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Accounts

Synthesis of Bifunctional Polycyclic Compounds and Their Application to Mechanistic Studies of Solvolysis Reactions

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The 1-adamantyl cation reacts with carbon monoxide and adamantane in the presence of a superacid to give 3-hydroxy-4-homoadamantyl 1-adamantanecarboxylate in good yields. This finding has permitted the development of a synthetic route by using ring-expansion of bridgehead aldehydes with benzoic trifluoromethanesulfonic anhydride to give various bicyclic and tricyclic 1,2-diols having different ring flexibility. The diols are transformed to bridgehead compounds having an oxo or a methylene substituent on the vicinal position, which can be used as substrates showing different degrees of π-conjugation between these substituents and the bridgehead cationic center in the transition state of solvolysis. The solvolysis rate ratio of 2-methylene vs. parent bridgehead compounds markedly increases with the ring-flexibility, indicating that the allylic conjugation can be enhanced by increasing ring flexibility. However, the rate ratios for 2-oxo (or α-carbonyl) vs. parent bridgehead compounds are essentially constant, irrespective of the ring flexibility, suggesting the unimportance of π conjugative stabilization of α-carbonyl carbocations. On the contrary, 3-oxo (or β-carbonyl) bridgehead compounds solvolyze markedly faster than expected and support the proposal of pC(1)$^+ \leftrightarrow \sigma$C(2)C-(3)$\leftrightarrow n$(CO) hyperconjugative interaction. The comparison of the solvolysis rates of (*Z*)- and (*E*)-2-ethylidene bridgehead compounds having a rigid structure provides a new method to evaluate the importance of F-strain effects in solvolysis.

Polycyclic compounds have been making a great contribution to the progress of carbocation chemistry. The first carbocation intermediate was postulated by Meerwein in the 1920's for the Wagner–Meerwein rearrangement of camphene hydrochloride to isobornyl chloride (Chart 1).[1] The most intensively studied carbocation in the history of solvolysis would be the 2-norbornyl cation, which was first proposed to have a bridged (nonclassical) structure on the basis of kinetic and stereochemical studies.[2,3] The question whether the 2-norbornyl cation is an energy-minimum nonclassical species or a pair of rapidly equilibrating classical ions has been a long-standing problem in the field of physical organic chemistry (Chart 2).[4] Both a recent theoretical study on the solvolysis intermediate[5] and solid-state ^{13}C NMR studies of the salt crystals in the range 5—200 K[6] suggest the nonclassical structure.

In contrast to the ready occurrence of the Wagner–Meerwein rearrangement of the carbocations where the cationic center is located on the C(2) position, the neighboring carbon participation is minimized in bridgehead carbocations. In addition, the solvolysis of a bridgehead compound is free from nucleophilic solvent participation from the rear side. Therefore, bridgehead substrates have very often been used for the studies of structure-reactivity relations in S_N1 solvolysis and substituent effects on the stability of carbocations. The effects of a substituent located at the β,[7a)] γ,[7a,8)] or δ[7b)] position on the stability of a carbocation have been examined by using solvolysis of bridgehead substrates of the bicyclo[2.2.2]octyl[7)] and adamantyl[8)] systems (Chart 3). The solvolysis reactivities of bridgehead compounds have successfully been used to correlate the theoretically calculated strain energies and stabilities of bridgehead carbocations.[9—11)] Various bridgehead carbocations have been generated in superacids and observed by

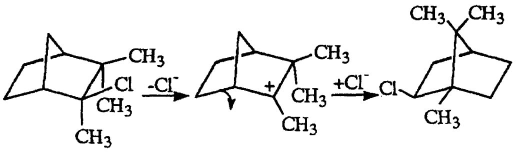


Chart 1.

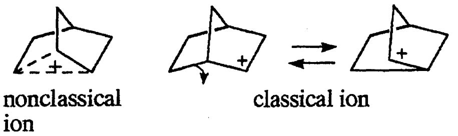


Chart 2.

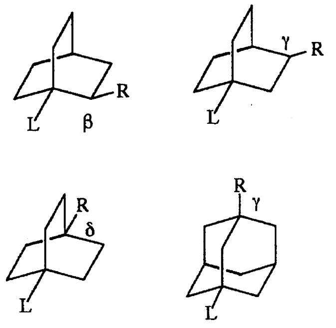


Chart 3. (L=leaving group).

NMR.[12] Recently, highly strained bridgehead carbocations such as the cubyl[13,14] and the bicyclo[1.1.1]pent-1-yl[15,16] cations have been generated as solvolysis intermediates and subjected to theoretical studies. In the fields other than the carbocation chemistry, many bridgehead halides have been subjected to $S_{RN}1$ reactions[17,18] and also used to generate bridgehead olefins.[19,20]

Despite the prosperous uses of the bridgehead compounds in carbocation chemistry, it was surprising that no general methods to synthesize 1,2-bifunctional polycyclic compounds had been reported until we found the ring-expansion of various bridgehead aldehydes with benzoic trifluoromethanesulfonic anhydride (Chart 4).[21,22] This method was expected to provide a new route to various bridgehead compounds having a functional group on the vicinal position. Therefore, we wished to make the best use of these compounds to shed light on some intriguing problems in physical organic chemistry. The subjects we selected were (i) examination of the stability of α- and β-carbonyl carbocations, (ii) design of typical substrates for quantitative evaluation of the F-strain effects in solvolysis, (iii) degenerate secondary and tertiary 4-homoadamantyl carbocations, and (iv) generation of 2-substituted adamantenes. In this Account we describe the development of a new method for 1,2-bifunctional polycyclic compounds, and some mechanistic studies on two of the above subjects, (i) and (ii).

In the 1980's, much attention was focused on the carbocations that are markedly destabilized by strongly electron-withdrawing groups such as a cyano, a trifluoromethyl, or a carbonyl.[23] Among the three substituents, the trifluoromethyl group is a rather simple, inductively electron-withdrawing group. On the contrary, it has been proposed that the cyano and carbonyl substituents directly attached to the cationic carbon significantly stabilize the carbocation by the mesomeric electron donating effect (**1a**↔**1b**, **2a**↔**2b**) just like allylic conjugation (**3a**↔**3b**) to such an extent as to offset the inductive electron-withdrawing effect (Chart 5). In those days we were working on the one-electron reducibility of α-carbonyl cations,[24] and have succeeded in isolating (4-methoxybenzoyl)[bis(4-methoxyphenyl)]methylium ion (**4^+**) as an SbF_6^- salt (Chart 6).[25] Although this salt was isolatable, we had the impression that the cation would not be kinetically so stable: it readily decomposed to give 2,3-bis(4-methoxyphenyl)-6-methoxybenzofuran (**5**) either in the solid state or in solution at or above room temperature (Chart 6).[25] Consequently, we decided to carry out a series of solvolysis studies to examine quantitatively the contribution of the carbonyl π-conjugation (**2a**↔**2b**) in stabilizing α-carbonyl carbocations in comparison with the allylic conjugation (**3a**↔**3b**).[26—29]

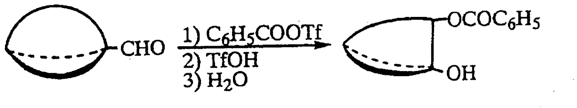


Chart 4.

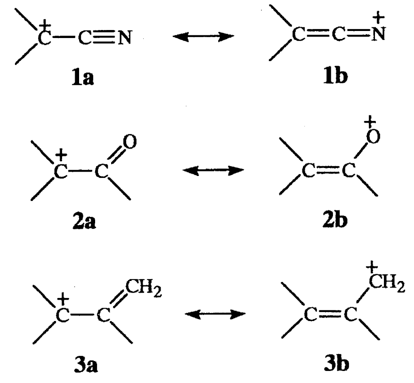
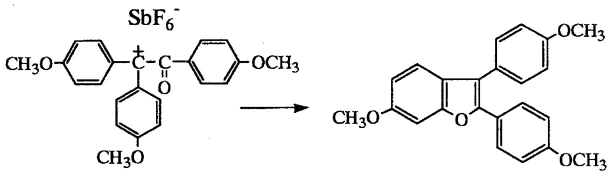


Chart 5.

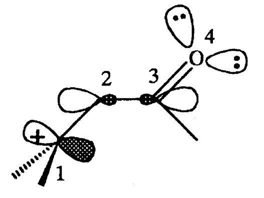
Another interesting feature of the carbonyl substituent is noted when it is attached to a β-carbon. In several reports published since 1978, Carrupt and Vogel have reported that a β-carbonyl cation may be stabilized by a through-bond $pC(1)^+ \leftrightarrow \sigma C(2)C(3) \leftrightarrow n(CO)$ hyperconjugative interaction between the oxygen lone pair and a vacant p orbital of a cationic carbon (Chart 7).[30] However, no quantitative experimental work has been published for evaluating the stabilizing effect of the through-bond hyperconjugative interaction. We showed that this effect amounts to the acceleration of solvolysis rates of bridgehead substrates by a factor of 10^3—10^4 when all the interacting orbitals are coplanar.[31—33]

The third problem was the search of a typical system that would show a large acceleration of solvolysis rate due to the F-strain (front strain) between the halogen leaving group



4^+ SbF_6^- **5**

Chart 6.



$pC(1)^+ \leftrightarrow \sigma C(2)C(3) \leftrightarrow n(CO)$

Chart 7.

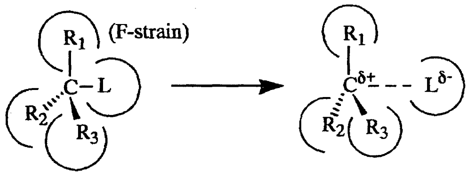


Chart 8.

and the skeleton (Chart 8). Although the theory had been proposed in the 1950's by Brown based on the well-known work on the alkylborane-amine complex formation,[34] no quantitative work has been reported on the F-strain effect of halogens with different sizes on solvolysis rates.[35] We were able to give some typical examples by utilizing the solvolysis of bridgehead compounds with markedly rigid frameworks.[36—41]

Throughout the three mechanistic studies described in this Account, we mainly used the bridgehead solvolyses of polycyclic compounds. Except for the work on the through-bond conjugation, all the substrates were prepared by the methods developed in our laboratories. Therefore, we wish to describe first the development of the new synthetic method.[21,22,42—44]

A Clue to the Development of a New Ring Expansion Reaction

Ring Expansion of 1-Adamantyl Cation in the Reaction with Carbon Monoxide. The carbonylation of carbocations with carbon monoxide under strongly acidic conditions is well known as the Koch (or the Koch–Haaf) reaction. The major products of this reaction are usually carboxylic acids. However, depending on the structure of a carbocation or by modifying reaction conditions, one can occasionally obtain ketones[45] or esters.[46] These products, however, do not appear synthetically useful because of their low yields and little structural characteristics. As one of our projects for the exploration of synthetic uses of carbocations, we selected the reaction of 1-adamantyl cation with CO.[42—44] The major reason was that we had succeeded in synthesizing highly reactive 1-adamantyl triflate (trifluoromethanesulfonate)[47] (**6**) as an 1-adamantyl cation precursor. This triflate is so reactive as to solvolyze in ethanol with a half life of 0.02 s at 25 °C ($k = 35.1\ \mathrm{s}^{-1}$).[48]

