Acetolysis of 4-Homoadamantyl Tosylate. Multiple Degenerate Rearrangements and Mechanism[1]

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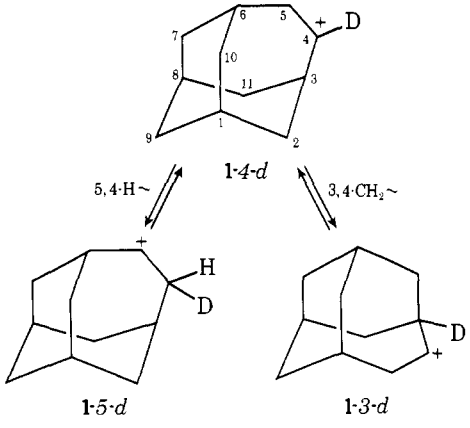
Abstract: Buffered acetolysis of 4-homoadamantyl tosylate (**6**) at 40 °C produces 75% of 4-homoadamantyl aacetate (**7**) and 25% of 4-homoadamantene (**8**). It is shown by deuterium labeling that the substitution process is accompanied by full degenerate stereospecific Wagner–Meerwein equilibration of the 4-homoadamantyl cation, **1**, together with its partial degenerate rearrangement by vicinal hydride shift. The nonstereoselectivity of the hydride migration and the absence of kinetic evidence for anchimeric assistance argue against a carbon-bridged structure for the intermediate carbenium ion, **1**. The elimination reaction, in contrast, is evidenced to involve preliminary Wagner–Meerwein equilibration but no appreciable hydride shift and is predominantly a syn E1 process. These and related results are interpreted as indicating that elimination takes place wholly from an initially formed Wagner–Meerwein pair of nonepimerizing intimate ion pairs, that irreversible dissociation of the latter precedes hydride migration, and that the formation of acetate takes place principally from solvent-separated ion pairs.

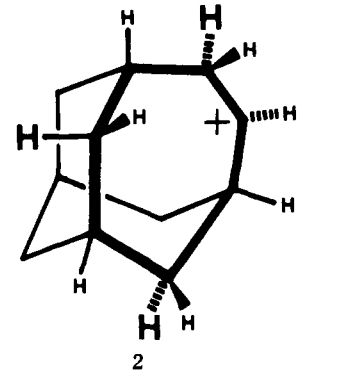
The analysis of multiple degenerate rearrangements in solvolytic or stable carbocations has provided insight into a number of dynamic systems.[2] In most of these a single type of rearrangement has been involved, usually a 1,2-carbon shift. Our attention has been directed to a system potentially degenerate under two different rearrangement processes, whose analysis under solvolytic reaction offered the prospect of extensive mechanistic information. The 4-homoadamantyl (4-tricyclo[4.3.1.1^{3,8}]undecyl) cation, **1**, is degenerate with respect both to Wagner–Meerwein rearrangement and to vicinal hydride shift, the two processes being distinguishable on the basis of deuterium label transpositions, as illustrated for **1**-*4*-*d*. We



have conducted a program of deuterium redistribution studies and rate measurements for solvolyses of 4-homoadamantyl tosylate (**6**) in several media. The results have, in fact, provided particular insight into the timing and stereochemistries of substitution, elimination, and ion pair return in this system and have allowed the formulation of mechanism in unusual detail. We report here our data and conclusions for the acetolysis reaction.

Several limiting rearrangement possibilities are apparent a priori. In terms of localized and unencumbered carbenium ions the potential degeneracy of **1** may be expressed as 11-fold with respect to carbon; by stereochemically unrestricted methylene and hydride shifts the charge could be exchanged among all of the carbon atoms with preservation of the skeletal identity. Under solvolysis conditions, however, ion pairing might be expected to impose a constraint of backside stereospecificity[3] upon both rearrangements. The consequences of this restriction are presented in structure **2**, in which a counterion is understood to be paired at the front side of the carbenium charge site. Peregrination of the charge under these conditions would be limited to one seven-membered face. Furthermore, only the large-type hydrogens in **2**, i.e., methylene hydrogens trans to the leaving group, could underrgo migration, while only the small-type hydrogens could become located at the charge site.

Also to be considered for 4-homoadamantyl cation is a symmetrically σ-delocalized structure, **3**. Direct formation of **3** from tosylate **6** would again entail backside methylene



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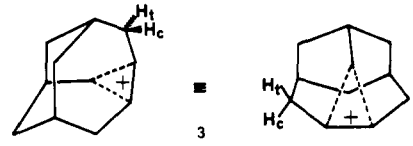

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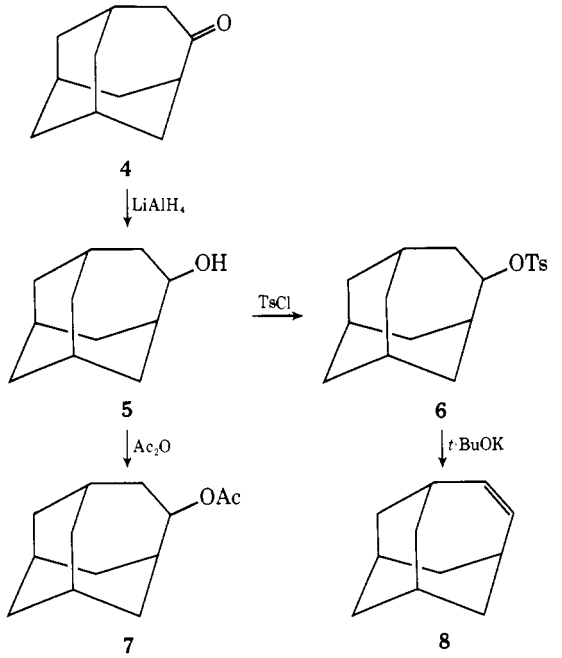
bridging. Vicinal hydride migration, however, would be predicted here to involve a hydrogen cis to the gegenion, H_c in **3** (discussed further below). The stereochemistry of degenerate hydride shift, then, offers a distinctive test for carbon bridging in the 4-homoadamantyl cation, a question of general concern in alicyclic carbocations, most notably the 2-norbornyl ion.[4]

Recently Majerski[5a-d] and Yamaguchi[5e] and respective co-workers have published studies of the chemistry of the 4-homoadamantyl cation generated under conditions complementary to those we have employed. Their results contrast with ours, as will be discussed, and demonstrate a marked dependence of the behavior of this species on its immediate environment.

