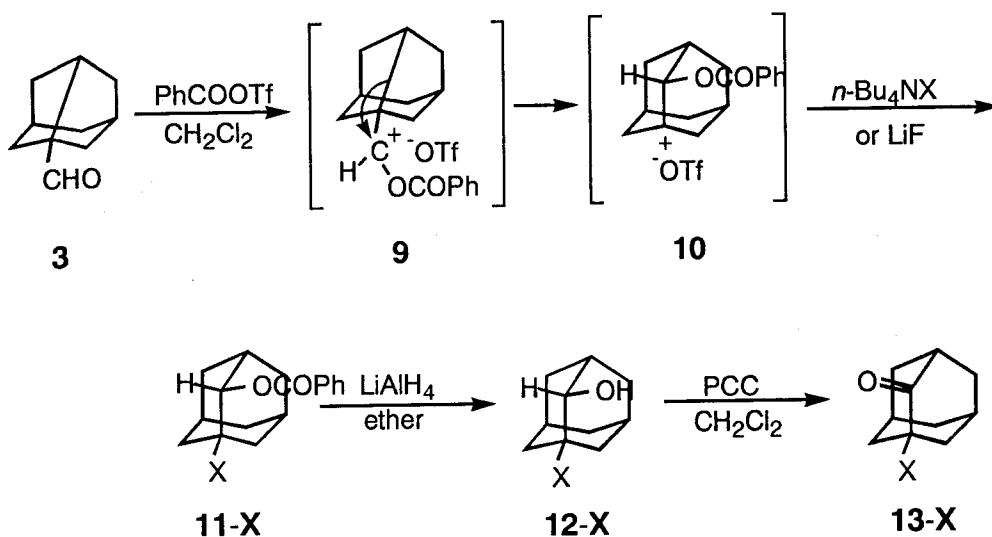
Acylative Ring Expansion of 3 in the Presence of Lithium Fluoride. In the beginning, commercially available n–Bu$_4$NF·3H$_2$O or a THF solution of n–Bu$_4$NF was used in the place of the ammonium halides n–Bu$_4$NX (X = Cl, Br, I) which were successfully utilized for the synthesis of **11–X**'s (X = Cl, Br, I). But, the hydrolyzed product **11–OH** was obtained as a major product (82%), because it was

Table 1.1. Yields, Melting Points, and Microanalytical Data for 1–Halo–2–adamantyl Benzoates

compound	yield[a](%)	mp (°C)	anal. obsd (calcd)
11–F	50	111.5–112.5	C; 74.27 (74.43)
		(hexane)	H; 7.04 (6.98)
			F; 6.84 (6.93)
11–Cl	61	86.0–87.0	C; 70.21 (70.22)
		(hexane)	H; 6.61 (6.59)
			Cl; 11.98 (12.19)
11–Br	59	84.5–85.0	C; 61.20 (60.91)
		(hexane)	H; 5.82 (5.71)
			Br; 23.59 (23.83)
11–I	70	118.5–119.0	C; 53.62 (53.42)
		(hexane)	H; 4.93 (5.01)
			I; 32.94 (33.20)

[a]Isolated yield.

Table 1.2. Yields, Melting Points, and Microanalytical Data for 1–Halo–2–adamantanols

compound	yield[a](%)	mp (°C)	anal. obsd (calcd)
12–F	92	224.5	C; 70.41 (70.56)
		(pentane)	H; 8.85 (8.88)
			F; 11.27 (11.16)
12–Cl	44	194.0–195.0[b]	——— [c]
		(pentane)	
12–Br	61	144.5–145.5	C; 51.83 (51.97)
		(hexane)	H; 6.55 (6.54)
			Br; 34.59 (34.57)
12–I	80	58.5–59.0	C; 43.33 (43.18)
		(pentane)	H; 5.53 (5.44)
			I; 45.40 (45.63)

[a]Isolated yield. [b]Melting point was not reported in ref 4c. [c]Reported in ref 4c.

Table 1.3. Yields, Melting Points, and Microanalytical Data for 1–Halo–2–adamantanones

compound	yield[a](%)	mp (°C)	anal. obsd (calcd)
13–F	90	308.5–309.5[b]	C; 71.28 (71.40)
			H; 8.02 (7.79)
			F; 11.41 (11.29)
13–Cl	92	188.0–189.0[c]	———[d]
		(hexane)	
13–Br	92	125.0–125.5[e]	C; 52.61 (52.42)
		(hexane)	H; 5.83 (5.72)
			Br; 34.95 (34.87)
13–I	87	116.0–117.0	C; 43.49 (43.50)
		(hexane–	H; 4.61 (4.75)
		benzene)	I; 45.75 (45.96)

[a]Isolated yield. [b]Lit. mp 213–216 °C; see ref 4a. [c]Melting point was not reported in ref 4c. [d]Reported in ref 4c. [e]Lit. mp 124–125 °C; see ref 4b.

difficult to prepare anhydrous $n-$Bu$_4$NF or its solution in THF. As a fluoride anion source, potassium fluoride was tried for acylative ring expansion, but the products were a mixture of **11-F** (17%), **11-OH** (34%), and 1,2-dibenzoate **11-OCOPh** (20%) (Scheme 1.5). Finally, the use of lithium fluoride was successful. Acylative ring expansion of **3** with 1.2 equivalent of PhCOOTf in CH$_2$Cl$_2$ at 0 °C followed by addition of large excess of finely powdered lithium fluoride to the reaction mixture with vigorous stirring gave **11-F** in a yield of 50%. Reduction followed by oxidation afforded **13-F** in 83% yield based on **11-F**.

Scheme 1.5
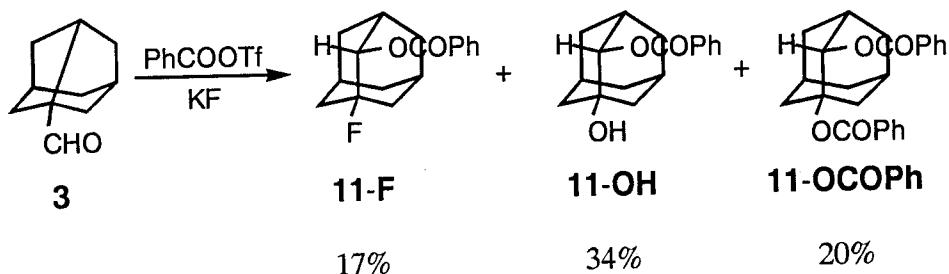
1-3. Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Hitachi 215 or Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi R-24 (60 MHz) or JEOL FX90A (89.55 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX90A (22.5 MHz) spectrometer. In all NMR measurements TMS was used as an internal standard. Elemental analyses were performed by the Microanalytical Center, Kyoto University, Kyoto. 7,7-

Dimethylbicyclo[2.2.1]heptane-1-carbaldehyde (**1**), bicyclo[2.2.1]heptane-1-carbaldehyde (**2**), and noradamantane-3-carbaldehyde (**3**) were prepared following literature methods.[1] Benzoyl triflate was prepared by the method of Brown and Koreeda.[5] n–Bu$_4$NCl, n–Bu$_4$NBr, n–Bu$_4$NI and LiF were dried at 100–120 °C in vacuo for longer than 6 h before use. All anhydrous solvents used for synthetic work were purified by standard procedure. Other commercially available reagents were of a reagent–grade quality and used as received. Medium–pressure liquid chromatography (MPLC) was conducted on Merck silica gel 60 (230–400 mesh).

1–Chloro–3,3–dimethylbicyclo[2.2.2]oct–2–yl Benzoate (6). To a stirred suspension of pulverized aluminum chloride (6.79 g, 50.9 mmol) in carbon disulfide (50 mL) was added a solution of 7,7–dimethylbicyclo[2.2.1]heptane-1-carbaldehyde (**1**) (2.28 g, 15.0 mmol) and benzoyl chloride (PhCOCl) (2.91 g, 20.7 mmol) in carbon disulfide (CS$_2$) (21 mL) at 3–4 °C over 14 min under N$_2$, and then stirring continued at room temperature for 90 min. The reaction mixture was poured into ice (110 g) and extracted with ether (120 mL). The combined extracts were washed with saturated aqueous NaHCO$_3$ (3 × 50 mL) and dried (MgSO$_4$). Evaporation of solvent afforded crude 1–chloro–3,3–dimethylbicyclo[2.2.2]oct-2–yl benzoate (**6**) (4.6 g). An analytical sample was obtained by recrystallization from hexane as colorless crystals: mp 96.5–97.0 °C; IR (CCl$_4$) 2970, 1730, 1600, 1450, 1395, 1370, 1280, 1180, 1120, 1030, 710 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.00 (s, 3 H), 1.36 (s, 3 H), 1.4–2.8 (m, 9 H), 4.94 (br s, 1 H), 7.3–8.2 (m, 5 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 39.1, 69.4 (C), 35.3, 82.3 (CH), 24.2, 24.6, 28.8, 34.0 (CH$_2$), 23.2, 29.1 (CH$_3$), 128.3, 129.6, 130.0, 132.8 (Ph), 166.0 (C=O). Anal. Calcd for C$_{17}$H$_{21}$O$_2$Cl: C, 69.73; H, 7.23. Found: C, 69.85; H, 7.46.

1–Chloro–3,3–dimethylbicyclo[2.2.2]octan–2–ol (7). An ether solution of

crude **4** (4.68 g) was added dropwise to $LiAlH_4$ (0.76 g, 20.0 mmol) in ether with stirring. The reaction mixture was further stirred for 30 min at room temperature and then worked up in a usual manner. Separation of **7** from benzyl alcohol by MPLC (SiO_2, hexane–ether (9:1)) gave pure **7** (1.33 g) in an overall yield of 47% based on aldehyde **1**: mp 43.5–44.0 °C; IR (CCl_4) 3600, 2950, 1460, 1325, 1270, 1080, 970, 910 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.05 (s, 3 H), 1.10 (s, 3 H), 1.2–2.6 (m, 9 H), 3.37 (s, 1 H, OH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 38.8, 75.8 (C), 35.6, 81.0 (CH), 24.6, 24.9, 27.6, 34.1 (CH_2), 22.7, 30.1 (CH_3). Anal. Calcd for $C_{10}H_{17}OCl$: C, 63.65; H, 9.08. Found: C, 63.37; H, 9.16.

1–Chloro–3,3–dimethylbicyclo[2.2.2]octan–2–one (8). To a suspension of pyridinium chlorochromate (2.29 g, 10.6 mmol) in CH_2Cl_2 (13 mL) was added a solution of **7** (1.33 g, 7.07 mmol) in CH_2Cl_2 (13 mL), and the mixture was magnetically stirred under N_2 at room temperature for 11 h. The reaction mixture was passed through a column of Florisil (13 g), and the residue was well washed with ether and passed through the same column. Evaporation of solvent afforded colorless crystals (1.33 g), which was purified by MPLC (SiO_2, hexane–ether (9:1)) to give pure **8** (1.29 g, 98%): mp 46.0–47.0 °C; IR (CCl_4) 2950, 1730, 1460, 1380, 970 cm^{-1}; ^1H NMR (89.55 MHz, $CDCl_3$) δ 1.21 (s, 6 H), 1.6–2.5 (m, 9 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 47.5, 72.1 (C), 37.3 (CH), 23.8, 33.3 (CH_2), 24.0 (CH_3), 211.3 (C=O). Anal. Calcd for $C_{10}H_{15}OCl$: C, 64.34; H, 8.10; Cl, 18.99. Found: C, 64.25; H, 8.40; Cl, 18.69.

1–Chlorobicyclo[2.2.2]oct–2–yl Benzoate. To a suspension of $AlCl_3$ (1.56 g, 11.7 mmol) in CS_2 (12 mL) was added a solution of bicyclo[2.2.1]heptane–1–carbaldehyde (**2**) (0.426 g, 3.43 mmol) and benzoyl chloride (0.654 g, 4.65 mmol)

in CS_2 (5 mL) at 3–6 °C over 12 min under N_2, and the resulting mixture was stirred for 2 h. The reaction mixture was poured into ice (25 g) and extracted with ether (35 mL). The extract was washed with saturated aqueous $NaHCO_3$ (3 × 15 mL) and dried ($MgSO_4$). Evaporation of solvent afforded crude 1–chlorobicyclo-[2.2.2]oct–2–yl benzoate (1.158 g) as brown liquid: ^1H NMR (60 MHz, CCl_4) δ 1.00–2.90 (m, 11 H), 5.00–5.30 (m, 1 H), 7.20–7.67 (m, 3 H), 7.87–8.20 (m, 3 H).

1–Chlorobicyclo[2.2.2]octan–2–ol. A solution of crude 1–chlorobicyclo-[2.2.2]oct–2–yl benzoate (1.158 g) in ether (11 mL) was added dropwise to $LiAlH_4$ (0.200 g, 5.27 mmol) in ether (22 mL) at room temperature. The reaction mixture was stirred for another 40 min and then worked up in a usual manner. Separation by MPLC (SiO_2, hexane–ether (9:1)) gave 1–chlorobicyclo[2.2.2]–octan–2–ol (0.395 g, 72% based on **2**) as colorless crystals: ^1H NMR (60 MHz, CCl_4) δ 1.33–2.73 (m, 11 H), 2.38 (s, 1 H), 3.66–4.00 (m, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 74.0 (C), 73.0, 23.9 (CH), 37.2, 33.7, 28.6, 27.5, 27.4 (CH_2).

1–Chlorobicyclo[2.2.2]octan–2–one. To a suspension of pyridinium chlorochromate (0.800 g, 3.71 mmol) in CH_2Cl_2 (4.6 mL) was added a solution of 1–chlorobicyclo[2.2.2]octan–2–ol (0.395 g, 2.46 mmol) in CH_2Cl_2 (4.6 mL), and the resulting mixture was stirred under N_2 at room temperature for 14.5 h. The reaction mixture was passed through a column of Florisil (4 g), and the residue was well washed with ether and passed through the same column. Evaporation of solvent afforded essentially pure 1–chlorobicyclo[2.2.2]octan–2–one (0.350 g, 90%) as colorless crystals: mp 118.5–119.0 °C (from hexane); IR (CCl_4) 2946, 2875, 1750, 1452, 1405, 1094, 1004, 955, 833, 625 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.60–2.53 (m, 11 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 206.5, 71.9 (C), 27.2 (CH), 44.8, 33.5, 27.2 (CH_2).

1-Chloro-2-adamantyl Benzoate (11-Cl). To a solution of benzoyl triflate (10.57 g, 41.6 mmol) in CH_2Cl_2 (40 mL) was added a solution of **3** (5.20 g, 34.6 mmol) in CH_2Cl_2 (40 mL) over 14 min under N_2, while the temperature was kept below 8 °C in an ice–water bath. After the mixture had been stirred for 10 min, n–Bu$_4$NCl (14.0 g, 50.4 mmol) was added. The mixture was stirred at room temperature for 17 h. The reaction mixture was poured into ice–water (80 mL) and extracted with ether (3 × 80 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 70 mL) and saturated aqueous NaCl (2 × 70 mL) and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (95:5)) afforded **11–Cl** (6.18 g, 61%) as colorless crystals: mp 86.0–87.0 °C (from hexane); IR (CCl_4) 3071, 2936, 2923, 2860, 1724, 1603, 1452, 1275, 1112, 709 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.46–2.73 (m, 13 H), 5.30 (d, 1 H, J = 3.62 Hz), 7.34–8.20 (m, 5 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 165.4, 130.4, 68.4 (C), 132.9, 129.6, 128.3, 79.5, 35.4, 30.7, 30.7 (CH), 47.0, 42.3, 35.2, 35.1, 30.1 (CH$_2$). Anal. Calcd for $C_{17}H_{19}O_2Cl$: C, 70.22; H, 6.59; Cl, 12.19. Found: C, 70.21; H, 6.61; Cl, 11.98.

1-Chloro-2-adamantanol (12-Cl). A solution of **11–Cl** (6.18 g, 21.2 mmol) in ether (80 mL) was added dropwise to a solution of LiAlH$_4$ (1.13 g, 29.8 mmol) in ether (100 mL) at room temperature. The reaction mixture was stirred for another 1 h and then worked up in a usual manner. Separation by MPLC (SiO_2, hexane–ether (95:5)) gave **12–Cl** (1.76 g, 44%) as colorless crystals: mp 194.0–195.0 °C (from pentane).[6] The spectral data satisfactorily coincided with the reported data.[4c]

1-Chloro-2-adamantanone (13-Cl). To a suspension of pyridinium chlorochromate (3.89 g, 18.0 mmol) in CH_2Cl_2 (35 mL) was added a solution of **12-Cl** (1.70 g, 9.11 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was stirred under N_2 at room temperature for 50 h. Ether (35 mL) was added to the reaction mixture, then the solution was passed through a column of Florisil (50 g). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (95:5)) afforded **13-Cl** (1.54 g, 92%) as colorless crystals: mp 188.0–189.0 °C (from hexane).[6] The spectral data satisfactorily coincided with the reported data.[4c]

1-Bromo-2-adamantyl Benzoate (11-Br). To a solution of benzoyl triflate (3.69 g, 15.6 mmol) in CH_2Cl_2 (16 mL) was added a solution of **3** (1.95 g, 13.0 mmol) in CH_2Cl_2 (13 mL) over 11 min under N_2, while the temperature was kept below 7 °C in an ice–water bath. After the mixture was stirred for 5 min, *n*–Bu_4NBr (5.20 g, 16.1 mmol) was added. The mixture was stirred for 18 h at room temperature and then poured into ice–water (40 mL) and extracted with ether (3 × 60 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 60 mL) and saturated aqueous NaCl (2 × 60 mL) and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (95:5)) afforded **11-Br** (2.57 g, 59%) as colorless crystals: mp 84.5–85.0 °C (from hexane); IR (CCl_4) 3071, 2935, 2861, 1724, 1603, 1452, 1274, 1112, 1027 cm^{-1}; ^1H NMR (89.55 MHz, $CDCl_3$) δ 1.42–2.90 (m, 13 H), 5.39 (d, 1 H, J = 3.5 Hz), 7.38–8.19 (m, 5 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 165.1, 130.2, 65.2 (C), 132.8, 129.5, 128.2, 79.8, 35.3, 31.3, 31.2 (CH). Anal. Calcd for $C_{17}H_{19}O_2Br$: C, 60.91; H, 5.71; Br, 23.83. Found: C, 61.20; H, 5.82; Br, 23.59.

1-Bromo-2-adamantanol (12-Br). A solution of **11-Br** (2.37 g, 7.07 mmol) in ether (30 mL) was added dropwise to $LiAlH_4$ (0.350 g, 9.22 mmol) in

ether (40 mL) at room temperature. The reaction mixture was stirred for another 25 min and then worked up in a usual manner. Separation by MPLC (SiO_2, hexane–ether (9:1)) gave **12-Br** (0.993 g, 61%) as colorless crystals: mp 144.5–145.5 °C (from hexane); IR (CCl_4) 3574, 2919, 2859, 1451, 1352, 1058, 1022 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.38–2.78 (m, 13 H), 2.59 (s, 1 H), 3.94 (d, 1 H, J = 3.4 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 74.6 (C), 78.4, 36.3, 32.0, 31.8 (CH), 47.8, 42.8, 35.6, 35.4, 28.9 (CH_2). Anal. Calcd for $C_{10}H_{15}OBr$: C, 51.97; H, 6.54; Br, 34.57. Found: C, 51.83; H, 6.55; Br, 34.59.

1–Bromo–2–adamantanone (13–Br). To a suspension of pyridinium chlorochromate (1.27 g, 5.89 mmol) in CH_2Cl_2 (11 mL) was added a solution of **12-Br** (0.908 g, 3.93 mmol) in CH_2Cl_2 (11 mL), and the resulting mixture was stirred under N_2 at room temperature for 68 h. Ether (15 mL) was added to the reaction mixture, and then the solution was passed through a column of Florisil (45 g). Evaporation of solvent afforded **13-Br** (0.832 g, 92%) as colorless crystals: mp 125.0–125.5 °C (from hexane) (lit.[4b] mp 124–125 °C); IR (CCl_4) 2935, 2861, 1743, 1454, 1287, 1052, 1029, 877, 635 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.70–2.34 (m, 8 H), 2.47–2.67 (m, 4 H), 2.95 (br s, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 206.0, 70.6 (C), 47.7, 30.8 (CH), 50.9, 38.0, 34.1 (CH_2). Anal. Calcd for $C_{10}H_{13}OBr$: C, 52.42; H, 5.72; Br, 34.87. Found: C, 52.61; H, 5.83; Br, 34.95.

1–Iodo–2–adamantyl Benzoate (11–I). To a solution of benzoyl triflate (5.74 g, 22.6 mmol) in CH_2Cl_2 (23 mL) was added a solution of **3** (2.83 g, 18.8 mmol) in CH_2Cl_2 (19 mL) over 15 min under N_2, while the temperature was kept below 6 °C in an ice–water bath. After stirring for 5 min, *n*–Bu$_4$NI (10.44 g, 28.3

mmol) was added. The mixture was stirred at 0 °C for 6 h and then at room temperature for 14 h. The reaction mixture was poured into ice–water (60 mL) and extracted with ether (3 × 120 mL). The combined extracts were washed with 10% aqueous $Na_2S_2O_3$ (2 × 120 mL) and saturated aqueous NaCl (2 × 120 mL) and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (95:5)) afforded **11-I** (5.00 g, 70%): mp 118.5–119.0 °C (from hexane); IR (CCl_4) 3071, 2933, 2860, 1725, 1603, 1451, 1341, 1273, 1176, 1111, 1070, 1027, 708, 689, 654 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.42–3.17 (m, 13 H), 5.37 (d, 1 H, J = 1.0 Hz), 7.18–7.62 (m, 3 H), 7.94–8.30 (m, 2 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 165.1, 130.4, 49.5 (C), 132.9, 129.7, 128.3, 81.6, 34.9, 32.1, 31.7 (CH), 51.3, 46.7, 35.4, 30.0 (CH_2). Anal. Calcd for $C_{17}H_{19}OI$: C, 53.42; H, 5.01; I, 33.20. Found: C, 53.62; H, 4.93; I, 32.94.

1–Iodo–2–adamantanol (12–I). A solution of **11-I** (4.75 g, 12.4 mmol) in ether (50 mL) was added dropwise to $LiAlH_4$ (0.566 g, 14.9 mmol) in ether (40 mL) at room temperature. The reaction mixture was stirred for another 40 min and then worked up in a usual manner. Separation by MPLC (SiO_2, hexane–ether (9:1)) gave pure **12-I** (2.76 g, 80%) as colorless crystals: mp 58.5–59.0 °C (from pentane); IR (CCl_4) 3563, 2917, 2858, 1451, 1350, 1287, 1225, 1107, 1070, 1057, 1020, 960, 940, 689, 650 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.23–3.06 (m, 13 H), 2.43 (s, 1 H), 4.04 (d, 1 H, J = 2.3 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 63.3 (C), 80.1, 36.1, 32.9, 32.3 (CH), 51.1, 45.6, 36.0, 35.6, 29.1 (CH_2). Anal. Calcd for $C_{10}H_{15}OI$: C, 43.18; H, 5.44; I, 45.63. Found: C, 43.22; H, 5.53; I, 45.40.

1–Iodo–2–adamantanone (13–I). To a suspension of pyridinium chloro-chromate (2.93 g, 13.6 mmol) in CH_2Cl_2 (24 mL) was added a solution of **12-I** (2.51 g, 9.0 mmol) in CH_2Cl_2 (34 mL) and the resulting mixture was stirred under

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N_2 at room temperature for 20 h. Ether (30 mL) was added to the reaction mixture, and then the solution was passed through a column of Florisil (40 g). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (9:1)) afforded **13–I** (2.18 g, 87%) as colorless crystals: mp 116.0–117.0 °C (from hexane–benzene); IR (CCl_4) 2933, 2859, 1729, 1452, 1285, 1050, 1024, 994, 876, 630 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.71–2.36 (m, 8 H), 2.54–3.10 (m, 5 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 206.7, 57.1 (C), 46.8, 31.3 (CH), 53.4, 38.3, 34.2 (CH_2). Anal. Calcd for $C_{10}H_{13}OI$: C, 43.50; H, 4.75; I, 45.96. Found: C, 43.49; H, 4.61; I, 45.75.

1–Fluoro–2–adamantyl Benzoate (11–F). To a solution of benzoyl triflate (7.55 g, 29.7 mmol) in CH_2Cl_2 (35 mL) was added a solution of **3** (3.93 g, 26.2 mmol) in CH_2Cl_2 (24 mL) over 12 min under N_2, while the temperature of the solution was kept below 8 °C in an ice–water bath. After 3 min of stirring, finely powdered LiF (13.0 g, 0.50 mol) was added. The mixture was stirred at room temperature for 16 h, and then ice–water (20 mL) was added. The excess LiF was removed by filtration and the filtrate was extracted with ether (2 × 30 mL). The extracts were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and saturated aqueous NaCl (2 × 50 mL) and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (95:5)) afforded **11–F** (3.58 g, 50%) as colorless crystals: mp 111.5–112.5 °C (from hexane); IR (CCl_4) 3072, 2925, 2859, 1724, 1603, 1452, 1271, 1028 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.43–2.57 (m, 13 H), 5.31 (m, 1 H), 7.30–8.14 (m, 5 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 165.3, 130.3, 91.2 (d, J = 192.8 Hz) (C), 132.7, 129.3, 128.0, 77.1 (d, J = 15.9 Hz), 34.9 (d, J = 8.2 Hz), 30.5 (d, J = 6.6 Hz), 30.1 (d, J = 6.6 Hz) (CH), 41.6 (d, J = 16.5 Hz), 37.1 (d, J = 18.1 Hz), 35.3 (d, J = 2.2 Hz), 34.8 (d, J = 1.1 Hz), 30.2 (d, J = 1.1 Hz) (CH_2). Anal. Calcd for $C_{17}H_{19}O_2F$: C, 74.43; H, 6.98; F, 6.93. Found:

C, 74.27; H, 7.04; F, 6.84.

1-Fluoro-2-adamantanol (12-F). A solution of **11-F** (3.58 g, 13.0 mmol) in ether (46 mL) was added dropwise to LiAlH$_4$ (0.600 g, 15.8 mmol) in ether (57 mL) at room temperature over 34 min. The reaction mixture was stirred for 30 min and then worked up in the usual manner. Separation by MPLC (SiO$_2$, hexane–ether (9:1)) gave **12-F** (2.04 g, 92%) as colorless crystals: mp 224.5 °C (from pentane); IR (CCl$_4$) 3611, 2917, 2864, 1453, 1355, 1235, 1077 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.29–2.18 (m, 13 H), 2.65 (s, 1 H), 3.87 (dd, 1 H, *J* = 3.3, 6.6 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 94.5 (d, *J* = 185.7 Hz) (C), 75.6 (d, *J* = 16.0 Hz), 35.9 (d, *J* = 21.5 Hz), 31.1 (d, *J* = 9.3 Hz), 30.6 (d, *J* = 9.9 Hz) (CH), 41.1 (d, *J* = 21.5 Hz), 36.2 (d, *J* = 1.6 Hz), 35.8 (d, *J* = 2.2 Hz), 35.1 (d, *J* = 2.2 Hz), 29.3 (d, *J* = 1.7 Hz) (CH$_2$). Anal. Calcd for C$_{10}$H$_{15}$OF: C, 70.56;, H, 8.88; F, 11.16. Found: C, 70.41; H, 8.85; F, 11.27.

1-Fluoro-2-adamantanone (13-F). To a suspension of pyridinium chlorochromate (3.88 g, 18.0 mmol) in CH$_2$Cl$_2$ (35 mL) was added a solution of **12-F** (2.04 g, 12.0 mmol) in CH$_2$Cl$_2$ (35 mL), and then the resulting mixture was stirred under N$_2$ at room temperature for 19 h. Ether (30 mL) was added to the reaction mixture; then the solution was passed through a column of Florisil (50 g). Evaporation of solvent afforded **13-F** (1.82 g, 90%) as colorless crystals: mp 308.5–309.5 °C (sealed tube. lit.[4a] mp 213–216 °C); ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.85–2.23 (m, 10 H), 2.39 (br s, 2 H), 2.77 (br 2, 1 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 209.3 (d, *J* = 14.0 Hz), 95.0 (d, *J* = 203.9 Hz) (C), 47.5 (d, *J* = 1.8 Hz), 30.0 (d, *J* = 9.2 Hz) (CH), 43.8 (d, *J* = 17.7 Hz), 37.5 (d, *J* = 1.2 Hz), 34.1 (d, *J* = 1.8 Hz) (CH$_2$). Although the melting point was higher than that reported by ca. 90 °C, the ^{13}C and ^{1}H NMR spectra were consistent with the structure and analyti-

cal data were satisfactory. Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79; F, 11.29. Found: C, 71.28; H, 8.02; F, 11.41.

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Chapter 2

Solvolysis of 2–Methylene Bicyclic Bridgehead Derivatives: A Model
for Gradual Variation of π–Conjugation in Carbocations

Abstract

The rates of solvolysis in ethanol or 80% ethanol at 25 °C have been deter-
mined on 2–methylenebicyclo[2.2.2]oct–1–yl triflate (**4a**), 2–methylenebicyclo-
[3.2.1]oct–1–yl triflate (**5a**), 2–methylenebicyclo[3.2.2]non–1–yl mesylate (**6a**),
2–methylenebicyclo[3.3.1]non–1–yl mesylate (**7a–OMs**) and heptafluorobutyrate
(**7a–OHFB**), 1–chloro–2–methylenebicyclo[4.2.2]decane (**8a**), 2–methylene-
bicyclo[4.3.1]dec–1–yl trifluoroacetate (**9a**), and 4–methylene–3–homoadamantyl
heptafluorobutyrate (**10a**) and on their corresponding parent 1–bicycloalkyl and 3–
homoadamantyl derivatives **4b–10b** containing the respective leaving group. The
rate ratios for **4a/4b**, **5a/5b**, **10a/10b**, **6a/6b**, **7a/7b**, **8a/8b**, and **9a/9b** are $10^{-3.9}$,
$10^{-1.9}$, $10^{-1.1}$, $10^{-0.8}$, $10^{0.9}$ (for mesylate), $10^{-0.2}$, and $10^{0.7}$, respectively. A plot of
the logarithms of the rate ratios against olefinic strain energies of their correspond-
ing unsubstituted bridgehead olefins shows that the smaller the olefinic strain
energy, the greater the rate ratio, providing a methodology to gradually change the
conjugative ability of bridgehead carbocations. The enhancement of allylic conju-
gation with increasing skeletal flexibility has been further verified by the enhanced
solvolysis rate of (*E*)–2–ethylidenebicyclo[3.2.2]non–1–yl mesylate ((*E*)–**6e**)
relative to **6a** by a factor of 259. A similar study on much more rigid (*E*)–2–ethy-

lidenebicyclo[2.2.2]oct–1–yl triflate ((*E*)–**4e**) gave a (*E*)–**4e/4a** rate ratio of 6.3. AM1 semiempirical molecular orbital calculations on pertinent 2–methylene and (*E*)–2–ethylidene bridgehead carbocations and corresponding hydrocarbons (L = hydrogen) also supported the increase in the conjugation with increasing skeletal flexibility. The solvolysis products were solely bridgehead substitution products, no indication for the formation of bridgehead olefin via an S_N1' mechanism having been obtained.

2–1. Introduction

It is well–known that the π–conjugative stabilization of allylic carbocations is highly sensitive to conformation. When the π–system is perpendicularly oriented relative to the cationic p orbital, the vinyl group exhibits only the inductive electron–withdrawing effect. In the 2–methylene–1–adamantyl cation the π–system is essentially perpendicular to the developing cationic p orbital. Thus, the rate of acetolysis of 2–methylene–1–adamantyl tosylate (**1a**) relative to 1–adamantyl tosylate (**1b**) is $10^{-4.2}$ at 25 °C.[1] On the other hand, in the compounds where the p orbitals can completely overlap with each other in the incipient carbocations, their rates of solvolysis relative to the corresponding parent compounds are $10^{2-2.8}$.[2,3]

1a   **1b**
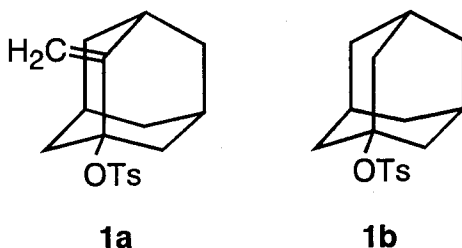
Consequently, if we establish a system in which the degree of allylic conjugation can be gradually changed, it will serve as a tool for examining the π–conjugative ability of a group adjacent to the carbocationic center, such as a carbonyl, thiocarbonyl, or imino group.

About three decades ago, Ferris and Miller[4] qualitatively showed that the rates of decarboxylation of various 2–oxobicycloalkane–1–carboxylic acids increase with the increase in the angle between the p orbital of the carbonyl group and the C–C σ bond connecting the bridgehead carbon and the carbonyl group. They interpreted the results to indicate the development of carbanion character in the transition state of decarboxylation (Scheme 2.1).[4]

Scheme 2.1
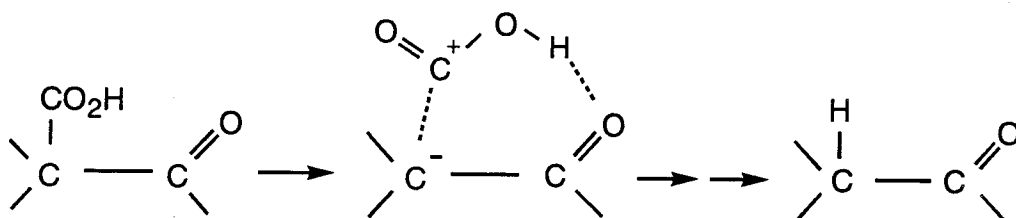
In the course of our study on α–keto cations,[5] we were interested in examining the resonance contribution of a canonical formula **2b**, [6] where the positive charge is delocalized on the carbonyl oxygen. For this purpose, the solvolysis

2a   **2b**   **3**
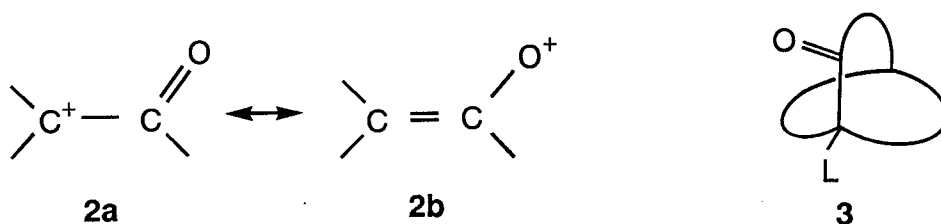
studies of the bridgehead substrates **3** containing the oxo substituent on the 2-position appeared to be appropriate for the reasons that the k_s process and carbonyl participation from the rear side are prohibited. If the conjugation as shown by **2b** is present and can be increased by making the ring system of **3** more and more flexible, the rates of solvolysis relative to the corresponding parent system are expected to rise with increased flexibility owing to concomitantly increased conjugative stabilization of incipient carbocations.[7] This 2-oxo system **3** has an additional advantage that the steric circumstances around the reaction center are kept essentially constant among a series of 2-oxo substrates. Before undertaking the 2-oxo system (see Chapter 3), it was required to examine the feasibility of this methodology by using the 2-methylene (or allylic) system.

Fortunately, a new route for synthesis of various bicyclic and tricyclic 2-oxo-1-alkanols[8] which can be transformed to corresponding 2-methylene-1-alkanols was developed in this laboratory. This Chapter describes the solvolysis of various newly prepared 2-methylene bridgehead compounds. The systems employed are bicyclo[2.2.2]oct-1-yl (**4**),[5c] bicyclo[3.2.1]oct-1-yl (**5**), bicyclo[3.2.2]non-1-yl (**6**),[5c] bicyclo[3.3.1]non-1-yl (**7**),[5d] bicyclo[4.2.2]dec-1-yl (**8**), bicyclo[4.3.1]dec-1-yl (**9**), and tricyclo[4.3.1.1[3,8]]undec-3-yl (3-homoadamantyl) (**10**).[5d] The rates of solvolysis of the parent compounds have also been determined and the $k(X = CH_2)/k(X = H_2)$ ratios at 25 °C compared between each system. In order to further substantiate the approach, (E)-2-ethylidene derivatives (E)-**4e** and (E)-**6e** have also been synthesized and subjected to solvolysis.[9,10] The usefulness of the present methodology has been supported by AM1 calculations.

X=CH$_2$
L=leaving group
X=H$_2$
L=leaving group
X=CH$_2$; L=OH
X=O ; L=OH
X=(E)-CHCH$_3$
L=leaving group
X=(Z)-CHCH$_3$
L=OH
X=(E)-CHCH$_3$
L=OH

4a (L=OTf)	**5a** (L=OTf)	**6a** (L=OMs)	**7a** (L=OMs,OHFB)	**8a** (L=Cl)	**9a** (L=OTFA)	**10a** (L=OHFB)
4b (L=OTf)	**5b** (L=OTf)	**6b** (L=OMs)	**7b** (L=OMs,OHFB)	**8b** (L=Cl)	**9b** (L=OTFA)	**10b** (L=OHFB)
4c	**5c**	**6c**	**7c**	**8c**	**9c**	**10c**
4d	**5d**	**6d**	**7d**	**8d**	**9d**	**10d**
(E)-**4e** (L=OTf)		(E)-**6e** (L=OMs)				
(Z)-**4f**		(Z)-**6f**				
(E)-**4f**		(E)-**6f**				
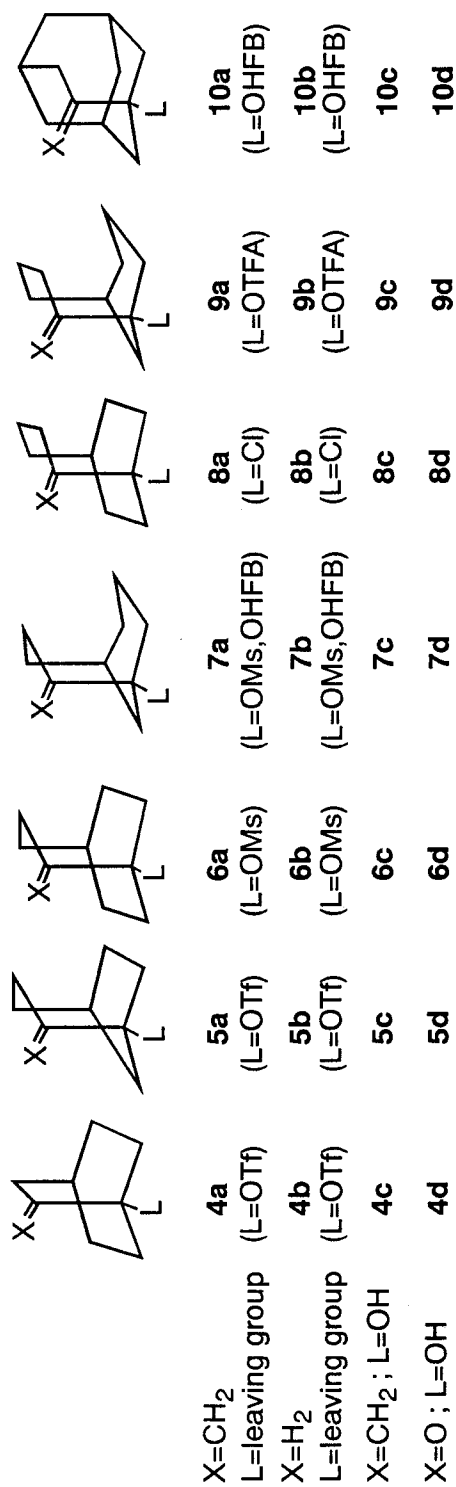
OTf; OSO$_2$CF$_3$ OMs; OSO$_2$CH$_3$ OHFB; OCOn-C$_3$F$_7$ OTFA; OCOCF$_3$

25

2-2. Results

Synthesis of 2–Methylene and Parent Substrates. The intermediate ketols were prepared by acylative ring expansion of bridgehead aldehydes following Scheme 2.2,[8] except that 1–hydroxybicyclo[2.2.2]octan–2–one was derived from 1–methoxybicyclo[2.2.2]oct–5–en–2–one which was provided by the Diels–Alder reaction of 1–methoxy–1,3–cyclohexadiene with 2–chloropropanenitrile.[11]

Scheme 2.2
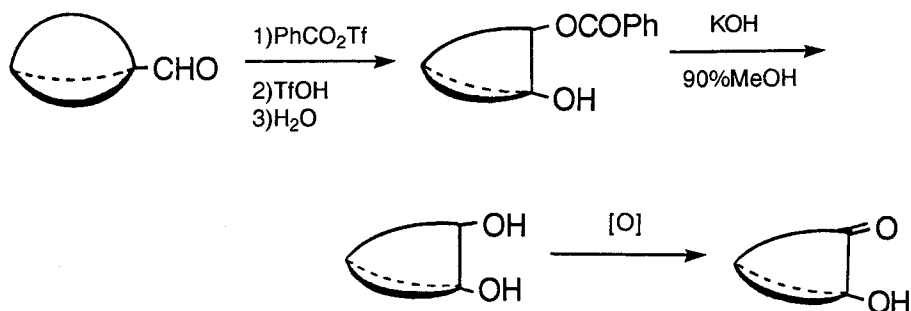
The ketols were subjected to Wittig methylenation,[12] in most cases after protection of the hydroxyl group by trimethyl– or *tert*–butyldimethylsilylation. 2–Methylenebicyclo[3.2.1]octan–1–ol (**5c**) was fortuitously obtained as a major product in the Wittig methylenation of 1–hydroxybicyclo[2.2.2]octan–2–one in DMSO, presumably owing to base–catalyzed ketol rearrangement[13] prior to the Wittig reaction. The parent substrates **4b–10b** were derived from known bridge-head alcohols. All the bridgehead alcohols were converted to the substrates containing an appropriate leaving group which were expected to solvolyze at the rates convenient for measurements.