1-Adamantyl triflate (**6**) is unreactive toward CO in carbon tetrachloride at atmospheric pressure. However, we found that **6** reacts with CO and adamantane in the presence of a superacid such as trifluoromethanesulfonic (triflic) acid to give 3-hydroxy-4-homoadamantyl 1-adamantanecarboxylate (**7**) as a major product, and 2-hydroxymethyl-2-adamantyl 1-adamantanecarboxylate (**8**) and (1-adamantyl)methyl 1-adamantanecarboxylate (**9**) as minor ones (Chart 9).[42,43] By controlling reaction conditions and relative amounts of 1-adamantyl triflate (**6**), triflic acid, and adamantane, the yields of **7**, **8**, and **9** were increased to 70, 7, and 21%, respectively, based on **6**. We later found that easily available 1-adamantyl methanesulfonate (mesylate) (**10**) could also be used in place of triflate **6**, but 1-adamantyl bromide gave the major product **7** only in 30% and 1-adamantanol yielded none of the three esters.[43] As strong acids, FSO_3H was much less effective and both 100% sulfuric acid and methanesulfonic acid were completely ineffective.[43]

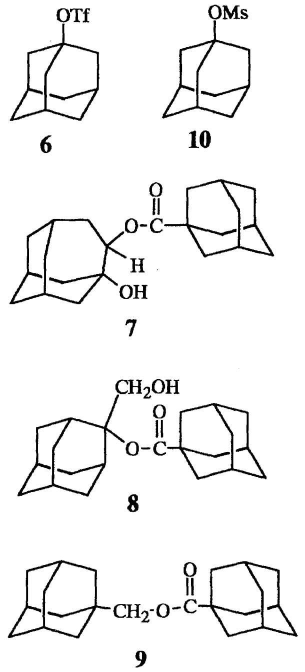


Chart 9.

Probable Pathways to the Esters. The formation of the three esters was explained by postulating transient formation of 1-adamantanecarbaldehyde (**12**) as a key intermediate (Chart 10).[43] The formation of the 1-adamantanecarbonyl cation (**11**) from triflate **6** or mesylate **10** and CO is the first step of the Koch reaction. The acyl cation **11** is presumed to abstract hydride from adamantane to give aldehyde **12** in the presence of triflic acid. Nucleophilic attack of **12** to **11** gives a triflate **9-OTf**, which gives **9** on hydride abstraction from adamantane (or **12**). The 1,2-alkyl shift of **9-OTf** gives triflate **7-OTf**. Subsequent intramolecular hydride shift in **7-OTf** followed by the 1,2-alkyl shift would afford **8-OTf**. When the mixture is worked up with water, **7-OTf** and **8-OTf** are expected to afford **7** and **8**, respectively. Summing up all the pathways, one can describe the stoichiometries for the formation of **7-OTf**, **8-OTf**, and **9** as shown in Chart 11. Actually, the carbonylation in the presence of aldehyde **12** in place of adamantane afforded **7** in 94% yield.[43]

Abstraction of a bridgehead hydride of adamantane by acyl cation **11** may be thermodynamically unfavorable. However, that this kind of process could occur has been postulated between the acetyl cation and isobutane in $HF–BF_3$ and explained by postulating a highly reactive, protonated acyl cation.[49] A patent describes the formation of 1-adamantanecarbaldehyde (**12**) from adamantane and carbon monoxide in the presence of anhydrous aluminum chloride.[50] Olah and his co-workers questioned if the hydride transfer could occur between 1-adamantanecarbonyl cation (**11**) and adamantane.[51] They carried out the reaction under pressure and detected a small amount (0.2—1.1%) of aldehyde **12**.[51]

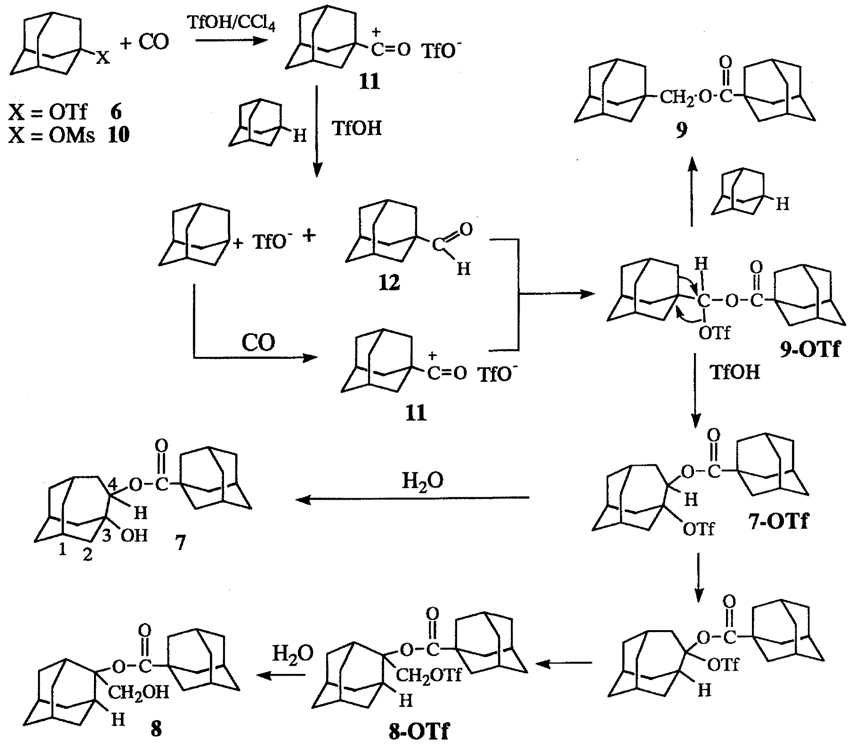


Chart 10.

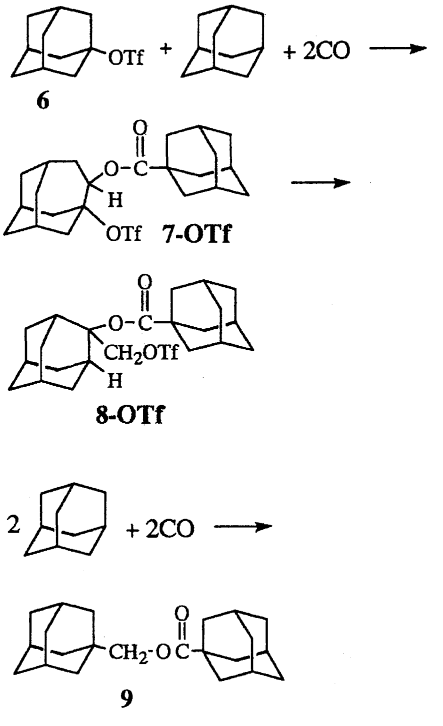


Chart 11.

The ester **7** is a monocarboxylate of 3,4-homoadamantanediol. Although 3,4-homoadamantanediol was thought to be a promising starting compound to 3,4-disubstituted homoadamantane derivatives, it had never been synthesized. Moreover, the formation of **7** from 1-adamantanecarbaldehyde (**12**) and 1-adamantanecarbonyl cation (**11**) suggested a possibility that a suitable acyl cation would react with a bridgehead aldehyde to give a monocarboxylate of a 1,2-diol having a ring-expanded skeleton. Therefore, we decided to develop a new ring-expansion method, as described in the following section.

Development of Acylative Ring Expansion

Synthesis of 1,2-Bifunctional Polycyclic Compounds. The acyl cation reacts not only with aromatic compounds (the Friedel–Crafts acylation), but also with unsaturated ones such as olefinic, acetylenic, and carbonyl compounds. Among these, the reactions with carbonyl compounds always give esters,[52] but the usefulness has been limited.

In order that the ring expansion of aldehydes become a useful synthetic method, a convenient acyl cation generator is required. We noticed that benzoic trifluoromethanesulfonic anhydride that had been developed by Effenberger[53] would be the best choice. This reagent can be prepared in moderate yields by simply distilling the mixture of benzoyl chloride and triflic acid.[53,54] The addition of benzoic trifluoromethanesulfonic anhydride to the formyl group is instantaneous and gives a benzoate-triflate (Chart 12).[21,22] If the aldehyde has a strained structure, the Wagner–Meerwein rearrangement proceeds spontaneously, but when the structure is strainless, the rearrangement only occurs by addition of a strong acid.[22] We postulate that the protonation of the ester makes the carbocation very unstable and facilitates the rearrangement so as to separate the two positive charges as far as possible (Chart 12). This "acylative rearrangement" reaction was also applicable to 2-methylpropanal, but was unsuccessful for cyclohexanecarbaldehyde.[21] Presumably, the secondary cation

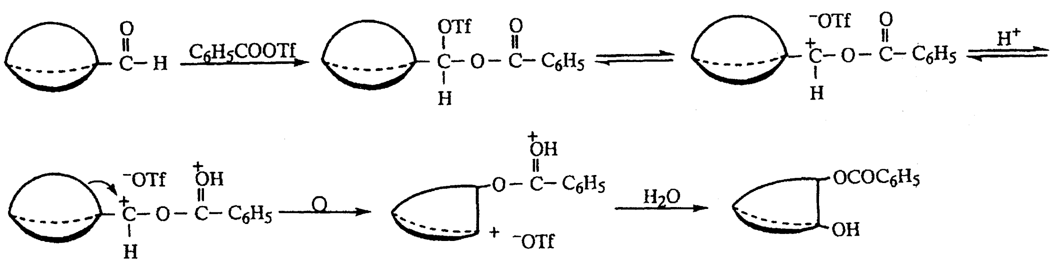
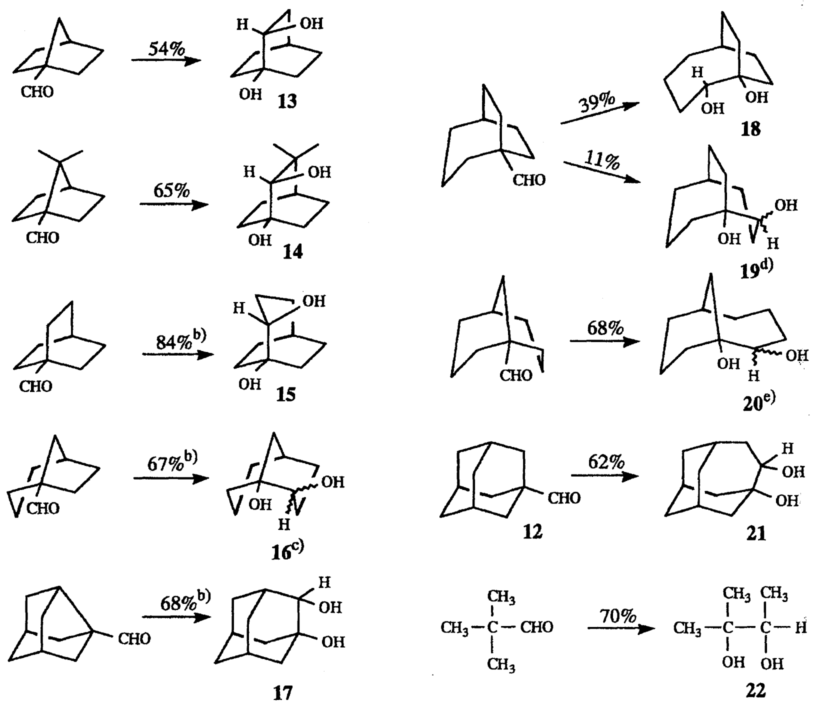


Chart 12.