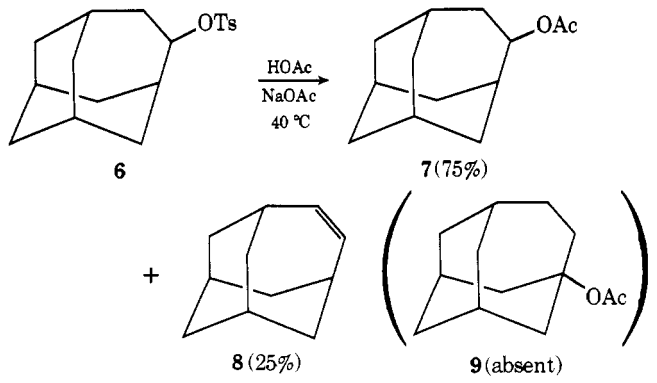
Results and Discussion

Synthesis. 4-Homoadamantanone (**4**) was prepared by the homologation of adamantanone, initially by a Tiffeneau–

Demjanov sequence[1a,6] and subsequently by the more direct reaction with diazomethane in methanol.[1b,7] 4-Homoadamantanone exhibits an unusually low ketone stretching frequency, 1698 cm^{-1} by our measurement (others have reported 1697,[1b] 1695,[7b,c] and 1700[6b] cm^{-1}); cf. cyclohexanone, 1714,[8] 1715[9] and cycloheptanone, 1702,[8] 1705[8,9] cm^{-1}. The special constraints of this ring system thus act to distend the C–CO–C bond angle significantly beyond its normal value.[10] Lithium aluminum hydride reduction of **4** gave 4-homoadamantanol (**5**)[1b,7b] from which the tosylate, **6**, and acetate, **7**, were prepared in the usual manner. Treatment of the tosylate with potassium *tert*-butoxide in *tert*-butyl alcohol furnished homoadamantene (**8**).[7b]



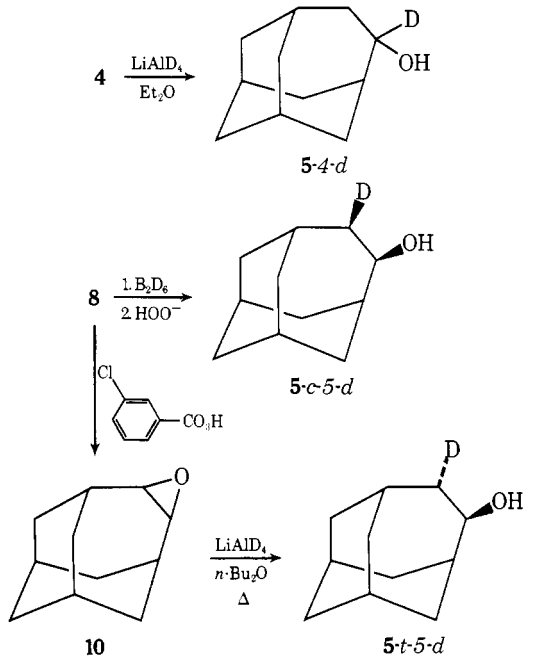
Acetolysis Products. The products (88% yield, 0.014-mol scale) of sodium acetate buffered acetolysis of 4-homoadamantyl tosylate (**6**) at 40 °C were readily identified as 75% 4-homoadamantyl acetate (**7**) and 25% homoadamantene (**8**). Control experiments showed the separate products to be stable to the reaction conditions, ruling out elimination–addition as a substitution route and substitution–elimination as a source of olefin.



3-Homoadamantyl acetate (**9**),[11] the product of possible 3,4-hydride shift, was specifically found absent from the product mixture (within gas chromatographic detectability of 0.5%). Models indicate that orbital overlap should be poor in thee transition state for this rearrangement; in the case of the 2-adamantyl cation, intramolecular shifts from the bridgehead have been shown to be strictly prohibited.[12]

Deuterium Labeling and Redistribution Analyses. Our experimental design was the solvolysis of 4-homoadamantyl tosylates labeled separately with deuterium at the 4, cis-5, and trans-5 positions, followed by isotopic analysis of the 4 and 5 positions of the products. Preparations of the required alcohols were conducted as outlined in Scheme I. In each case the extent

Scheme I



of deuterium incorporation was established mass spectrometrically using the derived trimethylsilyl ether. Degradative procedures together with mass spectrometry (MS) confirmed the labeling specificities (see Experimental Section).

Of note in the preparation of trans-5-d labeled alcohol, **5-*t*-5-*d***, was the low reactivity of homoadamantene oxide (**10**) toward lithium aluminum hydride or deuteride. Conversion to homoadamantanol (**5**) during 12 h was negligible in either ether or tetrahydrofuran at the boiling points. The reaction was successful in boiling di-*n*-butyl ether (142 °C). The effect is evidently one of steric hindrance to backside attack by hydride. Similar behavior is exhibited, for example, by *exo*-norbornene oxide[13] and certain steroidal epoxides.[14] Likewise, *cis*-4,5-homoadamantenimine has been reported[6b] to be exceptionally resistant to ring openings by azide ion or carbon disulfide.