Synthesis of 2–Ethylidene Substrates. In the beginning, we wished to prepare 2–isopropylidene derivatives, but various efforts to obtain 2–isopropylidenebicyclo[3.2.2]nonan–1–ol failed by using Wittig reaction in DMSO,[12] *i*–PrLi–SOCl$_2$,[14a] and McMurry reaction.[14b] Consequently, we employed 2–ethylidene substrates. Ethylidenation of the *tert*–butyldimethylsilyl (TBDMS) ether of **4d** (**4d–OTBDMS**) with ethylidenetriphenylphosphorane afforded only one product, which was determined as (*Z*)–2–ethylidenebicyclo–[2.2.2]octan–1–ol TBDMS ether ((*Z*)–**4f–OTBDMS**) by ^{1}H NMR NOE difference experiments; irradiation of the C(3) methylene hydrogens caused significant enhancement of the olefinic hydrogen (13%). To prepare an isomeric alcohol (*E*)–**4f**, (*Z*)–**4f–OTBDMS** was subjected to olefin inversion by using the phosphorus betaine method.[15] Application of NOE difference spectroscopy to (*E*)–**4f–OTBDMS** showed negligible enhancement of the olefinic hydrogen (<1%) when the C(3) methylene hydrogens were irradiated. Each of the TBDMS ethers was converted to (*Z*)–**4f** or (*E*)–**4f** by desilylating with tetrabutylammonium fluoride.[16]

Ethylidenation of **6d** TBDMS ether (**6d–OTBDMS**) afforded two products in isolated yields of 16% and 22%, which were separated from each other by repeated liquid chromatography on silica gel. These products were assigned as TBDMS ethers of (*Z*)–**6f** and (*E*)–**6f**, i.e., (*Z*)–**6f–OTBDMS** (minor product) and (*E*)–**6f–OTBDMS** (major product), respectively, on the basis of NOE difference spectroscopy. Enhancement of the olefinic hydrogen was 14% or 0.7% for (*Z*)–**6f–OTBDMS** or (*E*)–**6f–OTBDMS**, respectively, when the C(3) methylene hydrogens were irradiated. Cleavage of the TBDMS ethers afforded (*Z*)–**6f** and (*E*)–**6f**.[17]

Examinations of [1]H–[1]H coupling constants between the methyl and C(3) methylene hydrogens also supported the above structural assignments. The *J*(CH$_3$CH$_2$(3)) values are 1.98 and 1.59 Hz for (*Z*)–**4f** and (*E*)–**4f**, respectively, and

0.90 and 0.66 Hz for (Z)–**6f** and (E)–**6f**, respectively. (The geometry relation between the methyl and the 3–methylene group is *trans* in the Z isomers and *cis* in the E isomers.) Comparisons of the magnitude of these J values with $J(CH_3CH_3)$ values of *trans*–2–butene (1.60 Hz)[18] and *cis*–2–butene (1.18 Hz)[18] are qualitatively consistent with the structural assignments based on the NOE difference experiments. (E)–**4f** and (E)–**6f** were converted to triflate (E)–**4e** and mesylate (E)–**6e**, respectively.

Solvolysis Rates. The solvolysis rates of **6a**,[19] **6b**,[19] **7b–OMs**,[20] **9a**,[21] and **9b**[21] were previously determined in this labolatory. Because of requirement for covering a wide range of reactivity, the leaving group and solvent were appropriately selected as shown in Table 1.1. Most of the substrates were very unstable to water and column chromatography. In such cases, crude substrates were used for solvolysis studies without further purification. Except for **6b**, (E)–**6e**, **7a–OMs**, and **7b–OMs**, all the other substrates were essentially pure (>97%) on the basis of ^{13}C NMR spectra. In all the substrates, the sole impurity, if any, was the starting alcohol, which does not influence the solvolysis rates. For the triflates and mesylates, ethanol was used as solvolysis solvent, whereas for the heptafluorobutyrates, trifluoroacetates, and chlorides, 80% ethanol was used.[22] All measurements were conducted in the presence of 0.025 M 2,6–lutidine either titrimetrically or conductimetrically, showing good first–order kinetics over 80–90% reactions. The rate data, activation parameters, and the rates of the 2–methylene or the 2–ethylidene compounds relative to the parent ones [$k(X = CH_2)/k(X = H_2)$ or $k(X = CHCH_3)/k(X = H_2)$, respectively] at 25 °C are summarized in Table 2.1 together with those of **6a**, **6b**, **7b–OMs**, **9a**, and **9b**.

Table 2.1. Rate Data of solvolysis of 2–Methylene, 2–Ethylidene, or Parent Bridgehead Compounds in Ethanol or 80% Ethanol

compound system	L^d	solvent[a]	temp (°C)	k^b (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	$k(X = CH_2)/$ $k(X = H_2)^c$
4a[f]	OTf	EtOH	25.0	2.96 × 10^{-7} [e,f]	27.1	2.3	10$^{-3.9}$
			50.0	1.09 × 10^{-5} [f,g]			
			75.0	2.40 × 10^{-4} [f,g]			
(E)–4e[h]	OTf	EtOH	25.0	1.86 × 10^{-6} [g,h]	26.8	5.1	10$^{-3.1}$ [i]
			50.0	6.65 × 10^{-5} [g,h]			
4b[f]	OTf	EtOH	25.0	2.14 × 10^{-3} [f,i]	22.4	4.3	
			40.0	1.37 × 10^{-2} [f,i]			
5a	OTf	EtOH	25.0	1.26 × 10^{-6} [g]	27.8	7.5	10$^{-1.9}$
			50.0	5.10 × 10^{-5} [g]			
5b	OTf	EtOH	0.0	2.43 × 10^{-6} [g]			
			25.0	1.10 × 10^{-4} [g]	24.1	4.3	
6a[f]	OMs	EtOH	25.0	7.17 × 10^{-6} [f,g]	24.3	-0.4	10$^{-0.8}$
			50.0	1.86 × 10^{-4} [f,g]			
(E)–6e[h]	OMs	EtOH	25.0	1.86 × 10^{-3} [h,j]	21.6	1.3	10$^{1.6}$ [i]
			40.0	1.11 × 10^{-2} [h,j]			
6b[f]	OMs	EtOH	0.0	1.15 × 10^{-6} [f,g]			
			25.0	4.75 × 10^{-5} [f,g]	23.5	0.5	
7a	OMs	EtOH	25.0	2.83 × 10^{-3} [j]	20.3	-2.1	10$^{0.9}$
			40.0	1.53 × 10^{-2} [j]			
7b[k]	OMs	EtOH	25.0	3.28 × 10^{-4} [j,k]	22.7	1.7	
			40.0	2.16 × 10^{-3} [j,k]			
7a	OHFB	80% EtOH	25.0	1.58 × 10^{-7} [g]	26.4	-1.2	10$^{0.5}$
			50.0	5.34 × 10^{-6} [g]			

(Table 2.1 continued)

7b	OHFB	80% EtOH	25.0	5.22×10^{-8} [e]	26.3	–3.8	$10^{-0.2}$
			50.0	1.74×10^{-6} [g]			
			75.0	3.50×10^{-5} [g]			
8a	Cl	80% EtOH	25.0	3.14×10^{-4} [j]	22.5	0.7	
			40.0	2.02×10^{-3} [j]			
8b	Cl	80% EtOH	25.0	4.52×10^{-4} [j]	22.4	1.1	
			40.0	2.89×10^{-3} [j]			
9a[i]	OTFA	80% EtOH	0.0	1.41×10^{-6} [g,l]			
			25.0	6.88×10^{-5} [g,l]	24.5	4.8	$10^{0.7}$
9b[i]	OTFA	80% EtOH	25.0	1.46×10^{-5} [g,l]	24.5	1.7	
			50.0	3.90×10^{-4} [g,l]			
10a	OHFB	80% EtOH	25.0	1.04×10^{-7} [e]	26.6	–1.4	$10^{-1.1}$
			50.0	3.59×10^{-6} [g]			
			75.0	7.46×10^{-5} [g]			
10b	OHFB	80% EtOH	25.0	1.42×10^{-6} [g,m]	24.9	–2.0	
			50.0	3.93×10^{-5} [g,n]			

[a]Buffered with 0.025M 2,6–lutidine. [b]Determined by a single run. In all cases the correlation coefficient for the first order plot was greater than 0.999. [c]The rate ratio at 25.0 °C. [d]Leaving group: OTf, trifluoromethanesulfonate; OMs, methanesulfonate; OHFB, heptafluorobutyrate; OTFA, trifluoroacetate. [e]Extrapolated from data at other temperatures. [f]Reference 5c. [g]Determined titrimetrically within an experimental error ±2%. [h]Reference 10. [i]The $k(X = CHCH_3)/k(X = H_2)$ ratio. [j]Determined conductimetrically within an experimental error ±0.5%. [k]Reference 20. [l]Reference 21. [m]A reported value is 2.92×10^{-6} s⁻¹ (ref 42). [n]A reported value is 5.54×10^{-5} s⁻¹ (ref 42).

Solvolysis Products. The product(s) of solvolysis was determined only on 2–methylene and 2–ethylidene compounds in the solvent that was used for rate studies: no product studies have been conducted on the parent compounds **4b**–**10b**. Generally, the solvolysis was carried out on 0.04 M substrate solutions containing 20–50% excess amounts of 2,6–lutidine at convenient temperatures for a period longer than 10 half–lives. ^{13}C NMR analyses of crude products showed that the bridgehead substitution was the sole reaction, no other reactions such as elimination to form bridgehead olefins and allylic rearrangement to give S_N1' products having been detected within experimental errors (±3%).

2–3. Discussion

Leaving Group and Solvent. It has been well established that the bridgehead reactivity in solvolysis increases with the decrease in pyramidal strain in the transition state,[23,24] except for extremely strained molecules.[25,26] In the present work the most unreactive alkyl moiety is the 2–methylenebicyclo[2.2.2]oct–1–yl and the most reactive one is the bicyclo[4.2.2]dec–1–yl system. If the kinetic work is done with the same leaving group and the same solvent, the reactivity range would be estimated to be 10^{13} by using relative nucleofugalities of leaving groups[27] and the Y_{Cl} value (–2.5)[28] of ethanol. This extreme reactivity range suggested marked difficulties in both the synthesis and accurate rate measurements of highly reactive substrates even by using recently developed techniques.[29] Consequently, the leaving group and the solvent were appropriately chosen so as to make the synthesis and accurate rate measurements feasible.

These countermeasures may be justified by the data of Table 2.1 and hitherto accumulated ones. The rate ratios of ethanolysis at 25 °C of the 1–adamantyl[27,30]

to bicyclo[2.2.2]oct-1-yl[31] system are $10^{4.2}$ (= 35.1 : 2.14 × 10^{-3}) for triflates and $10^{3.9}$ (= 4.4 × 10^{-5} : 5 × 10^{-9}) for tosylates (the figures in parentheses are the first-order rate constants (s^{-1}) for 1-adamantyl and bicyclo[2.2.2]oct-1-yl systems). The rate ratios are markedly constant despite an enormous nucleofugality difference of ~10^6 between the TfO– and TsO– leaving groups. In 80% ethanol the tosylate rate ratio for 1-adamantyl / bicyclo[2.2.2]oct-1-yl is $10^{4.0}$ (= 4.03 × 10^{-3} : 3.6 × 10^{-7}) at 25 °C,[27,28] again very close to the above value of $10^{3.9}$ in ethanol. Therefore, comparisons of the $k(X = CH_2)/k(X = H_2)$ values between different systems are sound, even if the leaving group and solvent are different between the systems. However, as exemplified by the data of **7a/7b**, i.e., $10^{0.9}$ for mesylates in ethanol and $10^{0.5}$ for heptafluorobutyrates in 80% ethanol, an allowance of $10^{\pm 0.2}$–$10^{\pm 0.3}$ must be taken into account. The **8a/8b** rate ratio of $10^{-0.2}$ appears to be too small (vide infra). At the present stage we are not in the position to rationalize this value. This might be because of the use of the chlorides, but more probably **8a** and **8b** would be too flexible[32] for simple rate comparisons. In the light of considerably constant OTs/Cl rate ratios ($10^{5.1\pm 0.3}$ in 80% ethanol at 70 °C) for various bridgehead compounds,[33] we prefer the latter interpretation for the moment.

Scheme 2.3
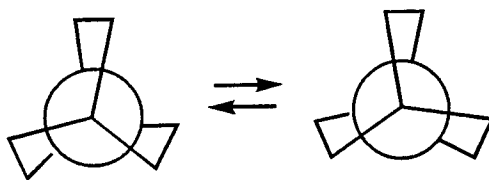
Ring Flexibility and Conjugative Ability. The most notable feature of the rate data of Table 2.1 is that the $k(X = CH_2)/k(X = H_2)$ ratio increases in the order **4a/4b** $(10^{-3.9})$, **5a/5b** $(10^{-1.9})$, **6a/6b** $(10^{-0.8})$, and **7a/7b** $(10^{0.9})$ as has been anticipated from variation of ring flexibility. Since the rate ratio has been shown to increase from 10^{-4} to $10^{2-2.8}$ as the conjugation in the incipient carbocation increases from null to full,[1-3] the rate ratios **6a/6b** and **7a/7b** indicate realization of ~50% and ~80% allylic conjugation in the solvolysis of **6a** and **7a**, respectively.

A measure of ring flexibility of bicyclic compounds would be given by the magnitude of the cross angle at which the twisted conformers show an energy minimum as exemplified by bicyclo[2.2.2]octane (Scheme 2.3). According to molecular mechanics calculations, bicyclo[2.2.2]octane shows very shallow energy minima at about $\pm 15°$, whereas in bicyclo[3.3.2]decane deeper energy minima appear at about $\pm 40°$.[34] Although these cross angles indicate that the former is less flexible than the latter, the use of cross angles is too qualitative to evaluate the relation between the structural flexibility and conjugative ability in the present study. A better measure for the conjugative ability would be given by the stability of a bridgehead olefin which corresponds to another resonance structure of the 2–methylene bridgehead carbocation (Scheme 2.4). Therefore, it is expected that the more stable the corresponding bridgehead olefin is, the easier the allylic conjugation will be.

Previously, Maier and Schleyer defined "olefinic strain energy", which is given by the difference between the strain energy of a bridgehead olefin and that of a corresponding saturated hydrocarbon, both being calculated by molecular mechanics for the most stable conformations.[35] A plot of log $[k(X = CH_2)/k(X = H_2)]$ against the olefinic strain energies (Figure 2.1) shows that the smaller the olefinic strain energy, the easier the allylic conjugation. Although the olefinic strain energies are concerned with the strain in neutral hydrocarbon molecules and

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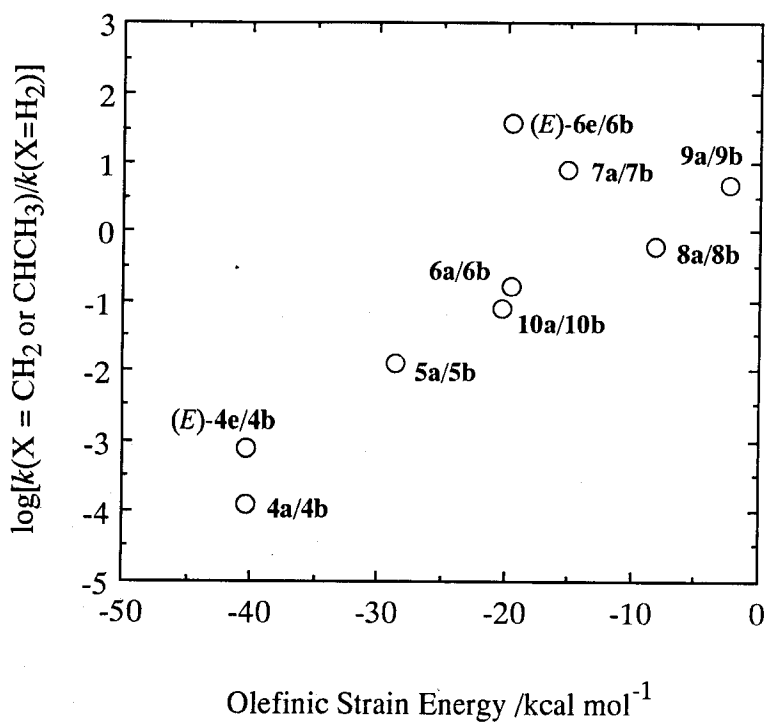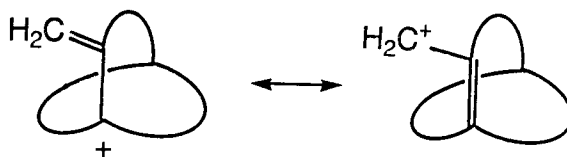Figure 2.1. Plot of log [k(X = CH$_2$ or CHCH$_3$)/k(X = H$_2$)] values against olefinic strain energies of the corresponding unsubstituted bridgehead olefins. For **7a/7b** the data of the mesylates were used. For olefinic strain energies, see ref 35.

Scheme 2.4

the log $[k(X = CH_2)/k(X = H_2)]$ values mainly with the stability of incipient carbo-cations, the plot of Figure 2.1 suggests that the olefinic strain energies may be used as an empirical measure of conjugative ability of 2–methylene bicyclic bridgehead carbocations.

Effects of 2–Ethylidene Substituent on Solvolysis Rates. Placement of a methyl substituent on the E position in **6a** markedly enhances the solvolysis rate; (E)–**6e** solvolyzes 259 times faster than **6a** in ethanol at 25 °C. As described above, the skeletal flexibility of **6a** enables approximately 50% allylic conjugation in the incipient carbocation. Therefore, a major part of this rate enhancement by introducing the methyl substituent is most probably ascribed to enhanced charge delocalization in the transition state, although other factors, in particular the steric strain between the methyl and the 3–methylene group in the ground state and its possible relief in the transition state, may also contribute to the rate acceleration.[36]

In contrast to the above methyl substituent effect in the bicyclo[3.2.2]nonyl system, the effect in the much more rigid bicyclo[2.2.2]octyl system is quite small; (E)–**4e** solvolyzes only 6.3 times faster than **4a** in ethanol at 25 °C. These results reinforce the notion that the allylic conjugation is enhanced with the increase in the ring flexibility.

Semiempirical MO Calculations on Bridgehead Carbocations. A series of 2–methylene and (E)–2–ethylidene bridgehead carbocations and the corresponding hydrocarbons (L; hydrogen in the place of leaving group) were subjected to AM1[38] and MNDO[39] calculations through the AMPAC[40] system. When two conformers are present as in the carbocations from **5a** and **7a**, the calculations were performed for the carbocation corresponding to the more stable conformer of the hydrocarbon

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Table 2.2. AM1 Calculated Bond Orders and Net Atomic Charges for Carbocations and Corresponding Hydrocarbons (L = Hydrogen)^a

| | bond order^b | | | | | | net atomic charge | | | | | |
| | carbocation | | hydrocarbon | | Δbond order^c | | carbocation | | | hydrocarbon | | |
system	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ	C_α	C_β	C_γ	C_α	C_β	C_γ
4a	1.028	1.912	0.972	1.933	0.056	-0.021	0.394	-0.245	-0.077	-0.073	-0.094	-0.232
(E)-4e	1.034	1.842	0.974	1.889	0.060	-0.047	0.402	-0.281	-0.003	-0.069	-0.104	-0.174
5a	1.048	1.900	0.974	1.932	0.074	-0.032	0.395	-0.241	-0.071	-0.078	-0.093	-0.232
6a	1.087	1.828	0.971	1.932	0.116	-0.104	0.379	-0.231	-0.046	-0.066	-0.088	-0.235
(E)-6a	1.138	1.722	0.973	1.890	0.165	-0.168	0.353	-0.247	0.045	-0.064	-0.096	-0.177
7a	1.157	1.737	0.972	1.931	0.185	-0.194	0.317	-0.219	0.005	-0.071	-0.090	-0.236
10a	1.026	1.898	0.972	1.930	0.054	-0.032	0.400	-0.232	-0.095	-0.061	-0.083	-0.245

^{a}When two conformers are present as in the carbocations from 5a and 7a, the calculations were preformed for the carbocation corresponding to the more stable conformer of the hydrocarbon. ^{b}C_α–C_β and C_β=C_γ denote the bonds in the allylic part C_α–C_β=C_γ. ^{c}The difference in the bond orders of C_α–C_β and C_β=C_γ between a carbocation and a hydrocarbon.

36
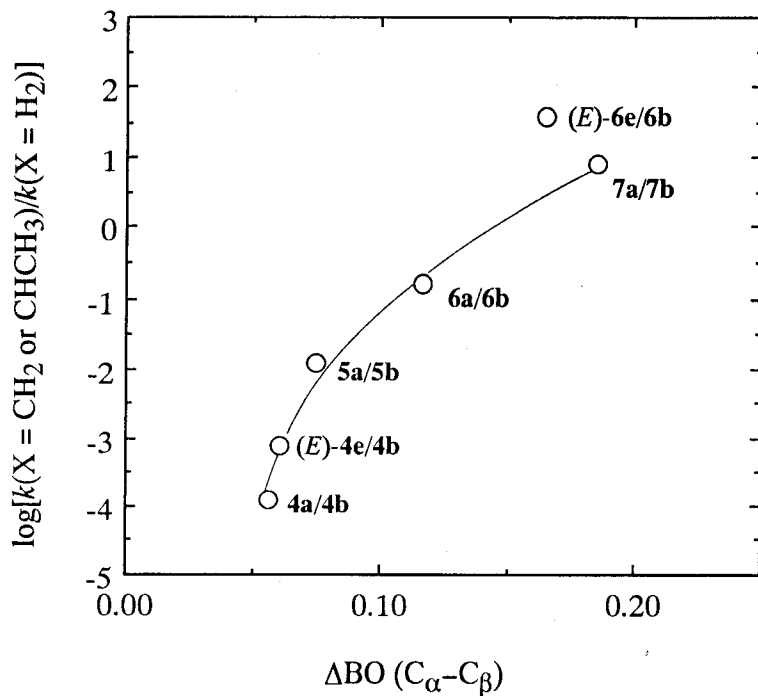
Figure 2.2. Plot of $\log[k(X = CH_2 \text{ or } CHCH_3)/k(X = H_2)]$ values against differences of C_α–C_β bond orders between bridgehead carbocations and the corresponding hydrocarbons. For **7a/7b** the data of the mesylates were used.

(L = hydrogen). **8a** and **9a** were not included in the calculations because of their complex conformations.[32] As indexes for the degree of allylic (C_α–C_β=C_γ) conjugation were employed the difference in C_α–C_β bond orders and that in C_β=C_γ bond orders between the carbocation and the corresponding hydrocarbon (L = hydrogen), denoted, respectively, by $\Delta BO(C_\alpha$–$C_\beta)$ and $\Delta BO(C_\beta$=$C_\gamma)$. The results of AM1 and MNDO calculations agreed well with each other. In Table 2.2 are summarized pertinent bond orders and net atomic charges calculated by AM1. Figure 2.2 gives the relation between log $[k(X = CH_2$ or $CHCH_3)/k(X = H_2)]$ and $\Delta BO(C_\alpha$–$C_\beta)$. .

A smooth curve in Figure 2.2 for a homologous series, **4a/4b, 5a/5b, 6a/6b,** and **7a/7b**, which shows gradual increases of allylic conjugation in this order, strongly supports the propriety of the present approach. It is also notable that the point for (E)–**4e/4b** is accommodated to the curve. However, a marked deviation of **10a/10b** suggests difficulty in applying AM1 (and MNDO) method to 4–methylene–3–homoadamantyl cation. The upward deviation of the point for (E)–**6e/6b** by 0.8 logarithmic unit suggests possible rate enhancement in (E)–**6e** due to steric origin (vide supra).

2–4. Experimental

Melting points are uncorrected. IR spectra were recorded on a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi R–24 (60 MHz), JEOL FX90A (89.55 MHz), or JEOL GSX270 (270.05 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX90A (22.5 MHz), JEOL FX100 (25.0 MHz), or JEOL GSX270 (67.8 MHz) spectrometer. In all NMR measurements TMS was used as an internal standard. Elemental analyses were performed by the

Microanalytical Center, Kyoto University, Kyoto. Ketol **7d**,[8b] **8d**[8b] and **10d**[8d,41] and 3–homoadamantyl heptafluorobutyrate[42] (**10b**) were described previously. Mesylate **6a**,[19] **6b**[19] and **7b–OMs**[20] and trifluoroacetate **9a**[21] and **9b**[21] were described previously. The purities of the unstable substrates for rate studies were generally higher than 97% on the basis of their ^{13}C NMR spectra even when a crude product was used. Exceptions were **6b**, (*E*)**–6e**, **7a–OMs**, and **7b–OMs**, whose purities were approximately 85, 70, 37, and 80 mol %, respectively, being contaminated by the respective bridgehead alcohols. Absolute ethanol as a solvolysis solvent was distilled from magnesium ethoxide. All the anhydrous solvents used for synthetic work were purified by standard procedures. *tert*–Butyldimethylsilyl trifluoromethanesulfonate (triflate) was prepared following a literature procedure.[43] Commercially available methyl– and ethyltriphenylphosphonium bromide were dried at 95–100 °C in vacuo for 1 h before use. Other commercially available reagents were of a reagent–grade quality and used as received. Medium–pressure liquid chromatography (MPLC) and conventional liquid chromatography were conducted on Merck silica gel 60 (230–400 mesh) and Nacalai Tesque silica gel No. I (60–200 mesh), respectively.

1–Hydroxybicyclo[2.2.2]octan–2–one (4d). A procedure described for the cleavage of methoxycyclohexane[44] was followed. To a solution of 1–methoxybicyclo[2.2.2]octan–2–one[45] (4.00 g, 25.9 mmol) and pyridine (0.83 g, 10 mmol) in $CHCl_3$ (8 mL) was added iodotrimethylsilane (6.8 g, 34 mmol) with stirring at room temperature. After 65 h at 60 °C, methanol (3.5 mL) was added and then volatile substances were evaporated with a rotary evaporator. The residue was subjected to MPLC (SiO_2, hexane–ether (4:1)) to afford **4d** (1.45 g, 40%): mp 187.5–188.0 °C (from hexane); IR (CCl_4) 3510, 2940, 2860, 1720, 1450, 1400,

1230, 1145, 1090, 960 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.49–2.26 (m, 9 H), 2.42 (d, 2 H, J = 2.7 Hz), 3.46 (s, 1 H, OH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 74.3 (C), 27.3 (CH), 25.9, 30.1, 43.1 (CH$_2$), 215.7 (C=O). Analytical data were unsatis-factory probably due to the hygroscopic nature. Anal. Calcd for C$_8$H$_{12}$O$_2$: C, 68.55; H, 8.63. Found: C, 67.73; H, 8.59. However, the p–nitrobenzoate gave satisfactory analytical data: mp 114.5–115.5 °C (from hexane–benzene). Anal. Calcd for C$_{15}$H$_{15}$O$_5$N: C, 62.28; H, 5.23. Found: C, 62.15; H, 5.29.

Protection of 4d by tert–Butyldimethylsilylation. To a solution of **4d** (1.45 g, 10.3 mmol) and 2,6–lutidine (2.4 mL) in CH$_2$Cl$_2$ (11 mL) was added *tert*–butyldimethylsilyl triflate[43] at 0 °C over 4 min. After being stirred for 1 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (15 mL), washed with water (2 × 15 mL), 10% aqueous HCl (2 × 15 mL), saturated aqueous NaHCO$_3$ (2 × 15 mL), and saturated aqueous NaCl (15 mL), and dried (MgSO$_4$). Evaporation of solvent, followed by MPLC (SiO$_2$, hexane–ether (9:1)) afforded *tert*–butyldimethylsilyl ether **4d–OTBDMS** (1.89 g, 71%) as a colorless oil: ^{1}H NMR (60 MHz, CCl$_4$) δ 0.1 (s, 6 H), 0.90 (s, 9 H), 1.6–2.4 (m, 11 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.2, 77.5 (C), 27.3 (CH), 26.2, 31.7, 44.5 (CH$_2$), –2.7, 25.8 (CH$_3$), 213.6 (C=O).

2–Methylenebicyclo[2.2.2]octan–1–ol (4c). Following a literature proce-dure,[12] *tert*–butyldimethylsilyl ether **4d–OTBDMS** (0.383 g, 1.51 mmol) was treated in DMSO (6 mL) under N$_2$ with methyltriphenylphosphorane, which was generated from methyltriphenylphosphonium bromide (1.62 g, 4.53 mmol) and NaH (60% dispersion 0.182 g, 4.53 mmol) in DMSO at 70 °C for 30 h. The reac-tion mixture was poured into ice–water (20 mL) and extracted with ether (4 × 15 mL). The combined extracts were washed with water (3 × 15 mL) and saturated aqueous NaCl (2 × 15 mL) and dried (MgSO$_4$). After evaporation of solvent, the

crude product was subjected to MPLC (SiO$_2$, hexane) to give the *tert*-butyldimethylsilyl ether of **4c** (**4c-OTBDMS**) (0.322 g), whose purity was estimated to be 86% from the ^{1}H NMR spectrum. The impure **4c-OTBDMS** (0.322 g) was dissolved in THF (6 mL). To this was added a 1.0 M solution of *n*-Bu$_4$NF in THF (2.6 mL), and the resulting solution refluxed for 46 h under N$_2$. The reaction mixture was stirred with 4% aqueous NH$_4$Cl (10 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with water (2 × 10 mL) and 10% aqueous NaCl (2 × 10 mL) and dried (MgSO$_4$). Evaporation of the ether followed by MPLC (SiO$_2$, hexane-ether (4:1)) afforded **4c** (0.136 g, 46% based on **4d**): mp 56.5–57.0 °C (from hexane); IR (CCl$_4$) 3610, 3475 br, 3080, 1650, 880 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.5–1.8 (m, 10 H), 2.38 (br s, 2 H, OH and H-4), 4.60 (br s, 1 H, =CH), 4.95 (br s, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 71.7, 153.1 (C), 26.0 (CH), 26.8, 33.7, 35.9, 102.3 (CH$_2$). Analytical data were unsatisfactory probably due to the hygroscopic nature. Anal. Calcd for C$_9$H$_{14}$O: C, 78.21; H, 10.21. Found: C, 75.75; H, 10.21. However, the *p*-nitrobenzoate gave satisfactory analytical data: mp 77.5–78.5 °C (from hexane). Anal. Calcd for C$_{16}$H$_{17}$O$_4$N: C, 66.89; H, 5.96. Found: C, 66.85; H, 5.98.

2-Methylenebicyclo[2.2.2]oct-1-yl Triflate (4a). To a solution of **4c** (0.143 g, 1.03 mmol) and pyridine (0.163 g, 2.06 mmol) in CH$_2$Cl$_2$ (2 mL) was added a solution of triflic anhydride (0.387 g, 1.37 mmol) in CH$_2$Cl$_2$ (1.2 mL) with stirring at 0 °C over 5 min, and then stirring continued for 45 min. After having been stored in a freezer overnight, the reaction mixture was diluted with CH$_2$Cl$_2$ (16 mL), washed at 0 °C with 10% aqueous HCl (30 mL), saturated aqueous NaHCO$_3$ (15 mL), and 10% aqueous NaCl (2 × 15 mL), and dried (MgSO$_4$). Evaporation of solvent with a rotary evaporator afforded **4a** (0.226 g, 81%) as an

unstable oil, which was used for solvolysis studies without further purification: IR (CCl$_4$) 3100, 1650, 1405, 1250, 1215, 1145, 930, 890 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.7–2.6 (m, 11 H), 4.81 (t, 1 H, J = 2.2 Hz), 5.10 (t, 1 H, J = 2.2 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 100.7, 146.0 (C), 25.3 (CH), 27.4, 31.4, 36.8, 106.0 (CH$_2$), 118.1 (q, CF$_3$, J = 319 Hz).

(Z)–2–Ethylidenebicyclo[2.2.2]octan–1–ol ((Z)–4f). Following a literature method for Wittig methylenation,[12] 4d–OTBDMS (1.89 g, 7.43 mmol) was treated in DMSO (34 mL) under N$_2$ with ethylidenetriphenylphosphorane, which was generated from ethylidenetriphenylphosphonium bromide (8.28 g, 22.3 mmol) and NaH (60% dispersion 0.892 g, 22.3 mmol) in DMSO at 70 °C for 3.5 h. The reaction mixture was poured into ice (120 g) and extracted with ether (4 × 70 mL). The combined extracts were washed with water (3 × 70 mL) and saturated aqueous NaCl (3 × 70 mL) and dried (MgSO$_4$). When most of the ether was removed with a rotary evaporator, hexane (10 mL) was added and insoluble solid was removed by filtration. Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded a colorless liquid (1.69 g, 85 %) whose ^{13}C NMR spectra and ^{1}H NMR NOE difference experiments showed the formation of (Z)–4f–OTBDMS, the E isomer being present in 5%: ^{1}H NMR (270.05 MHz, CDCl$_3$) δ 0.12 (s, 6 H), 0.88 (s, 9 H), 1.52–1.81 (m, 9 H), 1.84 (dt, 3 H, J = 7.1, 2.0 Hz), 2.27 (br s, 2 H), 5.14 (qt, 1 H, J = 7.1, 2.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.3, 77.2, 140.9 (C), 26.2, 116.9 (CH), 26.2, 27.2, 34.6, 38.9 (CH$_2$), –1.3, 14.3 (CH$_3$).

The cleavage of (Z)–4f–OTBDMS (0.660 g, 2.48 mmol) was conducted as described for 4c by refluxing with n–Bu$_4$NF (5.0 mmol) in THF (10 mL) for 19 h under N$_2$. After usual workup, MPLC (SiO$_2$, hexane–ether (9:1)) of the crude product afforded (Z)–4f (0.320 g, 84%): mp 92.0–92.5 °C (from pentane); IR (CCl$_4$) 3610, 3490 br, 2940, 2860, 1450, 1310, 1100, 1060, 960, 850 cm^{-1}; ^{1}H

NMR (89.55 MHz, CDCl$_3$) δ 1.34–1.80 (m, 10 H), 1.88 (dt, 3 H, J = 7.3, 2.0 Hz), 2.28 (br s, 2 H), 5.17 (qt, 1 H, J = 7.3, 2.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 74.5, 140.6 (C), 26.3, 116.3 (CH), 26.9, 34.7, 38.2 (CH$_2$), 13.5 (CH$_3$). Anal. Calcd for C$_{10}$H$_{16}$O: C, 78.90; H, 10.59. Found: C, 78.73; H, 10.80.

(E)–2–Ethylidenebicyclo[2.2.2]octan–1–ol ((E)–4f). Following a literature procedure,[15] (Z)–**4f–OTBDMS** was subjected to olefin inversion via an epoxide and phosphorous betaine. To a stirred solution of *m*–chloroperbenzoic acid (70% pure, 0.300 g, 1.22 mmol) in CH$_2$Cl$_2$ (2.7 mL) was added (Z)–**4f–OTBDMS** (0.300 g, 1.13 mmol) in CH$_2$Cl$_2$ (1.7 mL) at 0 °C over 3 min. During the addition *m*–chlorobenzoic acid precipitated. After the solution was stirred for 10 min, cold 10% aqueous NaOH (2.4 mL) was added. The organic layer was washed with 10% aqueous NaCl (2 × 15 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane–ether (9:1)) afforded (Z)–**4f–OTBDMS** epoxide (0.177 g, 56%): colorless oil; IR (CCl$_4$) 2930, 2860, 1470, 1460, 1260, 1150, 1125, 910, 835 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 0.08 (s, 3 H), 0.10 (s, 3 H), 0.85 (s, 9 H), 1.54 (d, 3 H, J = 5.8 Hz), 1.60–2.07 (m, 11 H), 2.79 (q, 1 H, J = 5.7 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.2, 64.7, 71.8 (C), 25.5, 63.3 (CH), 26.4, 26.8, 31.3, 32.2, 39.4 (CH$_2$), –1.7, –1.5, 14.5, 26.1 (CH$_3$).

The epoxide (0.177 g, 0.63 mmol) in THF (1.8 mL) was added under argon to lithium diphenylphosphide[15] (0.59 mmol) in THF (0.65 mL) with stirring at 25 °C over 2 min. After the solution was stirred at 25 °C for 2 h, iodomethane (0.137 g, 0.96 mmol) was added and stirring continued for 30 min. The reaction mixture was diluted with ether (10 mL), washed with 10% aqueous NaCl (8 mL), and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded essentially pure (E)–**4f–OTBDMS** (0.115 g, 69%), the Z isomer being present in

less than 2%, if any, colorless oil: IR (CCl$_4$) 2930, 2860, 1670, 1470, 1340, 1255, 1155, 1130, 980, 905 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.54 (dt, 3 H, J = 6.8, 1.5 Hz), 1.40–1.83 (m, 9 H), 2.27 (br s, 2 H), 5.38 (qt, 1 H, J = 6.8, 2.5 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.4, 74.2, 143.5 (C), 26.0, 111.8 (CH), 27.3, 33.6, 34.8 (CH$_2$), –1.6, 12.4, 26.0 (CH$_3$). The E configuration was verified by NOE difference experiments (vide infra).

(E)-**4f**-OTBDMS (0.409 g, 1.53 mmol) was desilylated as described for the preparation of **4c** by refluxing with n–Bu$_4$NF (3.00 mmol) in THF for 36 h under N$_2$. Usual workup followed by MPLC (SiO$_2$, hexane–ether (9:1)) afforded (E)-**4f** (0.214 g, 92%): mp 100.5–101.0 °C (from hexane); IR (CCl$_4$) 3600, 3475 br, 2940, 2865, 1675, 1455, 1335, 1105, 1060, 955, 890 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.14–1.74 (m, 10 H), 1.56 (dt, 3 H, J = 6.7, 1.59 Hz), 2.29 (br s, 2 H), 5.47 (qt, 1 H, J = 6.7, 2.7 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 71.6, 143.7 (C), 26.1, 110.7 (CH), 27.0, 33.4, 34.3 (CH$_2$), 12.2 (CH$_3$). Anal. Calcd for C$_{10}$H$_{16}$O: C, 78.90; H, 10.59. Found: C, 78.58; H, 10.78.