Table 1. Diols Prepared via Two Steps from Starting Aldehydes. Yields are the Values after Crystallization, Sublimation, or Distillation[a)]



a) The yields were taken from Ref. 21or Ref. 22. b) The improved yield by the authors. c) The major monobenzoate is the *endo* isomer, which can be isolated (Ref. 22). d) Mixture of the *endo* and *exo* isomers (Ref. 22). e) The *endo* and *exo* monobenzoates were isolated in 34 and 42% yields, respectively (Ref. 22).

to be formed on ring-expansion is too unstable to exist in a considerable amount in equilibrium with the first formed cation. Saponification of the esters to the diols is readily conducted in aqueous methanol. The starting aldehydes and the diols prepared by this method are summarized in Table 1.

It is generally highly difficult to selectively oxidize the secondary hydroxyl group in tertiary-secondary *vic*-diols by using chromium oxidizing reagents.[55)] In many cases, the carbon–carbon bond cleavage becomes a major reaction.[55)] For some of our compounds, we used chromic acid (Jones reagent) and PCC (pyridinium chlorochromate), but the results were very poor. It has been reported that dimethyl sulfide–chlorine complex[56)] works well for this purpose,[57)] but it was not necessarily good for our compounds. In some cases silver carbonate on celite worked nicely,[22,44)] but its use for **14**[58)] and **20**[44)] was almost or completely unsuccessful (Table 1). Eventually, essentially quantitative yields were attained by using dimethyldioxirane or methyl(trifluoromethyl)dioxirane through cooperation of three laboratories.[59)] In this way, we are now in a position to prepare various kinds of bridgehead alcohols having an oxo group on the vicinal carbon. Very recently, Eaton and his co-workers reported an elegant method to directly functionalize the bridgehead position adjacent to the carbonyl group of polycyclic ketones such as adamantanone (Chart 13).[60)] However, their method may not be useful to functionalize the C(3) position of 4-homoadamantanone, since the carbonyl group is connected to a methylene unit.

The acylative ring expansion is also applicable to the introduction of an isotope label or a substituent into a polycyclic skeleton.[44)] 1-Adamantanecarbaldehyde (**12**) labeled with ^{13}C or ^{2}H on the formyl group can be converted to 4-homoadamantanone labeled on the C(3) position by the process involving basic pinacol rearrangement (Chart 14).[44)]

Alkylation or arylation of 3-hydroxy-4-homoadamantanone, followed by acidic pinacol rearrangement, gives 3-R-4-homoadamantanones (Chart 15).[44] These processes have been applied to the preparation of some homoadamantyl substrates containing labels or substituents on the C(3) and/or C(4) positions, which have been used for the study of the nature of the secondary and tertiary 4-homoadamantyl cations in solvolysis:[61,62] These solvolysis studies are not included in this Account.

The replacement of the OH group of 2-oxo bridgehead alcohols with halogens is generally difficult because of the very high instability of intermediate carbocations. The synthesis of 1-chloro-3,3-dimethylbicyclo[2.2.2]octan-2-one[63] (**23**) and 1-halo-2-adamantanones[39—41] (**24-X**) has been accomplished by using benzoyl chloride–AlCl$_3$ for the former and by adding a halide salt after the addition of benzoic trifluoromethanesulfonic anhydride to noradamantane-3-carbaldehyde for the latter (Chart 16). Halo ketones **23** and **24-X**'s were used for exploration of a new S$_{RN}$1 reaction[63] and as starting compounds for the solvolysis substrates having large F-strain.[39—41]

Evaluation of π-Conjugative Stabilization of 2-Methylene and 2-Oxo Bridgehead Carbocations

Background. The π-conjugative stabilization of 2-oxo carbocation (Chart 5) was originally postulated by McDonald[64] and elaborated by Creary.[23] 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 (**25**) with an acyl group rather enhances the solvolysis rate (Chart 17).[65,66] By taking the σ^+ values[65] of the acyl substituents into account, the rates of 2-methyl-1-oxo-1-phenyl-2-propyl methanesulfonate (**26**) and 2,4,4-trimethyl-3-oxo-2-pentyl methanesulfonate (**27**) 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,[66] although the factor of 10^4—10^5 was later revised to be just a crude estimate.[23e]

The rigorous ab initio calculations[67] using a double-ζ plus polarization basis sets[67a] have been carried out on the formylmethyl cation. The planar cation is stabilized relative to the perpendicular cation by 2.5 kcal mol^{-1} (Chart 18).[67a] The later calculations of formaldehyde and formylmethyl cation based on the HF/6-31G*-optimized geometries and single point calculations at the MP2/6-31G** level indicated that there is essentially no double bond character in the C–C bond of the formylmethyl cation, as shown by **2b** in Chart 5.[67b] Very recently, Creary et al. calculated the fully optimized MP2/6-31G** geometry of the formylmethyl cation. The energy difference between the planar form and the perpendicular form is 1.7 kcal mol^{-1}.[67c] The stability of the planar form may be attributed to substantial π-donation of the

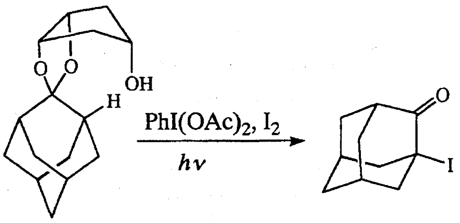


Chart 13.

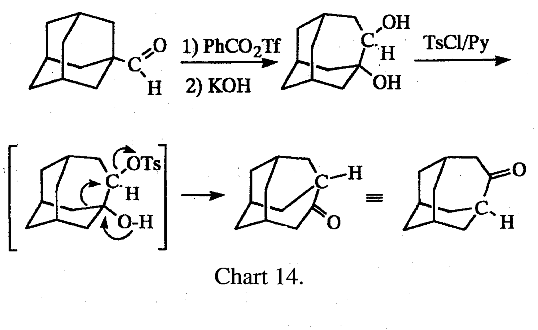


Chart 14.

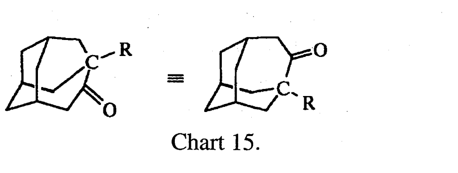
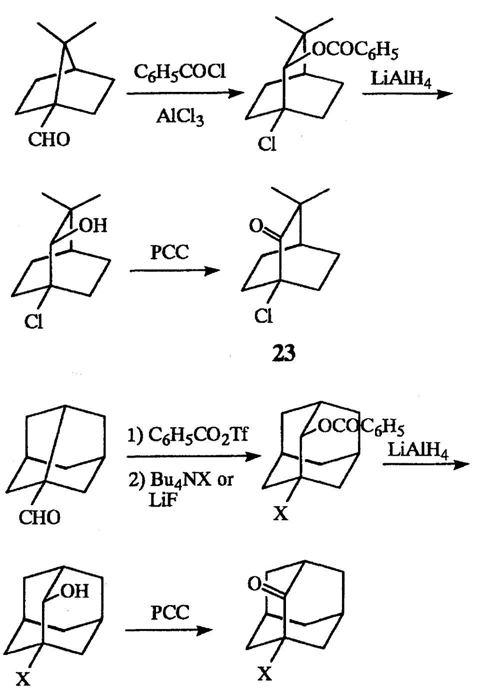
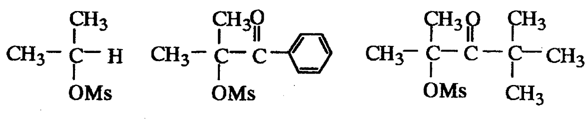


Chart 15.



24-X (X=F, Cl, Br, I)

Chart 16.



25 **26** **27**

Chart 17.

carbonyl group. However, this π-donation ability of the carbonyl group is expected to decrease with methyl substitution. So it follows that the π-donation would not be an important factor in the tertiary 2-oxo cation $(CH_3)_2C^+CHO$.

On the contrary, 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 effects. 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 (**28**) relative to 1-adamantyl tosylate (**29**) is $10^{-4.2}$ at 25 °C (Chart 19).[68] 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 $10^{2-2.8}$.[69] Therefore, it is expected that if the rate of solvolysis of the methylene system ($X=CH_2$) relative to the corresponding parent system ($X=H_2$) increases with increased flexibility of the ring system (Chart 20), we may be able to apply this methodology to the evaluation of carbonyl π-conjugation in the incipient carbocation. The usefulness of the present methodology has been supported by molecular mechanics calculations and semiempirical molecular orbital calculations.

Solvolysis Rates and Products. Because of requirement for covering a wide range of reactivity, the leaving group and solvent were appropriately selected or the rates were estimated by using the conversion factors for 1-adamantyl ethanolysis.[48] In Table 2 are summarized the rate ratios $k(X=CH_2)/k(X=H_2)$ and $k(X=O)/k(X=H_2)$ in ethanol or 80% ethanol–H_2O at 25 °C in the order of increasing ring flexibility.

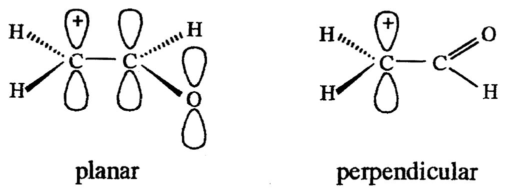


Chart 18.

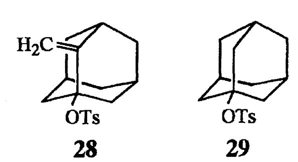


Chart 19.

The products from all the 2-methylene substrates and 4-oxo-3-homoadamantyl triflate were only the corresponding bridgehead substitution products, but the other 2-oxo substrates gave mixtures of bridgehead substitution products and rearranged ones (Chart 21).[27—29] It has been suggested that the preferred formation of rearrangement products might indicate σ-participation (k_Δ process) leading to a nonclassical ion.[23d,23e] At the present stage, the relative importance of σ-participation is difficult to assess. However, the S_N1 nature of solvolysis of 2-oxo substrates is provided by nicely linear mY relations (**31a**; $m=0.73$, $r=0.996$: **33a** (L=OTf); $m=0.77$, $r=0.997$: **35a**; $m=0.85$, $r=0.998$).[27] The exclusive bridgehead substitution in the solvolysis of **35a** suggests that the rearrangement is related to the skeletal structure of the first-formed, classical, bridgehead cation rather than the involvement of a nonclassical ion.