The acetate and olefin products of acetolysis of the labeled 4-homoadamantyl tosylates were analyzed for total deuterium and for that at the 4 and 5 positions according to Scheme II. Total deuterium in the acetate was measured by MS after conversion to the trimethylsilyl ether, **11**, while that in the olefin was determined directly. Alcohol from the acetate was then oxidized to the ketone (under conditions shown to effect no α-proton exchange in the product), whose mass spectrum gave by difference the fraction of 4-d acetate. The 5-d content was determined similaryl after either further oxidation to the 4,5-diketone, **12**,[6b] or else base-catalyzed exchange of deuterium from the ketone 5 position into water. Label analysis of the olefinic products was completed by removal of deuterium from the vinylic positions through the sequence hydroboration–oxidation–oxidation to the ketone plus further oxidation or exchange, as above, and repeated MS.

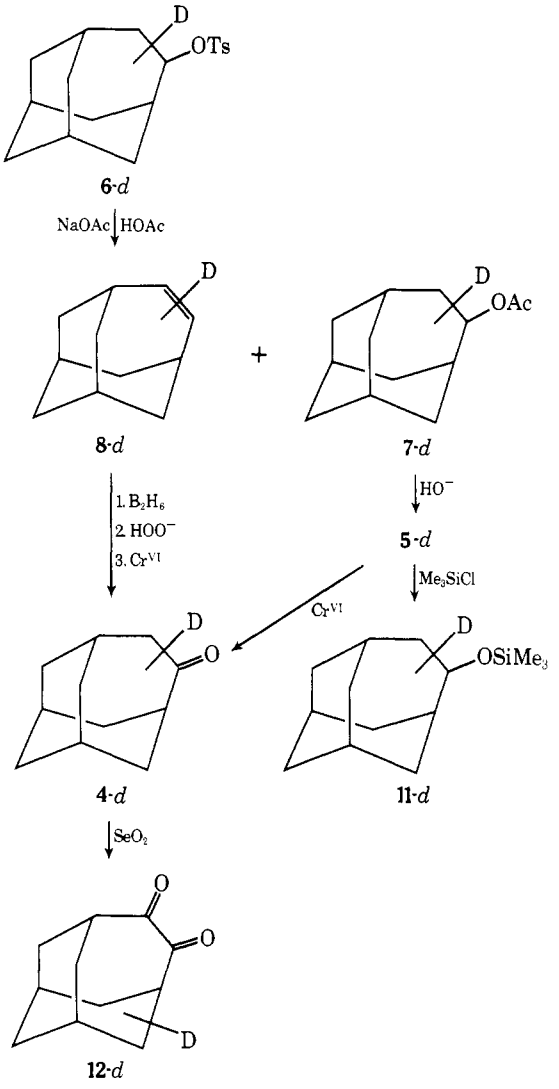
Label Redistribution Results. The analyses of label distribution in the acetolysis products of the deuterated 4-homoadamantyl tosylates are collected in Table I.[15] Each datum is an average for ten mass spectral scans, with precisions consistently better than 0.5%. The accuracies of the data are subject to somewhat larger uncertainties, derived from isotope effects during chemical degradations and mass spectral fragmentations and from possible background impurities and in-

Table I. Label Distributions[a] in the Acetolysis Products of Deuterated 4-Homoadamantyl Tosylates

Label position in tosylate **6**	Acetate product **7**			Olefin product **8**	
	Total % d	% 4-d	% 5-d	Total % d	% vinylic-d
4-d	99.6	40.7	5.4	99.8	45.3
cis-5-d		1.1	36.6	77.1	10.2
trans-5-d		2.1	37.2	98.1	48.5

[a] Product analyses normalized to reactant tosylate as 100.0% d_1.

Scheme II



strumental nonlinearity in mass spectrometry (see Experimental Section). We estimate that single measurements on the solvolysis products and their exocyclic derivatives—the total percent deuterium values of Tables I and II—are accurate to ±1.0% with high confidence. The remaining data in the tables are differences between two measurements, one following degradation on the ring, and are considered accurate to ±2.5%.

A. Counterion Return. Gegenion return was demonstrated by partial acetolysis of the α-deuterated substrate, **6-4-*d***. After 1.0 half-life (for the unlabeled reactant) at 40.0 °C recovered tosylate had 63% 4-d label (37% 4-h) by NMR analysis. As discussed below, the results of olefin-product label analysis demonstrate that the tosylate return occurs without appreciable 5,4-hydride shift or epimerization. Isotopic rearrangement of the tosylate, then, must be a Wagner–Meerwein process and is concluded below to take place entirely within first-formed tight ion pairs. (The observation of clean first-order kinetics for **6**, below, establishes the absence of return by free counterions.)

If full Wagner–Meerwein equilibration is assumed to accompany each ionization of tosylate, the rate of ionization, k_i, relative to solvolysis, k_t, may be derived from the fraction of unconsumed substrate, F_{recov}^{ROTs}, and the fraction of 4-d label in recovered reactant, $F_{4\text{-}d}^{ROTs}$, by eq 1. Adopting an approximate overall isotope-effect correction[16] of $k_h/k_d = 1.20$ for **6-4-*d***,

$$\frac{k_i}{k_t} = 1 + \frac{\log (2F_{4\text{-}d}^{ROTs} - 1)}{\log F_{recov}^{ROTs}} \quad (1)$$

including progressive 4-d dilution, the results correspond to $k_i/k_t = 3.3$; the fractional conversion of ion pairs to products is 0.30.