(E)-2-Ethylidenebicyclo[2.2.2]oct-1-yl Triflate ((E)-4e). Following the procedure described for the preparation of **4a**, treatment of (E)-**4f** (0.080 g, 0.53 mmol) with triflic anhydride (0.193 g, 0.65 mmol) in pyridine (0.083 g, 1.11 mmol) in CH$_2$Cl$_2$ (0.7 mL) at 0 °C for 2.5 h followed by usual workup at 0 °C afforded (E)-**4e** as a pale brown unstable oil (0.132 g), which was used for solvolysis studies without further purification: ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 101.6, 136.9 (C), 25.2, 114.6 (CH), 27.5, 31.8, 34.2 (CH$_2$), 12.4 (CH$_3$), 118.1 (q, CF$_3$, J = 319 Hz).

Bicyclo[2.2.2]oct-1-yl Triflate (4b). Bicyclo[2.2.2]octan-1-ol (mp 211.5–213.0 °C (lit.[46] mp 214–214.5 °C)) (0.170 g, 1.35 mmol), which was derived from

bicyclo[2.2.1]hept–1–ylmethyl tosylate,[47] was treated with triflic anhydride (0.478 g, 1.69 mmol) and pyridine (0.225 g, 2.85 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C for 14 h. Workup as described for the preparation of **4a** afforded an unstable oil which was used for rate studies without further purification: ^{13}C NMR (25 MHz, $CDCl_3$) δ 103.3 (C), 23.2 (CH), 27.7, 31.5 (CH_2), 118.1 (q, CF_3, J = 319 Hz).

2–Methylenebicyclo[3.2.1]octan–1–ol (5c). This was obtained as a major product on Wittig methylenation of **4d** following a literature method.[12] Treatment of **4d** (0.140 g, 1.00 mmol) in DMSO (5.3 mL) with methylenetriphenylphospho–rane, which was generated from methyltriphenylphosphonium bromide (0.89 g, 2.5 mmol) and NaH (60% dispersion 0.10 g, 2.5 mmol) in DMSO, at 35 °C for 18 h followed by usual workup as described for the preparation of **4c** afforded a mixture of **4c** and **5c** in an approximate ratio of 1:3, respectively, as determined by GLC. The separation of **4c** and **5c** by MPLC failed, but it was achieved by converting them to acetates. A mixture of **4c** and **5c** (1:3) (1.05 g, 7.60 mmol) from a scaled up reaction was dissolved in triethylamine (1.16 g, 11.5 mmol) containing acetic anhydride (1.17 g, 11.5 mmol). To this was added 4–(dimethylamino)pyridine (0.074 g, 0.61 mmol) with stirring. After 20 h at room temperature, the reaction mixture was poured into ice and extracted with ether (2 × 20 mL). The combined extracts were washed with 10% aqueous HCl (2 × 15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), saturated aqueous NaCl (20 mL), and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (9:1)) afforded 2–methylenebicyclo[2.2.2]oct–1–yl acetate (0.275 g, 20%) and 2–methylenebicyclo–[3.2.1]oct–1–yl acetate (0.844 g, 62%) in this sequence as colorless oils. **2–Methylenebicyclo[2.2.2]oct–1–yl acetate:** IR (CCl_4) 3090, 2950, 2860, 1740, 1650, 1430, 1365, 1240, 1070, 885 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.6–2.5 (m,

11 H), 1.97 (s, 3 H, CH$_3$), 4.62 (br s, 1 H, =CH), 4.80 (br s, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 81.6, 148.0 (C), 25.7 (CH), 26.5, 29.7, 36.2, 103.9 (CH$_2$), 22.0 (CH$_3$), 169.3 (C=O). Anal. Calcd for C$_{11}$H$_{16}$O$_2$: C, 73.30; H, 8.95. Found: C, 73.31; H, 9.16. **2-Methylenebicyclo[3.2.1]oct-1-yl acetate:** IR (CCl$_4$) 3090, 2950, 2870, 1745, 1645, 1450, 1365, 1240, 1080, 895 cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 1.23–2.46 (m, 11 H), 2.00 (s, 3 H), 4.27 (br s, 1 H, =CH), 4.48 (br s, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 88.2, 149.3 (C), 34.1 (CH), 27.7, 29.8, 33.0, 34.5, 45.2, 102.1 (CH$_2$), 21.4 (CH$_3$), 169.4 (C=O).

2-Methylenebicyclo[3.2.1]oct-1-yl acetate (0.671 g, 3.72 mmol) was reduced with LiAlH$_4$ in ether to give **5c** (0.482 g, 94%): mp 69.0–70.0 °C (from pentane); IR (CCl$_4$) 3630, 3400 br, 2950, 2870, 1650, 1455, 1110, 990, 900 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.13–2.47 (m, 11 H), 2.70 (s, 1 H, OH), 4.47 (s, 1 H, =CH), 4.77 (s, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 80.6, 154.4 (C), 35.4 (CH), 27.8, 29.2, 32.8, 36.8, 46.5, 100.9 (CH$_2$). Analytical data were unsatisfactory probably due to its hygroscopic nature. Anal. Calcd for C$_9$H$_{14}$O: C, 78.21; H, 10.21. Found: C, 77.55; H, 10.06. However, the p–nitrobenzoate prepared by the use of p–nitrobenzoyl chloride, triethylamine, and 4-(dimethylamino)pyridine gave satisfactory analytical data: mp 91.0–92.0 °C (from hexane). Anal. Calcd for C$_{16}$H$_{17}$O$_4$N: C, 66.89; H, 5.96. Found: C, 67.01; H, 5.96.

2-Methylenebicyclo[3.2.1]oct-1-yl Triflate (5a). Following the procedure described for the preparation of **4a**, treatment of **5c** (0.304 g, 2.20 mmol) with triflic anhydride (0.759 g, 2.69 mmol) and pyridine (0.349 g, 4.40 mmol) in CH$_2$Cl$_2$ (5.2 mL) at 0 °C for 12 h followed by usual workup at 0 °C afforded **5a** as a pale brown unstable liquid, which was used for solvolysis studies without further purification: IR (CCl$_4$) 2960, 2880, 1820, 1660, 1460, 1410, 1220, 1155, 1025, 905, 890 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.32–2.67 (m, 11 H), 4.70 (s, 1 H, =CH),

4.97 (s, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 103.9, 148.4 (C), 34.7 (CH), 26.7, 29.8, 32.0, 34.6, 44.7, 104.4 (CH$_2$), 118.2 (q, CF$_3$, J = 319 Hz).

Bicyclo[3.2.1]oct-1-yl Triflate (5b). Bicyclo[3.2.1]octan-1-ol was prepared by Baeyer–Villiger oxidation of bicyclo[3.2.1]octane-1-carboxylic acid[48] following a literature procedure.[49] To H$_2$SO$_4$ (18.5 mL) was added bicyclo[3.2.1]-octane-1-carboxylic acid (3.00 g, 19.5 mmol) at 0 °C, and then the yellowish mixture was further stirred at 0 °C for 30 min. To the magnetically stirred mixture was added 30% H$_2$O$_2$ (3.75 mL) at 0–8 °C over 1.5 h, and then stirring continued for 4 h. The reaction mixture was poured into ice (80 g) and extracted with ether (3 × 25 mL). The combined extracts were washed with 10% aqueous NaOH (3 × 20 mL) and 10% aqueous NaCl (2 × 20 mL) and dried (MgSO$_4$). Evaporation of the ether afforded a slightly pink solid (0.80 g) which was then recrystallized from hexane to give bicyclo[3.2.1]octan-1-ol (0.50 g, 20 %): mp 180.5–181.5 °C (from hexane);[50] IR (CCl$_4$) 3620, 3330 br, 2940, 2870, 1455, 1340, 1100, 1025 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.1–2.3 (m, 13 H), 2.60 (s, 1 H, OH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 78.5 (C), 35.1 (CH), 20.0, 27.5, 31.1, 35.7, 39.8, 45.7 (CH$_2$). Analytical data were unsatisfactory presumably because of the hygroscopic nature. Anal. Calcd for C$_8$H$_{14}$O: C, 76.14; H, 11.18. Found: C, 74.78; H, 11.43. *p*-Nitrobenzoate gave satisfactory analytical data: mp 136.5–137.5 °C. Anal. Calcd for C$_{15}$H$_{17}$O$_4$N: C, 65.44; H, 6.22. Found: C, 65.41; H, 6.22.

The triflate **5b** was prepared by using bicyclo[3.2.1]octan-1-ol (0.278 g, 2.20 mmol), pyridine (0.349 g, 4.40 mmol), and CH$_2$Cl$_2$ (5.2 mL) as described for the preparation of **4a**, as a yellowish liquid (0.489 g, 86%), which was used for solvolysis studies without further purification: ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 105.0 (C), 34.5 (CH), 20.2, 26.4, 30.3, 33.9, 37.7, 43.8 (CH$_2$), 118.1 (q, CF$_3$, J =

318 Hz).

1-Hydroxybicyclo[3.2.2]nonan-2-one (6d). Oxidation of bicyclo[3.2.2]-nonane-1,2-diol with Ag_2CO_3 on Celite was conducted as described in the literature.[51] To a suspension of Ag_2CO_3 on Celite[51] (161 g) in benzene (850 mL), from which contaminating water had been removed by azeotropic distillation, was added bicyclo[3.2.2]nonane-1,2-diol[8a] (5.32 g, 34.0 mmol) and then the mixture magnetically stirred vigorously at 80 °C for 1 h, during which period the suspension turned black. The reaction mixture was filtered and then the benzene evaporated to afford a semisolid (5.3 g), which on column chromatography (SiO_2, hexane–ether (4:1, 1:1)) gave **6d** (3.41 g, 65%): mp 150.5–151.5 °C (from hexane); IR (CCl_4) 3480 br, 2930, 2860, 1700, 1455, 1380, 1255, 1110, 1080 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.5–2.1 (m, 11 H), 2.50 (t, 2 H, J = 7.0 Hz), 3.60 (s, 1 H, OH); ^{13}C NMR (25 MHz, $CDCl_3$) δ 76.4 (C), 26.8 (CH), 24.9, 27.5, 29.7, 35.7 (CH), 214.9 (C=O). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.90; H, 9.37.

(Z)– and (E)–2-Ethylidenebicyclo[3.2.2]nonan-1-ol ((Z)– and (E)–6f). The hydroxyl group of **6d** was protected by *tert*-butyldimethylsilylation as described for the preparation of **4d–OTBDMS** by adding *tert*-butyldimethylsilyl triflate (1.72 g, 6.48 mmol) to a mixture of **6d** (1.00 g, 6.48 mmol) and 2,6–lutidine (1.4 g, 13 mmol) in CH_2Cl_2 (7 mL) at −78 °C and then stirring at room temperature for 2 h under N_2. Usual workup followed by MPLC (SiO_2, hexane–ether (9:1)) of the crude product afforded **6d–OTBDMS** (1.20 g, 69%): mp 40.5–42.0 °C. Further elusion with hexane–ether (1:1) afforded unchanged **6d** (0.235 g, 24%).

Following a literature method for Wittig methylenation,[12] the above **6d–OTBDMS** (1.20 g, 4.48 mmol) was treated in DMSO (31 mL) under N_2 with

ethylidenetriphenylphosphorane, which was generated from ethyltriphenylphos-phonium bromide (4.99 g, 13.4 mmol) and NaH (60% dispersion 0.537 g, 13.4 mmol) in DMSO, at 70 °C for 21 h. The reaction mixture was worked up as described for the preparation of (*Z*)–**4f** to give a pale yellow liquid (1.49 g). The crude product was subjected to MPLC (SiO$_2$, hexane) to give a mixture (0.495 g) of two components with R_f 0.52 and 0.60 on TLC (SiO$_2$, hexane). The mixture was separated to three fractions by MPLC (500 × 20 mm SiO$_2$, hexane), the first being a pure component (0.050 g), the second (0.415 g) a mixture of two components, and the third (0.004 g). The second fraction was again subjected to MPLC and separated to three fractions. This procedure was repeated five more times, finally affording (*Z*)–**6f–OTBDMS** (0.201 g, 16%) as the first and (*E*)–**6f–OTBDMS** (0.273 g, 22%) as the third fraction.[17] The assignments of the configurations are based on NOE difference spectroscopy (vide infra). (*Z*)–**6f–OTBDMS**: liquid; ^{1}H NMR (270.05 MHz, CDCl$_3$) δ 0.07 (s, 6 H), 0.87 (s, 9 H), 1.43–1.59 (m, 6 H), 1.81 (d, 3 H, *J* = 7.3 Hz), 1.86–1.89 (m, 3 H), 2.00–2.10 (m, 2 H), 2.18 (t, 2 H, *J* = 6.7 Hz), 5.27 (q, 1 H, *J* = 7.3 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.3, 77.3, 144.5 (C), 28.3, 121.8 (CH), 26.5, 33.9, 35.1, 38.2 (CH$_2$), –1.8, 15.6, 26.2 (CH$_3$). (*E*)–**6f–OTBDMS**: liquid; ^{1}H NMR (270.05 MHz, CDCl$_3$) δ 0.01 (s, 6 H), 0.85 (s, 9 H), 1.39–1.89 (m, 11 H), 1.60 (d, 3 H, *J* = 7.0 Hz), 2.27 (t, 2 H, *J* =7.0 Hz), 5.68 (q, 1 H, *J* = 7.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.2, 76.8, 146.5 (C), 28.1, 117.1 (CH), 23.4, 26.2, 35.8, 36.4 (CH$_2$), –1.9, 12.8, 26.0 (CH$_3$). A similar synthesis was repeated and the products were combined with each other of the above isomers.

The cleavage of (*Z*)–**6f–OTBDMS** (0.486 g, 1.73 mmol) was carried out as described for the preparation of (*Z*)–**4f** by treatment with *n*–Bu$_4$NF (3.5 mmol) in THF (10 mL) at 60 °C for 12 h and then at 70 °C for 72 h under N$_2$, while the

progress of reaction was monitored by TLC. The reaction mixture was worked up in the usual manner and the crude product subjected to MPLC (SiO$_2$, hexane–ether (9:1)) to give (Z)-**6f** (0.243 g, 84%) as colorless crystals: mp 90.0–90.5 °C (from pentane); IR (CCl$_4$) 3610, 3480 br, 2930, 2855, 1640, 1450, 1380, 1055, 925, 900 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.33–1.96 (m, 11 H), 1.85 (dt, 3 H, J = 7.2, 0.9 Hz), 2.02–2.31 (m, 3 H), 5.33 (qt, 1 H, J = 7.2, 0.9 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 74.8, 145.2 (C), 28.3, 121.4 (CH), 26.2, 33.7, 34.7, 37.7 (CH$_2$), 14.6 (CH$_3$). Anal. Calcd for C$_{11}$H$_{18}$O: C, 79.47; H, 10.91. Found: C, 79.28; H, 11.15.

The cleavage of (E)-**6f**-OTBDMS (0.273 g, 0.97 mmol) was similarly carried out, but it reacted much faster than the Z isomer, taking only 2 h for completion. Workup followed by MPLC afforded (E)-**6f** (0.140 g, 86%) as colorless crystals: mp 59.5–60.0 °C (from pentane); IR (CCl$_4$) 3610, 3470 br, 2950, 2860, 1655, 1460, 1060, 1010, 930 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.18–1.88 (m, 12 H), 1.63 (d, 3 H, J = 6.8 Hz), 2.32 (t, 2 H, J = 6.9 Hz), 5.72 (q, 1 H, J = 6.8 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 73.9, 147.8 (C), 27.9, 115.7 (CH), 23.3, 25.9, 33.4, 35.1 (CH$_2$), 12.8 (CH$_3$). Anal. Calcd for C$_{11}$H$_{18}$O: C, 79.47; H, 10.91. Found: C, 79.32; H, 11.04.

(E)–2–Ethylidenebicyclo[3.2.2]non–1–yl Mesylate ((E)–6e). The procedure is similar to that employed for the preparation of **6a**. (E)-**6f** (0.050 g, 0.301 mmol) was treated with methanesulfonyl chloride (0.039 g, 0.34 mmol) and triethylamine (0.046 g, 0.46 mmol) in CH$_2$Cl$_2$ (1.4 mL) at −20 °C for 50 min, and then the reaction mixture was worked up at 0 °C. The resulting wet CH$_2$Cl$_2$ solution was stabilized by 2,6–lutidine (9 mg) and dried (MgSO$_4$). Evaporation of the solvent afforded (E)-**6e** (0.057 g) contaminated by 30 mol % of (E)-**6f** as a colorless liquid. The crude product was used for solvolysis studies without further purification: ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 95.2, 141.9 (C), 27.6, 119.4 (CH),

23.1, 25.9, 33.4, 35.3 (CH$_2$), 12.9, 41.3 (CH$_3$).

2-Methylenebicyclo[3.3.1]nonan-1-ol (7c). The hydroxyl group of 1–hydroxybicyclo[3.3.1]nonan-2-one[8b] (7d) was protected by *tert*–butyldimethylsilylation as described for the preparation of **4d–OTBDMS** by treating **7d** (0.600 g, 3.89 mmol) with *tert*–butyldimethylsilyl triflate (1.56 g, 5.90 mmol) and 2,6–lutidine (0.544 g, 7.88 mmol) in CH$_2$Cl$_2$ (4.0 mL) for 1 h. Usual workup followed by MPLC (SiO$_2$, hexane–ether (9:1)) afforded **7d–OTBDMS** (0.496 g, 48%) as colorless crystals: mp 53.5–55.0 °C; ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 18.2, 78.6 (C), 30.5 (CH), 21.7, 29.3, 30.6, 37.7, 39.7, 42.6 (CH$_2$), –2.6, 25.8 (CH$_3$), 212.1 (C=O).

In a manner similar to that described for the preparation of **4c**, **7d–OTBDMS** (0.878 g, 3.27 mmol) was treated in DMSO (14 mL) with methylenetriphenylphosphorane, which was generated from methyltriphenylphosphonium bromide (3.505 g, 9.81 mmol) and NaH (60% dispersion 0.392 g, 9.81 mmol) in DMSO, at 70 °C for 19 h. Usual workup followed by MPLC (SiO$_2$, hexane) afforded **7c–OTBDMS** (0.677 g, 78%) as a colorless liquid: ^{1}H NMR (60 MHz, CDCl$_3$) δ 0.10 (s, 6 H), 0.87 (s, 9 H), 1.27–2.62 (m, 13 H), 4.70 (m, 1 H, =CH), 5.10 (m, 1 H, =CH).

To **7c–OTBDMS** (0.640 g, 2.40 mmol) in THF (10 mL) was added 1.0 M *n*–Bu$_4$NF in THF (6.0 mL) and the reaction mixture was heated at reflux for 45 h with stirring under N$_2$. Usual workup as described for the preparation of **4c** followed by MPLC (SiO$_2$, hexane–ether (4:1)) afforded **7c** (0.320 g, 87%) as colorless crystals: mp 44.5–45.5 °C (from pentane); IR (CCl$_4$) 3610, 3470 br, 3090, 1640, 1460, 1100, 905 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.30–2.87 (m, 14 H), 4.60 (m, 1 H, =CH), 4.93 (m, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 72.0,

154.5 (C), 31.2 (CH), 22.1, 30.3, 30.4, 32.4, 39.9, 43.3, 105.8 (CH_2). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.46; H, 10.61.

2–Methylenebicyclo[3.3.1]non–1–yl Mesylate (7a–OMs). The procedure is similar to that employed for the preparation of **6a**. Treatment of **7c** (0.120 g, 0.789 mmol) with methanesulfonyl chloride (0.099 g, 0.86 mmol) and triethylamine (0.120 g, 1.19 mmol) in CH_2Cl_2 (4 mL) at –12 °C for 30 min followed by workup at 0 °C afforded a mixture (0.10 g) of **7a–OMs** and **7c**, the latter being present in as much as 63% based on the ^{1}H NMR spectrum. ^{1}H NMR (60 MHz, CCl_4) δ 2.85 (s, 3 H, CH_3), 5.13 (m, 1 H, =CH), 5.27 (m, 1 H, =CH). The crude product was used for rate studies without further purification.

2–Methylenebicyclo[3.3.1]non–1–yl Heptafluorobutyrate (7a–OHFB). Following a literature method,[42] to a solution of **7c** (0.249 g, 1.64 mmol) in pyridine (2.3 mL) was added n–C_3F_7COCl (0.657 g, 2.83 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C and then the mixture stirred at 0 °C for 6 h. The reaction mixture was diluted with CH_2Cl_2, washed with 10% aqueous HCl (3 × 20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and 10% aqueous NaCl (2 × 20 mL), and dried ($MgSO_4$). Evaporation of solvent afforded **7a–OHFB** (0.515 g, 90%) as a pale yellow liquid, which was used for solvolysis studies without further purification: IR (CCl_4) 2935, 1765, 1635, 1450, 1300, 1220, 1140, 1080, 950, 905 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.87–3.08 (m, 13 H), 4.97 (m, 2 H, =CH_2); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 87.5, 149.3 (C), 28.7 (CH), 19.5, 26.0, 30.4, 31.9, 34.0, 39.2, 110.2 (CH_2).

Bicyclo[3.3.1]non–1–yl Heptafluorobutyrate (7b–OHFB). Bicyclo-[3.3.1]nonan–1–ol (mp 185.0–186.0 °C (lit.[52] mp 182.5–184.0 °C)) (0.202 g, 1.44 mmol) was treated with n–C_3F_7COCl (0.575 g, 2.47 mmol) and pyridine (2.0 mL)

in CH_2Cl_2 at 0 °C for 6 h. Usual workup as described for the preparation of **7a-OHFB** afforded a pale yellow liquid (0.451 g, 93%), which was used for solvolysis studies without further purification: IR (CCl_4) 2925, 1770, 1450, 1235, 1215, 1150, 1120, 1085, 965, 905 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.22–2.83 (m, 15 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 90.0 (C), 32.0 (CH), 22.5, 29.7, 34.7, 39.4 (CH_2).

2–Methylenebicyclo[4.2.2]decan–1–ol (8c). The hydroxyl group of **8d** was first protected by *tert*–butyldimethylsilylation. To a solution of **8d**[8b] (1.325 g, 7.88 mmol) and 2,6–lutidine (1.69 g, 15.8 mmol) in CH_2Cl_2 (8 mL) was added *tert*-butyldimethylsilyl triflate (2.08 g, 7.88 mmol) at –78 °C over 6 min. The reaction was allowed to warm to –30 °C over 30 min and then to 0 °C over 1 h. The reaction mixture was diluted with CH_2Cl_2, washed with water (2 × 30 mL), 10% aqueous HCl (3 × 30 mL), saturated aqueous $NaHCO_3$ (30 mL), and 10% aqueous NaCl (30 mL), and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane–ether (4:1)) afforded unchanged **8d** (0.460 g, 35%) and **8d-OTBDMS** (0.984 g, 44%): IR (CCl_4) 2940, 2860, 1700, 1465, 1360, 1255, 1120, 960, 840 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.28–2.82 (m, 15 H).

In a manner similar to that described for the preparation of **4c**, **8d-OTBDMS** (0.984 g, 3.48 mmol) was treated in DMSO (14.5 mL) with methylene-triphenylphosphorane, which was generated from methyltriphenylphosphonium bromide (3.75 g, 10.5 mmol) and NaH (60% dispersion 0.432 g, 10.5 mmol) in DMSO at 70 °C for 18 h. Usual workup afforded a mixture of a liquid and a solid, from which the liquid was extracted with pentane and hexane. Evaporation of solvent afforded **8c-OTBDMS** (0.981 g, 100%) as a pale yellow liquid: ^{1}H NMR

(60 MHz, CCl$_4$) δ 0.10 (s, 6 H), 0.93 (s, 9 H), 1.20–2.63 (m, 15 H), 4.90 (d, 1 H, =CH, J = 2.8 Hz), 5.18 (d, 1 H, =CH, J = 2.8 Hz).

Similar to the manner described for the preparation of **4c**, **8c–OTBDMS** (0.977 g, 3.48 mmol) was treated with n–Bu$_4$NF (7.0 mmol) in THF (22 mL) at reflux for 38 h under N$_2$. Usual workup followed by MPLC (SiO$_2$, hexane–ether (4:1)) afforded **8c** (0.485 g, 84%) as colorless crystals: mp 71.5–72.0 °C (from pentane); IR (CCl$_4$) 3610, 2930, 2855, 1620, 1470, 1450, 1050, 905 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.00–2.58 (m, 16 H), 4.67 (m, 1 H, =CH), 5.00 (d, 1 H, =CH, J = 2.4 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 73.5, 159.3 (C), 25.7 (CH), 24.1, 25.7, 34.3, 35.0, 35.6, 110.3 (CH$_2$). Anal. Calcd for C$_{11}$H$_{18}$O: C, 79.47; H, 10.91. Found: C, 79.21; H, 10.94.

1–Chloro–2–methylenebicyclo[4.2.2]decane (8a). To a stirred solution of SOCl$_2$ (0.537 g, 4.51 mmol) in benzene (0.8 mL) was added a solution of **8c** (0.150 g, 0.90 mmol) and pyridine (0.450 g, 5.69 mmol) in benzene (1.0 mL) at 0 °C over 5 min. The reaction mixture was stirred at 0°C for 40 min and at room temperature for 2 h, poured into ice–water (20 mL), and extracted with ether (3 × 20 mL). The combined extracts were washed at 0 °C with 10% aqueous HCl (3 × 20 mL) and saturated NaHCO$_3$ (3 × 20 mL) and dried (MgSO$_4$). Evaporation of solvent gave **8a** (0.141 g, 84%) as a pale yellow liquid, which was used for solvolysis studies without further purification: ^{1}H NMR (60 MHz, CCl$_4$) δ 1.10–2.77 (m, 15 H), 5.13 (br s, 1 H, =CH), 5.43 (d, 1 H, =CH, J = 1.6 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 73.7, 155.6 (C), 24.3 (CH), 24.8, 26.2, 34.3, 34.8, 37.4, 117.6 (CH$_2$). The purity of **8a** was 99% as estimated from the ^{13}C NMR spectrum.

1–Chlorobicyclo[4.2.2]decane (8b). The precursor bicyclo[4.2.2]decan-1-ol was prepared as follows. Bicyclo[4.2.2]decane[53] (mp 160–162 °C) (1.00 g, 7.23

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mmol), which was derived from bicyclo[4.2.2]decan–7–one[54] by Wolf–Kishner reduction,[54b] was brominated with NBS (1.35 g, 7.59 mmol) in the presence of dibenzoyl peroxide (0.05 g) in CCl_4 at reflux for 35 min under N_2. Filtration of succinimide followed by evaporation of CCl_4 afforded a yellow liquid (2.00 g), which was then hydrolyzed in 60% (v/v) aqueous acetone (60 mL) with stirring in the presence of $NaHCO_3$ (1.21 g, 14.4 mmol) at room temperature for 5 min, and then at reflux for 40 min. Evaporation of most of the acetone with a rotary evapo–rator separated a solid, which was extracted with ether (3 × 30 mL). The combined extracts were washed with water (3 × 50 mL) and saturated aqueous NaCl (50 mL) and dried ($MgSO_4$). Evaporation of the ether gave a yellow semisolid (1.02 g), which on column chromatography (SiO_2, hexane–ether (1:1, 1:4)) afforded un–changed bicyclo[4.2.2]decane (0.17 g, 17 %), unidentified liquid (0.14 g), and bicyclo[4.2.2]decan–1–ol (0.39 g, 35%) in this sequence. An analytical sample was provided by sublimation at 58–65 °C (2 mmHg): mp 165–171 °C (lit.[55] mp 73–74 °C)[56]; IR (CCl_4) 3600, 3400 br, 2920, 1470, 1450, 1075, 1060, 1020, 940 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 1.3–1.8 (m, 17 H), 2.0 (s, 1 H, OH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 72.6 (C), 27.1 (CH), 24.2, 24.7, 25.1, 34.2, 36.8, 45.5 (CH_2).

Chlorination of the above alcohol (0.154 g, 1.00 mmol) with $SOCl_2$ (1.11 g, 9.35 mmol) at 0 °C for 3 h followed by workup as described for the preparation of **8a** afforded crude **8b** as colorless crystals (0.106 g, 61%): mp 99.5–101.0 °C (lit.[55] mp 70–71 °C);[57] ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 76.7 (C), 26.3 (CH), 24.4, 26.0, 26.2, 36.3, 36.8, 47.9 (CH_2).

4–Methylene–3–homoadamantanol (10c). the hydroxyl group of **10d** was protected by treating **10d** (2.00 g, 11.1 mmol) with *tert*–butyldimethylsilyl triflate (3.64 g, 13.8 mmol) and 2,6–lutidine (2.39 g, 22.3 mmol) in CH_2Cl_2 (12 mL) at

room temperature for 1 h, giving **10d–OTBDMS** (2.62 g, 90%): mp 105.5–107.0 °C; ^{1}H NMR (60 MHz, CCl$_4$) δ 0.10 (s, 6 H), 0.82 (s, 9 H), 1.33–2.60 (m, 15 H). Wittig methylenation[12] of **10d–OTBDMS** (2.36 g, 8.00 mmol) was conducted in DMSO (34 mL) by treatment with methylenetriphenylphosphorane, which was generated from methyltriphenylphosphonium bromide (8.57 g, 24.0 mmol) and NaH (60% dispersion 0.950 g, 24.0 mmol) in DMSO, at 70 °C for 20 h under N$_2$. Worked up of the reaction mixture as described for the preparation of **4c** afforded crude **10c–OTBDMS** (2.24 g, 96%). The crude **10c–OTBDMS** (2.24 g, 7.66 mmol) was treated with n–Bu$_4$NF (19.1 mmol) in refluxing THF (50 mL) for 47 h, and then the reaction mixture was worked up in a usual manner. The crude product was subjected to MPLC (SiO$_2$, hexane–ether (4:1)), giving **10c** (1.30 g, 95%): mp 117.0–118.0 °C (from pentane); IR (CCl$_4$) 3600, 3460 br, 2910, 2850, 1620, 1440, 1050, 945, 910, 890 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.3–2.3 (m, 13 H), 1.43 (s, 1 H, OH), 4.63 (m, 1 H, =CH), 5.13 (m, 1 H, =CH); ^{13}C NMR (25 MHz, CDCl$_3$) δ 74.5, 157.4 (C), 28.1, 29.5 (CH), 35.5, 36.8, 40.8, 46.2, 107.5 (CH$_2$). Analytical data were unsatisfactory, presumably because of hygroscopic nature. Anal. Calcd for C$_{12}$H$_{18}$O: C, 80.85; H, 10.18. Found: C, 80.38; H, 10.16. The p–nitrobenzoate showed satisfactory analytical data: mp 150.5–152.0 °C. Anal. Calcd for C$_{19}$H$_{21}$O$_4$N: C, 69.71; H, 6.47. Found: C, 69.41; H, 6.43.

4–Methylene–3–homoadamantyl Heptafluorobutyrate (10a). To a mixture of **10c** (0.248 g, 1.39 mmol) and pyridine (1.9 mL, 23 mmol) was added n–C$_3$F$_7$COCl (0.556 g, 2.39 mmol) in CH$_2$Cl$_2$ (1.7 mL) at 0 °C over 1 min, and the resulting solution was stirred for 6 h. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed at 0 °C with 5% aqueous HCl (3 × 20 mL), water (2 × 20 mL), saturated aqueous NaHCO$_3$ (2 × 20 mL), and 10% aqueous NaCl (20 mL), and dried (MgSO$_4$). Evaporation of solvent afforded **10b** as a pale yellow liquid,

which was used for solvolysis studies without further purification: IR (CCl$_4$) 2910, 1780, 1450, 1300, 1265, 1240, 1210, 1190, 1080, 970, 940, 900, 840 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.3–2.7 (m, 15 H), 4.60 (s, 2 H, =CH$_2$); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 90.8, 150.8 (C), 27.9, 28.7 (CH), 35.5, 36.2, 40.9, 42.9, 109.7 (CH$_2$).

3–Homoadamantyl Heptafluorobutyrate (10b). The above procedure for **10a** and that described in the literature[42] were followed. To a mixture of 3–homoadamantanol[58] (0.333 g, 2.00 mmol) and pyridine (3.0 mL, 3.32 mmol) was added *n*–C$_3$F$_7$COCl (0.770 g, 3.32 mmol) in CH$_2$Cl$_2$ (2.4 mL) at 0 °C, and the resulting mixture stirred at 0 °C for 12 h. Usual workup afforded crude **10b** (0.682 g, 94%), which was used for solvolysis studies without further purification: liquid; ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 93.5 (C), 27.4, 30.7 (CH), 28.8, 35.0, 36.2, 37.0, 42.9 (CH$_2$).

Product of Solvolysis of 4a in Ethanol: A Typical Procedure. A solution of **4a** (0.164 g, 0.610 mmol) in 0.075 M 2,6–lutidine in ethanol (12.0 mL) was heated in a constant temperature bath (75.0 °C) for 20 h (25 half–lives). Analyses of the reaction mixture by GLC (PEG 20M, 3 mm × 2 m) exhibited the formation of a single product. After most of the ethanol had been removed with a rotary evaporator, the residue was dissolved in ether (20 mL) and the ether solution washed with water (10 mL), cold 2% aqueous HCl (10 mL), saturated aqueous NaHCO$_3$ (10 mL), and saturated aqueous NaCl (10 mL), and dried (MgSO$_4$). Evaporation of the ether afforded 1–ethoxy–2–methylenebicyclo[2.2.2]octane (**4a–OEt**) (0.072 g, 71%) as a colorless liquid: IR (CCl$_4$) 3080, 2950, 2860, 1645, 1430, 1395, 1120, 890 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.13 (t, 3 H, *J* = 7.0 Hz),

1.67 (br s, 10 H), 2.30 (br s, 1 H), 3.33 (q, 2 H, J = 7.0 Hz), 4.63 (q, 1 H, =CH, J = 2.0 Hz), 4.85 (q, 1 H, =CH, J = 2.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 76.2, 149.8 (C), 26.0 (CH), 26.7, 30.6, 36.5, 57.4, 104.0 (CH$_2$), 15.8 (CH$_3$).

Product of Solvolysis of (E)–4e in Ethanol. From (E)–4e (0.060 g, 0.211 mmol) in 0.050 M 2,6–lutidine in ethanol (5.3 mL) at 50.0 °C for 35 h (12 half–lives) was obtained 1–ethoxy–(E)–2–ethylidenebicyclo[2.2.2]octane ((E)–4e–OEt) (0.035 g, 92%) as a pale yellow oil: IR (CCl$_4$) 2950, 2865, 1670, 1455, 1380, 1120, 1045, 910 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.19 (t, 3 H, J = 7.0 Hz), 1.40–1.86 (m, 9 H), 1.56 (dt, 3 H, J = 6.7, 1.5 Hz), 2.27 (br s, 2 H), 3.44 (q, 2 H, J = 7.0 Hz), 5.40 (qt, 1 H, J = 6.9, 2.6 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 75.8, 140.3 (C), 26.0, 112.3 (CH), 26.9, 30.8, 33.3, 57.3 (CH$_2$), 12.3, 15.9 (CH$_3$).

Product of Solvolysis of 5a in Ethanol. From 5a (0.151 g, 0.559 mmol) in 0.051 M 2,6–lutidine in ethanol (14.0 mL) at 50.0 °C for 50.3 h (13.3 half–lives) was obtained 1–ethoxy–2–methylenebicyclo[3.2.1]octane (5a–OEt) (0.070 g, 75%) as a pale yellow liquid: IR (CCl$_4$) 3090, 2940, 2860, 1640, 1450, 1120, 1050, 910 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 1.00–2.57 (m, 11 H), 1.20 (t, 3 H, J = 7.0 Hz), 3.55 (q, 2 H, J = 7.0 Hz), 4.63 (m, 1 H, =CH), 4.77 (m, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 85.9, 151.8 (C), 35.1 (CH), 27.7, 29.9, 33.4, 33.5, 45.0, 59.8, 102.2 (CH$_2$), 15.7 (CH$_3$).

Product of Solvolysis of (E)–6e in Ethanol. From a mixture (0.042 g) of (E)–6e and (E)–6f (70 : 30 in mol) in 0.050 M 2,6–lutidine in ethanol (6.0 mL) at 25.0 °C for 1 h was obtained a pale yellow liquid, which on MPLC (SiO$_2$, hexane–ether (9:1, 7:3)) gave 1–ethoxy–(E)–2–ethylidenebicyclo[3.2.2]nonane ((E)–6f–OEt) (0.022 g, 100% based on (E)–6e) as a colorless liquid and (E)–6f (0.008 g) in

this sequence. (*E*)–**6f–OEt**: IR (CCl$_4$) 2910, 2860, 1655, 1460, 1390, 1130, 1085, 920 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.09 (t, 3 H, *J* = 7.0 Hz), 1.66 (dt, 3 H, *J* = 6.9, 0.9 Hz), 1.23–2.00 (m, 11 H), 2.27 (t, 2 H, *J* = 6.8 Hz), 3.25 (q, 2 H, *J* = 7.0 Hz) , 5.67 (qt, 1 H, *J* = 6.9, 1.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 78.8, 142.1 (C), 28.4, 116.9 (CH), 24.2, 25.8, 33.2, 35.9, 56.2 (CH$_2$), 12.9, 15.9 (CH$_3$).

Product of Solvolysis of 7a–OHFB in 80% Ethanol: A Typical Procedure. A solution of **7a–OHFB** (0.300 g, 0.86 mmol) in 0.050 M 2,6–lutidine in 80% ethanol (21.5 mL) was heated in a constant temperature bath (75.0 °C) for 21.5 h (12.1 half–lives). To the reaction mixture was added ether (200 mL), and the ether solution was washed with water (5 × 50 mL), saturated aqueous NaCl (50 mL), and dried (MgSO$_4$). Analyses of the ether solution by GLC (PEG 20M, 3 mm × 2 m) exhibited the formation of two products. Removal of the ether with a rotary evaporator afforded a yellow liquid, which on MPLC (SiO$_2$, hexane–ether (3:2, 1:4)) gave 1–ethoxy–2–methylenebicyclo[3.3.1]nonane (**7c–OEt**) (0.090 g, 56%) and **7c** (0.059 g, 44%) in this sequence. The ^{1}H NMR spectrum of **7c** obtained was in complete agreement with that of the specimen. **7c–OEt**: IR (CCl$_4$) 3080, 2930, 2850, 1630, 1450, 1390, 1090, 900 cm^{-1}; ^{1}H NMR (60 MHz, CCl$_4$) δ 0.90–2.57 (m, 16 H), 1.07 (t, 3 H, *J* = 7.1 Hz), 3.30 (q, 2 H, *J* = 7.1 Hz), 4.52 (m, 1 H, =CH), 4.63 (m, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 76.4, 150.8 (C), 29.2 (CH), 20.7, 27.9, 31.9, 35.3, 40.7, 56.4, 108.6 (CH$_2$), 16.0 (CH$_3$).

Product of Solvolysis of 8a in 80% Ethanol. From **8a** (0.115 g, 0.623 mmol) in 0.050 M 2,6–lutidine in 80% ethanol (16 mL) at 25.0 °C for 6 h (10 half–lives) was obtained a pale yellow oil (0.108 g), which on MPLC (SiO$_2$, hexane–ether (9:1, 1:1)) afforded 1–ethoxy–2–methylenebicyclo[4.2.2]decane

(**8c–OEt**) (0.030 g, 25%) and **8c** (0.040 g, 39%) in this sequence. **8c–OEt:** IR (CCl$_4$) 2920, 1625, 1465, 1450, 1390, 1110, 1080, 905 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.09 (t, 3 H, J = 7.0 Hz), 1.20–2.36 (m, 15 H), 3.27 (q, 2 H, J = 7.0 Hz), 5.08 (d, 1 H, J = 2.4 Hz), 5.16 (d, 1 H, J = 2.5 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 78.5, 154.9 (C), 25.4 (CH), 23.3, 26.5, 32.1, 34.9, 35.8, 56.0, 113.7 (CH$_2$), 15.9 (CH$_3$).