Ring Flexibility and Conjugative Ability. The most notable feature of the rate data of Table 2 is that the $k(X=CH_2)/k(X=H_2)$ ratio increases in the order **30b**/**30c** ($10^{-3.9}$), **32b**/**32c** ($10^{-1.9}$), **33b**(L=OMs)/**33c**(L=OMs) ($10^{-0.8}$) and **34b** (L=OMs)/**34c** (L=OMs) ($10^{0.9}$) 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,[68,69] the rate ratios for **33b** (L=OMs)/**33c** (L=OMs) and **34b** (L=OMs)/**34c** (L=OMs) indicate realization of ca.

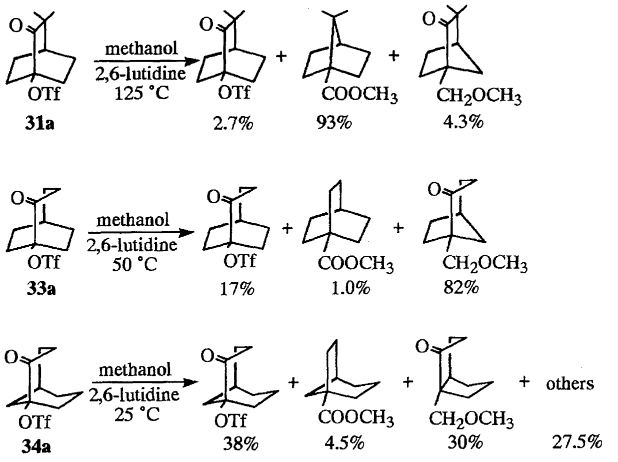


Chart 21.

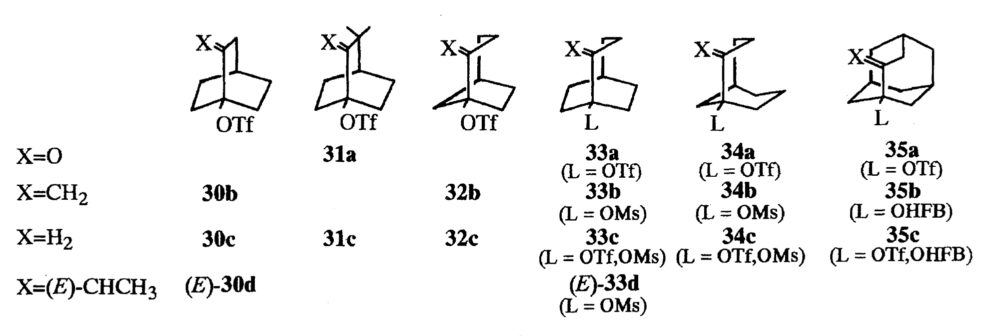
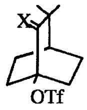
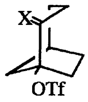
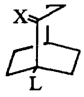
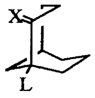
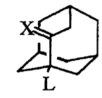


Chart 20.

Table 2. Rate Ratios [k(X=CH$_2$, (E)-CHCH$_3$, or O)/k(X=H$_2$)] for Solvolysis at 25.0 °C[a)]

	 **30**	 **31**	 **32**	 **33**	 **34**	 **35**
$\frac{k(\mathrm{X=CH_2})}{k(\mathrm{X=H_2})}$	$10^{-3.9}$		$10^{-1.9}$	$10^{-0.8}$ (L=OMs)	$10^{0.9}$ (L=OMs)	$10^{-1.1}$ (L=OHFB)
$\frac{k(\mathrm{X=}(E)\mathrm{-CHCH_3})}{k(\mathrm{X=H_2})}$	$10^{-3.1}$			$10^{1.6}$ (L=OMs)		
$\frac{k(\mathrm{X=O})}{k(\mathrm{X=H_2})}$		$10^{-8.4}$		$10^{-8.3}$ (L=OTf)	$10^{-8.2}$ (L=OTf)	$10^{-8.7}$ (L=OTf)
OS Value[b)]/kcal mol^{-1} [c)]	40.4	40.4	28.2	19.5	15.2	20.2

a) Buffered with 0.025 M 2,6-lutidine (M=mol dm^{-3}). b) Olefinic strain energy; see Ref. 70. c) 1 kcal mol^{-1}=4.184 kJ mol^{-1}.

50% and ca. 80% allylic conjugation in the solvolysis of **33b** (L=OMs) and **34b** (L=OMs), respectively.

A measure of ring flexibility of bicyclic compounds would be given by the stability of a bridgehead olefin, which corresponds to the resonance structure containing a double bond at the bridgehead. 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.[70)] A plot of log [k(X=CH$_2$)/k(X=H$_2$)] against the olefinic strain energy shows that the smaller the olefinic strain energy, the easier the allylic conjugation (Fig. 1).

In contrast with the marked variation of the k(X=CH$_2$)/k(X=H$_2$) ratio, the k(X=O)/k(X=H$_2$) ratios are sensibly constant with $10^{-8.2}$—$10^{-8.7}$ (Table 2 and Fig. 1).

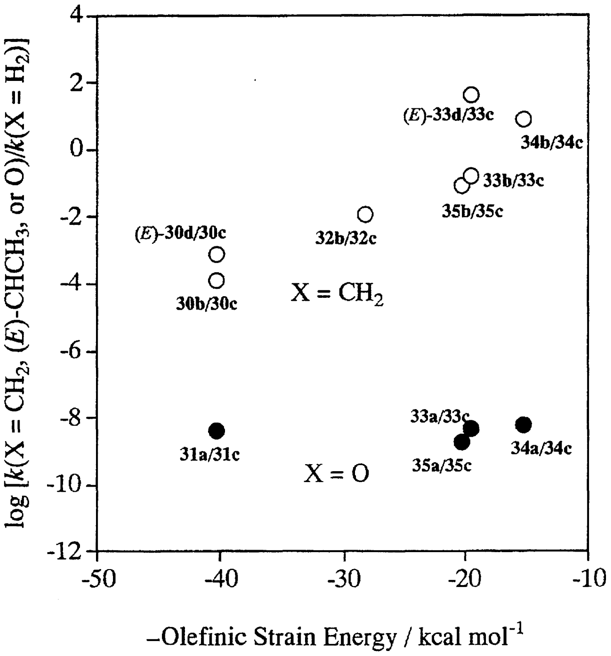


Fig. 1. Plot of log [k(X=CH$_2$, (E)-CHCH$_3$, or O)/k(X=H$_2$)] values against olefinic strain energies of corresponding unsubstituted bridgehead olefins.

This result leads us to conclude that the π-conjugative stabilization as depicted by Chart 5 is unimportant, at least in tertiary 2-oxo carbocations.

Placement of a methyl substituent on the E position in **33b** markedly enhances the solvolysis rate; (E)-**33d** solvolyzes 259 times faster than **33b** in ethanol at 25 °C. As described above, the skeletal flexibility of **33b** enables approximately 50% allylic conjugation. Therefore, a major part of this rate enhancement by introducing the methyl substituent can most probably be ascribed to enhanced charge delocalization in the transition state, although other factors, in particular the steric strain between the methyl and 3-methylene group in the ground state, may also contribute to the rate acceleration.

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)-**30d** solvolyzes only 6.3 times faster than **30b** in ethanol at 25 °C. These results reinforce the notion that the allylic conjugation is enhanced with the increase in the ring flexibility.

Semiempirical Molecular Orbital Calculations on Bridgehead Carbocations. A series of 2-methylene, (E)-2-ethylidene, and 2-oxo bridgehead carbocations and the corresponding hydrocarbons (L; hydrogen in the place of leaving group) were subjected to AM1 calculations. As indexes for the degree of allylic ($C_\alpha-C_\beta=C_\gamma$) conjugation, we employed the differences in C_α–C_β bond orders between the carbocation and the corresponding hydrocarbon denoted by ΔBO (C_α–C_β). Figure 2 gives the relation between log [k(X=CH$_2$, CHCH$_3$, or O)/k(X=H$_2$)] and ΔBO (C_α–C_β). A smooth curve in Fig. 2 for a homologous series, **30b/30c**, **32b/32c**,, **33b/33c**, and **34b/34c**, 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 of (E)-**30d/30c** is accommodated to the curve. The upward deviation of the point for (E)-**33d/33c** by 0.8 logarithmic units suggests possible rate enhancement in (E)-**33d** due to the back stain (B-strain) between the (E)-methyl group and the hydrogen atoms on the C(3) position. 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.

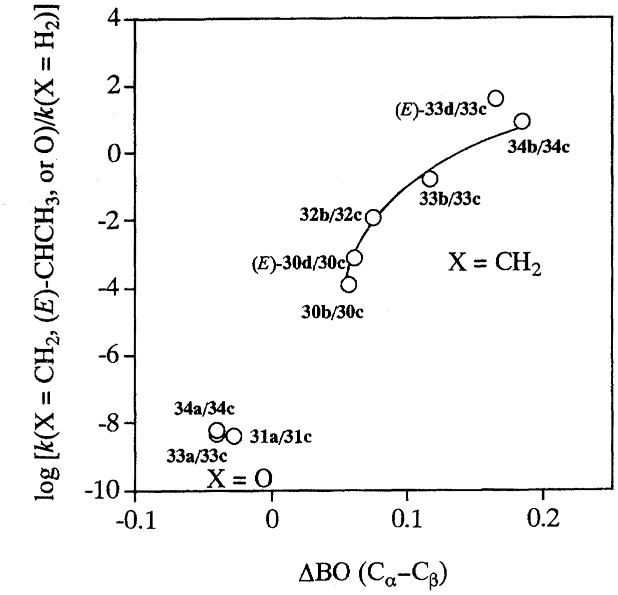
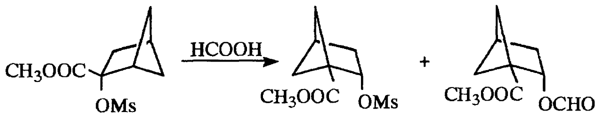


Fig. 2. Plot of log [k(X=CH$_2$, (E)-CHCH$_3$, or O)/k(X=H$_2$)] values against difference of C_α–C_β bond orders between carbocations and the corresponding hydrocarbons.