B. Acetate Products. Of first interest in the data of Table I is the formation of 40.7% 4-d acetate from 4-d tosylate. If either degenerate stereospecific Wagner–Meerwein or hydride-shift equilibration were complete, in the absence of the other, before product formation, 50% 4-d acetate would be produced (ignoring secondary isotope effects for the moment). Less than full equilibration would lead to >50% of this species. At the other extreme, complete equilibration of both types prior to solvent capture would leave $^1/_{17}$ = 5.9% of one deuterium at the 4 position in the absence of stereochemical restrictions, or $^1/_7$ = 14.3% under stereospecific backside methylene shift together with either front- or backside hydride migration. The experimental result suggests that full equilibration is attained through one of the two mechanisms while the other takes place in competition with acetate formation. This hypothesis is substantiated in the finding, presented below, that the olefinic product, **8**, is produced with complete Wagner–Meerwein equilibration but without hydride shift.

The generation of 5.4% 5-d acetate from 4-d tosylate demonstrates the significant incidence of 5,4-hydride shift in the course of the substitution process and accords also with the establishment of Wagner–Meerwein equilibration before product formation. If this were true instead for the hydride-shift rearrangement, the acetate would have equal 4-d and 5-d contents, taking hydride migration to be stereospecific, or else twice as much 5-d as 4-d, if hydride shift were stereorandom (again discounting secondary isotope effects).

To a first approximation the yield of 4-d acetate signifies that 100 − 2(40.7) = 18.6% of the substitution product is formed with net hydride shift. Taking account of an α-deuterium isotope effect on the Wagner–Meerwein equilibrium **1-4-*d*** ⇄ **1-3-*d***, however (see the olefin-product analysis below), would reduce this figure somewhat.

The simplest mechanistic hypothesis by which the data for 4-d acetate from 4-d tosylate may be treated is that presented in our preliminary communication,[1a] based on the stereochemical restrictions discussed above in association with structure **2**. Steady-state treatment of the intermediates in that scheme yields the relationship of eq 2[17] between the fraction, $F_{4\text{-}d}^{ROAc}$, of 4-d acetate from 4-d tosylate and the competitive rate constants k_h and k_p for hydride shift and acetate product formation, respectively. Equation 3, in turn, expresses the fraction of 5-d acetate from 4-d tosylate in terms of k_h and k_p.

$$F_{4\text{-}d}^{ROAc} = \frac{k_h^3 + 6k_h^2k_p + 10k_hk_p^2 + 4k_p^3}{7k_h^3 + 28k_h^2k_p + 28k_hk_p^2 + 8k_p^3} \quad (2)$$

$$F_{5\text{-}d}^{ROAc} = \frac{k_h^3 + 3k_h^2k_p + 2k_hk_p^2}{7k_h^3 + 28k_h^2k_p + 28k_hk_p^2 + 8k_p^3} \quad (3)$$

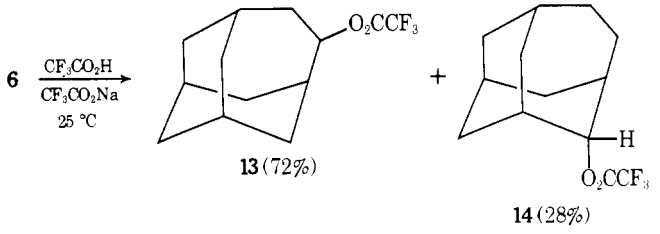
Equations 2 and 3 accommodate well the acetate product data from 4-d tosylate. From $F_{4\text{-}d}^{ROAc} = 0.407$, Table I, eq 2 gives

$k_h/k_p = 0.256$.[15] Insertion of this result into eq 3 generates 0.042 as the expectation value for $F_{5\text{-d}}^{ROAc}$; the experimental result is 0.054. The close agreement, at the least, supports effectively the hypothesis that Wagner–Meerwein equilibration is achieved prior to competitive solvent capture and hydride migration.

Consideration of the additional acetate data in Table I, however, shows this first mechanism to be an oversimplification. For stereospecific trans-hydride shifts, trans-5-d labeled 4-homoadamantyl tosylate should afford no 4-d acetate product. For exclusive cis-hydride shifts, on the other hand, no 4-d acetate should be produced from cis-5-d tosylate. The experimental indication is that neither limiting possibility is obeyed. From *cis*- and *trans*-4-homoadamantyl-*5-d* tosylate 1.1% and 2.1%, respectively, of 4-d acetate was observed, indicating negligible stereoselectivity in degenerate vicinal hydride shift. Consistent with these closely similar results are the 36.6 and 37.2% of 5-d acetates formed, respectively, from the cis- and trans-5-d tosylates.

The stereochemistry of hydride shift is a point of particular mechanistic significance, but conclusions from the foregoing data are qualified by the smallness of the measured values of 4-d acetate from the epimeric 5-d tosylates. More secure evidence was sought in solvolysis conducted in a less nucleophilic medium, where more extensive hydride migration would be anticipated. Trifluoroacetic acid was chosen for this purpose, based on its marked enhancement of carbocation rearrangements in other systems.[18]

C. Trifluoroacetolysis Products. The sodium trifluoroacetate buffered trifluoroacetolysis of 4-homoadamantyl tosylate (**6**) at 25 °C proceeded rapidly to yield essentially quantitatively a mixture of 72% of 4-homoadamantyl trifluoroacetate (**13**) and 28% of an isomeric ester identified as *exo*-2-homoadamantyl trifluoroacetate (**14**).[19] The synthesis and



13 (72%) **14** (28%)

characterization of the epimeric 2-homoadamantanols have been recently reported by Murray and co-workers[20] and Kawanisi and co-workers.[20] Repetition of the reaction with deuterated tosylates furnished 4-homoadamantyl trifluoroacetates whose label distributions are presented in Table II.