Product of Solvolysis of 10a in 80% Ethanol. From **10a** (0.391 g, 1.04 mmol) in 0.050 M 2,6–lutidine in 80% ethanol (26 mL) at 75.0 °C for 42.3 h (16.4 half–lives) was obtained a liquid (0.219 g), which on MPLC (SiO$_2$, hexane–ether (9:1, 4:1)) afforded 3–ethoxy–4–methylenehomoadamantane (**10c–OEt**) (0.090 g, 41%) and **10c** (0.108 g, 59%) in this sequence. **10c–OEt:** IR (CCl$_4$) 2930, 2850, 1630, 1450, 1395, 1125, 1070, 890 cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 0.86–2.57 (m, 15 H), 1.12 (t, 3 H, J = 7.0 Hz), 3.37 (q, 2 H, J = 7.0 Hz), 4.80 (m, 1 H, =CH), 5.00 (m, 1 H, =CH); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 79.2, 152.5 (C), 27.9, 29.2 (CH), 36.0, 36.6, 42.0, 43.9, 56.1, 109.5 (CH$_2$), 15.7 (CH$_3$).

Kinetic Studies. The preparation of 80% ethanol and kinetic methods followed a literature procedure.[27] All measurements were conducted in the presence of 0.025 M 2,6–lutidine with 0.02 M or (1–2) × 10^{-4} M substrate concentrations for titrimetric or conductimetric measurements, respectively. The first–order rate constants were calculated by the least–squares method on a microcomputer. The results are summarized in Table 2.1.

NOE Difference Experiments. Nuclear Overhauser enhancement of the olefinic proton of (*Z*)–**4f–OTBDMS**, (*E*)–**4f–OTBDMS**, (*Z*)–**6f–OTBDMS**, and (*E*)–**6f–OTBDMS** on irradiation of the C(3) methylene protons was determined at

270.05 MHz by the gated decoupling method using $CDCl_3$ solutions degassed under vacuum. An irradiation period of 3.5 times the T_1's of the C(3) methylene protons was employed for NOE generation, followed by a 90° pulse. For spin relaxation, a pulse interval of 3.5 times the T_1's of the olefinic proton was taken before the next pulse. The T_1 values for (Z)-4f-OTBDMS, (E)-4f-OTBDMS, (Z)-6f-OTBDMS, and (E)-6f-OTBDMS were determined by the inversion recovery method: C(3) methylene protons, 2.6, 1.9, 1.8, and 1.9 s, respectively; olefinic protons, 8.5, 7.9, 6.5, and 6.5 s, respectively.

Calculations. Semiempirical molecular orbital calculations and molecular mechanics calculations were preformed through the AMPAC[40] system and MM2,[37] respectively, on FACOM M–780/30, FACOM VP–400E, and FACOM VP–200 computers.

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Chapter 3

Solvolysis of 2–Oxo Bicyclic Bridgehead Derivatives: Evidence for the Unimportance of π–Conjugative Stabilization in Tertiary α–Keto Cations

Abstract

The solvolysis rate ratios of 2–methylene bicyclic and tricyclic compounds relative to the parent compounds $[k(X = CH_2)/k(X = H_2)]$ increased with increasing skeletal flexibility of the ring system, whereas the corresponding rate ratios related to 2–oxo homologues $[k(X = O)/k(X = H_2)]$ were essentially constant, suggesting the unimportance of π–conjugative stabilization in tertiary α–keto cations. Moreover, AM1 semiempirical molecular orbital calculations on 2–oxo bridgehead cations and the corresponding neutral compounds (L = hydrogen) also supported this notion. In the solvolysis of 2–oxo–3,3–dimethylbicyclo[2.2.2]oct–1–yl triflate, the possibility of the carbonyl addition of the solvent was ruled out by ^{18}O exchange study.

3–1. Introduction

The cyano and carbonyl groups are strongly electron withdrawing (–I and –M effects). In the past decade, a number of experimental data have been interpreted to support the notion that the α–cyano (Scheme 3.1) and α–keto (Scheme

Scheme 3.1

$$\underset{R}{\overset{R}{>}}\overset{+}{C}-C\equiv N \longleftrightarrow \underset{R}{\overset{R}{>}}C=C=\overset{+}{N}$$

Scheme 3.2

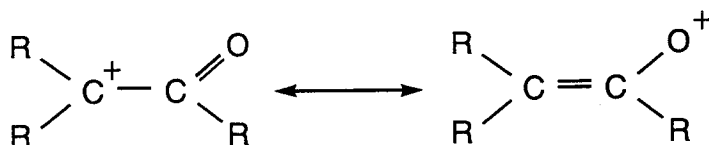$$\underset{R}{\overset{R}{>}}\overset{+}{C}-C\overset{O}{\underset{R}{\diagup}} \longleftrightarrow \underset{R}{\overset{R}{>}}C=C\overset{\overset{+}{O}}{\underset{R}{\diagdown}}$$
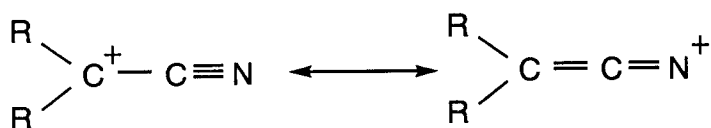
Scheme 3.3
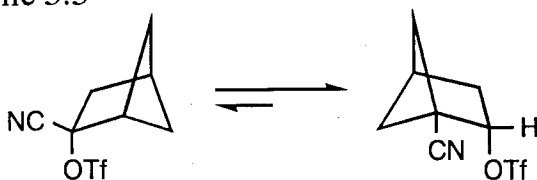
3.2) carbocations are stabilized by π–conjugation to an extent that partly offsets the destabilizing inductive effect of the substituents.[1] Recently, however, Kirmse and his co–workers pointed out that the cyano group and the leaving group attached to the same carbon atom interact with each other (geminal group interaction), result-ing in significant destabilizing (9–10 kcal mol^{-1}) of the ground state as compared with the β–cyano substrate (Scheme 3.3).[2] This has been used to explain why the α–cyano carbocations are relatively easily formed in solvolyses.[2a]

The π–conjugative stabilization of α–carbonyl cation was originally postu-lated by McDonald[3] and elaborated by Creary. The most important data used as evidence for the π–conjugative effect came from solvolysis work. Creary found that the replacement of the methine hydrogen in isopropyl mesylate **1** with an acyl

group rather enhances the solvolysis rate.[4] By taking the σ^+ values of the acyl substituents into account, the rates of **2** and **3** were evaluated to be faster by a factor of 10^4–10^5 than expected from the –I and –M effects of the substituents.
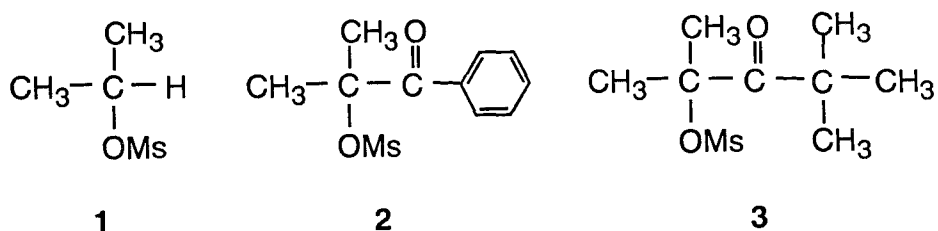
Such large rate enhancement corresponding to 5.5–7 kcal mol^{-1} was attributed to the stabilization of the incipient carbocation by π–conjugation as depicted in Scheme 3.2.[4] The rigorous ab initio calculations using a double-ζ plus polariza-tion basis sets have been carried out on the formylmethyl cation.[5] The planar cation is stabilized relative to the perpendicular cation by 2.5 kcal mol^{-1}.[5] The stability of the planar form is attributed to substantial π–donation of the carbonyl group. However, this π–donation ability of the carbonyl group is expected to de-crease with methyl substitution. So it follows that the π–donation would not be a important factor in the *tertiary* α–keto cation $(CH_3)_2C^+CHO$.
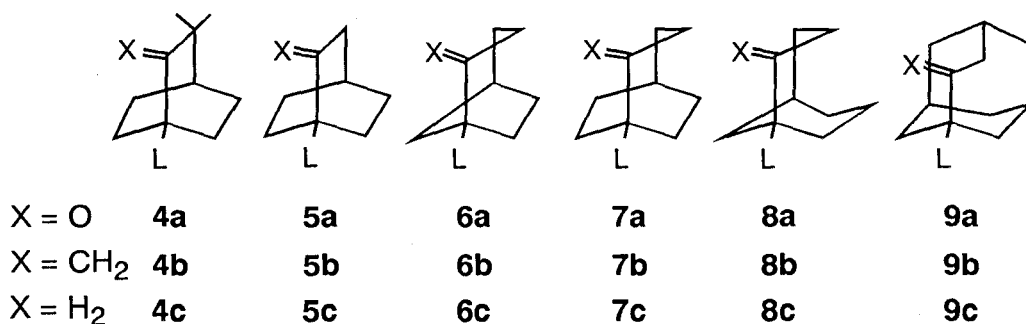

planar   perpendicular
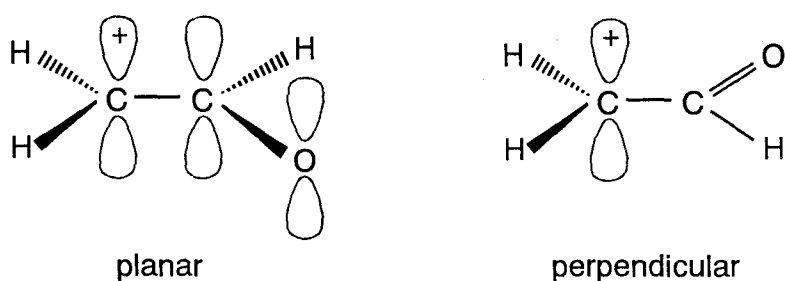
The preceding chapter described that the rates of solvolysis of the α–meth-ylene bicyclic and tricyclic compounds (**5b–9b**) relative to the corresponding

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parent compounds (**5c–9c**) markedly increase from $10^{-3.9}$ to $10^{0.9}$ with the increase in the structural flexibility (Table 3.1).[6] These rate studies and AM1 and MM2 calculations suggested the usefulness of our methodology to evaluate the conjugative ability of a group adjacent to the carbocationic center. Previously, we have determined the rates of solvolysis of 3,3–dimethyl–2–oxobicyclo[2.2.2]oct–1–yl triflate (**4a–OTf**), 2–oxobicyclo[3.2.2]non–1–yl mesylate (**7a–OMs**), 2–oxobicyclo[3.3.1]non–1–yl triflate (**8a–OTf**), and 4–oxo–3–homoadamantyl heptafluorobutyrate (**9a–OHFB**) relative to their corresponding parent compounds (**4c–OTf, 7c–OTf, 8c–OMs,** and **9c–OHFB,** respectively).[6a,b] The essentially identical rate ratios ($10^{-8.4}$ for **4a/4c**, $10^{-8.3}$ for **7a/7c**, $10^{-8.2}$ for **8a/8c**, and $10^{-8.7}$ for **9a/9c**) have been interpreted to indicate the unimportance of π–conjugative stabilization of α–keto cations. This chapter describes the semiempirical molecular orbital calculations (AM1) on 2–methylene and 2–oxo bridgehead carbocations and the corresponding neutral compounds (L = hydrogen).

Table 3.1. Rate Ratio [k(X = CH$_2$ or O)/k(X = H$_2$)] for Solvolysis at 25.0 °C[a]

system	k(X = CH$_2$)/k(X = H$_2$)	k(X = O)/k(X = H$_2$)
4	——[b]	$10^{-8.4\,c,d}$ (L = OTf[e])
5	$10^{-3.9\,c,d}$ (L = OTf[e])	——[b]
6	$10^{-1.9\,c,f}$ (L = OTf[e])	——[b]
7	$10^{-0.8\,c,d}$ (L = OMs[g])	$10^{-8.3\,c,d}$ (L = OTf[e])
8	$10^{0.9\,h,i}$ (L = OMs[g])	$10^{-8.2\,c,h}$ (L = OMs[g])
9	$10^{-1.1\,h,i}$ (L = OHFB[j])	$10^{-8.7\,c,h}$ (L = OTf[e])

[a]Buffered with 0.025 M 2,6–lutidine. [b]Not determined. [c]100% ethanol. [d]Reference 6a. [e]OSO$_2$CF$_3$. [f]Reference 6c. [g]OSO$_2$CH$_3$. [h]Reference 6b. [i]80% ethanol. [j]OCOC$_3$F$_7$–n.

X = O	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**
X = CH₂	**4b**	**5b**	**6b**	**7b**	**8b**	**9b**
X = H₂	**4c**	**5c**	**6c**	**7c**	**8c**	**9c**

Previously in this laboratory, the solvolysis of **4a–OTf** has been found to follow a good first–order kinetics and give a nicely linear $mY_{2-AdOTf}$ relation.[7] However, the major product from **4a–OTf** in methanol was methyl 7,7–dimethyl–bicyclo[2.2.1]heptane–1–carboxylate **10** (93%), accompanied by **4a–OMe** and **11** (4.3%) (Scheme 3.4). Recently, it has been suggested that the major formation of rearranged products might indicate the involvement of carbonyl addition process (Scheme 3.5).[1d] For the purpose of examining the possibility of the carbonyl addition process, in this chapter, the solvolysis of **4a–OTf** in 90% MeOH–10% $H_2^{18}O$ (10 atom% ^{18}O) in the presence of excess of 2,6–lutidine and the ^{18}O content at the carbonyl oxygen of recovered **4a–OTf** was determined by mass spectral analyses.

Scheme 3.4

	4a-OTf		**4a-OMe** (2.7%)	**10** (93%)	**11** (4.3%)

Scheme 3.5

4a-OTf   10
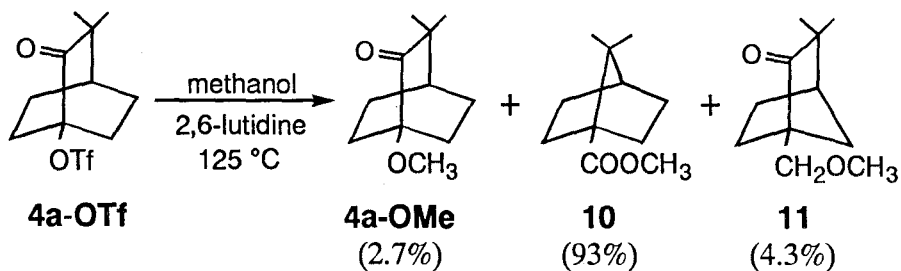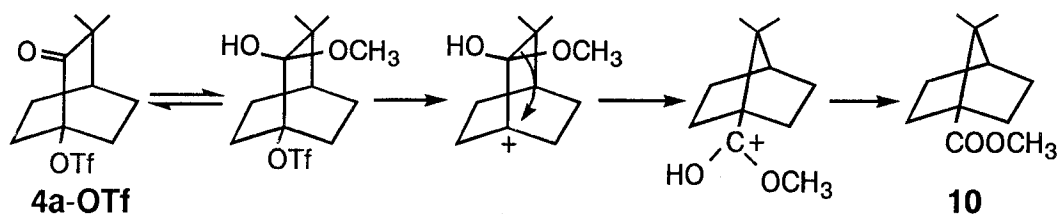
3-2. Results and Discussion

Synthesis of Solvolysis Substrates. 3,3–Dimethylbicyclo[2.2.2]octane–1,2–diol (12) and bicyclo[2.2.2]octane–1,2–diol (13) were prepared by the acylative ring expansion of 7,7–dimethylbicyclo[2.2.2]heptane–1–carbaldehyde and bicyclo[2.2.2]heptane–1–carbaldehyde, respectively, following the literature method.[8] Either with the silver carbonate (Ag_2CO_3) on Celite[9a] or with the Jones reagent,[9b,c] the oxidation of 13 to α–ketol (5a–OH) proceeded in low yields (15–20%). Recently, Curci and his co–workers reported the selective conversion of secondary and primary alcohols into carbonyl compounds by using dimethyldioxirane or methyl(trifluoromethyl)dioxirane in high yields.[10] Therefore, the oxidation of 13 with dimethyldioxirane was employed.[11] To a stirred solution of 13 in CH_2Cl_2 was added 1.2 equivalent of dimethyldioxirane in acetone, and then the resulting mixture was kept below 5 °C for 3 days. Removal of solvent afforded essentially pure 5a–OH in quantitative yields. Diol 12 was also quantitatively oxidized by dimethyldioxirane to give 4a–OH. 4a–OH and 5a–OH were converted to triflates 4a–OTf and 5a–OTf, respectively.

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Scheme 3.6
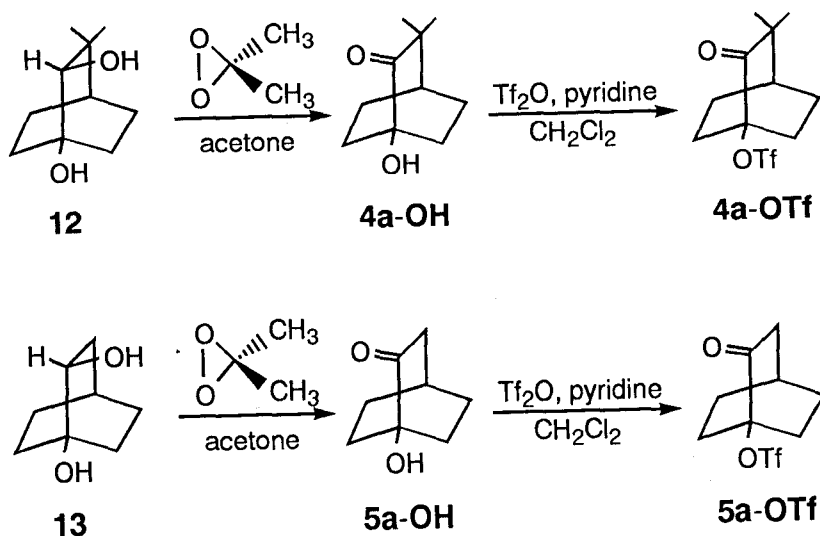
The Examination of π–Conjugative Ability of α–Keto Cations by Using Olefinic Strain Energies. The preceding chapter described the olefinic strain energies can be used as an empirical measure of conjugative ability of 2–methylene bicyclic bridgehead carbocations. A plot of $\log[k(X = CH_2)/k(X = H_2)]$ against the olefinic strain energies shows that the smaller the olefinic strain, the easier the allylic conjugation (Figure 3.1). However, $\log[k(X = O)/k(X = H_2)]$ values are sensibly constant. This result leads us to conclude that π–conjugative stabilization as depicted by Scheme 3.2 is unimportant, at least in tertiary α–keto cations.

AM1 Semiempirical Calculations. AM1 calculations wereconducted on the 2–oxo bicyclic bridgehead carbocations and the corresponding hydrocarbons (L = hydrogen) through the AMPAC system.[12] In Tables 3.2 and 3.3 are summarized pertinent bond orders and net atomic charges, respectively, in the allylic part
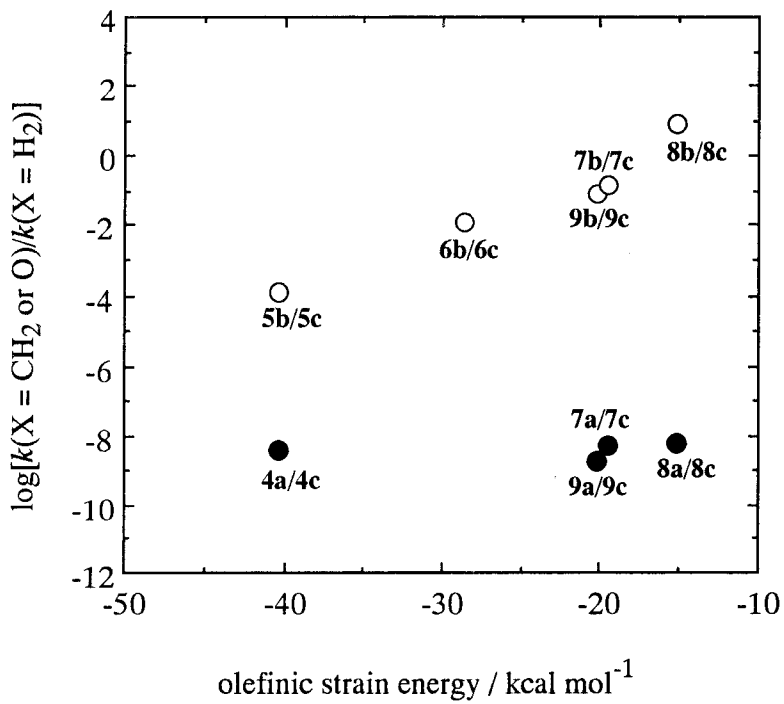
Figure 3.1. Plot of log[k(X = CH$_2$ or O)/k(X = H$_2$)] values against olefinic strain energies of corresponding unsubstituted bridgehead olefins.

Table 3.2. AM1 Calculated Bond Orders for Carbocations and Corresponding Hydrocarbons (L = Hydrogen)[a]

| | 2-oxo | | | | | | 2-methylene | | | | | |
| | carbocation | | hydrocarbon | | ΔBO | | carbocation | | hydrocarbon | | ΔBO | |
system	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ	C_α–C_β	C_β=C_γ
4	0.890	2.036	0.917	1.922	-0.027	0.114	1.041	1.917	—[b]	—[b]	—[b]	—[b]
5	0.877	2.030	—[b]	—[b]	—[b]	—[b]	1.028	1.912	1.034	1.842	0.056	-0.021
6	0.879	2.004	0.919	1.909	-0.040	0.095	1.087	1.828	1.087	1.828	0.116	-0.104
7	0.881	1.995	0.921	1.907	-0.040	0.088	1.157	1.737	1.157	1.737	0.185	-0.194

[a]The arrangement of atom is C_α–C_β=O or C_α–C_β=C_γ with C_α being the bridgehead cationic center. [b]Not calculated.

Table 3.3. AM1 Calculated Net Atomic Charges for Carbocations and Corresponding Hydrocarbons (L = Hydrogen)[a]

system	2-oxo			2-methylene		
	C_α	C_β	O	C_α	C_β	CH_2[b]
4	0.284	0.192	−0.127	0.390	−0.243	−0.078
5	0.288	0.197	−0.125	0.394	−0.245	−0.077
6	0.304	0.196	−0.145	0.379	−0.231	−0.046
7	0.279	0.194	−0.143	0.317	−0.219	0.005

[a]The arrangement of atoms is C_α–C_β=O or C_α–C_β=CH_2 with C_α being the bridgehead cationic center. [b]Net atomic charge on carbon.

together with those of the corresponding 2–methylene series calculated in Chapter 2. The relation between $\log[k(X = CH_2$ or $O)/k(X = H_2)]$ and $\Delta BO(C_\alpha$–$C_\beta)$ (Figure 3.2) shows that with the increases in $\log[k(X = CH_2)/k(X = H_2)]$ the C_α–C_β bond order increases, which indicates that the π–conjugative stabilization of an incipient carbocation becomes operative in the 2–methylene system with increasing structural flexibility. Whereas, in the 2–oxo system the changes appear to be too small in spite of increasing flexibility to evaluate the significance of the carbonyl π–conjugation. In addition, an inspection of net atomic charge reveals a decreasing trend of charge delocalization on the carbonyl oxygen with increasing ring flexibility, contrary to the expectation if carbonyl π–conjugation were important (Table 3.3).

The Origin of the Unexpectedly Fast Solvolysis Rates of 2 and 3. In this context, how can one rationalize the unexpectedly fast rates of solvolysis of **2** and **3**? The most important rate–enhancing factor would be geminal group interaction.
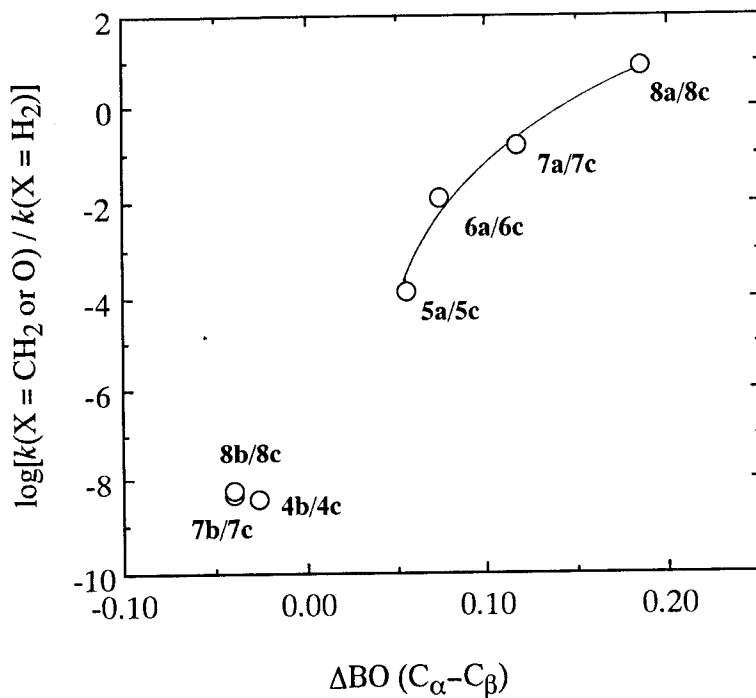
Figure 3.2. Plot of log[k(X = CH$_2$ or O) / k(X = H$_2$)] values against difference of C$_\alpha$–C$_\beta$ bond orders between bridgehead carbocations and the corresponding hydrocarbons.

Della and his co-workers reported that the solvolysis of 2–carbomethoxybicyclo[2.1.1]hex–2–yl mesylate **14** in formic acid gave rearranged 1–carbomethoxybicylo[2.1.1]hex–2–yl mesylate **15–OMs** and its formolysis product, indicating that **14** is far more destabilized than **15–OMs** by the geminal group interaction between the leaving group (OMs) and the methoxycarbonyl group (Scheme 3.7).[13]

Scheme 3.7

14	**15-OMs**	**15-OCHO**
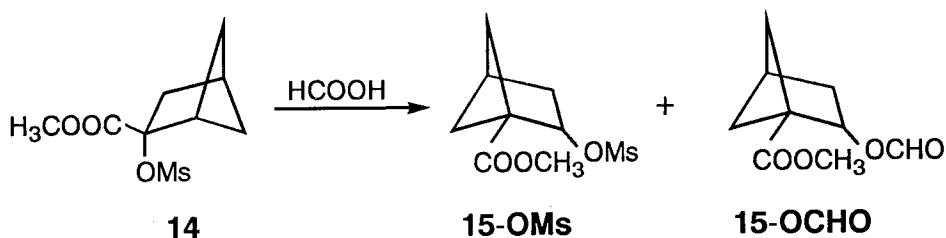
Another factor would be partial relief of back–strain of ground state on ionization. Molecular mechanics calculations indicated that **2** and **3** are more strained than **1** by 5–7 kcal mol^{-1}.[7]

Solvolysis of 4a–OTf in 90% MeOH–10% $H_2^{18}O$ at 100.0 °C. The solvolysis of **4a–OTf** was found to follow a good first–order kinetics and give a nicely linear $mY_{2-AdOTf}$ relation ($m = 0.73$, r = 0.996),[7] showing the S_N1 nature of its solvolysis.

The solvolysis of **4a–OTf** (natural abundance ratio M (300) : M + 2 (302) = 100 : (10.0 ± 0.6)) was conducted in 90% MeOH–10% $H_2^{18}O$ (10 atom% ^{18}O) in the presence of excess of 2,6–lutidine up to 50% and 75% reaction at 100.0 °C. The aliquot was worked up and the ^{18}O content at the carbonyl oxygen in the recovered **4a–OTf** was determined by comparing the intensities of mass spectral

peaks. The result of intensity ratio {[M+H] (301) : [M+H] + 2 (303)} was 100 : (10.1 ± 0.4) for 50% reaction and 100 : (10.4 ± 0.5) for 75% reaction. These mass spectral data indicated that the carbonyl oxygen could not be enriched by ^{18}O. If **4a–OTf** was completely enriched by the incorporation of 10 atom% ^{18}O in the carbonyl oxygen, the intensity ratio M : M + 2 would be (100 − 10) : ((10.0 ± 0.6) + 10) = 100 : (22.2 ± 0.7). Therefore, the possibility of the carbonyl addition process for the solvolysis of **4a–OTf** as shown in Scheme 3.5 was ruled out. The possible route in the solvolysis of **4a–OTf** is presented in Scheme 3.8. The rearrangement of the first–formed, classical, bridgehead carbocation **4a⁺** to acyl cation **16** gives ester **10**. Ether **11** is derived from the primary carbocation **17** which is formed by rearrangement of **4a⁺**. Ether **4a–OMe** is the product from direct capture of **4a⁺**.

Scheme 3.8
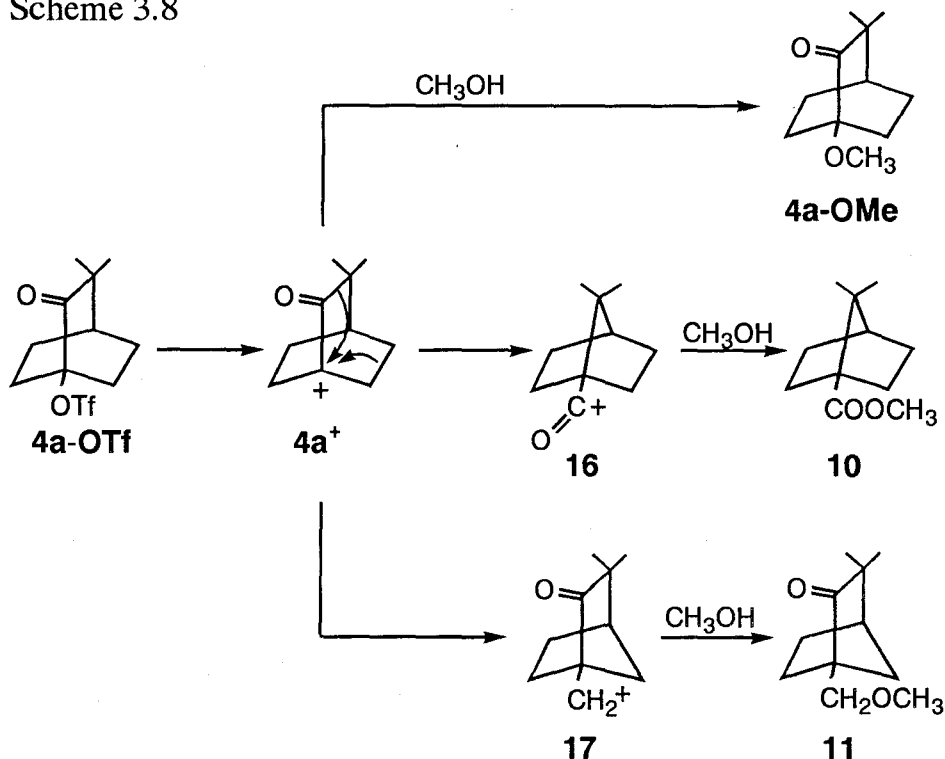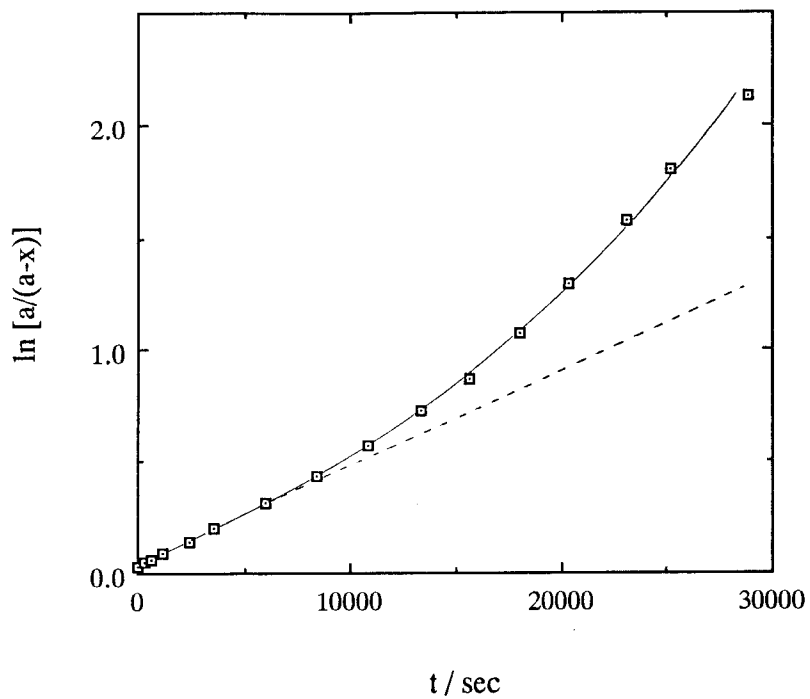
Figure 3.3. A first-order plot for solvolysis of 2-oxo-bicyclo[2.2.2]oct-1-yl triflate (**5-OTf**) in 90% methanol-10% H_2O at 100.0 °C.

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Solvolysis of 5a–OTf in 90% MeOH–10% $H_2^{18}O$ at 100.0 °C. On the contrary, the first order plot of **5a–OTf** showed an upward drift (Figure 3.3) and an $mY_{2-AdOTf}$ plot for the solvolysis of **5a–OTf** was not linear, but random,[7] indicating the occurrence of carbonyl addition of solvent in the solvolysis of **5a–OTf**.

The solvolysis of **5a–OTf** (natural abundance ratio M (272) : M + 2 (274) = 100 : (9.5 ± 0.9)) was conducted in 90% MeOH–10% $H_2^{18}O$ (10 atom% ^{18}O) in a similar manner described for **4a–OTf**. The result of intensity ratio M : M + 2 was 100 : (10.1 ± 1.0) for 50% reaction and 100 : (13.4 ± 0.6) for 75% reaction. If **5a–OTf** was completely enriched, the intensity ratio M : M + 2 would be (100 – 10) : ((9.5 ± 0.9) + 10) = 100 : (21.7 ± 1.0). Consequently, although being not completely enriched, the carbonyl oxygen was enriched by the incorporation of (3.4 ± 1.3) % ^{18}O at 75% reaction. It is highly probable that the solvolysis of **5a–OTf** involved the carbonyl addition process (Scheme 3.5).

3–3. Experimental Section

IR spectra were recorded on a Hitachi 215 spectrophotometer. ^1H NMR spectra were recorded on a JEOL FX90A (89.55 MHz) and JEOL GSX270 (270.05 MHz) spectrometer. ^{13}C NMR spectra were measured on a JEOL FX90A (22.5 MHz) and JEOL GSX270 (67.8 MHz) spectrometer. In all NMR measurements TMS was used as an internal standard. Mass spectra were recorded on a Hitachi M–80 GC–MS spectrometer equipped with a Hitachi M–003 data processor. 3,3–Dimethylbicyclo[2.2.2]octane–1,2–diol (**12**) and bicyclo[2.2.2]octane–1,2–diol (**13**) were prepared following the procedures developed in this laboratory.[8] A solution of dimethyldioxirane in acetone was obtained by reported procedure[10] and

standardized by iodometry prior to use. All anhydrous solvents used for synthetic work were purified by standard procedures. Other commercially available reagents were of a reagent–grade quality and used as received. Medium–pressure liquid chromatography (MPLC) was conducted on Merck silica gel 60 (230–400 mesh).

1–Hydroxy–3,3–dimethylbicyclo[2.2.2]octan–2–one (4a–OH). To a stirred solution of 3,3–dimethylbicyclo[2.2.2]octane–1,2–diol **12**[8] (0.772 g, 4.53 mmol) in CH_2Cl_2 (90 mL) was added 0.079 M dimethyldioxirane in acetone (69 mL). The resulting mixture was stored in a refrigerator at 3 °C for 69 h. After most of solvent had been removed with a rotary evaporator, ether was added. The ether solution was dried with $MgSO_4$. Evaporation of solvent gave 1–hydroxy–3,3–dimethylbicyclo[2.2.2]octan–2–one **4a–OH** (0.768 g, 100%) as colorless crystals: mp 116.5–117.0 °C; ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 220.9, 75.6, 74.3, 45.8, 38.0, 30.2, 23.7, 23.2. Analytical data were unsatisfactory probably due to its hygroscopic nature. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.08; H, 9.54. Satisfactory analytical data were obtained for the triflate **4a–OTf** as described below.

2–Oxo–3,3–dimethylbicyclo[2.2.2]oct–1–yl Triflate (4a–OTf) To a solution of **4a–OH** (0.300 g, 1.78 mmol) and pyridine (0.282 g, 3.57 mmol) in CH_2Cl_2 (2.1 mL) was added a solution of triflic anhydride (0.604 g, 0.214 mmol) in CH_2Cl_2 (2.1 mL) with stirring at 0 °C over 3 min, and then stirring continued at 0 °C for 2h. After having been stored in a freezer overnight, the reaction mixture was diluted with CH_2Cl_2 (25 mL), washed at 0 °C with water (2 × 15 mL), 10% aqueous HCl (3 × 15 mL), 10% aqueous NaCl (15 mL), saturated aqueous $NaHCO_3$ (15 mL), and 10% aqueous NaCl (15 mL) and dried ($MgSO_4$). Evapora–

tion of solvent with a rotary evaporator followed by recrystallization from hexane afforded **4a–OTf** (0.388 g, 73%) as colorless crystals: mp 112.0–114.0 °C; ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 210.2, 97.0, 48.0, 37.1, 28.3, 23.7, 23.3, 118.1 (q, CF$_3$, J = 318.7 Hz). Anal. Calcd for C$_{11}$H$_{15}$O$_4$SF$_3$: C, 44.00; H, 5.03. Found: C, 43.83; H, 4.84. The natural abundance of [18]O for **4a–OTf** was determined by analysis of mass spectral peaks at [M+H] (301) and [M+H] + 2 (303); the intensity ratio [M+H] : [M+H] + 2 was 100 : (10.0 ± 0.6).

1–Hydroxybicyclo[2.2.2]octan–2–one (5a–OH). To a stirred solution of bicyclo[2.2.2]octane–1,2–diol **13**[8] (0.722 g, 5.08 mmol) in CH$_2$Cl$_2$ (100 mL) was added 0.079 M dimethyldioxirane in acetone (77 mL) . The resulting mixture was stored in a refrigerator at 3 °C for 69 h. After most of solvent had been removed with a rotary evaporator, ether was added. The ether solution was dried with MgSO$_4$. Evaporation of solvent gave 1–hydroxybicyclo[2.2.2]octan–2–one **5a–OH** (0.703 g, 99%). The spectral data satisfactorily coincided with the reported data.[6c]

2–Oxobicyclo[2.2.2]oct–1–yl Triflate (5a–OTf). To a solution of **5a–OH** (0.300 g, 2.14 mmol) and pyridine (0.334 g, 4.22 mmol) in CH$_2$Cl$_2$ (2.5 mL) was added a solution of triflic anhydride (0.721 g, 2.56 mmol) in CH$_2$Cl$_2$ (2.5 mL) with stirring at 0 °C over 3 min, and then stirring continued for 1 h. After having been stored in a freezer overnight, the reaction mixture was diluted with CH$_2$Cl$_2$ (20 mL), washed at 0 °C with water (2 × 15 mL), 10% aqueous HCl (3 × 15 mL), 10% aqueous NaCl (15 mL), saturated aqueous NaHCO$_3$ (15 mL), and saturated aqueous NaCl (15 mL) and dried (MgSO$_4$). Evaporation of solvent with a rotary evaporator followed by recrystallization from hexane afforded **5a–OTf** (0.426 g,

73%) as colorless crystals: mp 81.5–82.5 °C; ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 204.6, 97.0, 44.5, 28.2, 26.6, 26.2, 118.1 (q, CF$_3$, J = 319.4 Hz). Anal. Calcd for C$_9$H$_{11}$O$_4$SF$_3$: C, 39.71; H, 4.07. Found: C, 39.93; H, 4.00.