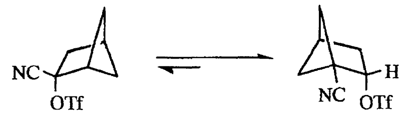
The Possible Origin of the Unexpectedly Fast Rate of Solvolysis of 26 and 27. In this context, how can one explain the unexpectedly fast rates of solvolysis of **26** and **27** (Chart 17)? The most important rate-enhancing factor would be geminal group interaction between the leaving group and the acyl substituent in the ground state. Della and his coworkers reported that the solvolysis of **36** in formic acid gave rearranged **37-OMs** and its formolysis product **37-OCHO** (Chart 22), indicating that **36** is far more destabilized than **37-OMs** by the geminal group interaction between the leaving group (OMs) and the methoxycarbonyl group.[71] We note that the importance of destabilizing geminal group interaction in α-cyano substituents has been pointed out from the finding that **38** is 9—10 kcal mol^{-1} more unstable than **39** (Chart 23).[72] Recent publications further emphasize the great importance of the geminal group interaction in chemical reactions, particularly in solvolysis.[73]

Another, perhaps less important, factor would be partial relief of back-strain on ionization. Molecular mechanics calculations on t-butyl phenyl ketone and di-t-butyl ketone as models for the substrates used by Creary indicated that **26** and **27** are more strained than **25** by ca. 7 kcal mol^{-1}.[27]



36 **37-OMs** **37-OCHO**

Chart 22.



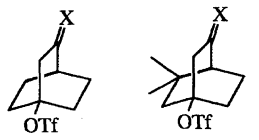
38 **39**

Chart 23.

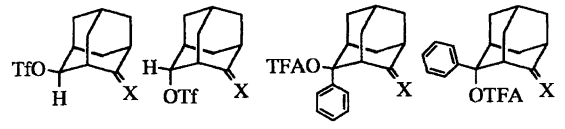
Through-Bond Stabilization of 3-Oxo Carbocations

Background. Interactions between two orbitals through framework σ orbitals have been studied not only for their theoretical interest[74] but also for their applications to synthetic organic chemistry.[75] In the 1960s, the stabilization of an incipient carbocation by the lone pair of an amino nitrogen attached to the C(3) position was first demonstrated by Grob; this effect was named the "frangomeric effect."[76] Since 1978, Vogel, Carrupt, and their co-workers have reported that a carbonyl oxygen has a similar effect, as illustrated in Chart 7 on regioselective electrophilic additions to the C=C bond of bicyclo[2.2.1]hept-5-en-2-one and related enones.[30] The interpretation in terms of a through-bond pC(1)$^+$$\leftrightarrow$$\sigma$C(2)C(3)$\leftrightarrow$$n$(CO) hyperconjugative interaction in a C(1)$^+$–C(2)–C(3)=O species is based on the concept of through-bond interaction recognized by Hoffmann: The lone pair of a carbonyl group interacts with the σ^* orbital of an adjacent C–C σ bond.[74] Lajunen and his co-workers used this concept to explain the preferred protonation of bicyclo[2.2.1]hept-5-en-2-one at the C(5) position.[77]

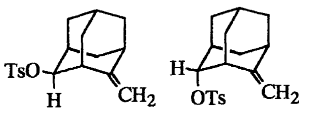
This sort of through-bond electronic effect may be best assessed quantitatively by the study of the solvolyses of appropriate compounds. In relation to our results of 2-oxo (α-carbonyl) effects (vide supra), we selected the 3-oxobicyclo[2.2.2]oct-1-yl triflate (**40a**) and its 5,5-dimethyl derivative **41a** (Chart 24) as a model in which the carbonyl lone pair and the developing cationic p orbital are in antiperiplanar arrangement.[31] As reference compounds we used 3-methylenebicyclo[2.2.2]oct-1-yl triflate (**40b**), bicyclo[2.2.2]oct-1-yl triflate (**30c**), and the 3,3-dimethyl deriva-



X=O	**40a**	**41a**
X=CH$_2$	**40b**	——
X=H$_2$	**30c**^{a}	**31c**^{a}



X=O	**42eq**	**42ax**	**44eq**	**44ax**
X=H$_2$	**43**	**43**	**45**	**45**



46eq **46ax**

Chart 24. ^{a}See Chart 20. TfO; CF$_3$SO$_3$; TFAO; CF$_3$CO$_2$.

tive **31c** (Chart 24).

The through-bond interaction is expected to decrease when coplanarity of the interacting orbitals is lost. This point has been examined by using the solvolysis of 4-oxo-2$_{eq}$- and -2$_{ax}$-adamantyl triflates (**42eq** and **42ax**).[32,33] It has also been shown that the through-bond stabilization of the equatorial transition state from **42eq** essentially vanishes in the solvolysis of the 2-phenyl substituted substrate **44eq**.[32] The oxo/methylene rate comparison has been attempted by the use of 4-methylene-2-adamantyl tosylates (**46eq** and **46ax**), but they react in quite different ways than **40b**,[78] which is briefly described in this Account.

Rates and Products of Solvolyses of 3-Oxobicyclo[2.2.2]oct-1-yl and Related Compounds. Solvolysis rates were determined in various solvents.[31] To allow the evaluation of the rates on the basis of Grob's data,[7a] the data in 80% ethanol at 25 °C are employed. Pertinent rate constants and rate ratios relevant to the 2-oxo-, 2-methylene-, 3-oxo, and 3-methylene-bicyclo[2.2.2]oct-1-yl systems are summarized in Chart 25.

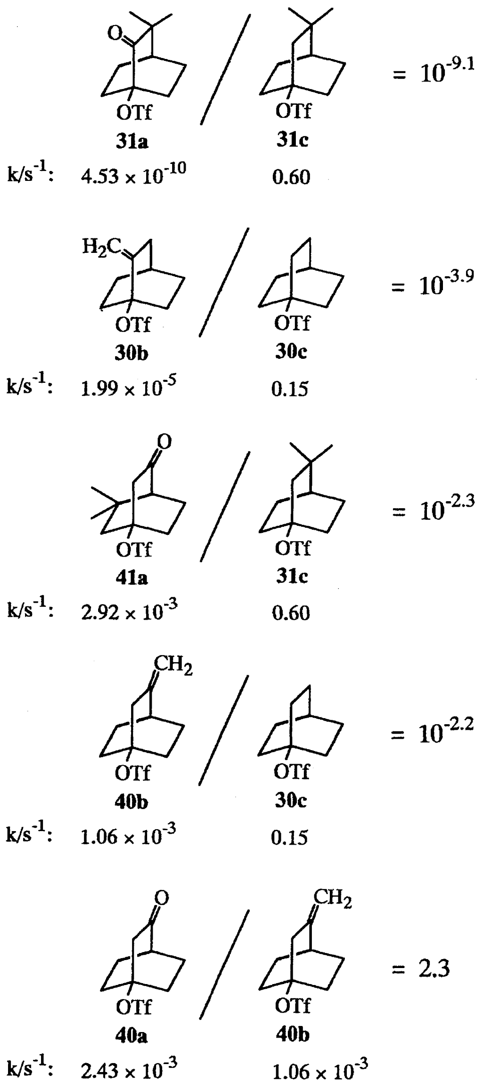


Chart 25. In 80% ethanol at 25 °C.

As described before in this Account, the 2-oxo and 2-methylene compounds solvolyze more slowly than the corresponding parent compounds; in 80% ethanol at 25 °C the rate ratios are $10^{-9.1}$ (**31a/31c**) and $10^{-3.9}$ (**30b/30c**), respectively.[31b)] Since the π system in **31a** and **30b** is essentially perpendicular to the developing cationic p orbitals, the rate decelerations are ascribed to the purely inductive effect of the 2-oxo and 2-methylene substituents.[29] Therefore, the 2-oxo substituent is markedly more electron-withdrawing than the 2-methylene substituent.

In contrast, when the oxo or the methylene substituent is attached to the C(3) position, the rate-decelerating effects are comparable, as evidenced by the rate ratios for **41a/31c** ($10^{-2.3}$) and **40b/30c** ($10^{-2.2}$).[31b)] A comparison of the rate of **40a** with that of **40b** results in a rate ratio of 2.3, making the 3-oxo substituent look less electron-withdrawing than the 3-methylene substituent. The through-bond electron donation from the carbonyl lone pair to the developing cationic p orbital as depicted in Chart 7 is a most reasonable explanation.

The rate data are quantitatively evaluated by comparing the rate ratios **41a/31c** and **40b/30c** with **31a/31c** and **30b/30c**, respectively,[31b)] and by employing the solvolysis rate data reported by Grob and his co-workers on **47**—**49** (Chart 26).[7a)] As Fig. 3 shows, the point for the methylene compounds conforms fairly well to the plot, indicating that the methylene group can be treated as an ordinary electron-withdrawing substituent. In contrast, the point for the oxo compounds deviates significantly upward. We estimate that the through-bond stabilization of the incipient 3-oxobicyclo[2.2.2]oct-1-yl cation amounts to a solvolysis rate factor of 10^3—10^4, which corresponds to a 4—5 kcal mol^{-1} stabilization.

The most notable feature of the solvolysis product from

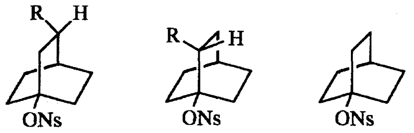


Chart 26. ONs; p-$NO_2C_6H_4SO_3$.

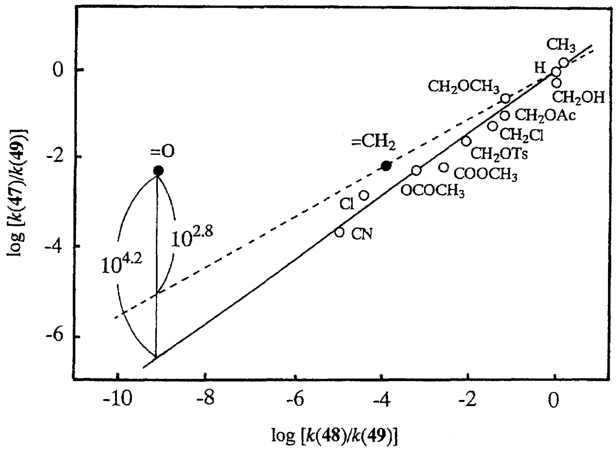


Fig. 3. Plot of log [k(**47**)/k(**49**)] vs. log [k(**48**)/k(**49**)] for the solvolysis in 80% ethanol at 25 °C.

3-oxo compound **41a** is that the fragmentation product **53** was formed in 9% yield, in addition to the normal substitution product **52** (91%) (Chart 27).[31b)] Since 3-methylene compound **40b** gives only a normal substitution product, the fragmentation observed for the oxo compounds indicates that the C(2)–C(3) σ bond is weakened in the intermediate carbocation **50** by the special electronic effect of the 3-oxo substituent, i.e., the through-bond interaction. Quantum mechanical calculations by Carrupt and Vogel on our system support the weakening of the C(2)–C(3) σ bond by a through-bond interaction.[79)] Similar fragmentation reactions have often been observed in other systems giving a 3-oxo carbocation.[30c,80)] The fragmentation product **53** is most probably formed via acyl cation **51** (Chart 27). The AM1 calculations on the (4-methylenecyclohex-1-yl)carbonyl cation (a cation formed by the removal of the methyl groups from **51**) with a twist-boat structure show that this cation is more stable by 9 kcal mol^{-1} than 3-oxobicyclo[2.2.2]oct-1-yl cation.[31b)]

Rates and Products of Solvolyses of Secondary 4-Oxo-2-adamantyl Triflates. In the 3-oxobicyclo[2.2.2]oct-1-yl cation, the carbonyl lone pair and the cationic p orbital are situated in antiperiplanar arrangement, bringing about the maximum through-bond interaction (Chart 27). On the other hand, it is not the case in either of the incipient 4-oxo-2$_{\mathrm{eq}}$- or -2$_{\mathrm{ax}}$-adamantyl cations: In the equatorial ion pair, the cationic p orbital is tilted from the C–C=O plane by approximately 60°, resulting in partial through-bond interaction, whereas in the axial ion pair, the overlap is completely prohibited (Chart 28).