Control experiments were conducted concerning the origin of **13**. 4-Homoadamantyl-*4-d* trifluoroacetate (**13-*4-d***) was found to be stable to the solvolysis conditions, but the possibility of an elimination–addition sequence was raised by the observation of clean rapid addition of trifluoroacetic acid to homoadamantene (**8**) at 25 °C to yield 83% of **13** and 17% of **14**.

$$\mathbf{8} \xrightarrow[CF_3CO_2Na]{CF_3CO_2H} \underset{83\%}{\mathbf{13}} + \underset{17\%}{\mathbf{14}}$$

Evidence that this pathway was not involved in the solvolysis reaction, however, was provided by the trifluoroacetolysis of 5,5-dideuterated tosylate, **6-*5,5-d*$_2$**, to produce trifluoroacetate **13** without appreciable deuterium loss, as shown in Table II.

As expected, hydride shift is more extensive in trifluoroacetic acid, the 4-d tosylate returning only 30.1% 4-d label in the 4-homoadamantyl trifluoroacetate product (cf. 40.7% in acetic acid). Of chief significance, the cis- and trans-5-d tosylates gave 5.4 and 5.3% 4-d trifluoroacetate, respectively, demonstrating again no stereoselectivity in the hydride migration,

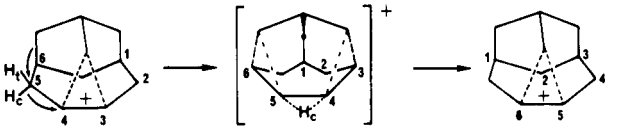
Table II. Label Distributions[a] in the 4-Homoadamantyl Products from Trifluoroacetolysis of Deuterated 4-Homoadamantyl Tosylates

Label position in tosylate **6**	Trifluoroacetate **13**		
	Total % d	% 4-d	% 5-d
4-d		30.1	5.1
cis-5-d		5.4	22.0
trans-5-d		5.3	21.8
5,5-d_2	99.0		

[a] Product analyses normalized to reactant tosylate as 100.0% d_1.

this time on the basis of values well beyond experimental uncertainty. The data for residual 5-deuterium in trifluoroacetates **13** from the epimeric 5-d tosylates are likewise essentially identical.

The distinct absence of hydride-shift stereospecificity in the trifluoroacetolysis of 4-homoadamantyl tosylate appears decisively inconsistent with direct formation of a fully σ-delocalized carbonium ion, **3**. Degenerate hydride shift in such a structure, **3** → **3'**, would seem strongly preferred stereoelectronically for the migration of hydrogen cis to the leaving group, H_c in **3**, i.e., trans and backside to the bridging carbon.[21] This pathway, but not that for H_t transposition, would permit a transition state with incipient new bridging, **15**.



3 **15** **3'**

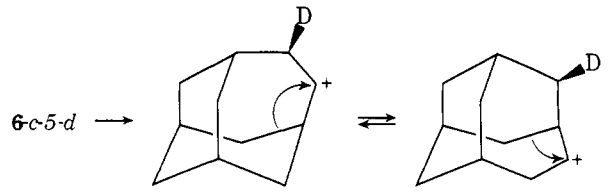
The results do not exclude, however, the production of bridged ion **3** as a second-stage intermediate from initially formed localized ion **1**. This possibility offers an attractive pathway for conversion of the 4- to the 2-homoadamantyl cation and thence 2-homoadamantyl ester, **14**. The corresponding 1,3-hydride shift would be facilitated by taking place within the protonated cyclopropane **3**.[19]

Since trifluoroacetic acid, by reason of its weak nucleophilicity, offers poor specific solvation to cations,[18] intramolecular modes of carbonium ion stabilization—bond polarization and neighboring group effects—are emphasized in this solvent relative to more nucleophilic media.[18] The evidence against direct formation of bridged carbonium ion **3** in trifluoroacetic acid, therefore, may be taken to disqualify it as well from the acetolysis mechanism (in accord with the rate data, below).

D. Olefin Products. Further insight into the acetolysis mechanism is provided by label-position analysis of the homoadamantenes formed from the deuterated 4-homoadamantyl tosylates, Table I.

Prominently, the nearly complete deuterium retention in acetolytic elimination from the trans-5-d tosylate reveals that loss of the elements of *p*-toluenesulfonic acid is predominantly a syn process. The stereochemical preference is reinforced in this reactant by a primary isotope effect which would operate against deuterium loss from the trans-5 position. Qualitatively in agreement with favored syn elimination is the 22.9% loss (77.1% preservation) of deuterium from cis-5-d tosylate on olefin formation. That the loss of label here is substantially less than 50% points to Wagner–Meerwein interconversion, **1-*c-5-d*** ⇄ **1-*enndo-2-d***, prior to hydrogen loss, with most of the syn elimination occurring for protium from the latter ion rather than for deuterium from the former (first-formed ion).

Additional evidence on the elimination stereochemistry is the finding that the olefin from cis-5-d tosylate retains 10.2% *vinylic* deuterium. This result is inconsistent with wholly syn elimination, by which no retained deuterium would be vinylic.



1-*c*-5-*d* 1-*endo*-2-*d*

The collective data show qualitatively that syn elimination is distinctly but not exclusively preferred.

A complementary result is the 48.5% vinylic deuterium content of the homoadamantene from trans-5-d tosylate. The closeness of this value to 50% suggests a mechanism in which elimination takes place subsequent to Wagner–Meerwein equilibration but without the incursion of any hydride shift, in contrast to the significant hydride shift found to have occurred in acetate product formation.