The natural abundance of ^{18}O for **5a–OTf** was determined by analysis of mass spectral peaks at M (272) and M + 2 (274); the intensity ratio M : M + 2 was 100 : (9.5 ± 0.9).

Product of Solvolysis of 2–Oxo–3,3–dimethylbicyclo[2.2.2]oct–1–yl Triflate (4a–OTf) in 90% MeOH–10% $H_2^{18}O$. A solution of **4a–OTf** ([M+H] : [M+H] + 2 = 100 : (10.0 ± 0.6), 0.120 g, 0.40 mmol) in 0.050 M 2,6–lutidine in 90% MeOH–10% $H_2^{18}O$ (10 atom% ^{18}O) (10 mL) was heated in a constant temperature bath (100.0 °C) for 22 h (75% reaction). After most of methanol had been removed with an oil pump at 0 °C, the residue was extracted with ether (10 mL), and the extract was dried (MgSO$_4$). Evaporation of solvent afforded colorless crystals (0.111 g). The isotopic composition of **4a–OTf** in the solvolysis products was determined by analysis of the mass spectral peaks at [M+H] (301) and [M+H] + 2 (303); the intensity ratio [M+H] : [M+H] + 2 was 100 : (10.4 ± 0.5), showing no incorporation of ^{18}O in the carbonyl group.

Product of Solvolysis of 2–Oxobicyclo[2.2.2]oct–1–yl Triflate (5a–OTf) in 90% MeOH–10% $H_2^{18}O$. A solution of **5a–OTf** (M : M + 2 = 100 : (9.5 ± 0.9), 0.109 g, 0.40 mmol) in 0.050 M 2,6–lutidine in 90% MeOH–10% $H_2^{18}O$ (10 atom% ^{18}O) (10 mL) was heated in a constant temperature bath (100.0 °C) for 6.3 h (75% reaction). After most of methanol had been removed with an oil pump at 0 °C, the residue was extracted with ether (10 mL), and the extract was dried (MgSO$_4$). Evaporation of solvent afforded colorless crystals (0.041 g). The isotopic composition of **5a–OTf** in the solvolysis products was determined by analy–

sis of the mass spectral peaks at [M+H] (273) and [M+H] + 2 (275); the intensity ratio [M+H] : [M+H] + 2 was 100 : (13.4 ± 0.6).

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Chapter 4

Solvolyses of Bicyclo[2.2.2]oct-1-yl and 1-Adamantyl Systems Containing an Ethylidene Substituent on the 2-Position: Typical Examples of Rate Enhancement Ascribed to Relief of F-Strain during Ionization

Abstract

The first typical examples are described on the solvolysis rate enhancements ascribed to the relief of F-strain between an alkyl group and the leaving group atom directly attached to the reaction center. The rates and products of solvolyses in ethanol were studied for 2-methylene- and (Z)- and (E)-2-ethylidenebicyclo-[2.2.2]oct-1-yl triflates. Solvolyses were also conducted in ethanol and 2,2,2-trifluoroethanol (TFE) on 2-methylene- and (Z)- and (E)-2-ethylidene-1-adamantyl compounds having OMs, F, Cl, Br, or I as a leaving group. All the substrates gave the corresponding bridgehead substitution products as kinetic control products. The Z:E rate ratios at 25 °C were 217 ± 6 for 2-ethylidenebicyclo[2.2.2]oct-1-yl triflates (ethanol) and 109 ± 11 (ethanol) and 117 ± 1 (TFE) for 2-ethylidene-1-adamantyl mesylates. ^{18}O scrambling studies on the ethanolyses of (Z)- and (E)-2-ethylidene-1-adamantyl mesylates showed that the titrimetrically determined Z:E rate ratios can be used as a measure of the rate ratios for the ionization step. The Z:E rate ratio in TFE at 25 °C for 2-ethylidene-1-adamantyl halides varied in the sequence F (ca. 70), Cl (1020 ± 160), Br (2230 ± 90), and I (9500 ± 280). The significant increases in the rate ratio with the increase

in the atomic size of halogen were explained in terms of the presence of F–strain in the Z substrates and its essential absence in the E substrates. Linear correlations were found in a plot of 1.36 × log[k_Z/k_E] against the MM2 steric energy difference between the Z and E isomers (slope 1.0) and against Hansch's Es, demonstrating the significance of F–strain effect in the enhanced rates of the (Z)–2–ethylidene–1–adamantyl system. These correlations showed an intercept of 0.8 kcal mol^{-1}, which suggested the greater stability of the (Z)–2–ethylidene–1–adamantyl cation than the corresponding E cation by this amount. Ab initio calculations (RHF/6–31G**) showed that the Z cation is more stable than the E cation by 1.0 kcal mol^{-1}, and that the large Z:E rate ratios are in part ascribed to the difference in the cation stability.

4–1. Introduction

Quantitative understanding of steric effects on the behavior of organic compounds has been one of major subjects in physical organic chemistry.[1] Such quantitative treatments have been most extensively done on the formation and breaking of chemical bonds, for example, coordination of amines with alkylboranes,[2] ester hydrolysis,[1a,3] solvolysis,[4] and carbon–carbon σ bond breaking.[5] Recent progress in molecular mechanics calculations has allowed for the explanation of various experimental data on a steric basis, and classic theories based on experiments are now being reassessed by calculations.[6] However, even now typical experimental data are not sufficient to generalize proposed theories.

The back strain (B–strain) and front strain (F–strain) theories were originally proposed by Brown in the 1950s to explain the enormous steric effects on the

heat of coordination of amines with alkylboranes.[2] These theories have played an important role in rationalizing markedly enhanced rates of S_N1 solvolyses.[7] In the transition state of ionization of crowded molecule R_3CX, both B–strain among the three groups (R) and F–strain between the leaving group and the alkyl groups (R) are partially relieved, resulting in enhancement of solvolysis rates (Scheme 4.1). Hitherto, many examples of the rate enhancement ascribable to the B–strain effect have been reported[1c,d,7] and rationalized by molecular mechanics calculations.[4b,8] However, it is not necessarily easy to evaluate the B– and F–strain effects separately, because increasing the bulkiness of the R groups to assess the B–strain effect inevitably increases the F–strain effect between the R groups and the leaving group X.[9] To author's knowledge, only three studies seem to be useful as supporting evidence for the F–strain effect in solvolysis.

Scheme 4.1
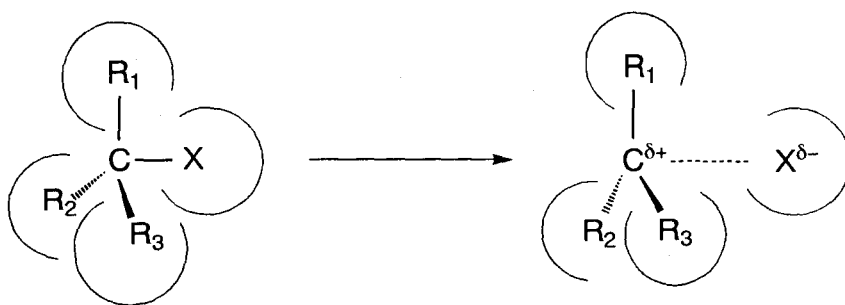
The most unambiguous example is the work reported by Schleyer and Brown.[10] They found that *trans,trans,trans*–perhydro–9b–phenalyl *p*–nitrobenzoate (1–OPNB) solvolyzes 2860 times faster than *trans*–9–decalyl *p*–nitrobenzoate (2–OPNB) in 80% acetone at 25 °C.[10] Since the rate enhancement essentially vanishes in the chloride (1–Cl), the major F–strain effect of 1–OPNB was attributed to the repulsion between the carbonyl group (and/or aryl group) and

the ring system, and the F–strain effect of a leaving group atom directly attached to the reaction center was taken as unimportant.[10] This notion was supported by molecular mechanics calculations.[4b] A similar example was provided by Dubois and his coworkers, who compared the t–Bu/Me rate ratios of solvolysis by changing the leaving group of 2–alkyl–2–adamantyl system 3.[11b,c] The large t–Bu/Me rate ratio at 25 °C of 225 000 for p–nitrobenzoate solvolyses[11a] as compared with 1820 for alcohol dehydration[11b,c] was ascribed to the greater F–strain effect for the p–nitrobenzoate than for the protonated alcohol.
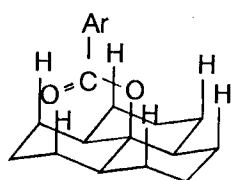
1-OPNB
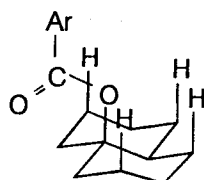
2-OPNB
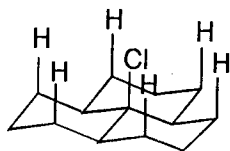
1-Cl
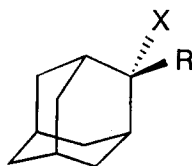
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R = t-Bu or Me
X = OPNB or OH⁺

The F–strain effect exerted by *the leaving group atom directly attached to the reaction center* was evaluated by Brown and Stern.[12] They reported that the t–Bu/Me rate ratio in the solvolysis of RMe_2CX (X = halogen) increases with the bulkiness of X in the manner 1.21 (X = Cl), 1.68 (X = Br), and 2.84 (X = I) in 80% ethanol at 25 °C.[12] These results show a small but definite trend supporting the

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leaving group strain effect. However, it appeared to the present authors that the changes were too small to warrant detailed analyses.

Consequently, we wished to design an appropriate system for evaluation of the F-strain effect of *the leaving group atom which is directly attached to the reaction center*. As such systems, we selected the bicyclo[2.2.2]oct-1-yl and 1-adamantyl systems having a (Z)-ethylidene substituent on the 2-position.[13,14] Since allylic conjugation in their carbocations had been shown to be insignificant,[15] the solvolysis rate ratios between the Z and E substrates were thought to afford a good measure of F-strain effect in the Z substrates with the B-strain effect being kept essentially constant. This Chapter describes the details of the solvolyses of various bicyclo[2.2.2]oct-1-yl (**4, 5**) and 1-adamantyl (**6-8**) derivatives.[13] The leaving group was variously changed, and a methylene, a (Z)-ethylidene, or an (E)-ethylidene substituent was placed on the 2-position. The rate data and the molecular mechanics calculations clearly showed a dramatic F-strain effect in the solvolyses of the (Z)-2-ethylidene substrates and its essential vanishing in the 2-methylene and (E)-2-ethylidene substrates.

(Z)-**4-X**　　(E)-**4-X**　　**5-X**

(Z)-**6-X**　　(E)-**6-X**　　**7-X**　　**8-X**
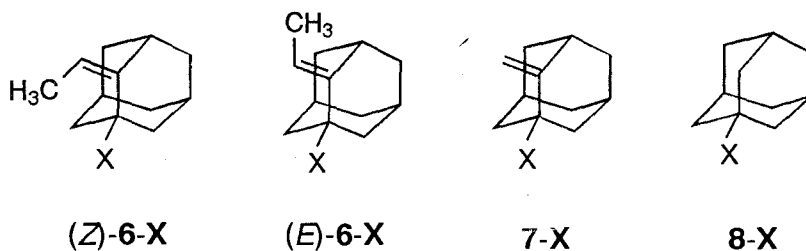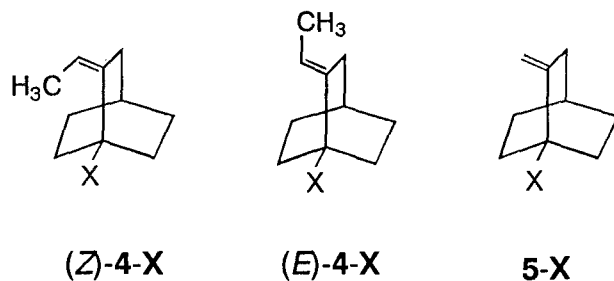
4-2. Results

Synthesis. The triflate (*Z*)-**4-OTf** was prepared from (*Z*)-**4-OH** which was synthesized in Chapter 2. Mesylate **7-OMs** was derived from the corresponding known alcohol **7-OH**[15a,b] which was provided by the Wittig methylenation of the *tert*-butyldimethylsilyl ether of 1-hydroxy-2-adamantanone (**9**). Mesylates (*Z*)- and (*E*)-**6-OMs** were derived from the corresponding alcohols [(*Z*)- and (*E*)-**6-OH**]. These alcohols were prepared as follows. The *tert*-butyldimethylsilyl ether of 1-hydroxy-2-adamantanone (**9**) was subjected to the Wittig ethylidenation in THF to give a mixture of (*Z*)- and (*E*)-**6-OTBDMS** in a ratio of 10:1 as estimated by ^{13}C NMR. After desilylation of the mixture with *n*-Bu$_4$NF, (*Z*)- and (*E*)-**6-OH** were separated by MPLC (SiO$_2$) from each other and their stereochemistry was determined by ^{1}H NMR NOE difference experiments (see Experimental Section). The (*E*)-**6-OH** was also synthesized via a different route (Scheme 4.2).

Scheme 4.2

(*E*)-**6-OTBDMS**   (*E*)-**6-OH**
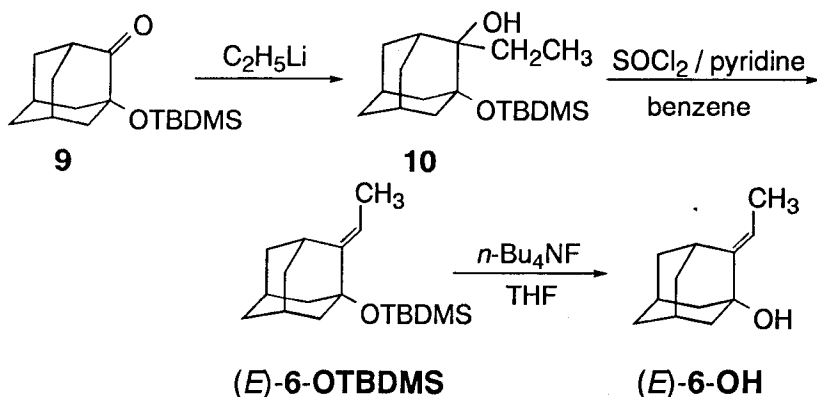
The *tert*-butyldimethylsilyl ether of 1–hydroxy–2–adamantanone (**9**) was treated with ethyllithium, and then the resulting alcohol (**10**) was dehydrated by treatment with thionyl chloride in benzene at reflux in the presence of excess of pyridine to give essentially pure (*E*)–**6**–**OTBDMS**, which was then converted into (*E*)–**6**–**OH**. These (*Z*)– and (*E*)–alcohols were converted to 2–ethylidene–1–adamantyl chlorides [(*Z*)– and (*E*)–**6**–**Cl**] or bromides [(*Z*)– and (*E*)–**6**–**Br**] by treatment with thionyl chloride or thionyl bromide, respectively, in the presence of pyridine. The Wittig ethylidenation of 1–fluoro–2–adamantanone which was prepared in Chapter 1 gave a mixture of (*Z*)– and (*E*)–2–ethylidene–1–adamantyl fluorides [(*Z*)– and (*E*)–**6**–**F**], which were separated from each other by means of MPLC (SiO$_2$) in yields of 45 and 41%, respectively. The Wittig ethylidenation of 1–iodo–2–adamantanone gave a mixture of (*Z*)– and (*E*)–2–ethylidene–1–adamantyl iodides [(*Z*)– and (*E*)–**6**–**I**] in a ratio of 95:5 as estimated by ^{13}C NMR. Treatment of this mixture with 0.01 M trifluoromathanesulfonic acid (TfOH) in CH$_2$Cl$_2$ at 0 °C gave essentially pure (*E*)–**6**–**I**. 2–Methylene–1–adamantyl halides [**7**–**X** (X = Cl, Br, I)] were prepared by the Wittig methylenation of 1–halo–2–adamantanones.

The determination of the *Z* or *E* stereochemistry of **6**–**F**'s and **6**–**I**'s rests upon comparisons of their ^{13}C NMR chemical shift data with those of **6**–**Cl**'s and **6**–**Br**'s whose stereochemistry has been unambiguously established. Two general characteristics are that the methyl and C(3) carbons of the *Z* compounds resonate at 1.5 ± 0.2 and 11.8 ± 1.5 ppm lower field than those of the *E* ones, respectively. It is also worth mentioning that the ^{13}C chemical shift difference (ppm) between the *Z* and *E* compounds with respect to the C(1) carbon decreases in the sequence **6**–**F** (2.9), **6**–**Cl** (–1.5), **6**–**Br** (–5.5), and **6**–**I** (–13.1), presumably because of increasing steric compression between the (*Z*)–methyl and the halogen atom.

Rate Studies. The solvolyses of (*E*)–**4–OTf** and **5–OTf** were described in Chapter 2. The rate studies of (*Z*)– and (*E*)–**6–OMs** and (*Z*)– and (*E*)–**6–I** were described in Chapter 6 in detail. All the substrates, except for (*Z*)–**4–OTf**, were purified by means of MPLC (SiO$_2$) and subsequent recrystallization. (*Z*)–**4–OTf** was very unstable to water and column chromatography. Therefore, the crude substrate which was essentially pure (>97%) on the basis of ^{13}C NMR was used for solvolysis without further purification; the sole impurity, if any, was the starting alcohol that did not influence the solvolysis rates. Except for the fluorides (*Z*)– and (*E*)–**6–F** and **8–F**, the solvolysis rates were measured either titrimetrically or conductimetrically in the presence of 2,6–lutidine to give good first–order kinetics (*r* > 0.997) over 80–90% of the reactions.

Initially, the rate measurement for 1–adamantyl fluoride (**8–F**) was attempted by using the titrimetric method, but it turned out that the produced HF was consumed, most probably owing to the reaction with glass, the material of the Pyrex ampules. Therefore, the rates of the fluorides were determined by following the substrate:product ratio by GLC (PEG 20M). Since the fluorides solvolyzed very slowly even in TFE, the reactions were followed over 4–16% at 100 and 125 °C. All the fluorides followed fairly good first–order kinetics within an experimental error of 1–7% for the rate constants at a 95% confidence limit. However, because of long extrapolations from data at 125 and 100 °C, the estimated rates of (*Z*)– and (*E*)–**6–F** at 25 °C are considered to include an error of ca. ±40%. All the first–order rate constants are summarized in Table 4.1.

The *Z*:*E* rate ratio in ethanol at 25 °C was 217 ± 6 for **4–OTf** and 109 ± 11 for **6–OMs**. Since the *Z*:*E* rate ratio for **6–OMs** in TFE (117 ± 1 at 25 °C) was very close to that in ethanol, the effect of changing the solvent on the rate ratio is small. The *Z*:*E* rate ratio for **6–X** (X = halogen) in TFE at 25 °C increased in the order **6–F** (ca. 70 or 28–160), **6–Cl** (1020 ± 160), **6–Br** (2230 ± 90), and **6–I**

Table 4.1. Rate Data of Solvolysis of 2–Ethylidene, 2–Methylene, or Parent Compounds

compound	solvent	temp(°C)	$k(\text{s}^{-1})$	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	relative rate	
(Z)-4-OTf	EtOH	25.0	$(4.04 \pm 0.04) \times 10^{-4}$ [a]	23.8 ± 0.3	5.6 ± 0.8	1370 ±100	217 ± 6
		40.0	$(2.89 \pm 0.03) \times 10^{-3}$ [a]				
(E)-4-OTf	EtOH	25.0	$(1.86 \pm 0.03) \times 10^{-6}$ [b,c]	26.8 ± 0.2	5.1 ± 0.8	6.3 ± 0.5	1
		50.0	$(6.65 \pm 0.10) \times 10^{-5}$ [b,c]				
5-OTf	EtOH	25.0	$(2.95 \pm 0.18) \times 10^{-7}$ [c,d]	27.1 ± 0.3	2.3 ± 1.0	1	
		50.0	$(1.09 \pm 0.04) \times 10^{-5}$ [b,c]				
		75.0	$(2.40 \pm 0.04) \times 10^{-4}$ [b,c]				
(Z)-6-OMs	EtOH	25.0	$(2.28 \pm 0.03) \times 10^{-6}$ [b]	25.8 ± 0.2	2.0 ± 0.7	745 ± 90	109 ± 11
		50.0	$(7.11 \pm 0.11) \times 10^{-5}$ [b]				
(E)-6-OMs	EtOH	25.0	$(2.09 \pm 0.17) \times 10^{-8}$ [d]	26.8 ± 0.3	-3.9 ± 0.8	6.8 ± 1.3	1
		75.0	$(1.59 \pm 0.02) \times 10^{-5}$ [b]				
		100.0	$(2.25 \pm 0.03) \times 10^{-4}$ [b]				
7-OMs	EtOH	25.0	$(3.06 \pm 0.30) \times 10^{-9}$ [d]	27.0 ± 0.4	-7.2 ± 1.1	1	
		75.0	$(2.42 \pm 0.04) \times 10^{-6}$ [b]				
		100.0	$(3.84 \pm 0.05) \times 10^{-5}$ [b]				
(Z)-6-OMs	TFE	4.1	$(4.04 \pm 0.04) \times 10^{-3}$ [e]	18.6 ± 0.1	-2.2 ± 0.4	1340 ± 30	117 ± 1
		25.0	$(4.65 \pm 0.02) \times 10^{-2}$ [e,f]				
(E)-6-OMs	TFE	25.0	$(3.96 \pm 0.02) \times 10^{-4}$ [e,f]	19.4 ± 0.2	-9.1 ± 0.6	11.4 ± 0.3	1
		40.0	$(1.99 \pm 0.02) \times 10^{-3}$ [e]				
7-OMs	TFE	25.0	$(3.46 \pm 0.05) \times 10^{-5}$ [b]	21.7 ± 0.2	-6.3 ± 0.7	1	
		50.0	$(6.32 \pm 0.09) \times 10^{-4}$ [b]				

(Table 4.1 continued)

		T/°C	k	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$		
(Z)-6-F	TFE	25.0	$(6.0 \pm 2.5) \times 10^{-11\,d}$	20.1 ± 1.4	-38.0 ± 3.7		ca.70(28–160)
		100.0	$(6.63 \pm 0.42) \times 10^{-8\,g}$				
		125.0	$(3.82 \pm 0.22) \times 10^{-7\,g}$				
(E)-6-F	TFE	25.0	$(8.8 \pm 3.4) \times 10^{-13\,d}$	25.6 ± 1.4	-28.0 ± 3.5		1
		100.0	$(6.30 \pm 0.28) \times 10^{-9\,g}$				
		125.0	$(5.77 \pm 0.39) \times 10^{-8\,g}$				
8-F	TFE	25.0	$(7.08 \pm 0.53) \times 10^{-9\,d}$	18.7 ± 0.3	-33.0 ± 0.7		
		75.0	$(7.57 \pm 0.11) \times 10^{-7\,g}$				
		100.0	$(5.09 \pm 0.15) \times 10^{-6\,g}$				
		125.0	$(2.52 \pm 0.08) \times 10^{-5\,g}$				
(Z)-6-Cl	TFE	25.0	$(3.95 \pm 0.21) \times 10^{-6\,d}$	19.5 ± 0.3	-17.8 ± 0.8	6690 ± 1530	1020 ± 160
		50.0	$(5.46 \pm 0.08) \times 10^{-6\,b}$				
		75.0	$(5.17 \pm 0.08) \times 10^{-4\,b}$				
(E)-6-Cl	TFE	25.0	$(3.86 \pm 0.36) \times 10^{-9\,d}$	23.4 ± 0.7	-18.5 ± 0.9	6.5 ± 1.8	1
		75.0	$(1.30 \pm 0.02) \times 10^{-6\,b}$				
		100.0	$(1.33 \pm 0.02) \times 10^{-5\,b}$				
7-Cl	TFE	25.0	$(5.90 \pm 0.84) \times 10^{-10\,d}$	22.2 ± 0.4	-26.3 ± 0.9	1	
		100.0	$(1.35 \pm 0.02) \times 10^{-6\,b}$				
		125.0	$(9.31 \pm 0.14) \times 10^{-6\,b}$				
(Z)-6-Br	TFE	25.0	$(2.50 \pm 0.03) \times 10^{-4\,e}$	18.5 ± 0.2	-13.0 ± 0.8	29980 ± 3490	2230 ± 90
		40.0	$(1.17 \pm 0.01) \times 10^{-3\,e}$				
(E)-6-Br	TFE	25.0	$(1.12 \pm 0.03) \times 10^{-7\,d}$	22.5 ± 0.2	-15.1 ± 0.4	13.4 ± 1.8	1
		75.0	$(2.99 \pm 0.04) \times 10^{-5\,b}$				
		100.0	$(2.75 \pm 0.04) \times 10^{-4\,b}$				

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(Table 4.1 continued)

		Temp	k				
7-Br	TFE	25.0	$(8.34 \pm 0.78) \times 10^{-9\,d}$	23.3 ± 0.3	-17.6 ± 0.9		1
		75.0	$(2.68 \pm 0.04) \times 10^{-6\,b}$				
		100.0	$(2.69 \pm 0.04) \times 10^{-5\,b}$				
(Z)-6-I	TFE	25.0	$(9.78 \pm 0.10) \times 10^{-4\,e}$	19.6 ± 0.2	-6.5 ± 0.5	136200 ± 16350	9500 ± 280
		40.0	$(5.26 \pm 0.05) \times 10^{-3\,e}$				
		50.0	$(1.36 \pm 0.01) \times 10^{-2\,f}$				
(E)-6-I	TFE	25.0	$(1.03 \pm 0.02) \times 10^{-7\,d}$	24.1 ± 0.1	-9.9 ± 0.3	14.3 ± 1.9	1
		50.0	$(2.51 \pm 0.02) \times 10^{-6\,b,f}$				
		75.0	$(4.19 \pm 0.06) \times 10^{-5\,b}$				
		100.0	$(4.27 \pm 0.06) \times 10^{-4\,b}$				
7-I	TFE	25.0	$(7.18 \pm 0.71) \times 10^{-9\,d}$	24.7 ± 0.4	-13.2 ± 1.0		1
		75.0	$(3.25 \pm 0.05) \times 10^{-6\,b}$				
		100.0	$(3.74 \pm 0.07) \times 10^{-5\,b}$				

[a]Determined conductimetrically for 0.00020 M substrate in the presence of 0.025 M 2,6-lutidine within an experimental error of ±1.0%. [b]Determined titrimetrically for 0.020 M substrate in the presence of 0.025 M 2,6-lutidine within an experimental error of ±1.5%. [c]Reference 15c. [d]Extrapolated from data at other temperatures. [e]Determined conductimetrically for 0.00074 M substrate in the presence of 0.00119 M 2,6-lutidine within an experimental error of ±1.0%. [f]Reference 14. [g]Determined by GLC method within an experimental error at 95% confidence limit.

(9500 ± 280).

Product Studies. The solvolyses were carried out in ethanol and TFE on 0.040 M substrate solutions containing 0.050 M 2,6–lutidine at convenient temper- atures for 10 half–lives or longer periods. Solvolysis products were identified by ^{13}C NMR and GLC (PEG 20M). The substrates gave solely the corresponding bridgehead ethers, except for **7–Cl** in TFE and **7–OMs** in ethanol. **7–Cl** afforded a mixture of bridgehead trifluoroethyl ether **7–OTFE** (71%), 1,2–bis(2,2,2–trifluo- roethoxy)–2–methyladamantane (**11**) (20%), and 2–methyl–4–protoadamantanone (**12**) (9%) after 10 half–lives at 125 °C (Scheme 4.3). These products were sepa- rated by MPLC (SiO$_2$), and trifluoroethyl ether **7–OTFE** and **11** were identified by ^{13}C and ^{1}H NMR. The identification of **12** was conducted by comparing its spec- tral and GLC data with those of authentic **12** that was synthesized by the pinacol rearrangement of 2–methyl–1,2–adamantanediol. The ethanolysis of **7–OMs** also gave a mixture of **7–OEt**, 1,2–diethoxy–2–methyladamantane, and ketone **12**.

Scheme 4.3
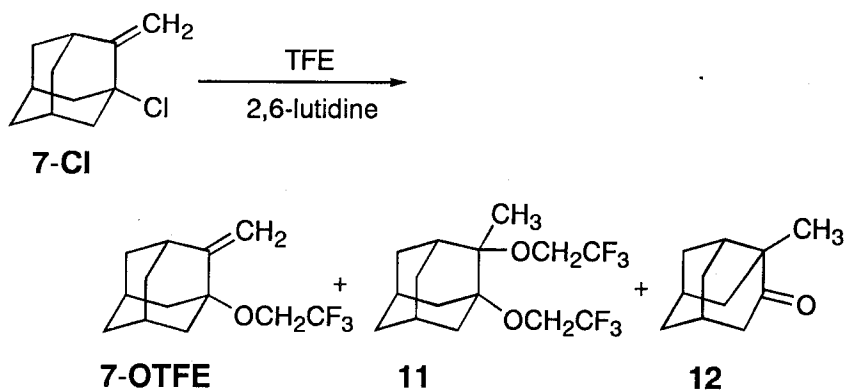
Table 4.2. Product Distribution in the Trifluoroethanolysis of **7–Cl** at 125.0 °C Determined by GLC

compound	$0.1 \times t_{1/2}$	$0.3 \times t_{1/2}$	$t_{1/2}$	$2 \times t_{1/2}$	$10 \times t_{1/2}$	$11.5 \times t_{1/2}$
7–Cl	91	83	52	27	0	$0(0^a)$
7–OTFE	9	17	48	73	71	$60(56^a)$
11	0	0	0	0	20	$27(29^a)$
12	0	0	0	0	9	$13(14^a)$

^{a}Isolated yield.

Scheme 4.4
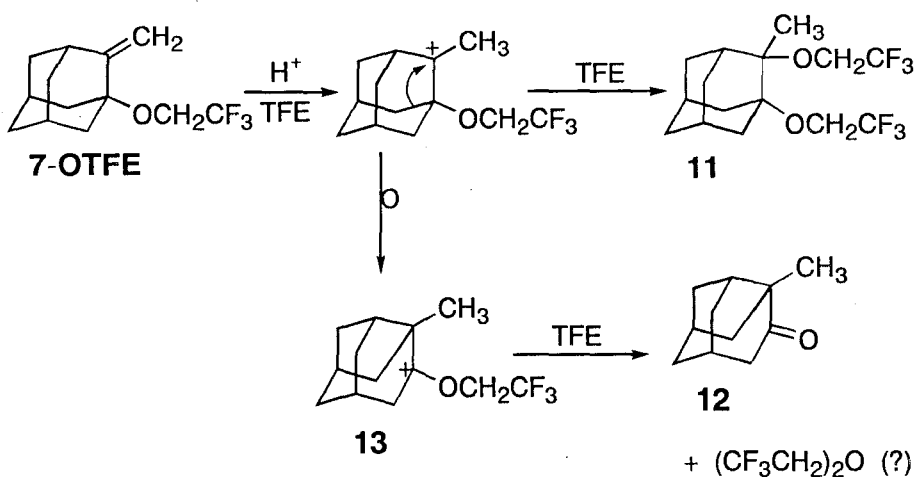
In order to elucidate the route to **11** and **12**, the product distribution in the trifluoroethanolysis of **7–Cl** was followed by GLC: the results are summarized in Table 4.2. The data of Table 4.2 clearly show that both **11** and **12** were formed from normal substitution product **7–OTFE** and not directly from the substrate.

Since the solvolyses of **7–Cl** in TFE and of **7–OMs** in ethanol were conducted at 125 °C because of their slow rates, once–formed products **7–OTFE** and **7–OEt** presumably underwent acid–catalyzed addition of the solvent molecule to the double bond to give 1,2–dialkoxy–2–methyladamantane even in the presence of excess 2,6–lutidine. Although we were unable to detect diethyl ether or bis(trifluoroethyl) ether, the ketone **12** is presumed to have been formed through the reaction of protoadamantyl cation **13** with the solvent molecule (Scheme 4.4). Previously, the formation of an unidentified compound was reported for the acetolysis of **7–OTs**.[15b] It is now highly probable that the unidentified product was **12**.

Oxygen–18 Scrambling Study. Any rate of S_N1 solvolysis as determined by following the rate of product formation is intrinsically slower than that of the ionization step because such an overall rate additionally includes those of product formation and ion–pair return steps. In the present objective in which the F–strain effect on the ionization step is to be investigated, we should determine the rate of ionization. At present, however, there is no method available to precisely measure the rates of ionization in solvolysis reactions. One approach is to measure the rate of oxygen scrambling of a sulfonate leaving group, which is much closer to the rate of the ionization step than a titrimetrically or conductimetrically determined one. Consequently, we followed the rates of oxygen scrambling of (Z)– and (E)–2–ethylidene–1–adamantyl mesylates labeled with a 10% excess of ^{18}O on the ether oxygen of the methanesulfonyloxyl moiety by means of mass spectrometric analysis.

The two ^{18}O–labeled mesylates ([^{18}O]–(Z)–2–ethylidene–1–adamantyl and [^{18}O]–(E)–2–ethylidene–1–adamantyl [$^{18}O_1$]–mesylates) were prepared by hydrolyzing unlabeled mesylates in 90% THF–10% $H_2^{18}O$ (10 excess atom %) in the presence of excess 2,6–lutidine. The resulting 2–ethylidene–1–adamantanols were

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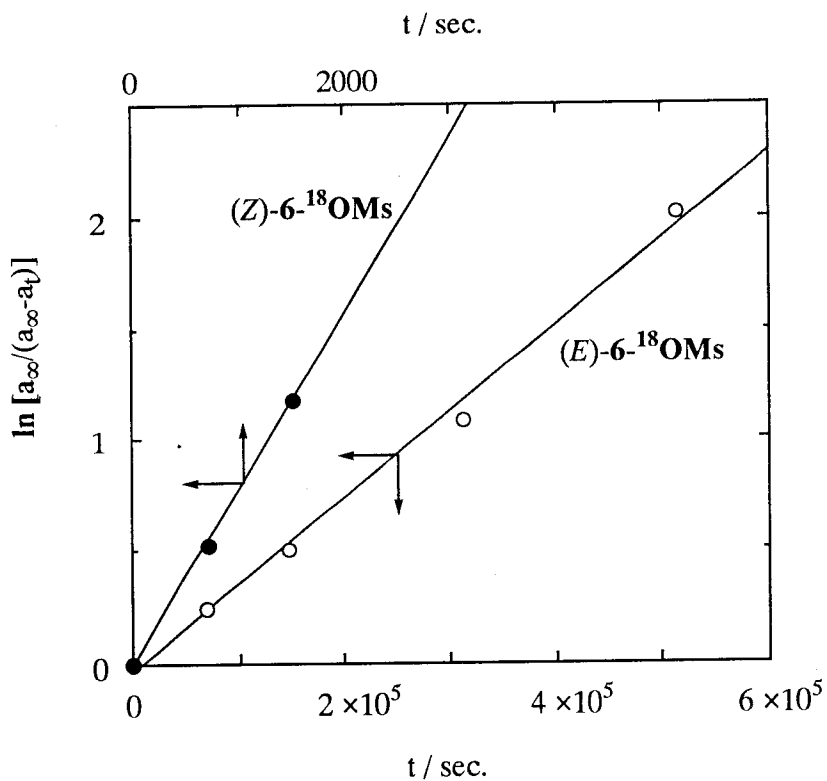
Figure 4.1. The first-order plot of ^{18}O-scrambling study for (Z)- and (E)-**6**-^{18}**OMs** in ethanol at 50.0 °C. a_∞ and a_t denote the decrease of ^{18}O content on the ether site at $t_{1/2} \times 10$ and t, respectively.

found to contain 10.9 ± 0.1% ^{18}O as determined by comparing the intensities of the mass spectral peaks at M (178) and M + 2 (180). Lithiation of the alcohols with n–BuLi in THF and subsequent treatment with methanesulfonyl chloride (MsCl) gave the desired labeled mesylates.

The solvolysis was carried out in ethanol on 0.040 M substrate in the presence of 0.050 M 2,6–lutidine at 50.0 °C. At intervals aliquots were worked up in the usual manner and the unchanged mesylate was recovered by MPLC (SiO$_2$) at –40 °C. The recovered mesylate was cleaved to the alcohol by treatment with t–BuOK in DMSO.[17] Control experiments showed that oxygen scrambling did not occur throughout the overall treatment within an absolute error of ±0.5% (or relative error of ±5%). The first–order plots are shown in Figure 4.1, and the first–order rate constants of ^{18}O scrambling (k_{sc}) are summarized in Table 4.3 along with titrimetric ones (k_t). Because of a relative error of ±5% in each ^{18}O scrambling determination, the k_{sc} values include ±(16–21)% errors. It was found that k_{sc} was greater than k_t by 9–13 times for (Z)–6–OMs and 4.6–6.3 times for (E)–6–OMs. The Z/E rate ratios were 95 ± 5 for k_t and 190 ± 80 for k_{sc} at 50 °C.

Table 4.3. Rate Constants for Solvolysis (k_t) and Oxygen Scrambling (k_{sc}) for Ethanolysis of 2–Ethylidene–1–adamantyl Mesylates at 50.0 °C

	(Z)–6–OMs	(E)–6–OMs	Z/E
k_t	$(7.11 \pm 0.11) \times 10^{-5}$	$(7.46 \pm 0.31) \times 10^{-7}$	95 ± 5
k_{sc}	$(7.86 \pm 1.46) \times 10^{-4\,a}$	$(4.06 \pm 0.64) \times 10^{-6\,a}$	190 ± 80

^{a}Error is expressed as a standard deviation at 95% confidence limit.

4-3. Discussion

Essential Absence of Solvent Effects on the Z:E Rate Ratios. Ethanol and TFE are two extreme solvents in S_N1 solvolysis although their dielectric constants are very similar (24.32 and 26.14, respectively, at 25 °C).[18] The Y_{OTs} (= $Y_{2-AdOTs}$) values of ethanol and TFE are –1.75 and 1.80, and the respective N_{OTs} values are 0.00 and –3.0.[19] These values show that TFE is much more ionizing and much less nucleophilic than ethanol. Despite these marked dissimilarities, the Z:E rate ratios for **6–OMs** are almost identical, 109 ± 11 in ethanol and 117 ± 1 in TFE at 25 °C (Table 4.1). Interestingly, the (Z)–methyl group does not appear to affect the magnitude of electrophilic solvation by the protic solvents toward the leaving group in the transition state. This reasoning may be supported by two–point $mY_{1-AdOMs}$ relations by using the ethanol and TFE data.[20] The approximate m values are calculated to be 1.1 for (Z)–**6–OMs** and 1.0 for (E)–**6–OMs** and **7–OMs**. These results suggest that we can safely discuss the Z:E rate ratios on the basis of the shape of the molecules without much worrying about the solvation effects.