The first order rate constants and rate ratios of solvolysis of **42eq** and **42ax** (Chart 24) are summarized for several solvents at 25 °C (Table 3).[33)] In all the solvents used, **42eq** solvolyzes faster than **42ax** by a factor of 15—24. Although small, this factor would be attributed to the presence of the through-bond stabilization of the transition state of ionization in **42eq** and its unimportance in **42ax**. From the conclusion in the last section, the maximum rate enhancement when all the interacting orbitals are coplanar would be 10^3—10^4. By assuming that the cationic p orbital is tilted from the C–C=O plane by about 60° in the transition state of ionization of **42eq** and that the orbital interaction is proportional to $\cos^2\phi$ in energy scale,[81)] the rate enhancement is predicted to be $10^{0.75}$ (ca. 6)—10, which is fairly close to the value 15—24 obtained for **42eq** : **42ax**. Molecular mechanics calculations (MM2(87)) on the corresponding alcohols indicated that **42ax** is unstable than **42eq** by merely 0.2 kcal mol^{-1}, which may not significantly affect the relative rates.

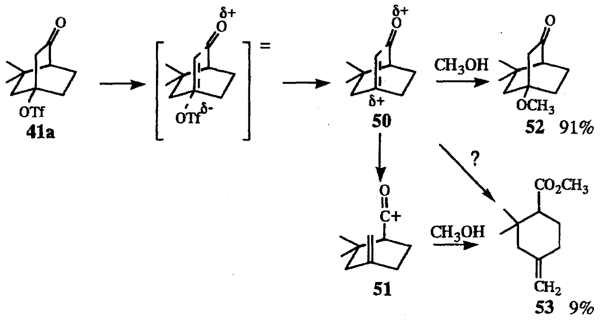


Chart 27.

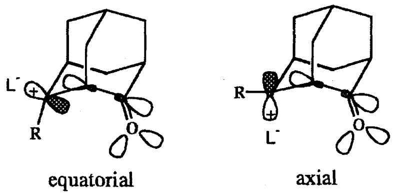


Chart 28.

Table 3. Rate Constants and Rate Ratios for the Solvolysis of **42eq** and **42ax** in Various Solvents at 25 °C[a,b)]

Solvent	k_1/s^{-1}		Rate ratio
	42eq	**42ax**	**42eq/42ax**
EtOH	1.87×10^{-3}	1.08×10^{-4}	17
80% EtOH	1.82×10^{-2}	1.19×10^{-3}	15
60% EtOH	6.86×10^{-2}	4.56×10^{-3}	15
MeOH	6.93×10^{-3}	3.24×10^{-4}	21
TFE	1.10×10^{-2}	4.60×10^{-4}	24

a) Taken from Ref. 33. b) For the rate constants of **43**, see Ref. 33.

The rate ratio **42eq** : **42ax** in TFE (24) is similar to that in MeOH (21), but product distributions are considerably different (Tables 4 and 5). The formation of fragmentation products, the 2,2,2-trifluoroethyl and methyl esters (**56** and **57**, respectively) (Chart 29) of bicyclo[3.3.1]non-2-ene-7-carboxylic acid, similarly to the formation of **53** (Chart 27), indicates that the reaction proceeds through carbocations in the two solvents.

In trifluoroethanolysis, both **42eq** and **42ax** gave the equatoial product **54eq** in greater amounts than **54ax** with the **54eq** : **54ax** ratio 35 : 10 from **42eq** and 51 : 3.2 from **42ax**. The results suggest that the equatorial ion pair is in equi-

Table 4. Product Distributions in the Trifluoroethanolysis of **42eq** and **42ax** at 25 °C

	Product distribution/%		
Substrate	**54eq**	**54ax**	**56**
42eq[a)]	35	10	52
42ax[b)]	51	3.2	44

a) An unidentified product of 3% was detected. b) An unidentified product of 2% was detected.

Table 5. Product Distributions in the Methanolysis of **42eq** and **42ax** at 25 °C[a)]

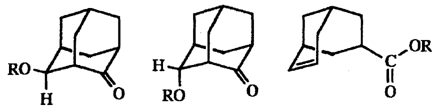
	Product distribution/%		
Substrate	**55eq**	**55ax**	**57**
42eq	3	54	43
42ax[b)]	82	2	14

a) Taken from Ref. 33. b) An unidentified product of 2% was detected.

librium with the axial ion pair and that the former is favored, being stabilized by the through-bond orbital interaction (Chart 30). It has been suggested by ab initio calculations that the 2-adamantyl cation may exist as a pair of rapidly equilibrating ion pairs having nonplanarity at the cation center.[82] The formation of a greater amount of **54ax** from **42eq** than from **42ax** (10% vs. 3.2%) may be explained in terms of partial involvement of an S_N2 (intermediate)[83] mechanism. The role of the S_N2 (intermediate) mechanism appears to become more important in more nucleophilic methanol, since both **42eq** and **42ax** gave greater amounts of inversion products with the **55eq** : **55ax** ratio 3 : 54 from **42eq** and 82 : 2 from **42ax**. Such characteristic behavior was actually utilized in the synthesis of **55eq** and the corresponding alcohol from relatively readily available **42eq**.[84] It is worth noting that the nucleophilic solvent attack from the rear side of the leaving group can happen even in a 2-adamantyl system in spite of the typical k_c character[83a,83b] of the parent 2-adamantyl system.

Essential Vanishing of the Through-Bond Interaction in 4-Oxo-2-phenyl-2_{eq}-adamantyl Solvolysis. Evaluation of neighboring participation in solvolysis by changing the electron demand of a cationic center is a familiar tool for physical organic chemists.[85] According to this tool, substitution of a phenyl group for the hydrogen on the C(2) position of **42eq** is expected to decrease the through-bond stabilization of the incipient carbocation and to give a small eq : ax rate ratio. We carried out the trifluoroethanolysis of **44eq**, **44ax**, and **45** (Chart 24) and showed the rate ratio **44eq** : **44ax** : **45** of $10^{-2.9} : 10^{-2.5} : 1$ with **44eq** : **44ax**=0.61 : 1 at 25 °C.[32] This result should be compared with the secondary rate ratio **42eq** : **42ax**=24 : 1 (Table 3), and is consistent with the essential vanishing of the through-bond interaction in the transition state of ionization of **44eq**.

In contrast to the secondary substrates, neither **44eq** nor **44ax** gave any detectable amounts of a fragmentation product that has a structure similar to **56**. This finding strongly supports the essential vanishing of the through-bond interaction in the tertiary carbocation intermediate that is stabilized by the phenyl substituent. In addition, the equatorial : axial trifluoroethyl ether product ratios were essentially identical to each other for the substrates **44eq** and **44ax**, which were 18 : 82 from the former and 17 : 83 from the latter.[32] The formation of a smaller amount of the equatorial product is in harmony with the vanishing of the through-bond stabilization of the transition state leading to the equatorial product. The predominant axial attack is interpreted to result from smaller steric hindrance, because of the absence of one axial hydrogen due to the substitution with the oxo group.



$R=CF_3CH_2$	**54eq**	**54ax**	**56**
$R=CH_3$	**55eq**	**55ax**	**57**

Chart 29.

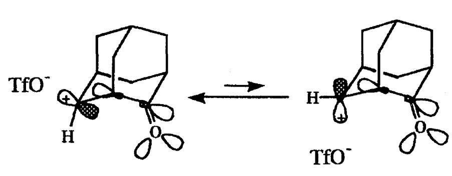


Chart 30.

Solvolyses of 4-Methylene-2_{ax}- and -2_{eq}-adamantyl Tosylates. In the study of the through-bond interaction between a cationic center and carbonyl lone pair electrons by using the bicyclo[2.2.2]octyl system, 4-methylenebicyclo[2.2.2]oct-1-yl triflate (**40b**) has been utilized very effectively as a structurally similar model compound that does not show the through-bond interaction. Therefore, we extended our research project to 4-methylene-2-adamantyl tosylates (**46eq** and **46ax**) (Chart 24) in the hope that they would also become model compounds for evaluating the through-bond interaction for the corresponding 4-oxo-2-adamantyl triflates (**42eq** and **42ax**) (Chart 24).[78] Unfortunately, both **46eq** and **46ax** have been found to solvolyze with anchimeric assistance by the methylene group. Product distributions suggest that the most probable intermediate from **46eq** is a π-bridged carbocation and that from **46ax** is a pair of rapidly equilibrating classical ones (Chart 31). Although the stability and behavior of these cations are interesting in the light of the purely inductive nature of the methylene group of **40b**, the discussion is beyond the scope of this Account.

Typical Examples of F-Strain Effect in Solvolysis

Background. 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.[34] These theories have played an important role in explaining markedly enhanced rates of S_N1 solvolyses.[4] In the transition state of ionization of a crowded molecule R_3CX, both B-strains among the three alkyl groups (R) and F-strains between the leaving group and the alkyl groups (R) are partially relieved, resulting in enhancement of solvolysis rates (Chart 8). Hitherto, many examples of the rate enhancement ascribed to the B-strain effect have been reported[4,86] and rationalized by molecular mechanics calculations.[11,87] However, it is not necessarily easy to evaluate the B- and F-strain effects separately, because increasing the bulkiness of the R groups to

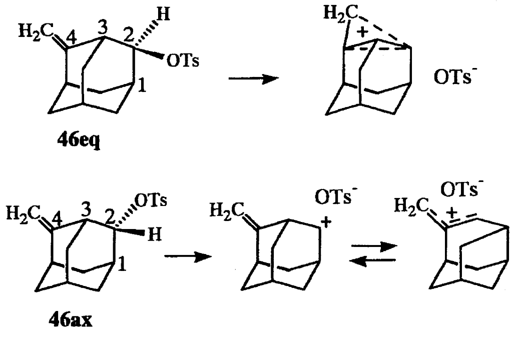
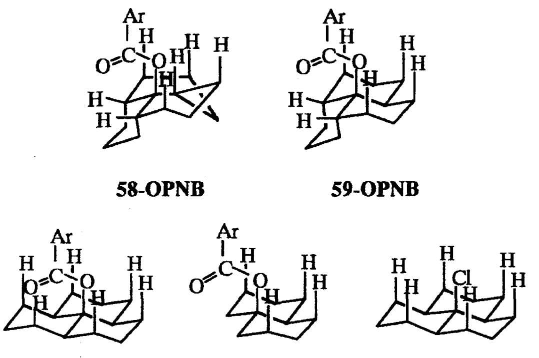


Chart 31.

assess the B-strain effect inevitably increases the F-strain effect.[88] When we published the latest paper in 1994, there were only three studies that seemed to be useful as supporting evidence for the F-strain effect in solvolysis.