This hypothesis is supported by the data from 4-d labeled reactant, where no deuterium is lost and the homoadamantene contains 45.3% vinylic deuterium. Here the initially formed carbenium ion, **1**-*4*-*d*, should be disfavored by an α-deuterium isotope effect relative to its Wagner–Meerwein congener, **1**-*3*-*d*, which should reduce to slightly below 50% the fraction of deuterium at vinylic carbon in the product, as observed.

Elimination Mechanism. Quantitative treatment of the elimination reaction as an E1 process with Wagner–Meerwein equilibration, but without hydride shift, may be developed from Scheme III, which traces the products from cis- and trans-5-deuterated tosylates. Let F_{vd}^{c} and F_{zd}^{c} be the fractions of 4-homoadamantene from cis-labeled reactant which possess a vinylic deuterium and zero deuterium (beyond normal isotopic abundance), respectively, F_{vd}^{t} and F_{zd}^{t} be the corresponding data from the trans-labeled substrate, k^{h}_{syn} and k^{h}_{anti} be thee rate constants for elimination from the carbenium ion of protium syn and anti, respectively, with reference to the tosylate group, and k^{d}_{syn} and k^{d}_{anti} be the corresponding values for deuterium elimination. Equations 4 and 5 relate F_{vd}^{c} and F_{zd}^{c}, respectively, to the pertinent rate constants.[22]

$$F_{vd}^{c} = \frac{k^{h}_{anti}}{2k^{h}_{anti} + k^{h}_{syn} + k^{d}_{syn}} \quad (4)$$

$$F_{zd}^{c} = \frac{k^{d}_{syn}}{2k^{h}_{anti} + k^{h}_{syn} + k^{d}_{syn}} \quad (5)$$

Simultaneous solution of these equations yields the syn/anti rate ratio for protium loss, eq 6, and the primary isotope effect for syn deuterium loss, eq 7, in terms of the experimentally observed deuterium distributions.

$$\frac{k^{h}_{syn}}{k^{h}_{anti}} = \frac{1 - 2F_{vd}^{c} - F_{zd}^{c}}{F_{vd}^{c}} \quad (6)$$

$$\frac{k^{h}_{syn}}{k^{d}_{syn}} = \frac{1 - 2F_{vd}^{c} - F_{zd}^{c}}{F_{zd}^{c}} \quad (7)$$

By analogous derivation for the pathways from trans-5-d substrate, eq 8 and 9 result, the former an independent measure of the syn/anti protium-loss rate ratio and the latter the primary isotope effect for anti elimination.

$$\frac{k^{h}_{syn}}{k^{h}_{anti}} = \frac{F_{vd}^{t}}{1 - 2F_{vd}^{t} - F_{zd}^{t}} \quad (8)$$

$$\frac{k^{h}_{anti}}{k^{d}_{anti}} = \frac{1 - 2F_{vd}^{t} - F_{zd}^{t}}{F_{zd}^{t}} \quad (9)$$

Insertion of the data from Table I generates values for k^{h}_{syn}/k^{h}_{anti} of 5.56 (eq 6) and 44.1 (eq 8), with k^{h}_{syn}/k^{d}_{syn} = 2.48 and $k^{h}_{anti}/k^{d}_{anti}$ = 0.579. The independent evaluations of k^{h}_{syn}.k^{h}_{anti} are thus in disagreement, while the isotope effect for anti elimination is unrealistically inverse. These anomalies result, however, from the sensitivities of the functions of eq 8 and 9 to the experimental data from trans-5-d substrate. A reconciliation was achieved by computer survey of the functions of eq 6–9 under variation of the isotope-distribution data within the limits of experimental uncertainty. The best fit is found for F_{zd}^{c} = 0.224 and F_{zd}^{t} = 0.020, both values within 0.5% of the experimental data, and F_{vd}^{c} = 0.078 and F_{vd}^{t} = 0.461, both values within 2.4% of the experimental data, whereby k^{h}_{syn}/k^{h}_{anti} = 7.95 together with reasonable[23] isotope effects k^{h}_{syn}/k^{d}_{syn} = 2.77 and $k^{h}_{anti}/k^{d}_{anti}$ = 2.90.

A possible contribution to the remaining discrepancies could be a slight incursion of ion pair epimerization competitive with elimination. The results leave little doubt, however, that any such rearrangement occurs to a very minor extent and that acetolytic elimination proceeds by an E1 mechanism essentially according to Scheme III, with predominant syn stereochemistry. Our conclusion conflicts with the recent judgment of Cavazza[24] that acetolytic elimination from 2-butyl reactants occurs by a concerted mechanism.

Skell and Hall[25] in 1963 observed that in solvolyses of 2-butyl-*3*-*d* tosylates the degree of syn elimination increased with decreesing solvent basicity. They proposed that proton removal in the syn pathway was effected from the carbenium ion intermediate by tightly paired tosylate ion. Several subsequent workers have invoked this gegenion-as-base mechanism in explanation of other syn E1 eliminations.[26]

This hypothesis finds attractive application to the present elimination results for the 4-homoadamantyl system. The fact that the formation of olefin, in contrast to that of acetate, takes place without hydride shift may be restated to signify that once hydride shift does occur within the first Wagner–Meerwein carbenium ion pair only acetate product ensues. This departure is most reasonably rationalized by tight ion pair dissociation concomitant with hydride shift. Either the gegenion cannot maintain a contact relationship with the carbenium center under transposition through hydride migration and rapid second-generation Wagner–Meerwein equilibration, or, as will be argued below, intimate ion pair dissociation is prerequisite to hydride shift. The failure of 4-homoadamantyl cations not tightly anion paired to undergo significant elimination and the predominant syn stereochemistry of elimination from the first-generation tightly paired cations are jointly accommodated by considering the effective base in syn elimination to be contact tosylate ion. A rationalization for the remaining requirement of tight ion pairing for the minor anti elimination, where the base is presumably acetic acid or acetate ion, is as follows. From the tight ion pair direct acetate product formation is sterically precluded at the frontside by the gegenion and could well be sterically disadvantaged by the ring system at the backside relative to elimination; the latter requires attack by a solvent species only at a peripheral atom (H) rather than a less accessible frame atom (C). Subsequent to first-stage ion pair dissociation substitution could be enhanced relative to elimination by skeletal relaxation or by solvent polarization within the field of the opposite ions at the frontside[27] (see the discussion of stereochemistry below.)