Origin of the Large Z:E Rate Ratios. Previously, the groups of Martin[15a] and Schleyer[15b] independently reported that the allylic conjugation is essentially prohibited in the incipient carbocation from **7–OTs** because of perpendicular relation between the developing cationic p orbital and the methylene π system. We also reported that it is also the case for **5–OTf** and (E)–**4–OTf**[15c], which was described in Chapter 2. The faster rates of (E)–**4–OTf** than **5–OTf** and of (E)–**6–OMs** than **6–OMs** by respective factors of 6.3 (= 1.86×10^{-6} / 2.95×10^{-7} in ethanol) and 11.4 (= 3.96×10^{-4} / 3.46×10^{-5} in TFE) at 25 °C may be principally
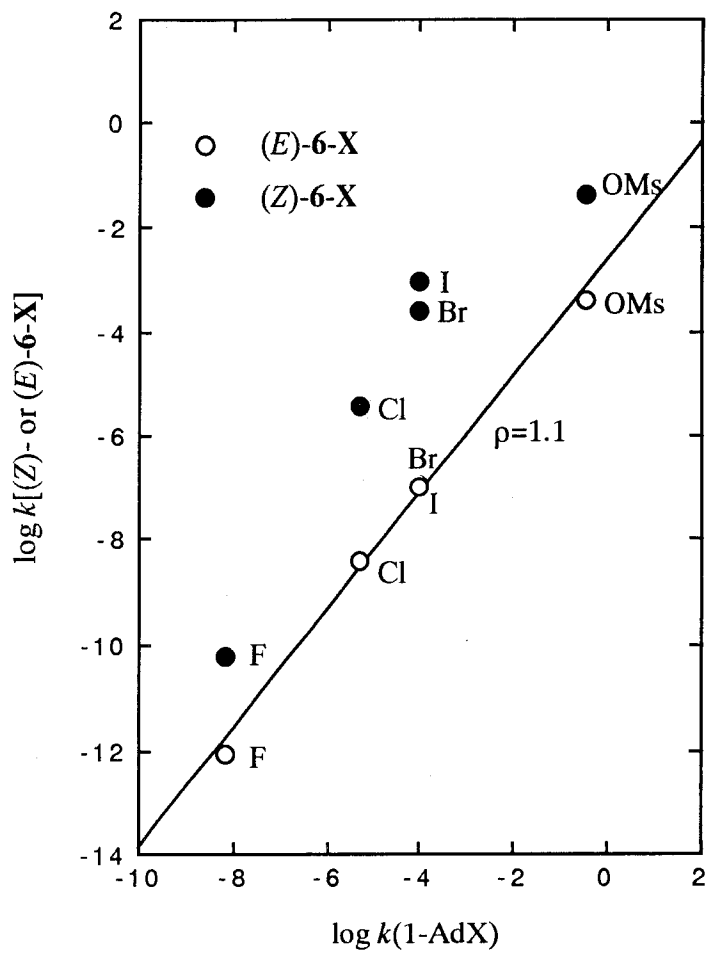
Figure 4.2. Plot of log k for (Z)- and (E)-**6-X** in 100% TFE against log k for **8-X** in 97% or 100% TFE at 25 °C.

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attributed to the electron–donating character (inductive and hyperconjugative) of the (*E*)–methyl substituent.

The variation of the leaving group of (*Z*)– and (*E*)–**6–X** significantly influenced the *Z*:*E* rate ratio, which increased in the order F (ca. 70 or 28–160), OMs (117 ± 1), Cl (1020 ± 160), Br (2230 ± 90), and I (9500 ± 280) in TFE at 25 °C (Table 4.1). As discussed below, the large *Z*:*E* rate ratios cannot wholly be ascribed to steric origin. However, they strongly suggest that in (*Z*)–**6–X** the F–strain between the (*Z*)–methyl group and the leaving group atom directly attached to the reaction center increases in the above sequence of atomic size, whereas in (*E*)–**6–X** there would be no serious F–strain between the hydrogen atom in the *Z* position and the leaving group. Figure 4.2 gives a plot of log *k* values for **6–X**'s against those for the corresponding parent 1–adamantyl compounds **8–X** (X = OMs,[21a] F,[22] Cl,[21b] Br,[21b] I[21c]) in 97% TFE. A good linear correlation with a slope of 1.1 for (*E*)–**6–X**'s indicates the essential absence of an extra F–strain effect. In contrast, the points for (*Z*)–**6–X**'s scatter, supporting the development of F–strain.

The present result is in striking contrast to the solvolysis of *trans,trans,trans*–perhydro–9b–phenalyl system **1** where the marked F–strain in the *p*–nitrobenzoate **1–OPNB** completely vanishes in the chloride **1–Cl**.[10] The deuterium kinetic isotope effect on the *Z*:*E* rate ratios by using methyl–d_3 compounds of (*Z*)– and (*E*)–**6–X** showed a large steric isotope effect in the (*Z*)–iodide but its marked decrease in the (*Z*)–mesylate,[14] which was described in Chapter 6.

Z:*E* *Rate Ratios Based on* [18]*O Scrambling.* The internal return in the solvolysis of 1–adamantyl derivatives has only recently been disclosed. Kevill and his co–workers reported that 1–adamantyl chloroformate in hydroxylic solvents reacts with loss of carbon dioxide to give solvolysis product (**1–AdOS**) and decomposition product (**1–AdCl**).[23a] The fraction of the decomposition product, which was

20–72.5% in several solvents, was regarded as a minimum fraction of internal return during solvolysis of 1–adamantyl chloride. Recently, Stoelting and Shiner examined the [18]O scrambling of 2–methyl– and 2,2–dimethyl–1–adamantyl pentamethylbenzenesulfonates (pemsylates) in 95% ethanol and found respective minimum fractions of internal return of 81% and 89%.[23b] Our data of Table 4.3 provide the values $(100 \times k_{sc} / (k_{sc} + k_t))$[23b] of 92% and 84% for (Z)– and (E)–6–OMs, respectively.

Despite significant internal return in the present solvolyses, the Z/E rate ratio for k_{sc} is 190 ± 80 in ethanol at 50 °C, which is only twice as large as the Z/E rate ratio 95 ± 5 for k_t. Consequently, it has been shown that the Z/E rate ratios determined from k_t can be used as a measure of the F–strain effect on the ionization step.

Molecular Mechanics (MM2) Calculations. In order to obtain information on geometries and steric energies in the ground state, MM2(87) calculations were performed on (Z)– and (E)–2–ethylidene–1–adamantyl substrates.[24] From the lack of parameters of sulfonates, the calculations for mesylates were carried out on the corresponding alcohols as surrogates. As pertinent data, the bond lengths included in the $X–C_\alpha–C_\beta=C_\gamma–CH_3$ part (where C_α denotes the bridgehead carbon) were compared between the Z and E substrates; however, the effect of changing the leaving group X on the geometry was very small.[25] On the other hand, steric energies significantly changed depending on the leaving group (Table 4.4).

The data of Table 4.4 show that the difference in steric energy between the Z and E isomers ($SE_Z – SE_E$, kcal mol^{-1}) increases in the sequence of the leaving group, F (1.5), OH (2.3), Cl (3.2), Br (3.9), and I (4.6). Figure 4.3 shows a plot of $1.36 \times \log[k_Z/k_E]$ values against $SE_Z – SE_E$ for 2–ethylidene–1–adamantyl halides
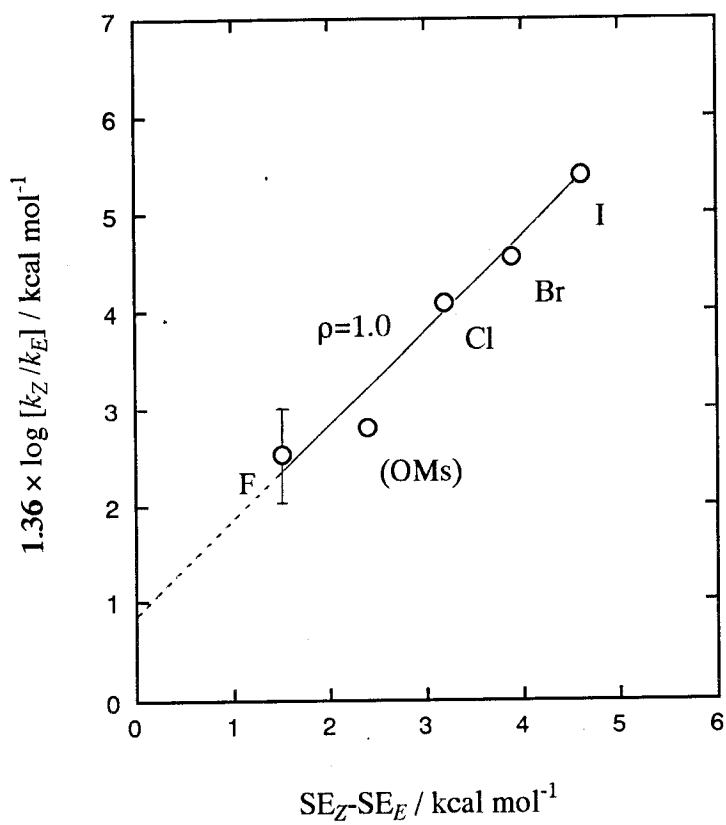
Figure 4.3. Plot of 1.36 × log [k_Z / k_E] against steric energy difference between (Z)-**6-X** and (E)-**6-X** calculated by MM2.

Table 4.4. Pertinent Bond Lengths and Steric Energies for (Z)– and (E)–2–Ethylidene–1–adamantyl Substrates (6–X) Calculated by MM2(87)

compound	bond length,[a] Å				steric energy (kcal mol⁻¹)
	X–C_α	C_α–C_β	C_β=C_γ	C_γ–CH_3	
(Z)–6–OH[b]	1.426	1.519	1.346	1.505	20.4
(E)–6–OH[b]	1.429	1.520	1.346	1.507	18.1
Δ	–0.003	–0.001	0.000	–0.002	2.3
(Z)–6–F	1.395	1.518	1.345	1.504	20.8
(E)–6–F	1.397	1.520	1.345	1.507	19.3
Δ	–0.002	–0.002	0.000	–0.003	1.5
(Z)–6–Cl	1.810	1.526	1.347	1.504	24.8
(E)–6–Cl	1.815	1.527	1.347	1.508	21.6
Δ	–0.005	–0.001	0.000	–0.004	3.2
(Z)–6–Br	1.979	1.530	1.348	1.504	26.7
(E)–6–Br	1.985	1.530	1.347	1.508	22.8
Δ	–0.006	0.000	0.001	–0.004	3.9
(Z)–6–I	2.186	1.531	1.348	1.503	27.5
(E)–6–I	2.191	1.531	1.347	1.508	22.9
Δ	–0.005	0.000	0.001	–0.005	4.6

[a]C_α–C_β and C_β=C_γ denote the bonds in the allylic part X–C_α–C_β=C_γ–CH_3 with C_α being the bridgehead carbon. [b]Surrogate of mesylate.

Scheme 4.5
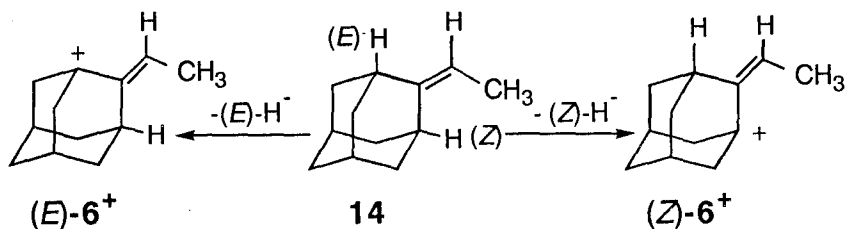
and mesylates. A linear correlation with a slope of 1.0 indicates that a change in $SE_Z - SE_E$ on changing the leaving group is exactly reflected to the change in the $\Delta G^{\ddagger}$ difference between the two isomers. The intercept value of 0.8 kcal mol^{-1} should be taken as meaningful and not due to inherent errors in MM2 calculations. The value suggests that the hypothetical heterolysis of 2–ethylideneadamantane (14) (Scheme 4.5) would be more favorable by 0.8 kcal mol^{-1} for the bridgehead hydrogen at the Z position than that at the E position. In other words, it is suggested that the transition state from (Z)–6–X is more stable than that from (E)–6–X by 0.8 kcal mol^{-1}. MM2 calculations on 2–ethylideneadamantane (14) have indicated that the van der Waals repulsion between the methyl group and the (Z) hydrogen is greater than that between the vinylic hydrogen and the (E) hydrogen by 0.6 kcal mol^{-1}. This value can account for 75% of the intercept value. As shown below, ab initio (RHF/6–31G**) calculations showed that the (Z) cation [(Z)–6$^+$] is more stable than the (E) cation [(E)–6$^+$] by 1.0 kcal mol^{-1}.

Correlation with Hansch's Es. Kutter and Hansch improved Taft's steric parameters Es by using average van der Waals radii of various substituents.[26] By employing Hansch's Es as an empirical parameter, we evaluated the Z:E rate ratios.
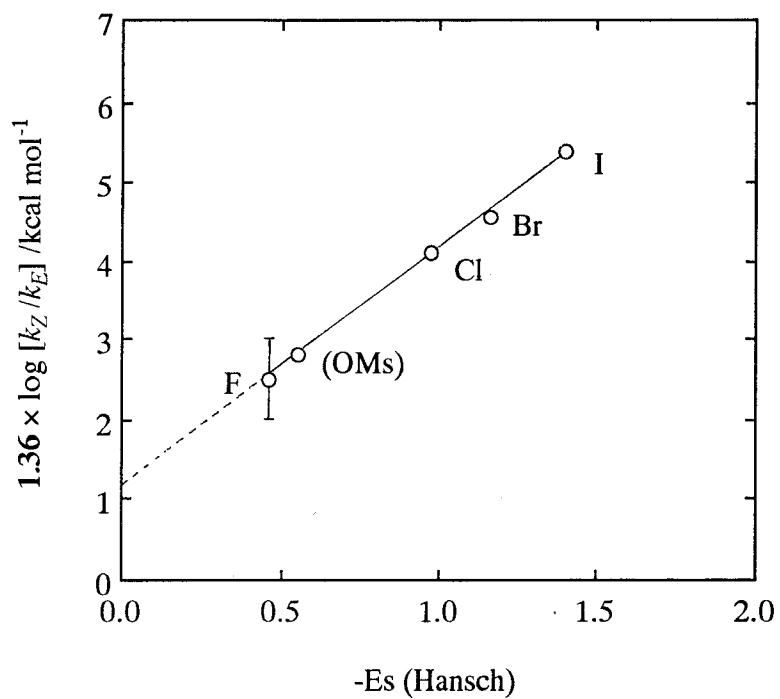
110

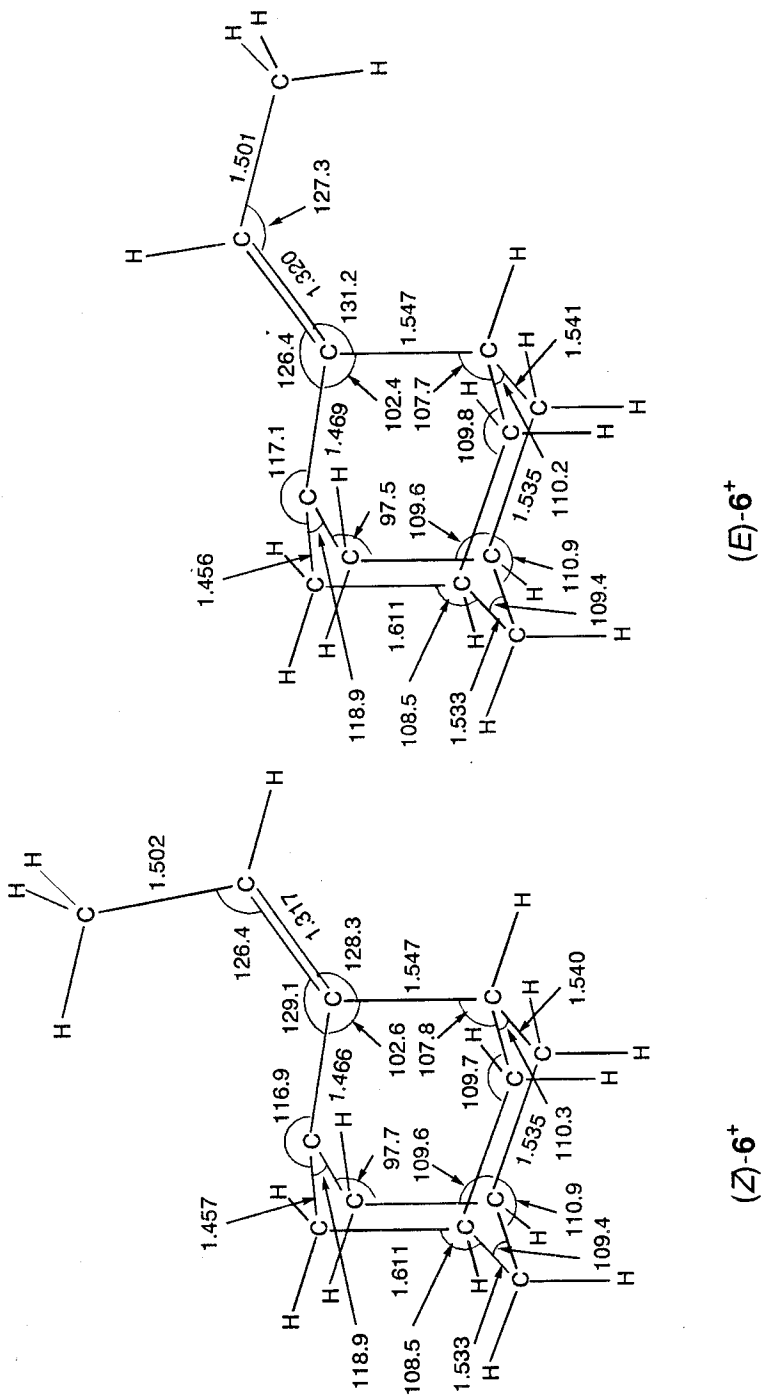Figure 4.4. Plot of 1.36 × log [k_Z/k_E] against Hansch's Es.

Figure 4.5. Optimized geometries of (Z)-**6**$^+$ and (E)-**6**$^+$ at RHF/6-31G**.

(E)-**6**$^+$

(Z)-**6**$^+$

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Figure 4.4 shows a plot of 1.36 × log[k_Z/k_E] values against Hansch's Es. The nicely linear plot reinforces the conclusion reached by MM2 calculations that the major origin of the large $Z:E$ rate ratios is F–strain between the (Z)–methyl group and the leaving group atom directly attached to the reaction center. Furthermore, the intercept that corresponds to the value for the hydride leaving group (Es = 0) is 1.1 kcal mol^{-1}, which is comparable with the intercept obtained in Figure 4.3.

Ab Initio (RHF/6–31G**) Calculations on 2–Ethylidene–1–adamantyl Cations. With a view to seeing the structure and energies of the cations, the optimization of (Z)– and (E)–6$^+$ was made by applying the Gaussian 90 program.[27] Here a C_s symmetry was assumed, in which the external double bond and the methyl carbon was placed in the symmetry plane. The calculated total energies of (Z) and (E) cations were –464.0842945 and –464.0826948 au, respectively, at the RHF/6–31G** level, suggesting that the former cation is more stable than the latter one by 1.0 kcal mol^{-1}. Notably, this value is in very good agreement with the intercept values of 0.8 and 1.1 kcal mol^{-1} which were obtained in the plots of Figure 4.3 and 4.4. It is now almost certain that the $Z:E$ rate ratios in the 2–ethylidene–1–adamantyl solvolyses include a rate factor of approximately 5 coming from the greater stability of (Z)–6$^+$ than (E)–6$^+$ by 0.8–1.1 kcal mol^{-1}. If allowances are made for the observed rate ratios by this factor, the net $Z:E$ rate ratios ascribed solely to the F–strain effect in the trifluoroethanolysis of 6–X are 23 (6–OMs), ca. 14 (6–F), 200 (6–Cl), 450 (6–Br), and 1900 (6–I) at 25 °C.

As shown in Figure 4.5, the cationic center has the arrangement of bonds that is close to an sp^2–hybridized carbon, the C–C$^+$–C bond angles being 116.9–117.1°. The bond length between the cationic center and the adjacent sp^2 carbon is seen to be almost the same as those between the cationic center and the adjacent

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sp^3 carbons. This is natural because the 2pπ atomic orbital of the cationic center is not allowed to conjugate with the double bond in these configurations. Having an sp^2–like cationic center in an adamantyl cage, two sp^3 carbon–carbon bonds are seen to be stretched to have an unusually long length of 1.611 Å. These geometric data are very close to those of 3,5,7–trimethyl–1–adamantyl cation which were determined by X–ray structural analysis of the $Sb_2F_{11}^-$ salt.[28] The 3,5,7–trimethyl–1–adamantyl cation was found to have the C–C$^+$–C angles of 116°, 118°, and 120° and a C(2)–C(3) bond of 1.62 Å.

4–4. Experimental Section

Melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 1640 spectrophotometer. ^1H NMR spectra were recorded on a Hitachi R–24 (60 MHz), JEOL FX90A (89.55 MHz), or JEOL GSX270 (270.05 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX90A (22.5 MHz) or JEOL GSX270 (67.8 MHz) spectrometer. In all NMR measurements TMS was used as an internal standard. Mass spectra were recorded on a Hitachi M–80 GC–MS spectrometer equipped with a Hitachi M–003 data processor. Elemental analyses were performed by the Microanalytical Center, Kyoto University, Kyoto. 1–Chloro–2–adamantanone, 1–bromo–2–adamantanone, 1–iodo–2–adamantanone, and 1–fluoro–2–adamantanone were described in Chapter 1. (Z)–4–OH,[15c] (E)–4–OTf,[15c] and 5–OTf were described in Chapter 2. 8–F was prepared by following a literature method.[29] Ethanol was refluxed over magnesium ethoxide and distilled. 2,2,2–Trifluoroethanol (TFE) was stored over 5A molecular sieves and distilled. Benzoyl triflate was prepared by the method of Brown and Koreeda.[30] Commercially available methyl– and ethyltriphenylphosphonium

bromides were dried at 95–100 °C in vacuo for 1 h before use. All anhydrous solvents used for synthetic work were purified by standard procedures. Other commercially available reagents were of a reagent–grade quality and used as received. Medium–pressure liquid chromatography (MPLC) was conducted on Merck silica gel 60 (230–400 mesh).

(Z)–2–Ethylidenebicyclo[2.2.2]oct–1–yl Triflate ((Z)–4–OTf). To a solution of (Z)–4–OH[15c] (0.152 g, 1.00 mmol) and pyridine (0.156 g, 1.97 mmol) in CH_2Cl_2 (1.2 mL) was added a solution of triflic anhydride (0.369 g, 1.31 mmol) in CH_2Cl_2 with stirring at 0 °C over 5 min, and then stirring continued for 1.5 h. After having been stored in a freezer overnight, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed at 0 °C with water (2 × 8 mL), 10% aqueous HCl (2 × 8 mL), 10% aqueous NaCl (8 mL), saturated aqueous $NaHCO_3$ (8 mL), and 10% aqueous NaCl (8 mL), and dried ($MgSO_4$). Evaporation of solvent with a rotary evaporator afforded (Z)–4–OTf (0.214 g, 75%) as an unstable brown oil, which was used for solvolysis studies without further purification: ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 135.0, 102.9 (C), 119.0, 25.4 (CH), 39.2, 31.4, 27.5 (CH_2), 13.3 (CH_3), 118.0 (q, CF_3, J = 319.2 Hz).

2–Oxo–1–adamantyl tert–Butyldimethylsilyl Ether. To a solution of 1–hydroxy–2–adamantanone (**9**) (3.25 g, 19.0 mmol) and 2,6–lutidine (5.5 mL) in CH_2Cl_2 (21 mL) was added *tert*–butyldimethylsilyl triflate (5.1 mL, 23.1 mmol) at 0 °C for 9 min. After having been stirred for 1 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with water (2 × 40 mL), 10% aqueous HCl (2 × 40 mL), saturated aqueous $NaHCO_3$ (2 × 40 mL), and saturated aqueous NaCl (2 × 40 mL), and dried ($MgSO_4$). Evaporation of solvent, followed by MPLC (SiO_2,

hexane–ether (95:5)) afforded **9** (3.94 g, 74%) as colorless crystals: mp 57.0–58.0 °C; IR (CCl$_4$) 2929, 2857, 1730, 1472, 1348, 1248, 1173, 1127, 1056, 990, 920 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 0.13 (s, 6 H), 0.87 (s, 9 H), 1.66–2.34 (m, 12 H), 2.69 (br s, 1 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 79.0, 18.3 (C), 47.6, 30.0 (CH), 48.0, 38.5, 35.0 (CH$_2$), 25.9, –2.4 (CH$_3$), 213.5 (C=O).

(Z)– and (E)–2–Ethylidene–1–adamantanol ((Z)– and (E)–6–OH). To a suspension of ethyltriphenylphosphonium bromide (13.46 g, 36.3 mmol) in THF (90 mL) was added dropwise 1.6 M *n*–BuLi in hexane (22.7 mL) at room temperature under N$_2$. After stirring for 30 min, a solution of **9** (3.39 g, 12.1 mmol) in THF (25 mL) was added. The mixture was stirred at room temperature for 19 h and then at reflux for 2 h. The reaction mixture was poured into ice–water (90 mL) and extracted with ether (3 × 70 mL). The combined extracts were washed with water (2 × 85 mL) and 10% aqueous NaCl (2 × 85 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded a mixture of (Z)– and (E)–**6–OTBDMS** (2.28 g, 65%) in an approximate ratio of 10:1. (Z)–**6– OTBDMS**: ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 0.15 (s, 6 H), 0.91 (s, 9 H), 1.26– 1.94 (m, 13 H), 2.12 (br s, 2 H), 2.41 (br s, 1 H), 5.13 (q, 1 H, *J* = 7.1 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 147.1, 113.1, 77.9, 47.7, 44.6, 38.8, 36.0, 31.0, 26.4, 18.4, 14.3, –1.1.

To a 10:1 mixture of (Z)– and (E)–**6–OTBDMS** (2.28 g, 7.8 mmol) in THF (35 mL) was added a 1.0 M THF solution of *n*–Bu$_4$NF (15.6 mL) and the resulting solution was refluxed for 17 h under N$_2$. The reaction mixture was stirred with 4% aqueous NH$_4$Cl (40 mL) and extracted with ether (3 × 60 mL). The combined extracts were washed with water (2 × 60 mL) and 10% aqueous NaCl (2 × 60 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane– ether (9:1)) afforded (Z)–**6–OH** (1.24 g, 89%) and (E)–**6–OH** (0.13 g, 9%) in this

sequence. **(Z)-6-OH**: mp 104.5–105.0 °C (from hexane); IR (CCl$_4$) 3612, 2919, 2852, 1446, 1343, 1212, 1177, 1118, 1092, 966, 937 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.57–2.29 (m, 13 H), 1.89 (d, 3 H, J = 7.3 Hz), 2.43 (br s, 1 H), 5.15 (q, 1 H, J = 7.2 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 146.8, 74.8 (C), 112.4, 43.8, 30.6 (CH), 47.4, 38.6, 35.6 (CH$_2$), 13.4 (CH$_3$). Analytical data were unsatisfactory, probably owing to its hygroscopic nature. Anal. Calcd for C$_{12}$H$_{18}$O: C, 80.85; H, 10.18. Found: C, 80.43; H, 9.92. Satisfactory analytical data were obtained for the mesylate **(Z)-6-OMs** as described below. **(E)-6-OH**: mp 77.0–77.5 °C (from pentane); IR (CCl$_4$) 3601, 2923, 2852, 1550, 1451, 1341, 1220, 1178, 1121, 1091, 1007, 936 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.66–2.29 (m, 13 H), 1.60 (d, 3 H, J = 6.7 Hz), 3.03 (br s, 1 H), 5.34 (q, 1 H, J = 6.8 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 148.4, 71.8 (C), 108.0, 32.9, 30.5 (CH), 47.2, 37.7, 35.7 (CH$_2$), 11.9 (CH$_3$). Analytical data were unsatisfactory, probably owing to its hygroscopic nature. Anal. Calcd for C$_{12}$H$_{18}$O: C, 80.85; H, 10.18. Found: C, 80.26; H, 10.09. Satisfactory analytical data were obtained for the mesylate **(E)-6-OMs** as described below.

(Z)-2-Ethylidene-1-adamantyl Mesylate ((Z)-6-OMs). To a solution of **(Z)-6-OH** (0.300 g, 1.68 mmol) in THF (3.0 mL) was added dropwise 1.6 M *n*-BuLi in hexane (1.05 mL) at −40 °C over 2 min. After stirring at −40 °C for 50 min, methanesulfonyl chloride (0.193 g, 1.68 mmol) in THF (3.0 mL) was added and stirring continued for 4 h, then the solution allowed to warm slowly to 10 °C over 1.5 h. After most of the solvent had been removed with a rotary evaporator, hexane was added. An insoluble white precipitate was removed by filtration. Evaporation of solvent followed by MPLC at −40 °C (SiO$_2$, hexane–ether (9:1)) afforded pure **(Z)-6-OMs** (0.206 g, 48%) and a mixture of **(Z)-6-OMs** and

(Z)-6-OH (0.117 g) in this sequence. (Z)-6-OMs: mp 61.0-61.5 °C (from pentane); IR (CCl$_4$) 2925, 2855, 1550, 1452, 1362, 1345, 1177, 1051, 1040, 970, 938, 899, 879 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.11-2.91 (m, 13 H), 1.80 (d, 3 H, J = 7.1 Hz), 3.04 (s, 3 H), 5.25 (q, 1 H, J = 7.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 142.5, 94.1 (C), 113.6, 44.7, 31.1 (CH), 43.8, 37.9, 34.8 (CH$_2$), 41.0, 13.3 (CH$_3$). Anal. Calcd for C$_{13}$H$_{20}$O$_3$S: C, 60.91; H, 7.86. Found: C, 60.71; H, 8.07.

(E)-2-Ethylidene-1-adamantanol ((E)-6-OH) by Using Ethyllithium. To a 0.45 M solution of C$_2$H$_5$Li in pentane (15.5 mL), which was generated from Li shots and ethyl bromide in pentane, was added a solution of **9** (1.49 g, 5.32 mmol) in benzene (15 mL) at 0 °C over 23 min. After the solution had been stirred for 10 min at room temperature and then at reflux for 1 h , water (25 mL) was added. The reaction mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with 10% aqueous NaCl (3 × 35 mL) and dried (MgSO$_4$). Evaporation of solvent with a rotary evaporator afforded 1-*tert*-butyldimethylsilyloxy-2-ethyl-2-adamantanol (**10**) (1.88 g, 100%) as a pale yellow oil. ^{1}H NMR (60 MHz, CCl$_4$) δ 0.10 (s, 6 H), 0.72-0.90 (m, 12 H), 1.37-2.48 (m, 16 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 77.4, 76.3, 18.1 (C), 33.7, 33.1, 30.2 (CH), 41.7, 41.5, 37.2, 31.5, 30.6, 25.2 (CH$_2$), 25.8, 6.4, −1.9, −2.0 (CH$_3$).

To a solution of SOCl$_2$ (0.186 g, 6.85 mmol) in benzene (21 mL) was added a solution of **10** (1.652 g, 6.04 mmol) and pyridine (1.467 g, 18.5 mmol) in benzene (10.5 mL) at 0 °C over 17 min. The resulting mixture was stirred for another 25 min at 0 °C, then for 45 min at room temperature, and heated at reflux for 30 min. The reaction mixture was poured into ice-water (70 g) and extracted with ether (3 × 40 mL). The combined extracts were washed with 10% HCl (3 × 30 mL) and saturated aqueous NaCl (3 × 30 mL) and dried (MgSO$_4$). Evaporation of

solvent followed by MPLC (SiO$_2$, hexane) afforded essentially pure (*E*)–6–**OTBDMS** (1.400 g, 90% based on **9**) as a colorless oil. ^{1}H NMR (60 MHz, CDCl$_3$) δ 0.10 (s, 6 H), 0.92 (s, 9 H), 1.30–1.93 (m, 10 H), 1.55 (d, 3 H, *J* = 6.6 Hz), 2.07 (br s, 2 H), 3.02 (br s, 1 H), 5.47 (q, 1 H, *J* = 7.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 148.2, 108.9, 74.5, 47.9, 37.8, 36.1, 32.9, 30.8, 26.0, 18.4, 12.0, –1.5.

(*E*)–6–**OTBDMS** (1.400 g, 4.79 mmol) was desilylated as described for the preparation of (*Z*)–6–**OH** by refluxing with *n*–Bu$_4$NF (9.8 mmol) in THF for 24 h under N$_2$. The usual workup followed by MPLC (SiO$_2$, hexane–ether (9:1)) afforded (*E*)–6–**OH** (0.627 g, 75%).

(E)–2–Ethylidene–1–adamantyl Mesylate ((E)–6–OMs). The procedure described for the preparation of (*Z*)–**6**–**OMs** (0.200 g, 1.12 mmol) was followed. A solution of (*E*)–6–**OH** (0.200 g, 1.12 mmol) in THF (3.0 mL) was treated with 1.6 M *n*–BuLi in hexane (0.7 mL) and then with methanesulfonyl chloride (0.129 g, 1.12 mmol) at –40 °C for 4 h. Workup followed by MPLC at –30 °C (SiO$_2$, hexane–ether (9:1)) afforded (*E*)–6–**OMs** (0.163 g, 57%) and (*E*)–6–**OH** (0.073 g, 37%) in this sequence. (*E*)–6–**OMs**: colorless crystals: mp 61.5–62.0 °C (from pentane); IR (CCl$_4$) 2923, 2855, 1550, 1451, 1341, 1178, 1044, 1000, 971, 935, 897 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.31–2.73 (m, 13 H), 1.62 (d, 3 H, *J* = 6.8 Hz), 3.06 (s, 3 H), 5.45 (q, 1 H, *J* = 6.8 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 143.0, 92.7 (C), 110.8, 33.9, 31.2 (CH), 44.5, 37.1, 35.2 (CH$_2$), 40.9, 12.0 (CH$_3$). Anal. Calcd for C$_{13}$H$_{20}$O$_3$S: C, 60.91; H, 7.86. Found: C, 60.83; H, 8.00.

2–Methylene–1–adamantyl Mesylate (7–OMs). To a solution of **7–OH** (0.200 g, 1.22 mmol) in THF (2.4 mL) was added dropwise 1.6 M *n*–BuLi in

hexane (0.78 mL) at −40 °C over 3 min. After the mixture had been stirred at −40 °C for 1.5 h, methanesulfonyl chloride (0.140 g, 1.22 mmol) in THF (2.4 mL) was added and stirring continued for 4.5 h, then the solution was allowed to warm slowly to 10 °C over 2 h. After most of the solvent had been removed with a rotary evaporator, hexane was added. An insoluble white precipitate was removed by filtration. Evaporation of solvent by MPLC (SiO$_2$, hexane–ether (9:1)) afforded **7–OMs** (0.112 g, 38%) and **7–OH** (0.052 g, 26%) in this sequence. **7–OMs**: mp 58.0–59.0 °C (from hexane); IR (CCl$_4$) 2927, 2858, 1657, 1454, 1331, 1174, 1042, 931, 910, 846 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.67–2.89 (m, 13 H), 3.06 (s, 3 H), 4.76 (br s, 1 H), 4.86 (br s, 1 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 152.7, 92.0 (C), 42.0, 31.5 (CH), 102.1, 44.2, 38.0, 35.2 (CH), 40.9 (CH$_3$). Anal. Calcd for C$_{12}$H$_{18}$O$_3$S: C, 59.48; H, 7.49. Found: C, 59.37; H, 7.73.

(Z)–2–Ethylidene–1–chloroadamantane ((Z)–6–Cl). To a solution of SOCl$_2$ (0.163 g, 1.37 mmol) in benzene (1.0 mL) was added a solution of (Z)–**6–OH** (0.050 g, 0.28 mmol) and pyridine (0.225 g, 2.84 mmol) in benzene (1.0 mL) at room temperature over 6 min. The reaction mixture was stirred at room temperature for 22 h. The reaction mixture was poured into ice–water (10 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed with 10% aqueous HCl (2 × 10 mL) and saturated aqueous NaHCO$_3$ (2 × 10 mL) and dried (MgSO$_4$). Evaporation of solvent gave (Z)–**6–Cl** (0.049 g, 89%) as colorless crystals: mp 60.0 °C (from pentane); IR (CCl$_4$) 3063, 2928, 2855, 1661, 1449, 1299, 1206, 1042, 880 cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 1.57–2.50 (m, 13 H), 1.96 (d, 3 H, J = 7.4 Hz), 5.31 (q, 1 H, J = 7.3 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 143.6, 72.9 (C), 115.5, 46.1, 31.5 (CH), 50.8, 38.4, 35.5 (CH$_2$), 13.9 (CH$_3$). Anal. Calcd for C$_{12}$H$_{17}$Cl: C, 73.21; H, 8.71; Cl, 18.02. Found: C, 72.98; H, 8.92; Cl, 18.00.

(E)-2-Ethylidene-1-chloroadamantane ((E)-6-Cl). To a solution of SOCl$_2$ (0.163 g, 1.37 mmol) in benzene (0.5 mL) was added a solution of *(E)-6-OH* (0.050 g, 0.28 mmol) and pyridine (0.225 g, 2.84 mmol) in benzene (1.0 mL) at room temperature over 5 min. The reaction mixture was stirred at room temperature for 30 min and then at 50 °C for 3 h. The reaction mixture was worked up as described for the preparation of *(Z)-6-Cl* and the crude product subjected to MPLC (SiO$_2$, hexane) to give *(E)-6-Cl* (0.039 g, 71%) as pale yellow crystals: mp 43.0–43.5 °C (from pentane); IR (CCl$_4$) 2926, 2854, 1671, 1449, 1380, 1338, 1289, 1107, 1034, 997, 899 cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 1.25–2.40 (m, 12 H), 1.59 (d, 3 H, *J* = 6.8 Hz), 3.10 (s, 1 H), 5.47 (q, 1 H, *J* = 7.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 144.7, 73.6 (C), 113.0, 34.1, 29.7 (CH), 50.2, 37.3, 35.3 (CH$_2$), 12.2 (CH$_3$). Anal. Calcd for C$_{12}$H$_{17}$Cl: C, 73.27; H, 8.71; Cl, 18.02. Found: C, 73.01; H, 8.82; Cl, 17.89.

(Z)-2-Ethylidene-1-bromoadamantane ((Z)-6-Br). To a solution of SOBr$_2$ (0.697 g, 3.35 mmol) in benzene (3.0 mL) was added a solution of *(Z)-6-OH* (0.300 g, 1.68 mmol) and pyridine (0.538 g, 6.80 mmol) in benzene (6.0 mL) at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 45 min and then poured into ice–water (30 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with 10% aqueous HCl (3 × 30 mL) and saturated aqueous NaHCO$_3$ (3 × 30 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded *(Z)-6-Br* (0.341 g, 84%) as colorless crystals: mp 58.5–59.0 °C (from hexane); IR (CCl$_4$) 3061, 2929, 2855, 1450, 1402, 1292, 1206, 1039 cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 1.81–2.98 (m, 13 H), 2.02 (d, 3 H, *J* = 7.0 Hz), 5.43 (q, 1 H, *J* = 7.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 143.7, 67.3 (C), 116.1, 47.1, 32.3 (CH), 52.6, 38.4, 35.2 (CH$_2$), 14.0 (CH$_3$).

Anal. Calcd for $C_{12}H_{17}Br$: C, 59.76; H, 7.10; Br, 33.13. Found: C, 59.46; H, 7.18; Br, 32.92.

(E)-2-Ethylidene-1-bromoadamantane ((E)-6-Br). To a solution of $SOBr_2$ (0.697 g, 3.35 mmol) in benzene (3.0 mL) was added a solution of *(E)*-**6**-**OH** (0.300 g, 1.68 mmol) and pyridine (0.538 g, 6.80 mmol) in benzene (6.0 mL) at 0 °C over 5 min. The reaction mixture was stirred at 0 °C for 30 min and at 30 °C for 5 h and then poured into ice–water (30 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with 10% aqueous HCl (3 × 30 mL) and saturated aqueous $NaHCO_3$ (3 × 30 mL) and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane) afforded *(E)*-**6**-**Br** (0.277 g, 68%) as colorless crystals: mp 27.0–27.5 °C (from hexane); IR (CCl_4) 3055, 2930, 2856, 1450, 1379, 1288, 1029, 893 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.63 (d, 3 H, $J = 6.6$ Hz), 1.82–2.47 (m, 12 H), 3.19 (s, 1 H), 5.43 (q, 1 H, $J = 7.0$ Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 144.9, 72.8 (C), 115.7, 34.6, 32.4 (CH), 51.8, 37.3, 35.2 (CH_2), 12.4 (CH_3). Anal. Calcd for $C_{12}H_{17}Br$: C, 59.76; H, 7.10; Br, 33.13. Found: C, 59.92; H, 7.10; Br, 33.29.