The most unambiguous example is the work reported by Schleyer and Brown.[89,90] They found that *cis*, *cis*, *cis*-perhydro-9b-phenalyl *p*-nitrobenzoate (**58-OPNB**) solvolyzes 4×10^6 times faster than *cis*, *cis*, *trans*-stereoisomer (**59-OPNB**[89]) and *trans*, *trans*, *trans*-stereoisomer (**60-OPNB**) solvolyzes 2860 times faster than *trans*-9-decalyl *p*-nitrobenzoate (**61-OPNB**) in 80% acetone at 25 °C (Chart 32).[90] Since the rate enhancement essentially vanishes in the chloride (**60-Cl**), the major F-strain effect of **60-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.[90] This notion was supported by molecular mechanics calculations.[11,87] A similar example was provided by Dubois and his co-workers, who compared the *t*-Bu/Me rate ratios for solvolysis by changing the leaving group of 2-alkyl-2-adamantyl system **62** (Chart 33).[91] The large *t*-Bu/Me rate ratio at 25 °C of 225000 for *p*-nitrobenzoate solvolyses[92] as compared with 1820 for alcohol dehydration[91] was ascribed to the greater F-strain effect for the *p*-nitrobenzoate than for the protonated alcohol.

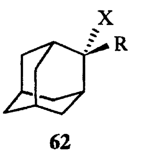
The F-strain effect exerted by the leaving group atom directly attached to the reaction center was evaluated by Brown and Stern.[35] They reported that the *t*-Bu/Me rate ratio in the solvolysis of $\mathrm{RMe_2CX}$ (X=halogen) increases with the bulkiness of X in the manner 1.21 (X=Cl), 1.68 (X=Br), and 2.84 (X=I) in 80% ethanol at 25 °C.[35] These results show a small but definite trend supporting the leaving group strain effect. However, it appeared to us that the changes were too small to warrant detailed analyses.



58-OPNB **59-OPNB**

60-OPNB **61-OPNB** **60-Cl**

Chart 32.



62

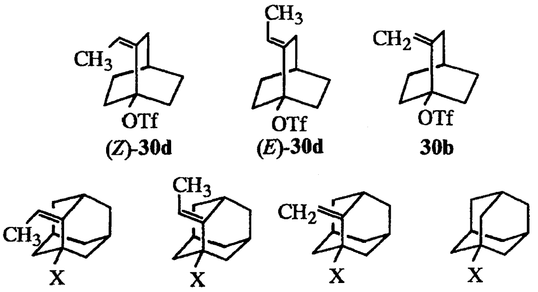
R = *t*-Bu or Me
X = OPNB or $\mathrm{OH_2}^+$

Chart 33.

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 C(2) position (Chart 34).[36—41] Since allylic conjugation in their carbocations had been shown to be insignificant,[29,68] 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. Very recently, Lomas et al. reported that the rate of solvolysis of 1-chlorospiro[adamantane-2,2′-adamantane] (**66**) is about 10^8 times larger than that of 1-chloroadamantane (**65-Cl**) (Chart 35).[93] MM2 calculations indicated that the extremely large acceleration is due very largely to steric interactions between the chloride leaving group and the closest methylene hydrogens on the nonsubstituted adamantyl moiety.[93]

The Large *Z*/*E* Rate Ratios and the Origin. The allylic conjugation is essentially prohibited in the incipient carbocations from **30b**, (*E*)-**30d**, and **28** because of perpendicular relation between the developing cationic p orbital and the methylene π system. The faster rates of (*E*)-**30d** than **30b** and of (*E*)-**63-OMs** than **64-OMs** by respective factors of 6.3 and 11.4 at 25 °C may be principally attributed to the electron-donating character (inductive and hyperconjugative) of the (*E*)-methyl substituent (Table 6).

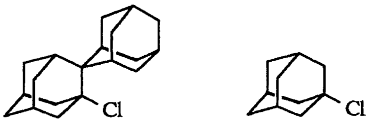
The variation of the leaving group of (*Z*)- and (*E*)-**63-X** significantly influences the *Z*/*E* rate ratio, which increases in the order F (ca. 70 or 28—160), OMs (117±1), Cl (1020±160), Br (2230±90), and I (9500±280) in TFE at 25 °C (Table 6). As discussed below, the large *Z*/*E* rate ratios cannot wholly be ascribed to steric origin. However, they strongly suggest that, in (*Z*)-**63-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*)-**63-X** there would be no serious F-strain between the hydrogen atom in the *Z* position and the leaving



(*Z*)-30d **(*E*)-30d** **30b**

(*Z*)-63-X **(*E*)-63-X** **64-X** **65-X**

Chart 34.



66 **65-Cl**

Chart 35.

Table 6. Rates of Solvolysis[a] and Calculated Steric Energies[b] of 2-Ethylidene and 2-Methylene Bridgehead Compounds

Compound	Solvent	k	Relative rate		Steric energy
		s^{-1}			kcal mol^{-1} [c]
(*Z*)-**30d**	Ethanol	$(4.04\pm0.04)\times10^{-4}$	1370 ± 100	217 ± 6	—[d]
(*E*)-**30d**	Ethanol	$(1.86\pm0.03)\times10^{-6}$	6.3 ± 0.5	1	—[d]
30b	Ethanol	$(2.95\pm0.18)\times10^{-7}$	1		—[d]
(*Z*)-**63-OMs**	Ethanol	$(2.28\pm0.03)\times10^{-6}$	745 ± 90	109 ± 11	20.4[e]
(*E*)-**63-OMs**	Ethanol	$(2.09\pm0.17)\times10^{-8}$	6.8 ± 1.3	1	18.1[e]
64-OMs	Ethanol	$(3.06\pm0.30)\times10^{-9}$	1		—[d]
(*Z*)-**63-OMs**	TFE	$(4.65\pm0.02)\times10^{-2}$	1340 ± 30	117 ± 1	20.4[e]
(*E*)-**63-OMs**	TFE	$(3.96\pm0.02)\times10^{-4}$	11.4 ± 0.3	1	18.1[e]
64-OMs	TFE	$(3.46\pm0.05)\times10^{-5}$	1		—[d]
(*Z*)-**63-F**	TFE	$(6.0\pm2.5)\times10^{-11}$		ca. 70(28-160)	20.8
(*E*)-**63-F**	TFE	$(8.8\pm3.4)\times10^{-13}$		1	19.3
(*Z*)-**63-Cl**	TFE	$(3.95\pm0.21)\times10^{-6}$	6690 ± 1530	1020 ± 160	24.8
(*E*)-**63-Cl**	TFE	$(3.86\pm0.36)\times10^{-9}$	6.5 ± 1.8	1	21.6
64-Cl	TFE	$(5.90\pm0.84)\times10^{-10}$	1		—[d]
(*Z*)-**63-Br**	TFE	$(2.50\pm0.03)\times10^{-4}$	29980 ± 3490	2230 ± 90	26.7
(*E*)-**63-Br**	TFE	$(1.12\pm0.03)\times10^{-7}$	13.4 ± 1.8	1	22.8
64-Br	TFE	$(8.34\pm0.78)\times10^{-9}$	1		—[d]
(*Z*)-**63-I**	TFE	$(9.78\pm0.10)\times10^{-4}$	136200 ± 16350	9500 ± 280	27.5
(*E*)-**63-I**	TFE	$(1.03\pm0.02)\times10^{-7}$	14.3 ± 1.9	1	22.9
64-I	TFE	$(7.18\pm0.71)\times10^{-9}$	1		—[d]

a) At 25.0 °C. b) Calculated by MM2(87). c) 1 kcal mol^{-1}=4.184 kJ mol^{-1}. d) Not calculated. e) The calculations were carried out on the corresponding alcohol as surrogate.

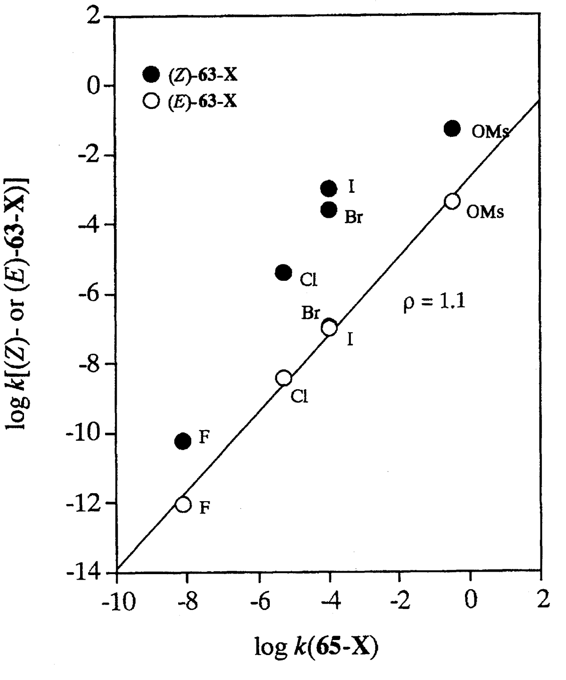


Fig. 4. Plot of log *k* for (*Z*)- and (*E*)-2-ethylidene-1-adamantyl derivatives ((*Z*)- and (*E*)-**63-X**) in 100% TFE against log *k* for 1-adamantyl derivatives (**65-X**) in 97 or 100% TFE at 25 °C.

group. Figure 4 gives a plot of log *k* values for **63-X**'s against those for the corresponding parent 1-adamantyl compounds **65-X** (X=OMs,[94] F, Cl,[83d] Br,[83d] I[95]) in 97% TFE. A good linear correlation with a slope of 1.1 for (*E*)-**63-X**'s indicates the essential absence of an extra F-strain effect. In contrast, the points for (*Z*)-**63-X**'s scatter, supporting the development of F-strain. The result is in striking contrast to the solvolysis of *trans*, *trans*, *trans*-perhydro-9b-phenalyl system **60**, where the marked F-strain in the *p*-nitrobenzoate **60-OPNB** completely vanishes in the chloride **60-Cl**.[90]

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).[96] The $Y_{\rm OTs}$ (=$Y_{\rm 2\text{-}AdOTs}$) values of ethanol and TFE are −1.75 and 1.80, and the respective $N_{\rm OTs}$ values are 0.00 and −3.0.[83b] 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 **63-OMs** are almost identical (109±11 in ethanol, 117±1 in TFE at 25.0 °C) (Table 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 a solvolysis product (1-AdOS) and a decomposition product (1-AdCl).[97] 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. Stoelting and Shiner examined the ^{18}O scrambling of 2-methyl- and 2,2-dimethyl-1-adamantyl pentamethylbenzenesulfonates in 95% ethanol and found respective minimum fractions of internal return of 81 and 89%.[98] Our data provide the values of 92 and 84% for (*Z*)- and (*E*)-**63-OMs**, respectively.[41]

Despite significant internal return in the present solvolyses, the *Z*/*E* rate ratio for k_{sc} is 190±80 (=(7.86±1.46)×10^{-4}/(4.06±0.64)×10^{-6}) in ethanol at 50 °C, which is only twice as large as the *Z*/*E* rate ratio 95±5 (=(7.11±0.11)×10^{-5}/(7.46±0.31)×10^{-7}) for k_t.[41] 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. Due to the lack of parameters of sulfonates, the calculations for mesylates were carried out on the corresponding alcohols as surrogates.