Rate Studies. Kinetics have been determined for the solvolysis of 4-homoadamantyl tosylate in acetic acid and in trifluoroacetic acid (TFA). Good first-order behavior was observed throughout. The data are collected in Table III. (Owing to the relatively narrow temperature range of the trifluoroacetolysis measurements, the resultant activation entropy may not be closely accurate. The five rate constants, however, fit an Eyring plot with an average deviation for the observed values of only ±0.41%.)

The rate data have been subjected to two mechanistic analyses.

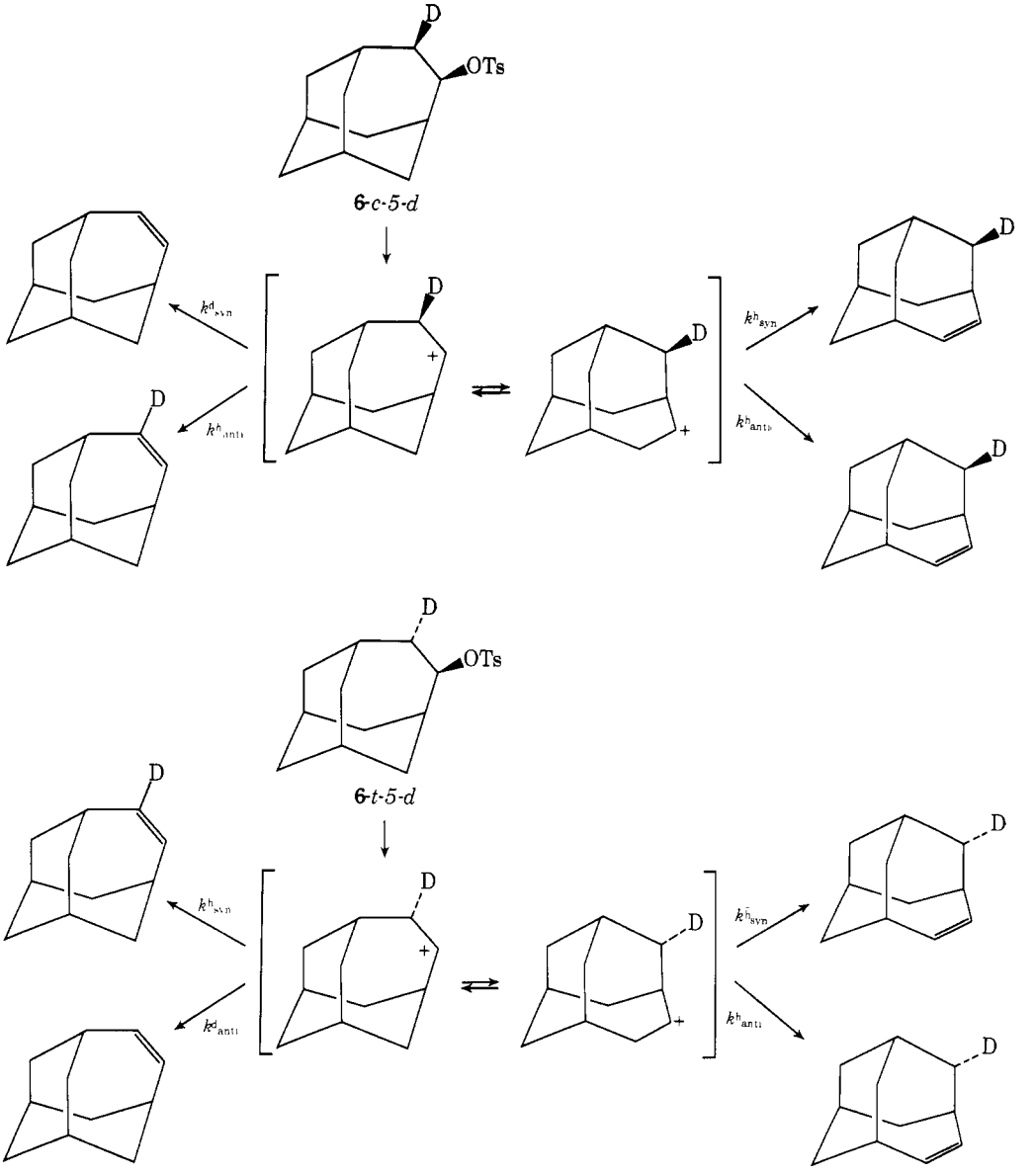
Foote[9] and Schleyer[28] have correlated secondary tosylate acetolysis reactivities with corresponding ketone stretching frequencies and torsional energy changes on ionization. While

Table III. Rate Data for Solvolyses of 4-Homoadamantyl Tosylate (**6**)

Acetic acid[a]				Trifluoroacetic acid[b]			
Temp, °C	$10^5 k_1$, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	Temp, °C	$10^2 k_1$, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
55.0	49.7			25.0	22.6[c]		
40.0	8.17	22.7	−4.9	22.0	18.6		
25.0	1.35[c]			18.0	14.6	10.3	−27.0
24.9	1.34			16.0	12.8		
				14.3	11.4		
				7.8	7.32		

[a] Purified acetic acid containing 1.0 wt % acetic anhydride; initial substrate concentrations ca. 0.07 M. [b] Purified trifluoroacetic acid containing 0.060 M sodium trifluoroacetate and 1.0 wt % sodium trifluoroacetate; initial substrate concentrations ca. 0.006 M. [c] Interpolated or extrapolated from the data at other temperatures.