1-Chloro-2-methyleneadamantane (7-Cl). To a suspension of methyltriphenylphosphonium bromide (4.10 g, 11.5 mmol) in THF (25 mL) was added dropwise 1.6 M *n*–BuLi in hexane (7.2 mL) at room temperature under N_2. After the mixture was stirred for 1 h, a solution of 1–chloro–2–adamantanone (0.700 g, 3.79 mmol) in THF (14 mL) was added. The resulting mixture was stirred for another 3 h and then poured into ice–water (60 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and 10% aqueous NaCl (2 × 50 mL) and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane) afforded **7**–**Cl** (0.553 g, 80%) as colorless crystals: mp

71.5–72.5 °C (from pentane); IR (CCl$_4$) 3094, 2996, 2929, 2856, 1810, 1654, 1450, 1034, 903 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.76–2.19 (m, 12 H), 2.79 (br s, 1 H), 4.77 (d, 1 H, J = 1.6 Hz), 5.08 (d, 1 H, J = 1.6 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 154.4, 71.6 (C), 41.7, 31.5 (CH), 104.0, 49.7, 38.1, 35.2 (CH$_2$). Anal. Calcd for C$_{11}$H$_{15}$Cl: C, 72.32; H, 8.28; Cl, 19.41. Found: C, 72.19; H, 8.44; Cl, 19.12.

1–Bromo–2–methyleneadamantane (7–Br). To a suspension of methyltriphenylphosphonium bromide (3.90 g, 10.9 mmol) in THF (25 mL) was added dropwise 1.6 M *n*–BuLi in hexane (6.8 mL) at room temperature under N$_2$. After the mixture was stirred for 45 min, a solution of 1–bromo–2–adamantanone (0.832 g, 3.63 mmol) in THF (14 mL) was added. The resulting mixture was stirred for another 40 min, poured into ice–water (60 mL), and extracted with ether (3 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and 10% aqueous NaCl (2 × 50 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded **7–Br** (0.687 g, 83%) as colorless crystals: mp 23.5–24.5 °C (from pentane); IR (CCl$_4$) 3093, 2995, 2925, 2856, 1652, 1449, 1029, 903 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.81–2.83 (m, 13 H), 4.84 (d, 1 H, J = 1.5 Hz), 5.15 (d, 1 H, J = 1.7 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 154.7, 69.8 (C), 42.0, 32.2 (CH), 106.7, 51.3, 38.2, 35.1 (CH$_2$). Anal. Calcd for C$_{11}$H$_{15}$Br: C, 58.17; H, 6.66; Br, 35.18. Found: C, 58.41; H, 6.90; Br, 35.05.

(Z)–2–Ethylidene–1–iodoadamantane ((Z)–6–I). To a suspension of ethyltriphenylphosphonium bromide (3.62 g, 10.1 mmol) in THF (23 mL) was added dropwise 1.6 M *n*–BuLi in hexane (6.3 mL) at room temperature under N$_2$. After stirring for 30 min, a solution of 1–iodo–2–adamantanone (1.40 g, 5.10

mmol) in THF (18 mL) was added. The resulting mixture was stirred for another 15 min, poured into ice–water (80 mL) and extracted with ether (3 × 90 mL). The combined extracts were washed with water (2 × 90 mL) and 10% aqueous NaCl (2 × 90 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded (Z)-6-I (1.17 g, 80%) as colorless crystals: mp 25.0–26.0 °C (from pentane); IR (CCl$_4$) 2926, 2854, 1654, 1448, 1294, 1203, 1034, 1014, 982, 946, 873, 708, 648 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.88 (br s, 8 H), 2.05 (d, 3 H, J = 7.5 Hz), 2.46 (br s, 1 H), 2.78 (br s, 3 H), 5.41 (q, 1 H, J = 7.5 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 144.7, 48.7 (C), 116.5, 47.7, 33.2 (CH), 56.7, 38.6, 35.4 (CH$_2$), 14.1 (CH$_3$). Anal. Calcd for C$_{12}$H$_{17}$I: C, 50.02; H, 5.95; I, 44.04. Found: C, 49.93; H, 5.92; I, 44.07.

(E)–2–Ethylidene–1–iodoadamantane ((E)–6–I). A solution of (Z)-6-I (0.682 g, 2.37 mmol) in 0.01 M trifluoromethanesulfonic acid (TfOH) in CH$_2$Cl$_2$ (24 mL) was stirred at 0°C for 1 h. The resulting mixture was diluted with ether (20 mL), washed with saturated aqueous NaHCO$_3$ (2 × 20 mL) and saturated aqueous NaCl (2 × 20 mL) and dried (MgSO$_4$). Evaporation of solvent with a rotary evaporator afforded essentially pure (E)-6-I (0.670 g, 98%) as colorless crystals: mp 24.0–25.0 °C (from pentane); IR (CCl$_4$) 2942, 2855, 1666, 1448, 1285, 1215, 1107, 1024, 943, 879, 658, 607 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.63 (d, 3 H, J = 6.7 Hz), 1.69–2.07 (m, 8 H), 2.46–3.23 (m, 5 H), 5.76 (q, 1 H, J = 6.7 Hz), ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 146.3, 61.8 (C), 120.4, 34.4, 33.3 (CH), 55.3, 37.5, 35.3 (CH$_2$), 12.9 (CH$_3$). Anal. Calcd for C$_{12}$H$_{17}$I: C, 50.02; H, 5.95; I, 44.04. Found: C, 50.26; H, 5.95; I, 44.12.

2–Methylene–1–iodoadamantane (7–I). To a suspension of methyltri-phenyphosphonium bromide (3.30 g, 9.24 mmol) in THF (21 mL) was added

dropwise 1.6 M *n*–BuLi in hexane (5.8 mL) at room temperature over 10 min under N_2. After the mixture had been stirred for 50 min, a solution of 1–iodo–2–adamantanone (0.852 g, 3.09 mmol) in THF (12 mL) was added. The resulting mixture was stirred for another 30 min, poured into ice–water (60 mL), and extracted with ether (3 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and 10% aqueous NaCl (2 × 50 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded **7–I** (0.483 g, 57%) as colorless crystals: mp 25.5–26.5 °C (from pentane); IR (CCl$_4$) 3086, 2990, 2904, 2854, 1648, 1447, 899 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.89 (m, 8 H), 2.51–2.90 (m, 5 H), 4.95 (d, 1 H, *J* = 1.2 Hz), 5.13 (d, 1 H, *J* = 1.3 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 156.1, 56.7, (C), 41.1, 32.7 (CH), 111.2, 54.6, 38.4, 35.2 (CH$_2$). Anal. Calcd for C$_{11}$H$_{15}$I: C, 48.19; H, 5.51; I, 46.29. Found: C, 48.47; H, 5.57; I, 46.54.

(Z)– and (E)–2–Ethylidene–1–fluoroadamantanes ((Z)– and (E)–6–F). To a suspension of ethyltriphenylphosphonium bromide (4.46 g, 12.0 mmol) in THF (28 mL) was added dropwise 1.6 M *n*–BuLi in hexane (7.5 mL) at room temperature under N_2. After 1 h of stirring, a solution of 1–fluoro–2–adamantanone (0.673 g, 4.00 mmol) in THF (17 mL) was added. The resulting mixture was stirred for another 17 h, poured into ice–water (50 mL), and extracted with ether (3 × 40 mL). The combined extracts were washed with water (2 × 40 mL) and 10% aqueous NaCl (2 × 40 mL) and dried (MgSO$_4$). Evaporation of solvent afforded a mixture of *(Z)*– and *(E)*–**6–F**. The mixture was separated by MPLC (SiO$_2$, hexane–ether (95:5)), the first fraction being pure *(Z)*–**6–F** (0.326 g, 45%) as a colorless liquid, the second being pure *(E)*–**6–F** (0.295 g, 41%) a colorless crystals. *(Z)*–**6–F**: IR (CCl$_4$) 3068, 2934, 2911, 2854, 1471, 1453, 1392,

1210, 1084 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.66–2.21 (m, 13 H), 1.76 (dd, 3 H, J = 2.9, 7.1 Hz), 5.15 (dq, 1 H, J = 1.7, 7.1 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 143.7 (d, J = 12.6 Hz), 96.7 (d, J = 192.3 Hz) (C), 112.7, 43.8 (d, J = 6.6 Hz), 31.3 (d, J = 9.9 Hz) (CH), 44.5 (d, J = 18.1 Hz), 38.3 (d, J = 1.6 Hz), 35.4 (d, J = 2.2 Hz) (CH$_2$), 13.0 (d, J = 11.5 Hz) (CH$_3$). Anal. Calcd for C$_{12}$H$_{17}$F: C, 79.96; H, 9.51; F, 10.54. Found: C, 79.82; H, 9.62; F, 10.45.

(*E*)-6-F: mp 53.0–53.5 °C (from pentane); IR (CCl$_4$) 3067, 2934, 2920, 2854, 1470, 1451, 1341, 1083 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.60 (d, 3 H, J = 6.9 Hz), 1.69–1.97 (m, 11 H), 2.25 (br s, 1 H), 3.07 (br s, 1 H), 5.37 (q, 1 H, J = 6.8 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 144.4 (d, J = 12.1 Hz), 93.8 (d, J = 193.4 Hz) (C), 108.4 (d, J = 12.1 Hz), 33.5 (d, J = 3.9 Hz), 31.2 (d, J = 9.9 Hz) (CH), 44.7 (d, J = 18.1 Hz), 37.3 (d, J = 1.7 Hz), 35.5 (d, J = 1.6 Hz) (CH$_2$), 11.7 (CH$_3$). Anal. Calcd for C$_{12}$H$_{17}$F: C, 79.96; H, 9.51; F, 10.54. Found: C, 79.68; H, 9.79; F, 10.48.

Product of Solvolysis of (Z)–4–OTf in Ethanol. A solution of (Z)–4–OTf (0.207 g, 0.73 mmol) in 0.050 M 2,6–lutidine in ethanol (18 mL) was heated in a constant temperature bath (25.0 °C) for 5 h (10 half–lives). GLC analysis (PEG 20M, 3 mm × 2 m) of the reaction mixture exhibited the formation of a single product. After most of solvent had been removed with a rotary evaporator, the residue was diluted with ether (15 mL) and the ether solution was washed with water (15 mL), 10% aqueous HCl (15 mL), saturated aqueous NaHCO$_3$, and saturated aqueous NaCl (15 mL), and dried (MgSO$_4$). Evaporation of solvent afforded 1–ethoxy–(Z)–2–ethylidenebicyclo[2.2.2]octane ((Z)–4–OEt) (0.099 g, 76%) as a yellowish brown oil: IR (CCl$_4$) 2939, 2866, 1732, 1454, 1381, 1317, 1202, 1156, 1115, 1045, 960 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.19 (t, 3 H, J = 7.0 Hz), 1.31–1.89 (m, 9 H), 1.81 (dt, 3 H, J = 7.3, 1.8 Hz), 2.22 (br s, 2 H), 3.44 (q, 2 H,

J = 7.0 Hz), 5.21 (qt, 1 H, J = 7.1, 1.9 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 139.0, 77.8 (C), 117.8, 26.5 (CH), 57.5, 39.2, 31.1, 26.5 (CH$_2$), 15.7, 13.3 (CH$_3$).

Product of Solvolysis of (Z)–6–OMs in Ethanol. From (Z)–6–OMs (0.050 g, 0.20 mmol) in 0.050 M 2,6–lutidine in ethanol (4.9 mL) at 50.0 °C for 38 h (13.7 half–lives) was obtained 1–ethoxy–(Z)–2–ethylideneadamantane ((Z)–6–OEt) (0.038 g, 95%) as a pale yellow oil: IR (CCl$_4$) 2928, 2852, 1709, 1450, 1388, 1341, 1211, 1178, 1116, 1095, 1056, 967, 936, 897 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.20 (t, 3 H, J = 6.9 Hz), 1.34–1.97 (m, 10 H), 1.83 (d, 3 H, J = 7.2 Hz), 2.14 (br s, 2 H), 2.43 (br s, 1 H), 3.53 (q, 2 H, J = 6.9 Hz), 5.17 (q, 1 H, J = 7.3 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 145.6, 78.1 (C), 113.3, 44.5, 30.6 (CH), 56.5, 43.3, 39.1, 36.1 (CH$_2$), 15.9, 13.4 (CH$_3$).

Product of Solvolysis of (Z)–6–OMs in TFE. A solution of (Z)–6–OMs (0.080 g, 0.31 mmol) in 0.050 M 2,6–lutidine in TFE (7.8 mL) was stirred at 25.0 °C for 5 min (20 half–lives). GLC analysis (PEG 20M, 3 mm × 2 m) of the reaction mixture exhibited the formation of a single product. After most of solvent had been removed with a rotary evaporator, the residue was diluted with ether (20 mL) and the ether solution was washed with water (15 mL), 10% aqueous HCl (15 mL), saturated aqueous NaHCO$_3$ (15 mL), and water (15 mL), and dried (MgSO$_4$). Evaporation of solvent afforded 1–(2,2,2–trifluoroethoxy)–(Z)–2–ethylideneadamantane ((Z)–6–OTFE) (0.080 g, 99%) as a pale yellow oil: IR (CCl$_4$) 2927, 2854, 1700, 1539, 1448, 1280, 1163, 1127, 1101, 972 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.25–2.47 (m, 13 H), 1.82 (d, 3 H, J = 7.4 Hz), 3.84 (q, 2 H, J = 8.6 Hz), 5.20 (q, 1 H, J = 7.3 Hz): ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 144.1, 80.0 (C), 114.3, 44.2, 30.6 (CH), 41.8, 38.7, 35.7 (CH$_2$), 13.5 (CH$_3$), 59.2 (q, J = 34 Hz,

$-O\underline{C}H_2CF_3$), 124.5 (q, J = 278 Hz, CF$_3$).

Product of Solvolysis of (E)-6-OMs in Ethanol. From (*E*)-6-OMs (0.035 g, 0.14 mmol) in 0.050 M 2,6-lutidine in ethanol (3.4 mL) at 100.0 °C for 9.5 h (11.3 half-lives) was obtained 1-ethoxy-(*E*)-2-ethylideneadamantane ((*E*)-6-**OEt**) (0.026 g, 93%) as a pale yellow oil: IR (CCl$_4$) 2927, 2853, 1729, 1449, 1392, 1341, 1295, 1218, 1124, 1093, 1055, 964 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.21 (t, 3 H, J = 7.0 Hz), 1.37–1.90 (m, 10 H), 1.60 (d, 3 H, J = 6.9 Hz), 2.17 (br s, 2 H), 3.03 (br s, 1 H), 3.54 (q, 2 H, J = 7.0 Hz), 5.31 (q, 1 H, J = 6.9 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 145.5, 75.8 (C), 109.0, 32.9, 30.4 (CH), 56.4, 43.7, 37.9, 36.2 (CH$_2$), 16.0, 12.0 (CH$_3$).

Product of Solvolysis of (E)-6-OMs in TFE. From (*E*)-6-OMs (0.071 g, 0.28 mmol) in 0.050 M 2,6-lutidine in TFE (6.9 mL) at 25.0 °C for 5.5 h (11 half-lives) was obtained 1-(2,2,2-trifluoroethoxy)-(*E*)-2-ethylideneadamantane ((*E*)-6-**OTFE**) (0.075 g, 100%) as a pale yellow oil: IR (CCl$_4$) 2923, 2854, 1671, 1448, 1418, 1380, 1276, 1219, 1158, 1101, 1087, 1005, 974, 854 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.41–1.91 (m, 10 H), 1.60 (d, 3 H, J = 6.8 Hz), 2.22 (br s, 2 H), 3.06 (br s, 1 H), 3.89 (q, 2 H, J = 8.6 Hz), 5.37 (q, 1 H, J = 6.8 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 144.4, 77.3 (C), 109.9, 33.0, 30.4 (CH), 43.0, 37.6, 35.8 (CH$_2$), 11.9 (CH$_3$), 60.0 (q, J = 34.2 Hz, $-O\underline{C}H_2CF_3$), 124.4 (q, J = 277.3 Hz, CF$_3$).

Product of Solvolysis of 7-OMs in Ethanol. A solution of 7-OMs (0.078 g, 0.32 mmol) in 0.050 M 2,6-lutidine in ethanol (8.0 mL) was heated in a constant temperature bath (100.0 °C) for 55 h (11.0 half-lives). After most of solvent had been removed with a rotary evaporator, the residue was diluted with

CHCl$_3$ (20 mL). The organic layer was washed with water (10 mL), 10% aqueous HCl (10 mL), saturated aqueous NaHCO$_3$ (10 mL), and water (10 mL), and dried (MgSO$_4$). Evaporation of solvent afforded a mixture of 1–ethoxy–2–methyleneadamantane (**7–OEt**) (94%), 1,2–diethoxy–2–methyladamantane (3%), and 2–methyl–4–protoadamantanone (**12**) (3%). The product distribution was determined by GLC (PEG 20M, 3 mm × 2 m) analysis for crude products. **7–OEt:** ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 155.8, 76.0 (C), 41.3, 30.6 (CH), 100.4, 56.6, 43.9, 38.8, 36.1 (CH$_2$), 15.9 (CH$_3$). **1,2–Diethoxy–2–methyladamantane:** ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 81.0, 77.2 (C), 37.5, 30.2, 30.1 (CH), 57.7, 55.0, 40.1, 37.4, 35.4, 33.7, 32.1 (CH$_2$), 16.7, 16.5, 16.2 (CH$_3$). **12:** The ^{13}C NMR spectral data were consistent with those of authentic **12** that was synthesized by the pinacol rearrangement of 2–methyl–1,2–adamantanediol.

Product of Solvolysis of (Z)–6–Cl in TFE. A solution of (Z)–6–Cl (0.076 g, 0.39 mmol) in 0.050 M 2,6–lutidine in TFE (9.6 mL) was heated in a constant temperature bath (75.0 °C) for 4 h (10.8 half–lives). GLC analysis (PEG 20M, 3 mm × 2 m) of the reaction mixture exhibited the formation of a single product. After most of solvent had been removed with a rotary evaporator, the residue was diluted with ether (20 mL) and the ether solution was washed with water (12 mL), 10% aqueous HCl (15 mL), saturated aqueous NaHCO$_3$ (2 × 15 mL), and water (15 mL), and dried (MgSO$_4$). Evaporation of solvent afforded 1–(2,2,2–trifluoroe–tho–xy)–(Z)–2–ethylideneadamantane ((Z)–**6–OTFE**) (0.078 g, 77%) as a yellow oil.

Product of Solvolysis of 7–Cl in TFE. A solution of **7–Cl** (0.066 g, 0.36 mmol) in 0.050 M 2,6–lutidine in TFE (9.0 mL) was heated in a constant tempera-

ture bath (125.0 °C) for 237 h (11.5 half–lives). After most of solvent had been removed with a rotary evaporator, the residue was diluted with ether (20 mL) and the ether solution was washed with water (15 mL). The aqueous layer was extracted with ether (2 × 15 mL). The combined extracts were washed with 10% aqueous HCl (15 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), and water (15 mL), and dried ($MgSO_4$). Evaporation of solvent followed by MPLC (SiO_2, hexane, hexane–ether (9:1)) afforded 1–(2,2,2–trifluoroethoxy)–2–methyleneadamantane (**7–OTFE**) (0.047 g, 56%), 1,2–bis(2,2,2–trifluoroethoxy)–2–methyladamantane (**11**) (0.035 g, 29%), and 2–methyl–4–protoadamantanone (**12**) (0.008 g, 14%) in this sequence. **7–OTFE**: pale yellow oil; IR (CCl_4) 3099, 3000, 2929, 2856, 1654, 1450, 1379, 1356, 1278, 1157, 1128, 977 cm^{-1}; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.73–1.88 (m, 10 H), 2.25 (br s, 2 H), 2.68 (br s, 1 H), 3.92 (q, 2 H, J = 8.7 Hz), 4.74 (dd, 1 H, J = 5.1, 1.8 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 154.4, 77.5 (C), 41.4, 30.7 (CH), 101.2, 42.9, 38.5, 35.5 (CH_2), 60.0 (q, J = 34.1 Hz, –O$\underline{C}H_2CF_3$), 124.3 (q, J = 278.0 Hz, CF_3). **11**: pale yellow oil; ^{1}H NMR (89.55 MHz, $CDCl_3$) δ 1.26–2.09 (m, 12 H), 1.35 (s, 3 H), 2.52 (m, 1 H), 3.83 (qd, 2 H, J = 8.6, 2.7 Hz), 3.99 (qd, 2 H, J = 8.8, 2.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 83.1, 78.0 (C), 38.3, 30.0, 29.9 (CH), 40.1, 36.8, 34.8, 33.5, 31.5 (CH_2), 61.1 (q, J = 34.2 Hz), 59.8 (q, J = 34.2 Hz) (–O$\underline{C}H_2CF_3$), 16.2 (CH_3), 124.4 (q, J = 277.2 Hz), 124.3 (q, J = 277.1 Hz) (CF_3). **12**: ^{13}C and ^{1}H NMR spectral data were consistent with those of authentic **12** that was synthesized by the pinacol rearrangement of 2–methyl–1,2–adamantanediol.

Preparation of 2–Methyl–4–protoadamantanone (12) by the Pinacol Rearrangement of 2–Methyl–1,2–adamantanediol. To a solution of 1–hydroxy–2–adamantanone (0.200 g, 1.20 mmol) in benzene (25 mL) was added dropwise CH_3Li in ether (0.381 M, 19 mL) over 5 min at room temperature under N_2. The

reaction mixture was stirred at 70 °C for 23 h and then cold water (10 mL) was added. The resulting mixture was stirred for another 10 min and then extracted with ether (3 × 20 mL) and dried (MgSO$_4$). Evaporation of solvent gave 2–methyl–1,2–adamantanediol (0.218 g, 99%) as pale yellow crystals: mp 269.5–271.5 °C (dec sealed tube, from hexane–benzene); IR (CCl$_4$) 3599, 3580, 3455, 3014, 2925, 2862, 1449, 1080 cm^{-1}; ^{1}H NMR (60 MHz, CDCl$_3$) δ 0.87–2.12 (m, 15 H), 1.33 (s, 3 H); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 76.4, 72.3 (C), 40.9, 30.4, 30.3 (CH), 41.2, 40.8, 36.8, 34.2, 31.7 (CH$_2$), 22.3 (CH$_3$). Anal. Calcd for C$_{11}$H$_{18}$O$_2$: C, 72.49; H, 9.95. Found: C, 72.21; H, 10.12. A solution of 2–methyl–1,2–adamantanediol (0.658 g, 3.61 mmol) in ether (60 mL) was vigorously stirred with 4 N H$_2$SO$_4$ (40 mL) at 45 °C for 118 h. The reaction mixture was extracted with ether (3 × 20 mL). The combined extracts were washed with saturated aqueous NaHCO$_3$ (3 × 15 mL) and saturated aqueous NaCl (2 × 15 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane–ether (4:1)) afforded 2–methyl–4–protoadamantanone (**12**) (0.553 g, 93%) as colorless crystals: mp 122.0–122.5 °C (from hexane); IR (CCl$_4$) 3401, 2925, 2863, 1712, 1458, 1445, 1072 cm^{-1}; ^{1}H NMR (270.05 MHz, CDCl$_3$) δ 1.10 (s, 3 H), 1.26–2.59 (m, 13 H); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 217.0, 52.9 (C), 45.6, 38.9, 29.8 (CH), 45.9, 45.3, 40.1, 37.8, 35.0 (CH$_2$), 22.8 (CH$_3$). Analytical data were unsatisfactory presumably because of the sublimating nature. Anal. Calcd for C$_{11}$H$_{16}$O: C, 80.44; H, 9.82. Found: C, 79.84; H, 10.03. HRMS calcd for C$_{11}$H$_{16}$O 164.1202, found 164.1198.

Product of Solvolysis of (Z)–6–Br in TFE. From (Z)–6–Br (0.054 g, 0.22 mmol) in 0.050 M 2,6–lutidine in TFE (5.5 mL) at 40.0 °C for 2 h (12.1 half-lives) was obtained 1–(2,2,2–trifluoroethoxy)–(Z)–2–ethylideneadamantane ((Z)–

6–OTFE) (0.051 g, 88%) as a pale yellow oil.

Product of Solvolysis of (E)–6–Br in TFE. From (*E*)–**6–Br** (0.049 g, 0.20mmol) in 0.050 M 2,6–lutidine in TFE (5.0 mL) at 100.0 °C for 7.4 h (10.6 half–lives) was obtained 1-(2,2,2-trifluoroethoxy)-(*E*)-2-ethylideneadamantane ((*E*)–**6–OTFE**) (0.051 g, 96%) as a pale yellow oil.

Product of Solvolysis of (Z)–6–I in TFE. From (*Z*)–**6–I** (0.055 g, 0.19 mmol) in 0.050 M 2,6–lutidine in TFE (4.8 mL) at 40.0 °C for 30 min (13.6 half–lives) was obtained 1-(2,2,2-trifluoroethoxy)-(*Z*)-2-ethylideneadamantane ((*Z*)–**6–OTFE**) (0.044 g, 88%) as a pale yellow oil.

Product of Solvolysis of (E)–6–I in TFE. From (*E*)–**6–I** (0.048 g, 0.17 mmol) in 0.050 M 2,6–lutidine in TFE (4.2 mL) at 100.0 °C for 3.5 h (7.7 half–lives) was obtained 1-(2,2,2-trifluoroethoxy)-(*E*)-2-ethylideneadamantane ((*E*)–**6–OTFE**) (0.035 g, 82%) as a pale yellow oil.

Product of Solvolysis of 7–I in TFE. From **7–I** (0.055 g, 0.20 mmol) in 0.050 M 2,6–lutidine in TFE (5.0 mL) at 100.0 °C for 51.5 h (10 half–lives) was obtained 1-(2,2,2-trifluoroethoxy)-2-methyleneadamantane (**7–OTFE**) (0.048 g, 98%) as a pale yellow oil.

[^{18}O]–(Z)–2–Ethylidene–1–adamantanol ((Z)–6–^{18}OH). A solution of (*Z*)–**6–OMs** (0.818 g, 3.19 mmol) in 0.50 M 2,6–lutidine in 90% THF–10% $H_2^{18}O$ (10 atom % ^{18}O) (8.0 mL) was heated in a constant temperature bath (75.0 °C) for 96 h. After most of solvent had been removed with a rotary evaporator, the residue was extracted with pentane (10 mL + 2 × 4 mL). The combined extracts were

washed with 10% aqueous HCl (7 mL), saturated aqueous NaHCO₃ (7 mL), and water (7 mL), and dried (MgSO₄). Evaporation of solvent afforded (Z)-6-^{18}OH (0.581 g, 100%). The isotopic composition of the product was determined by analysis of the mass spectral peaks at M (178) and M + 2 (180); the intensity ratio M : (M + 2) was 100 : 13.8.

[^{18}O]–(E)–2–Ethylidene–1–adamantanol ((E)–6–^{18}OH). From (E)-6-OMs (0.923 g, 3.60 mmol) in 0.50 M 2,6-lutidine in 90% THF–10% H₂^{18}O (10 atom % ^{18}O) (9.0 mL) at 100.0 °C for 115 h was obtained (E)-6-^{18}OH (0.640 g, 100%). The isotopic composition of the product was determined by analysis of the mass spectral peaks at M (178) and M + 2 (180); the intensity ratio M : (M + 2) was 100 : 13.8.

[^{18}O]–(Z)–2–Ethylidene–1–adamantyl [$^{18}O_1$]Mesylate ((Z)–6–^{18}OMs). To a solution of (Z)-6-^{18}OH (0.400 g, 2.24 mmol) in THF (5.0 mL) was added dropwise 1.6 M n-BuLi in hexane (1.4 mL) at –40 °C under N₂. After the mixture had been stirred for 50 min, a solution of methanesulfonyl chloride (0.258 g, 2.25 mmol) in THF (5.0 mL) was added. The resulting mixture was stirred at –40 °C for 3 h and then allowed to warm slowly to 10 °C over 2 h. After most of solvent had been removed with a rotary evaporator, hexane was added. An insoluble precipitate was removed by filtration. Evaporation of solvent followed by MPLC at –40 °C (SiO₂, hexane–ether (9:1)) afforded pure (Z)-6-^{18}OMs (0.396 g, 69%) and a mixture of (Z)-6-^{18}OMs and (Z)-6-^{18}OH (0.127 g) in this sequence.

[^{18}O]–(E)–2–Ethylidene–1–adamantyl [$^{18}O_1$]Mesylate ((E)–6–^{18}OMs). The procedure described for the preparation of (Z)-6-^{18}OMs was followed. A

solution of (*E*)–**6**–[18]OH (0.400 g, 2.24 mmol) in THF (5.0 mL) was treated with 1.6 M *n*–BuLi in hexane (1.4 mL) and then with methanesulfonyl chloride (0.252 g, 2.20 mmol) at –40 °C for 4 h. Workup followed by MPLC at –40 °C (SiO$_2$, hexane–ether (9:1)) afforded (*E*)–**6**–[18]OMs (0.371 g, 65%) and (*E*)–**6**–[18]OH (0.120 g, 30%) in this sequence.

NOE Difference Experiments. Nuclear Overhauser enhancement of the C(3) bridgehead proton of (*Z*)– and (*E*)–**6**–**OH** on irradiation of the olefinic proton was determined at 270.05 MHz by the gated decoupling method using CDCl$_3$ solution degassed under vacuum. An irradiation period of 3.5 times the T_1's of the olefinic proton was employed for NOE generation, followed by a 90° pulse. For spin relaxation, a pulse interval of 3.5 times the T_1's of the olefinic proton was taken before the next pulse. The T_1 values were determined by the inversion recovery method. Irradiation of the olefinic proton of (*Z*)–**6**–**OH** caused enhancement both of the C(3) bridgehead proton and the methyl protons, 17.0% and 2.6%, respectively. Only the methyl protons showed NOE's (3.4%) when the olefinic proton of (*E*)–**6**–**OH** was irradiated.

Kinetic Methods. The preparation of solvents and kinetic methods followed a literature procedure.[14,20] Titrimetric rates were obtained for solutions containing 0.025 M 2,6–lutidine and 0.020 M substrate in ethanol or TFE, whereas conductimetric rates were determined for solutions containing 2,6–lutidine (0.025 M in ethanol and 0.0012 M in TFE) and 0.0002 M substrate. For the fluorides, the solvolysis rates were determined by GLC as follows. The solvolysis was conducted for TFE solutions containing 0.025 M 2,6–lutidine and 0.020 M substrates, and the concentrations of the substrates and the produced trifluoroethyl ether were determined by GLC (PEG 20M, 3 mm × 2 m) for reaction solutions by

using separately determined peak intensity factors. The first–order rate constants were calculated by the least–squares method on a microcomputer.

Oxygen–18 Scrambling Study: Typical Procedure. A solution of (Z)–6–^{18}OMs (0.090 g, 0.35 mmol) in 0.050 M 2,6–lutidine in ethanol (9.0 mL) was heated at 50.0 °C for 12 min (5% reaction). Evaporation of solvent with an oil pump at 0 °C followed by MPLC at –40 °C (SiO$_2$, hexane–ether (9:1)) gave (Z)–6–^{18}OMs (0.070 g, 78%). To a solution of the recovered (Z)–6–^{18}OMs (0.070 g, 0.27 mmol) in DMSO (4.5 mL) was added 0.5 M t–BuOK in DMSO (4.5 mL). The resulting mixture was heated at 50 °C for 40 h. The reaction mixture was poured into ice–water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined extracts were washed with water (2 × 10 mL) and dried (MgSO$_4$). Evaporation of solvent afforded (Z)–6–^{18}OH (0.048 g, 98%). The isotopic composition of (Z)–6–^{18}OH was determined by analysis of the mass spectral peaks at M (178) and M + 2 (180).

Control Experiment for ^{18}O Scrambling Study. A solution of (E)–6–^{18}OH (0.079 g, 0.44 mmol, M : (M + 2) = 1 : 7.69) in THF (1.0 mL) was treated with 1.6 M n–BuLi in hexane (0.28 mL) and then with methanesulfonyl chloride (0.050 g, 0.44 mmol) at –40 °C for 5 h. Workup followed by MPLC at –35 °C (SiO$_2$, hexane–ether (9:1)) afforded (E)–6–^{18}OMs (0.065 g, 57%) and (E)–6–^{18}OH (0.021 g, 27%) in this sequence. A solution of the recovered (E)–6–^{18}OMs (0.065 g, 0.25 mmol) in DMSO (4.3 mL) was treated with 0.5 M t–BuOK in DMSO (4.3 mL) at 60 °C for 45 h. The reaction mixture was poured into ice–water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined extracts were washed with water (2 × 10 mL) and dried (MgSO$_4$). Evaporation of solvent afforded (E)–6–

¹⁸OH (0.012 g, 27%). The isotopic composition of the recovered (*E*)-**6**-¹⁸**OH** was determined by analysis of the mass spectral peaks at M (178) and M + 2 (180); the intensity ratio M : (M + 2) was 100 : 7.75, showing no scrambling of the ether oxygen during MPLC and the cleavage reaction.

4–5. References

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the O–H between C(8)–C(1)–C(2) than between C(8)–C(1)–C(9). The
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Chapter 5

Solvolysis of (Z)– and (E)–2–Ethylidenebicyclo[3.2.2]non–1–yl Mesylates: Significant Relief of F–Strain Effect

Abstract

The rate of ethanolysis at 25 °C of (Z)–2–ethylidenebicyclo[2.2.2]oct–1–yl triflate ((Z)–**1**–OTf) is 217 times faster than that of its E isomer ((E)–**1**–OTf). On the other hand, more flexible (Z)–2–ethylidenebicyclo[3.2.2]non–1–yl mesylate ((Z)–**3**–OMs) solvolyzes 3.4 times slower than the E isomer ((E)–**3**–OMs). This striking contrast suggests the importance of a rigid structure and coplanar arrangement of the Z–methyl group and the reaction center for exerting the F–strain. The unexpectedly small Z/E rate ratio for **3** (0.30 ± 0.01) can be explained in terms of the relief of internal strain between the (E)–methyl group and C(3)–hydrogen on ionization of (E)–**3**. These experimental data are supported by molecular mechanics calculations ((MM2(87)) and semiempirical molecular orbital calculations (AM1).

5–1. Introduction

In Chapter 4, the first typical examples were described on the solvolysis rate enhancement ascribed to the relief of ground state F–strain.[1] MM2 calculations indicated that the origin of the F–strain effects is most probably attributed to the

repulsion between the (Z)–methyl group and the leaving group atom directly attached to the reaction center. We were also successful in a quantitative treatment of the F–strain effect for the trifluoroethanolysis of (Z)–2–ethylidene–1–adamantyl compounds by using MM2 steric energies and Hansch's Es values. This Chapter describes the solvolysis of (Z)– and (E)–2–ethylidenebicyclo[3.2.2]non–1–yl mesylates [(Z)– and (E)–3–OMs]. The more flexible bicyclo[3.2.2]nonyl system than the rigid bicyclo[2.2.2]octyl system showed a significant decrease in the F–strain effect in the Z substrate.

(Z)-1-OTf   (E)-1-OTf   2-OTf

(Z)-3-OMs   (E)-3-OMs   4-OMs
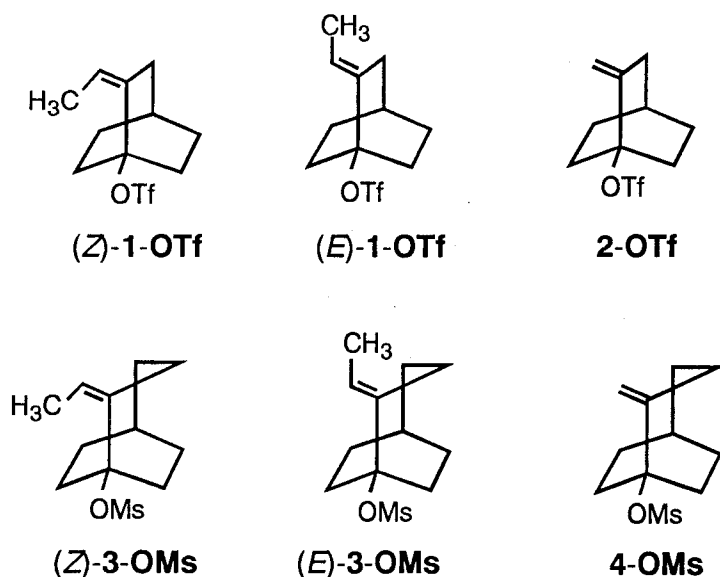
5-2. Results and Discussion

Synthesis. Mesylate (Z)-3-OMs was derived from the corresponding

bridgehead alcohol (*E*)–3–OH which was prepared in Chapter 2. Mesylates (*E*)–3–OMs and 4–OMs were described in Chapter 2.

Solvolysis Rates and Product Study. The solvolysis of (*Z*)–3–OMs was conducted in ethanol in the presence of 0.025 M 2,6–lutidine, and the rate was followed conductimetrically, showing good first–order kinetics over 80–90% reaction. The product of solvolysis of (*Z*)–3–OMs was studied in ethanol on 0.040 M substrate solution containing 0.050 M 2,6–lutidine at 25.0 °C for a period longer than 10 half–lives. GLC analysis of the reaction mixture and ^{13}C NMR analysis of the crude product showed that the corresponding bridgehead ethyl ether was the sole product. The solvolysis and product studies of (*E*)–3–OMs and 4–OMs were described in Chapter 2. The first–order rate constants and activation parameters are summarized in Table 5.1 together with the data for (*Z*)– and (*E*)–1–OTf and 2–OTf which were determined in Chapters 2 and 4.

Z/E Rate Ratios. In the more flexible 2–ethylidenebicyclo[3.2.2]non–1–yl system the *Z/E* rate ratio is 0.30 ± 0.01, which should be compared with that for the rigid 2–ethylidenebicyclo[2.2.2]oct–1–yl system (217 ± 6). This result shows that the F–strain effect was reduced in (*Z*)–2–ethylidenebicyclo[3.2.2]nonyl system. In addition, this striking contrast of *Z/E* rate ratios reveals the importance of a rigid structure and coplanar arrangement of the methyl group and the reaction center for exerting the marked F–strain effect in solvolysis.

In Chapter 2, it has been shown that the allylic conjugation in 4$^+$ is approximately 50% attained in the incipient carbocation from 4–OMs. A major origin for the faster rates of (*Z*)–3–OMs and (*E*)–3–OMs than 4–OMs by the factors of 77 ± 2 and 259 ± 7, respectively, is ascribed to enhanced allylic conjugation by the electron–donating character (inductive and hyperconjugative) of the methyl sub–

Table 5.1. The Rate Data of Ethanolysis of 2–Ethylidene and 2–Methylenebicyclo[3.2.2]non–1–yl Mesylates

compound	T (°C)	k (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (eu)	relative rate	
(Z)–1–OTf	25.0	$(4.04 \pm 0.04) \times 10^{-4}$[a]	23.8 ± 0.3	5.6 ± 0.5	1370 ± 100	217 ± 6
	40.0	$(2.89 \pm 0.03) \times 10^{-3}$[a]				
(E)–1–OTf	25.0	$(1.86 \pm 0.03) \times 10^{-6}$[b]	26.8 ± 0.2	5.1 ± 0.8	6.3 ± 0.5	1
	50.0	$(6.65 \pm 0.10) \times 10^{-5}$[b]				
2–OTf	25.0	$(2.95 \pm 0.18) \times 10^{-7}$[c]	27.1 ± 0.3	2.3 ± 1.0	1	
	50.0	$(1.09 \pm 0.04) \times 10^{-5}$[b]				
	75.0	$(2.40 \pm 0.04) \times 10^{-4}$[b]				
(Z)–3–OMs	25.0	$(5.49 \pm 0.05) \times 10^{-4}$[a]	23.2 ± 0.3	4.3 ± 1.0	77 ± 2	0.30 ± 0.01
	40.0	$(3.76 \pm 0.04) \times 10^{-3}$[a]				
(E)–3–OMs	25.0	$(1.86 \pm 0.02) \times 10^{-3}$[a]	21.6 ± 0.3	1.3 ± 1.0	259 ± 7	1
	40.0	$(1.11 \pm 0.01) \times 10^{-2}$[a]				
4–OMs	25.0	$(7.17 \pm 0.11) \times 10^{-6}$[b]	24.3 ± 0.3	-0.4 ± 0.8	1	
	50.0	$(1.86 \pm 0.03) \times 10^{-4}$[b]				

[a]Determined conductimetrically for 0.00020 M substrate in the presence of 0.025 M 2,6–lutidine within an experimental error of ±1.0%. [b]Determined titrimetrically for 0.020 M substrate in the presence of 0.025 M 2,6–lutidine within an experimental error of ±1.5%. [c]Extrapolated from data at other temperatures.

stituent in the transition state. The unexpectedly small Z/E rate ratio for **3**, which is even smaller than unity, can be explained in terms of the relief of internal strain between the (E)–methyl group and C(3)–hydrogen on ionization of (E)–**3**.