The data of Table 6 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 5 shows a plot of 1.36×log $[k_Z/k_E]$ values against SE_Z–SE_E for 2-ethylidene-1-adamantyl halides and mesylates. A linear correlation with a slope of 1.0 indicates that a change in SE_Z–SE_E on changing he leaving group is exactly reflected to the change in the $\Delta G^{\neq}$ 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 (**67**) (Chart 36) 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*)-**63-X** is more stable than that from (*E*)-**63-X** by 0.8 kcal mol^{-1}. MM2 calculations on 2-ethylideneadamantane (**67**) have indicated that the van der Waals repulsion between the methyl group and the (*Z*) hydrogen and the (*E*) hydrogen by 0.6 kcal mol^{-1}. This value can account for 75% of the intercept value. Ab initio (RHF/6-31G**) calculations show that the (*Z*) cation [(*Z*)-**63**$^+$] is more stable than the (*E*) cation [(*E*)-**63**$^+$] by 1.0 kcal mol^{-1} (vide infra).[41]

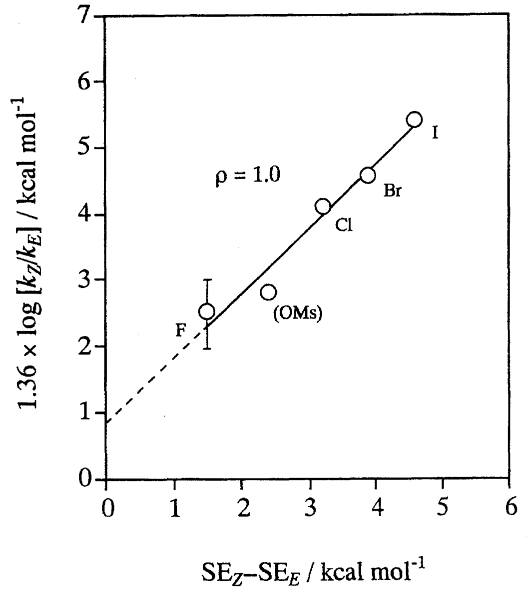


Fig. 5. Plot of 1.36×log $[k_Z/k_E]$ against steric energy difference between (*Z*)-**63-X** and (*E*)-**63-X** calculated by MM2.

Correlation with Hansch's Es. Kutter and Hansch improved Taft's steric parameters E_s by using average van der Waals radii of various substituents.[99] By employing Hansch's E_s as an empirical parameter, we evaluated the *Z*/*E* rate ratios. Figure 6 shows a plot of 1.36×log $[k_Z/k_E]$ values against Hansch's E_s. 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 ($E_s = 0$) is 1.1 kcal mol^{-1}, which is comparable with the intercept obtained in Fig. 5.

Ab Initio Calculations on 2-Ethylidene-1-adamantyl Cations. With a view to seeing the structure and energies of the cations, we optimized (*Z*)- and (*E*)-**63**$^+$ by applying the Gaussian 90 program. The calculated total energies of (*Z*) and (*E*) cations were −464.084295 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}.[41] 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 Figs. 5 and 6. 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

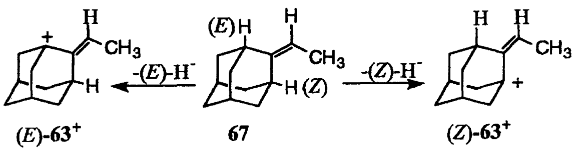


Chart 36.

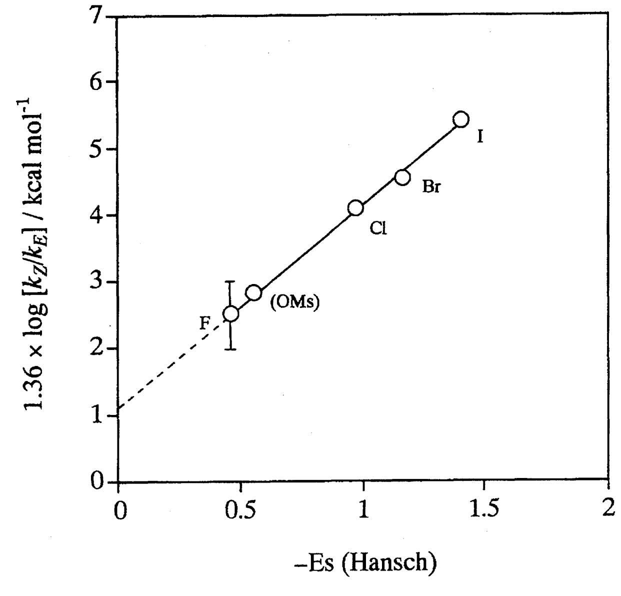


Fig. 6. Plot of 1.36×log $[k_Z/k_E]$ against Hansch's E_s.

from the greater stability of (*Z*)-**63**$^+$ than (*E*)-**63**$^+$ by 0.8—1.1 kcal mol^{-1}. If allowances are made for the rate ratios observed by this factor, the net *Z*/*E* rate ratios ascribed solely to the F-strain effect in the trifluoroethanolysis of **63-X** are 23 (**63-OMs**), ca. 14 (**63-F**), 200 (**63-Cl**), 450 (**63-Br**), and 1900 (**63-I**) at 25 °C.

Kinetic Steric Deuterium Isotope Effects. 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 ways, i.e., hyperconjugative, inductive, and steric effects. The steric effect was proposed by Bartell more than three decades ago,[100] and many pieces of supporting evidence have been reported.[101] 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. 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.

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 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 in TFE at 25.0 °C, respectively) (Chart 37 and Table 7). Hence, the difference between the $(Z/E)_H$ and $(Z/E)_D$ rate ratios would be a good measure for the difference in the F-strain effect between CH_3 and 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 in TFE at 50.0 °C). This indicates that (*Z*)-**63h-I** has greater F-strain than (*Z*)-**63d-I** by as much as 0.04±0.02 kcal mol^{-1}.

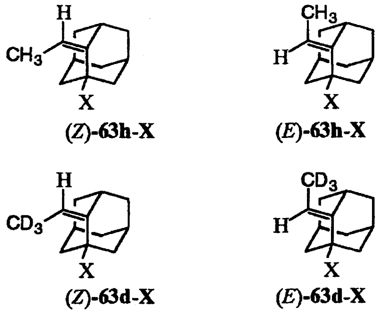

(*Z*)-**63h-X** (*E*)-**63h-X**
(*Z*)-**63d-X** (*E*)-**63d-X**

Chart 37.

On the basis of Bartell's procedure,[100] we estimated the non-bonded isotope effect in (*Z*)-2-ethylidene-1-adamantyl derivatives. Due to a 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[102] and the geometries which were obtained by MM2(87) calculations. The calculated non-bonded isotope effects, 0.007, 0.008, and 0.011 kcal mol^{-1} for (*Z*)-**63-OH** (in place of (*Z*)-**63-OMs**), (*Z*)-**63-Cl**, and (*Z*)-**63-Br**, respectively, are in line with the observed value for (*Z*)-**63-I** of 0.04±0.02 kcal mol^{-1}. MM2(87) calculations also showed resonable values of 0.012, 0.017, 0.020, and 0.023 kcal mol^{-1} for (*Z*)-**63-OH**, (*Z*)-**63-Cl**, (*Z*)-**63-Br**, and (*Z*)-**63-I**, respectively. Hence both Bartell's theory and MM2 appear to give reasonable estimates of steric deuterium isotope effects in solvolysis.

Conclusion

The fixed geometries of substituents in polycyclic (or cage) compounds having rigid frameworks permit detailed studies of electronic and steric effects of various substituents. The lack of freedom of the structural mobility makes the interpretation of experimental results clear-cut. This characteristic enables molecular orbital or molecular mechanics calculations of substrates and intermediates easier than for open-chain and monocyclic systems. Another advantage of the polycyclic compounds is the impossibility for a reagent or a solvent molecule to access from the rear side of a bridgehead position. These characteristics have been fully utilized in quantitatively assessing the magnitude of through-bond stabilization of carbocations by the oxo group located on

Table 7. Solvolysis Rates, CD_3/CH_3 Rate Ratios and *Z*/*E* Rate Ratios for 2-Ethylidene-1-adamantyl Derivatives in TFE

Compound	Temp	k	CD_3/CH_3	Z/E rate ratio[a]	
	°C	s^{-1}	rate ratio[a]	for CH_3	for CD_3
(*E*)-**63h-OMs**	25.0	$(3.961\pm0.023)\times10^{-4}$	1	1	
(*E*)-**63d-OMs**	25.0	$(3.998\pm0.018)\times10^{-4}$	1.009±0.010		1
(*Z*)-**63h-OMs**	25.0	$(4.646\pm0.022)\times10^{-2}$	1	117±1	
(*Z*)-**63d-OMs**	25.0	$(4.624\pm0.023)\times10^{-2}$	0.995±0.013		116±1
(*E*)-**63h-I**	50.0	$(2.507\pm0.019)\times10^{-6}$	1		1
(*E*)-**63d-I**	50.0	$(2.597\pm0.021)\times10^{-6}$	1.036±0.016		1
(*Z*)-**63h-I**	50.0	$(1.357\pm0.004)\times10^{-2}$	1	5413±57	
(*Z*)-**63d-I**	50.0	$(1.322\pm0.004)\times10^{-2}$	0.974±0.008		5090±58

a) The ratios are at 25.0 °C for mesylates and at 50.0 °C for iodides.

the C(3) position, and also in developing some systems that show marked solvolysis reactivities attributed to the F-strain effect. On the other hand, by making the polycyclic system more and more flexible, the overlap between the bridgehead vacant p orbital and the adjacent π system such as a methylene or an oxo substituent can be increased. As exemplified in this Account, this tool may be effectively used in evaluating the π conjugative ability of various unsaturated substituents. In executing such studies the development of new synthetic methods is indispensable.

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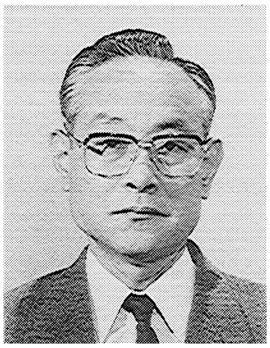

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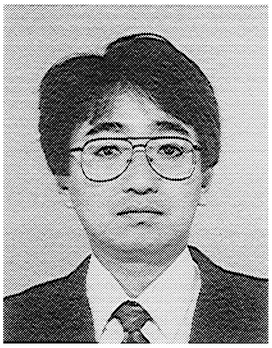

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