Semiempirical Molecular Orbital (AM1) and Molecular Mechanics Calculations (MM2). Semiempirical molecular orbital calculations were performed for bicyclo[3.2.2]nonyl and bicyclo[2.2.2]octyl systems by using AM1 through the AMPAC system.[2] AM1 calculations included the bridgehead carbocations and the corresponding hydrocarbons containing a hydrogen atom on the bridgehead position. Net atomic charges are summarized in Table 5.2. In Table 5.3 are summarized pertinent bond lengths in the allylic part C_α–C_β= C_γ with C_α being the bridgehead carbon. Molecular mechanics calculations (MM2(87))[3] were performed on (Z)–**3–OH** and (E)–**3–OH**. From the lack of parameters of a sulfonate, the calculations were carried out on the corresponding alcohols as surrogates by assuming *anti* conformation of the hydroxyl group, and lone pair electrons were placed on the oxygen atom.

Steric energies of (Z)–**1–OH** and (E)–**1–OH** calculated by MM2 were 23.7 and 21.2 kcal mol^{-1}, respectively, (Z)–**1–OH** being more strained than (E)–**1–OH** by 2.5 kcal mol^{-1}. About 80% of this energy is explicable in terms of the sum of repulsion between the (Z)–methyl group and the oxygen atom and thereby induced deformation of the skeleton. The origin of the F–strain in (Z)–**1–OMs** is most probably attributed to the repulsion between the (Z)–methyl group and the ether oxygen atom on the bridgehead position. AM1 calculations on (Z)–**1**$^+$ and (E)–**1**$^+$ indicated that charge delocalization is smaller in the two cations: the net atomic charge on the cationic carbon (C_α) is 0.403 for (Z)–**1**$^+$ and 0.402 for (E)–**1**$^+$. Furthermore, the very close values of $\Delta(C_\alpha$–$C_\beta)$ and also of $\Delta(C_\beta$=$C_\gamma)$ in bicyclo–

Table 5.2. Net Atomic Charges on the Carbons[a] for Bridgehead Cations Calculat–
ed by AM1

compound	C_α	C_β	C_γ
(Z)-1⁺	0.403	−0.275	−0.009
(E)-1⁺	0.402	−0.281	−0.003
2⁺	0.395	−0.245	−0.077
(Z)-3⁺	0.363	−0.252	0.039
(E)-3⁺	0.353	−0.247	0.045
4⁺	0.379	−0.231	−0.046

[a]C_α, C_β, and C_γ denote the carbons in the allylic part C_α–C_β=C_γ with C_α being the bridgehead carbon.

Table 5.3. Pertinent Bond Lengths for Bridgehead Cations and Corresponding Hydrocarbons Calculated by AM1

	bond length[a] (Å)				Δbond length[c]	
	cation		hydrocarbon[b]			
system	$C_\alpha-C_\beta$	$C_\beta=C_\gamma$	$C_\alpha-C_\beta$	$C_\beta=C_\gamma$	$\Delta(C_\alpha-C_\beta)$	$\Delta(C_\beta=C_\gamma)$
(Z)-1	1.4512	1.3353	1.4996	1.3383	−0.0484	−0.0030
(E)-1	1.4504	1.3373	1.5012	1.3388	−0.0508	−0.0016
2	1.4533	1.3287	1.5015	1.3325	−0.0482	−0.0038
(Z)-3	1.4312	1.3519	1.4974	1.3433	−0.0662	0.0086
(E)-3	1.4334	1.3541	1.5005	1.3433	−0.0671	0.0108
4	1.4395	1.3405	1.4990	1.3372	−0.0595	0.0033

[a]$C_\alpha-C_\beta$ and $C_\beta=C_\gamma$ denote the bonds in the allylic part $C_\alpha-C_\beta=C_\gamma$ with C_α being the bridgehead carbon. [b]The hydrocarbon containing a hydrogen on the bridgehead position. [c]The difference in the bond length between the cation and the corresponding hydrocarbon.

[2.2.2]octyl system indicate that the methyl substituent is essentially ineffective in stabilizing (Z)-$\mathbf{1^+}$ and (E)-$\mathbf{1^+}$.

On the other hand, MM2 calculations on (Z)-$\mathbf{3}$-$\mathbf{OH}$ and (E)-$\mathbf{3}$-$\mathbf{OH}$ gave similar respective steric energies of 26.6 and 26.3 kcal mol^{-1}, respectively, suggesting that F–strain is markedly reduced in (Z)-$\mathbf{3}$-$\mathbf{OMs}$. A close inspection of the MM2 steric energies has revealed that (E)-$\mathbf{3}$-$\mathbf{OH}$ is destabilized by the repulsive interaction amounting to 1.0 kcal mol^{-1} between (E)–methyl group and the hydrogen on the C(3) position. On ionization of (E)-$\mathbf{3}$-$\mathbf{OMs}$, the flexible carbocation (E)-$\mathbf{3^+}$ is expected to bend to attain greater allylic conjugation, thereby partially releasing the steric repulsion between the methyl group and the C(3)–methylene hydrogen. The net atomic charge on the cationic carbon calculated by AM1 is 0.353 for (E)-$\mathbf{3^+}$ and 0.363 for (Z)-$\mathbf{3^+}$. This means that the positive charge of (E)-$\mathbf{3^+}$ is more delocalized than that of (Z)-$\mathbf{3^+}$. This might be partly responsible for the faster rate of (E)-$\mathbf{3^+}$ than (Z)-$\mathbf{3^+}$. The much faster rates of (Z)-$\mathbf{3}$-$\mathbf{OMs}$ and (E)-$\mathbf{3}$-$\mathbf{OMs}$ than $\mathbf{4}$-$\mathbf{OMs}$ are explicable in terms of enhancement of allylic conjugation by the methyl substituent. This notion is supported by significant increases in $\Delta(C_\beta{=}C_\gamma)$ values and decreases in $\Delta(C_\alpha{-}C_\beta)$ values on going from the system $\mathbf{4}$ to (Z)-$\mathbf{3}$ or (E)-$\mathbf{3}$.
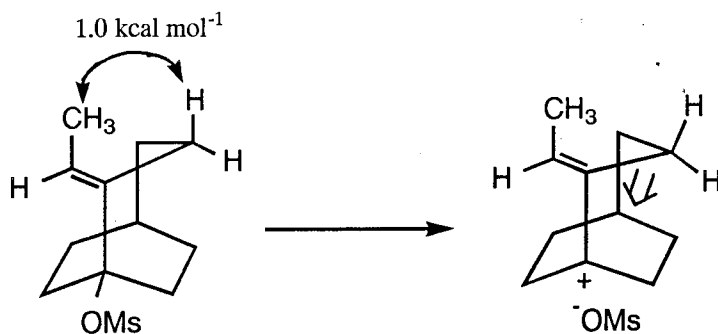
5–3. Experimental Section

IR spectra were recorded on a Hitachi 215 spectrophotometer. ^1H NMR spectra were recorded on a Hitachi R–24 (60 MHz) or JEOL FX90A (89.55 MHz) spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX90A (22.5 MHz) spectrometer. In all NMR measurements TMS was used as an internal standard. (Z)–2–Ethylidenebicyclo[3.2.2]nonan–1–ol ((Z)–**3**–**OH**) was prepared in Chapter 2. Ethanol was refluxed over magnesium ethoxide and distilled. All anhydrous solvents used for synthetic work were purified by standard procedures. Other commercially available reagents were of a reagent–grade quality and used as received.

(Z)–2–Ethylidenebicyclo[3.2.2]non–1–yl Mesylate ((Z)–3–OMs). The procedure in the literature was followed.[4] To a solution of (Z)–**3**–**OH** (0.100 g, 0.601 mmol) and triethylamine (0.094 g, 0.93 mmol) in CH_2Cl_2 (2.8 mL) was added methanesulfonyl chloride (0.076 g, 0.66 mmol) at –15 °C over 3h, and then the mixture was stirred at –10 °C for 50 min. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and then washed at 0 °C with water (2 × 8 mL), 10 % aqueous HCl (2 × 8 mL), saturated aqueous $NaHCO_3$ (2 × 8 mL), and saturated aqueous NaCl (8 mL). The resulting CH_2Cl_2 solution was stabilized by 2,6–lutidine (8 mg) and dried ($MgSO_4$). Evaporation of solvent afforded a mixture (0.145 g) of (Z)–**3**–**OMs** and (Z)–**3**–**OH** as a pale yellow liquid, the latter being present in 15% based on ^{13}C NMR spectrum. The crude product was used for solvolysis studies without further purification: ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 140.1, 94.3 (C), 123.2, 27.7 (CH), 37.3, 33.0, 31.9, 26.1 (CH_2), 40.7, 14.8 (CH_3).

Product of Solvolysis of (Z)–3–OMs in Ethanol. A solution of a mixture of (Z)–3–OMs and (E)–3–OH (85:15 in mol) (0.122 g) in 0.050 M 2,6–lutidine in ethanol (12.5 mL) was placed in a constant temperature bath (25.0 °C) for 3.5 h (10 half–lives). After most of the ethanol had been removed with a rotary evaporator, the residue was dissolved in ether (20 mL) and the ether solution washed with water (4 × 15 mL) and saturated aqueous NaCl (15 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane–ether (9:1, 7:3)) gave 1–ethoxy–(Z)–2–ethylidenebicyclo[3.2.2]nonane ((Z)–3–OEt) (0.065 g, 0.335 mmol) and (Z)–3–OH (0.010 g, 0.060 mmol) in this sequence. (Z)–3–OMs: colorless liquid; IR (CCl$_4$) 2930, 2820, 1650, 1450, 1390, 1130, 1085, 930 cm^{-1}; ^{1}H NMR (89.55 MHz, CDCl$_3$) δ 1.14 (t, 3 H, *J* = 7.0 Hz), 1.26–2.29 (m, 13 H), 1.79 (dt, 3 H, *J* = 7.3, 1.0 Hz), 3.33 (q, 2 H, *J* = 7.0 Hz), 5.40 (qt, 1 H, *J* = 7.1, 1.0 Hz); ^{13}C NMR (22.5 MHz, CDCl$_3$) δ 140.8, 79.1 (C), 121.9, 28.5 (CH), 56.3, 37.8, 34.6, 32.0, 25.9 (CH$_2$), 15.9, 13.9 (CH$_3$).

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Chapter 6

Steric Deuterium Isotope Effect in the Solvolysis of (Z)–[*Methyl*–d_3]–2–ethylidene–1–adamantyl Iodide Accelerated by F–Strain

Abstract

The deuterium isotope effect in the solvolysis of (Z)– and (E)–[*methyl*–d_3]–2–ethylidene–1–adamantyl mesylates [(Z)– and (E)–**1d**–OMs] and iodides [(Z)– and (E)–**1d**–I] was studied in 2,2,2–trifluoroethanol at 25.0 °C for mesylates and at 50.0 °C for iodides. For the mesylates, which show a relatively small F–strain effect, the $(Z/E)_H$ rate ratio (117 ± 1) is essentially identical with the $(Z/E)_D$ rate ratio (116 ± 1) at 25.0 °C. On the other hand, for the iodides, which show a large F–strain effect, the $(Z/E)_H$ rate ratio (5413 ± 57) is greater than the $(Z/E)_H$ rate ratio (5040 ± 58) at 50.0 °C. This indicates that (Z)–**1h**–I has greater F–strain effect than (Z)–**1d**–I in the ground state. These results again confirm that the F–strain effect in the (Z)–2–ethylidene–1–adamantyl derivatives exists between the (Z)–methyl group and the leaving group atom directly attached to the reaction center.

6–1. Introduction

Deuterium substitution in organic compounds at the β or more distant positions with respect to the reaction center exerts isotope effects on their reactivity in three different ways, i.e., hyperconjugative, inductive, and steric effects. The steric effect was proposed by Bartell[1] more than three decades ago,[1] and many pieces of

supporting evidence have been reported.[2] According to this proposal, protium atoms behave as if they were larger than deuterium atoms as a consequence of the greater amplitude of vibration of their bonds.[1] Therefore, if a reaction proceeds with relief of ground–state strain, the protium derivatives should react at a faster rate than the corresponding deuterium derivatives.

This theory has been applied to solvolysis to support the importance of steric acceleration of ionization.[3-5] However, the difference in hyperconjugative and inductive effects between protium and deuterium always had to be taken into account.[2] To the author's knowledge, only three examples relate to kinetic *steric* isotope effects in solvolysis. Karabatsos and coworkers[3] studied the solvolysis of [8–(*methyl–d_3*)]–1–naphthoyl chloride where the hyperconjugative effect is not transmitted to the cationic center. The isotope effect, $k_H/k_D = 1.029$, was interpreted to show non–bonded interaction in the ground state.[3] Fry and Badger[4] examined the solvolysis of [2–(*tert–butyl–d_9*)]–2–adamantyl *p*–nitrobenzoate, and the isotope effect, $k_H/k_D = 1.1072$, was explained similarly. Creary *et.al.*[5] studied the solvolysis of 3–methyl–*exo*–tricyclo[3.2.1.0^{2,4}]oct–*exo*–3–yl tosylate and the *methyl–d_3* analogue. The isotope effect, $k_H/k_D = 1.33$ at 50.0 °C, was interpreted in terms of non–bonded interaction between the 3–methyl group and the C–8 hydrogen.[5] In these three studies, however, the intramolecular non–bonded interaction examined was mainly the back–side strain (B–strain) or, most probably, a combination of both the back–side and front–side (F–strain) effects.

In Chapter 4, the first typical examples were described on the solvolysis rate enhancements ascribed to the relief of F–strain between an alkyl group and the leaving group atom directly attached to the reaction center.[6] We succeeded also in a quantitative treatment of solvolysis rate enhancement by using MM2 steric energies.[6d] This Chapter describes further supporting evidence for the F–strain effect

in the solvolyses of (Z)–2–ethylidene–1–adamantyl derivatives. The rates of solvolysis in 2,2,2–trifluoroethanol (TFE) were studied for the mesylates and iodides of the (Z)– and (E)–[*methyl–d₃*]–2–ethylidene–1–adamantyl and the corresponding *methyl–d₀* systems. The results for the iodides provide the first example in which the kinetic steric isotope effect has been observed in the F–strain effect in solvolysis.
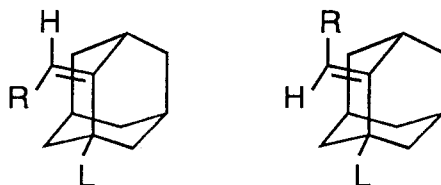
R = CH₃   (Z)-1h-L   (E)-1h-L

R = CD₃   (Z)-1d-L   (E)-1d-L

(L = OMs, I)

6–2. Results

Isotopic Purity. For introducing the *methyl–d₃* group, [*methyl–d₃*]ethylidenetriphenylphosphorane containing 99 atom % deuterium was used. No evidence for isotope scrambling was found in the final products by NMR and mass spectral analyses.

Synthesis. The unlabelled mesylates ((Z)– and (E)–1h–OMs) and iodides ((Z)– and (E)–1h–I) were prepared in Chapter 4. The labeled mesylates ((Z)–1d–

Scheme 6.1

(Z)-**1d-OTBDMS**   (E)-**1d-OTBDMS**

3

10   :   1

$Z:E = 7:3$ $\xrightarrow{\textit{n}\text{-Bu}_4\text{NF}}{\text{THF}}$

(Z)-**1d-OH**   (E)-**1d-OH**

Scheme 6.2

8

(Z)-**1h-I**   (E)-**1h-I**

$Z:E = 95:5$

154
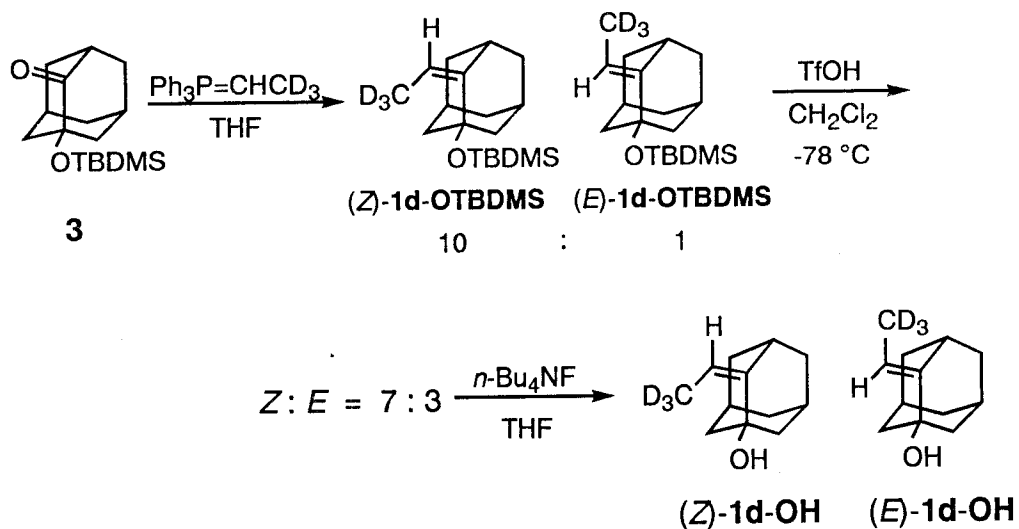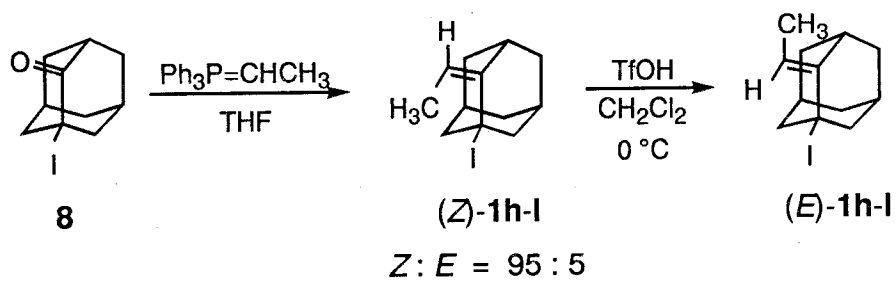
OMs) was prepared by using [*methyl–d₃*]ethylidenetriphenylphosphorane at the Wittig ethylidenation step. For the preparation of (*E*)-**1d–OMs**, the olefin inversion of (*Z*)-**1d–OTBDMS** was employed. Treatment of a 10:1 mixture of (*Z*)- and (*E*)-**1d–OTBDMS** with 0.01 M trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 at −78 °C gave a 7:3 mixture of (*Z*)- and (*E*)-**1d–OTBDMS**, which was then desilylated and the *E* alcohol ((*E*)-**1d–OH**) was separated chromatographically (Scheme 6.1). The corresponding mesylate (*E*)-**1d–OMs** was prepared in the usual manner.

The labeled iodides were prepared by using [*methyl–d₃*]ethylidenetriphenylphosphorane at the Wittig ethylidenation step as a 95:5 mixture of (*Z*)- and (*E*)-**1d–I**. Treatment of this mixture with 0.01 M TfOH in CH_2Cl_2 at 0 °C gave essentially pure (*E*)-**1d–I** (Scheme 6.2).

Solvolysis Studies. In all the solvolysis experiments, substrates which had been purified by medium–pressure liquid chromatography (MPLC) at −40 °C or recrystallization were used. Accurate determination of rates at 25.0 °C was feasible for the mesylates owing to the relatively small *Z/E* rate ratio (117 ± 1 for unlabelled mesylates), but it was difficult for the iodides because of the very slow rates for the *E* isomers. Therefore, the isotope effect for the mesylates was evaluated at 25.0 °C and that for the iodides at 50.0 °C. The solvolysis was conducted in anhydrous TFE in the presence of an excess of 2,6–lutidine and the rates were determined conductimetrically or titrimetrically. In the former method, the concentration of hydrogen iodide showed a linear correlation with conductivity over an [HI] range of 0 – 3.24 × 10^{-3} M in the presence of 9.52 × 10^{-3} M 2,6–lutidine in TFE at 50.0 °C. In contrast, methanesulfonic acid (MsOH) showed a slightly curved plot over an [MsOH] range 0 – 7.11 × 10^{-4} M in the presence of 1.19 ×

Table 6.1. Solvolysis Rates, CD_3/CD_3 Rate Ratios and Z/E Rate Ratios for 2–Ethylidene–1–adamantyl Derivatives in 2,2,2–Trifluoroethanol

compound	temp (°C)	k (s^{-1})	CD_3/CH_3 rate ratio[a]	Z/E rate ratio[a] for CH_3	Z/E rate ratio[a] for CD_3
(E)–1h–OMs	25.0	$(3.961 \pm 0.023) \times 10^{-4\,b,c}$	1	1	
(E)–1d–OMs	25.0	$(3.998 \pm 0.018) \times 10^{-4\,b}$	1.009 ± 0.010		1
(Z)–1h–OMs	25.0	$(4.646 \pm 0.022) \times 10^{-2\,b,d}$	1	117 ± 1	
(Z)–1d–OMs	25.0	$(4.624 \pm 0.023) \times 10^{-2\,b}$	0.995 ± 0.013		116 ± 1
(E)–1h–I	50.0	$(2.507 \pm 0.019) \times 10^{-6\,e,f}$	1	1	
(E)–1d–I	50.0	$(2.597 \pm 0.021) \times 10^{-6\,e}$	1.036 ± 0.016		1
(Z)–1h–I	50.0	$(1.357 \pm 0.004) \times 10^{-2\,g}$	1	5413 ± 57	
(Z)–1d–I	50.0	$(1.322 \pm 0.004) \times 10^{-2\,g}$	0.974 ± 0.008		5090 ± 58

[a]The ratios are at 25.0 °C for mesylates and at 50.0 °C for iodides. [b]Determined conductimetrically for 0.00074 M substrate in the presence of 0.00119 M 2,6–lutidine. Error is expressed as avarage deviation for three runs ($r > 0.9998$). [c]The reported value which was determined for 0.00020 M substrate in the presence of 0.00119 M 2,6–lutidine is 3.51×10^{-2} s^{-1}; see reference 6b. [d]The reported value which was determined for 0.00020 M substrate in the presence of 0.00119 M 2,6–lutidine is 4.41×10^{-2} s^{-1}; see reference 6b. [e]Determined titrimetrically by a single run for 0.020 M substrate in the presence of 0.025 M 2,6–lutidine ($r > 0.9998$). Error is expressed as a standard deviation at the 95% confidence limit ($n = 24$). [f] A reported value is 2.48×10^{-6} s^{-1} under the same conditions; see reference 6d. [g]Determined conductimetrically for 0.00491 M substrate in the presence of 0.00952 M 2,6–lutidine. Error is expressed as anerage deviation for three runs ($r > 0.9999$).

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10^{-3} M 2,6–lutidine in TFE at 25.0 °C, although the first–order plot obtained by conductivity measurements was satisfactorily linear. Consequently, for the solvolysis of mesylates the conductivity was converted into concentration and used for rate calculations. The rate constants obtained from three runs for the mesylates at 25.0 °C were accurate to within ±0.6%.

The rates for (E)–**1h–I** and (E)–**1d–I** were too slow, with a half–life of *ca* 3 days at 50.0 °C. Therefore, their solvolysis was followed titrimetrically, and the rates were calculated for a single run by using 24 points with an estimated error of ±0.6% at a 95% confidence limit. The rates for (Z)–**1h–I** and (E)–**1d–I** were determined conductimetrically at 50.0 °C. The rates obtained from three runs were accurate to within ±0.3%. All the rate data are summarized in Table 6.1. All the substrates used in this study gave the corresponding bridgehead trifluoroethyl ether as the sole product (>99% by GLC) in trifluoroethanolysis.

6–3. Discussion

F–strain Effect in the Z Substrates. In Chapter 4, it was described that the Z/E rate ratio in the solvolysis of (Z)– and (E)–**1h–L** increases with increase in the size of the leaving group L, i.e., 117 ± 1 (L = OMs) (a previously reported value[6b,c,d] is 126 ± 3), 1020 ± 60 (L = Cl), 2230 ± 90 (L = Br), and 9680 ± 400 (L = I) in TFE at 25.0 °C.[6d] A plot of 1.36 × log[k_Z/k_E] values against MM2 steric energy differences between the Z and E isomers gives a good linear correlation with a slope of 0.83.[6d] Consequently, it was concluded that the origin of the large Z/E rate ratios arises principally from the relief of the strain between the (Z)–methyl group and the leaving group atom directly attached to the reaction center on ionization.[6d] The F–strain effect in the (Z)–2–ethylidene–1–adamantyl system

(Z)–**1h–L** is in contrast to that in *trans,trans,trans*–perhydro–9b–phenalyl *p*–nitrobenzoate (**2**),[7] where the F–strain has been found to exist between the axial hydrogen and the carbonyl oxygen atom (and/or the aryl group).

(Z)-**1h-L**   (E)-**1h-L**   **9**
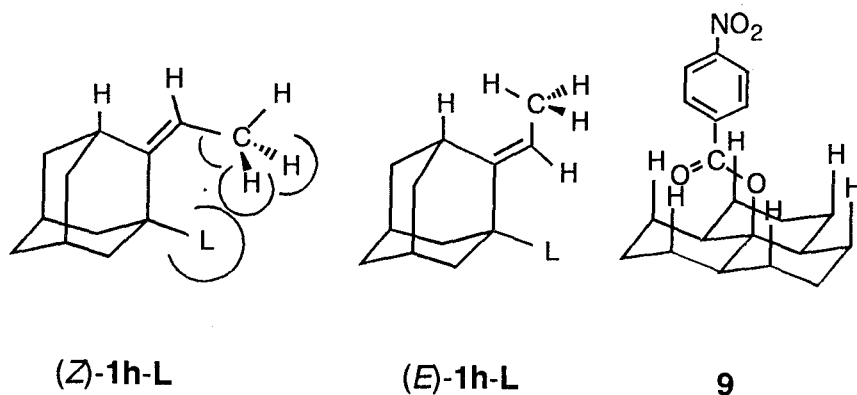
Kinetic Isotope Effects in the E Substrates. Obviously, there is no steric interaction between the (E)–methyl and the leaving group. Therefore, should a kinetic isotope effect be observed, it would to a first approximation be ascribed to electronic effects. Partial relief of steric repulsion between the (E)–methyl and the hydrogen at the 3–position is expected on ionization owing to flattening of the reaction center. However, it would be slight. If such a back–strain (B–strain) effect were operative, it would work to decelerate the rate of solvolysis of (E)– *methyl–d₃* derivatives because of the smaller steric requirement of deuterium than protium. In fact, we observed k_D/k_H ratios greater than unity: 1.009 ± 0.010 for (E)–**1–OMs** at 25.0 °C and 1.036 ± 0.016 for (E)–**1–I** at 50.0 °C.

It has been well recognized that protium is hyperconjugatively more electron donating but inductively less so than deuterium.[8] Therefore, the k_D/k_H ratios greater than unity for the E substrates would most probably be attributed to the

inductive effect. The greater k_D/k_H ratio of the E iodides than that of the E mesylates would be rationalized by assuming a later transition state (more progressed ionization) for the iodides because of their lower reactivity. The more progressed ionization in the transition state would be more susceptible to inductive effects to give a greater k_D/k_H ratio.

Kinetic Isotope Effects in the Z Substrates. In contrast to the E substrates, both the Z mesylates and Z iodides gave k_D/k_H ratios smaller than unity: 0.995 ± 0.013 for **(Z)-1-OMs** at 25.0 °C and 0.974 ± 0.008 for **(Z)-1-I** at 50.0 °C. In the present adamantyl system, hyperconjugative effects are precluded, since allylic conjugation in the transition state is prohibited for geometric reasons.[9] As stated above, an inductive effect would have resulted in k_D/k_H being greater than unity. Only steric reasons based on the smaller steric requirement of deuterium than protium can account for the results. The slower rates of the deuterium than those of protium compounds provide strong evidence for the presence of F–strain in the ground state of the Z substrates and its relief on ionization.

Kinetic Isotope Effects on the Z/E Rate Ratios. The Z/E rate ratio presumably includes various factors, such as steric, electronic and solvation effects. However, it would be reasonable to assume that the change of the stability of carbocations on replacement of CH_3 with CD_3 would be of similar magnitude for the Z and E carbocations. Solvation of carbocations would be assumed to be essentially constant even on replacing CH_3 with CD_3. These premises may be supported by the fact that the mesylates, which show a relatively small F–strain effect, exhibit essentially identical Z/E rate ratios for protium and deuterium (117 ± 1 and 116 ± 1, respectively). Hence the difference between the $(Z/E)_H$ and $(Z/E)_D$ rate ratios would be a good measure of the difference in the F–strain effect between CH_3 and

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CD_3. In contrast to the mesylates, for the iodides where the F–strain effect is enormous, the $(Z/E)_H$ rate ratio is greater than the $(Z/E)_D$ rate ratio by a factor of 1.063 ± 0.024 (5413 ± 57 vs 5090 ± 58). This indicates that (Z)–**1h**–**I** has greater F–strain than (Z)–**1d**–**I** by as much as 0.04 ± 0.02 kcal mol^{-1}.

Previously, we have shown from solvolysis rates and MM2 calculations that the net F–strain in (Z)–**1h**–**I** of *ca* 4.5 kcal mol^{-1} decreases to *ca* 1.5 kcal mol^{-1} in (Z)–**1h**–**OMs**.[6d] Since the steric isotope effect would decrease similarly, (Z)–**1h**–**OMs** is expected to have greater F–strain than (Z)–**1d**–**OMs** by *ca* 0.013 kcal mol^{-1}. This predicts that the $(Z/E)_H$ rate ratio is greater than the $(Z/E)_D$ ratio by 1%, in good agreement with the rate ratios of 117 ± 1 and 116 ± 1 for $(Z/E)_H$ and $(Z/E)_D$, respectively.

On the basis of Bartell's procedure,[1] we estimated the non–bonded isotope effect in (Z)–2–ethylidene–1–adamantyl derivatives. From lack of the parameters for H⋯I interaction, the calculations were performed for H⋯O, H⋯Cl, and H⋯Br interactions for the two methyl–hydrogen atoms in the close positions (the interaction between the furthest methyl–hydrogen and the bridgehead heteroatom was negligibly small) by using the potential function of Scott and Scheraga[10] and the geometries which were obtained by MM2(87) calculations.[11] The calculated non–bonded isotope effects, 0.007, 0.008, and 0.011 kcal mol^{-1} for (Z)–**1**–**OH** (in place of (Z)–**1**–**OMs**), (Z)–**1**–**Cl**, and (Z)–**1**–**Br**, respectively, are in line with the observed value for (Z)–**1**–**I** of 0.04 ± 0.02 kcal mol^{-1}. MM2(87) calculations also showed reasonable values of 0.012, 0.017, 0.020, and 0.023 kcal mol^{-1} for (Z)–**1**–**OH**, (Z)–**1**–**Cl**, (Z)–**1**–**Br**, and (Z)–**1**–**I**, respectively. Hence both Bartell's theory and MM2 appear to give reasonable estimates of steric deuterium isotope effects in solvolysis.

6–4. Conclusion.

The notion that the relief of F–strain between the leaving group atom direct-ly attached to the reaction center and the (Z)–methyl group in (Z)–2–ethylidene–1–adamantyl derivatives has again been supported by applying steric kinetic isotope effects. The results also represent the first example of the demonstration of the deuterium kinetic isotope effect on F–strain in solvolysis.

6–5. Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1640 spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi R–24 (60 MHz) or JEOL FX90A (89.55 MHz) spectrometer with TMS as internal standard. ^{13}C NMR spectra were obtained on a JEOL FX90A (22.5 MHz) spectrometer with the δ values being calculated on the basis of the central line of the chloroform–d triplet (77.0 ppm). Mass spectra were recorded on a Hitachi M–80 gas chromatograph–mass spectrometer equipped with a Hitachi M–003 data processor. 2,2,2–Trifluoroethanol (TFE) was stored over 5A molecular sieves and distilled. The other solvents used for syntheses were dried by standard methods. Elemental analyses were performed by the Microanalytical center, Kyoto Universi-ty, Kyoto.

(Z)– and (E)–[Methyl–d_3]–2–ethylidene–1–adamantyl Mesylates ((Z)– and (E)–1d–OMs). Ethyl–2,2,2–d_3–triphenylphosphonium bromide was prepare following a literature procedure.[11] A mixture of ethyl–2,2,2–d_3 bromide (12.3 g, 0.11 mol), which was prepared from ethyl–2,2,2–d_3 alcohol (Aldrich, 99 atom %

D) and PBr$_3$, and triphenylphosphine (28.1 g, 0.11 mol) in benzene (27 mL) was heated at 135 °C in an autoclave for 21 h. The resulting crude solid was recrystallized from water and dried to give ethyl–2,2,2–d_3–triphenylphosphonium bromide (39.8 g, 99%). ^{1}H NMR analysis showed no signal at δ 1.40 due to unlabelled ethyltriphenylphosphonium bromide within a detection limit (2%).

To a suspension of ethyl–2,2,2–d_3–triphenylphosphonium bromide (7.45 g, 20.0 mmol) in THF (46 mL) was added dropwise 1.6 M n–BuLi in hexane (15 mL) at room temperature under N$_2$. After stirring for 30 min, a solution of 2–oxo–1–adamantyl *tert*–butyldimethylsilyl ether (2.90 g, 10.3 mmol) in THF (36 mL) was added. The mixture was stirred at room temperature for 19 h and then at reflux for 2 h. The reaction mixture was poured into ice–water (80 mL) and extracted with ether (3 × 60 mL). The combined extracts were washed with water (2 × 70 mL) and 10% aqueous NaCl (3 × 70 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded a 10:1 mixture of (Z)– and (E)–1d–OTBDMS (1.32 g, 43%).

To above mixture (0.600 g, 2.06 mmol) of (Z)– and (E)–1d–OTBDMS was added 0.01 M TfOH in CH$_2$Cl$_2$ (20 mL) at –78 °C, and the resulting solution was stirred for 1 h. The reaction mixture was diluted with ether (40 mL), washed with saturated aqueous NaHCO$_3$ (20 mL) and saturated aqueous NaCl (20 mL) and dried (MgSO$_4$). Evaporation of solvent with a rotary evaporator afforded a mixture of (Z)– and (E)–1d–OTBDMS in an approximate ratio of 68:32 as estimated by ^{1}H NMR. To a solution of the above mixture (1.16 g, 3.91 mmol) of (Z)– and (E)–1d–OTBDMS in THF (18 mL) was added a 1.0 M solution of n–Bu$_4$NF in THF (8.0 mL) and the resulting mixture was refluxed for 17 h under N$_2$. The reaction mixture was stirred with 4% aqueous NH$_4$Cl (20 mL) and extracted with ether (3 × 30 mL). The combined extracts were washed with water (2 × 30 mL) and 10%

aqueous NaCl (2 × 30 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane–ether (9:1)) afforded (Z)–**1d–OH** (0.497 g, 70%) and (E)–**1d–OH** (0.113 g, 16%). Mass spectra for the labeled alcohol gave a molecular ion peak at *m/z* 181 which is greater than the molecular ion peak for the unlabelled alcohol by 3 mu. Analysis of the peak intensities of *m/z* 181 and 178 for the labeled alcohol indicated that the isotopic purity was greater than 99%.

A solution of (Z)–**1d–OH** (0.150 g, 0.83 mmol) in THF (1.5 mL) was treated with 1.6 M *n*–BuLi in hexane (0.53 mL) and then with methanesulfonyl chloride (MsCl) (0.096 g, 0.83 mmol) at –50 °C for 4.5 h. The usual work–up followed by MPLC (SiO$_2$, hexane–ether (9:1)) at –40 °C afforded (Z)–**1d–OMs** (0.092 g, 43%) and unreacted (Z)–**1d–OH** (0.057 g, 38%) in this sequence.

(E)–**1d–OMs** was also synthesized in a similar way from (E)–**1d–OH** (0.104 g, 0.57 mmol) and 1.6 M *n*–BuLi in hexane (0.36 mL) and MsCl (0.065 g, 0.57 mmol). Separation of the crude product by MPLC (SiO$_2$, hexane–ether (9:1)) gave (E)–**1d–OMs** (0.081 g, 54%) and (E)–**1d–OH** (0.048 g, 46%) in this sequence.

(Z)–[Methyl–d$_3$]–2–ethylidene–1–iodoadamantane ((Z)–1d–I). To a suspension of ethyl–2,2,2–d$_3$–triphenylphosphonium bromide (3.65 g, 9.75 mmol) in THF (23 mL) was added dropwise 1.6 M *n*–BuLi in hexane (6.1 mL) at room temperature under N$_2$. After stirring for 30 min, a solution of 1–iodo–2–adamantanone (1.40 g, 5.07 mmol) in THF (18 mL) was added. The resulting mixture was stirred for another 15 min, poured into ice–water (80 mL) and extracted with ether (3 × 90 mL). The combined extracts were washed with water (2 × 90 mL) and 10% aqueous NaCl (2 × 90 mL) and dried (MgSO$_4$). Evaporation of solvent followed by MPLC (SiO$_2$, hexane) afforded (Z)–**1d–I** (0.950 g, 64%).

(E)-[Methyl-d₃]-2-ethylidene-1-iodoadamantane (E)-1d-I). A solution of (*Z*)-**1d-I** (0.630 g, 2.16 mmol) in 0.01 M TfOH in CH_2Cl_2 (22 mL) at 0 °C for 1 h. The reaction mixture was diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and saturated aqueous NaCl (2 × 20 mL) and dried ($MgSO_4$). Evaporation of solvent with a rotary evaporator afforded essentially pure (*E*)-**1d-I** (0.594 g, 94%).

Kinetic Methods. For the titrimetric method, the solvolysis was conducted in the presence of 0.025 M 2,6-lutidine with 0.020 M substrate concentration in TFE. The developed acid was titrated with 0.01 M KOH–ethanol by using bromcresol green–methyl red as indicator after an aliquot in an ampule (1.000 mL) had been quenched in 10 mL of cold acetone. Good first–order kinetics were obtained over three half–lives.

For the conductimetric method, a conductivity cell (cell constant 0.1005) was filled with TFE solution (20 mL) containing 0.00119 M 2,6–lutidine (for mesylate solvolysis) or 0.00952 M 2,6–lutidine (for iodide solvolysis) and the system was thermally equilibrated. A 20 µl volume of THF solution containing a substrate at a concentration of 25–60% was injected under magnetic stirring and the specific conductance (κ) of the reaction mixture was recorded against reaction time.

Treatment of Conductance Data. The specific conductance (κ) of methanesulfonic acid (MsOH) in TFE in the presence of 0.00119 M 2,6–lutidine was measured in the concentration range of MsOH from 0 to 7.11 × 10⁻⁴ M. The plot of κ vs concentration of MsOH (*C*) was non–linear. The conductance data were fitted with the least–squares method to the equation $\kappa = \alpha + \beta C + \gamma C^{1/2}$, giving $\alpha =$

4.23, $\beta = 4.73 \times 10^5$ and $\gamma = -1.71 \times 10^3$. The $C_{calc.}$ values calculated from measured κ values by using this equation gave good first–order kinetics. For hydrogen iodide, the plot of κ vs C was linear within the concentration ranges of this work. Therefore, first–order rate constants were determined by using measured κ values.

6–6. References

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