Scheme III



the method ignores contributions to the solvolysis rate from nucleophilic solvent participation,[29] differential ion pair return,[30] and steric hindrance to ionization,[4j,k,31] it does show significant upward deviations of experimental rates from those predicted for a number of substrates believed independently to undergo carbon-assisted ionization.

Models of **6** reveal no clearly preferred conformation around the functional position, but a range of reasonable dihedral-angle combinations, ϕ_i, was charted[6a] which led to limits for the value of the torsional term. In this manner 4-homoadamantyl tosylate was predicted to react faster than cyclohexyl tosylate by a factor of from $10^{3.94}$ (ϕ_i = 28, 46°) to $10^{4.76}$ (ϕ_i = 60, 0°, i.e., an untwisted two-carbon bridge).[32] Experimentally, **6** undergoes acetolysis at 25 °C 275 = $10^{2.44}$ times faster than cyclohexyl tosylate ($k = 4.88 \times 10^{-8}$ s^{-1}),[34] a rate *slower* than predicted by from $10^{1.50}$ to $10^{2.32}$, indicating the

importance of factors other than those included in the original correlation.[9,28] In any event, the results provide no evidence for anchimeric assistance to ionization of 4-homoadamantyl tosylate. This conclusion complements that reached earlier against the intermediacy of bridged ions, **3**, on the basis of the absence of stereoselectivity in hydride migration.

The second test applied was that recently developed by Schleyer et al.[29] for the estimation of nucleophilic solvent contributions to rates of secondary alkyl sulfonates (ROTs), given by the following equation (2-Ad = 2-ademantyl):

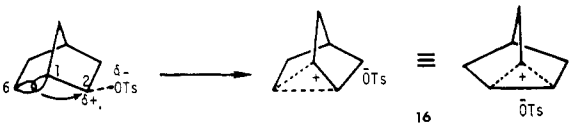
$$\left(\frac{k_s}{k_c}\right)^{\mathrm{ROTs}}_{\mathrm{solvent}} = \frac{(k_{\mathrm{ROTs}}/k_{\text{2-AdOTs}})_{\mathrm{solvent}}}{(k_{\mathrm{ROTs}}/k_{\text{2-AdOTs}})_{\mathrm{TFA}}} \qquad (10)$$

By this measure $(k_s/k_c)_{\mathrm{HOAc}}$ for 4-homoadamantyl tosylate = 9.0, which may be compared with values in the literature[35] for isopropyl tosylate, 547; cyclopentyl tosylate, 93; and *endo*-2-norbornyl tosylate, 30. The 4-homoadamantyl acetolysis thus receives meager nucleophilic solvent assistance; its mechanism is indicated to be close to the k_c limit. This result could be anticipated from the similarity of steric limitations to backside accessibility of the 4-homoadamantyl and 2-adamantyl structures.

Overall Mechanism. The collective results allow stepwise formulation of the acetolysis mechanism in the following detail.

Ionization of 4-homoadamantyl tosylate takes place without participation by neighboring carbon or hydrogen (beyond ordinary hyperconjugative stabilizations) to form a localized tight ion pair. Degenerate Wagner–Meerwein rearrangement of this species reaches equilibrium rapidly before product formation. Return from the tight ion pairs to covalent tosylate competes with their forward reactions, the fraction of return being 0.70. Neither hydride shift nor front-to-backside movement of the counterion occurs appreciably within the tight ion pairs.

The conclusions to this point deserve comment with respect to two central questions in solvolysis theory. There is, first, a salient contrast between the 4-homoadamantyl cation, for which a classical structure is indicated, and the 2-norbornyl cation, where diverse evidence supports a strongly carbon-bridged structure.[4,36] The two systems are analogous in their potential for formation of a symmetrically bridged carbonium ion and in their steric hindrance to backside nucleophilic attack. The evident key to their distinctive behavior is the strained nature of the C(1)–C(6) bond in the norbornyl framework, which facilitates its participation in positive charge stabilization at C(2), the minimum energy corresponding to a structure at or near the symmetrically bridged limit, **16.** In



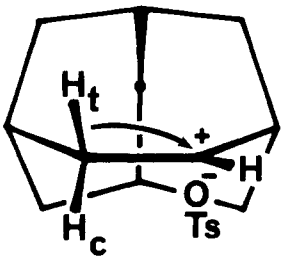
16

the 4-homoadamantyl system, in comparison, the corresponding β,γ-C–C bonds appear to be normal σ linkages.

The foregoing conclusions bear also on the question of the degree of internal ion pair return which can be observed in solvolysis reactions. While much has been learned about ion pair behavior from studies[36] of substrate racemization, oxygen-label scrambling, and related isomerizations, these probes leave undetected the fraction of return which occurs with simple re-formation of the originally ionized bond. Shiner and co-workers in 1969, on the basis of comparative addition and solvolysis rates for the 2-propyl system, postulated that this ordinarily "hidden" return of tight ion pairs may typically be much faster than solvolysis.[37] A sizably faster trifluoroacetolysis rate observed for 3,3-dimethyl-2-butyl brosylate over 2-propyl brosylate was then attributed to the preemption of return by methyl migration in the pinacolyl reaction.[38] Schleyer et al. have challenged these studies and argued contrariwise that there is in general little support for major hidden return.[39] Our present results favor the latter view.

Schleyer et al. have presented evidence that, where nucleophilic solvent participation is unimportant, pinacolyl, 1-adamantylmethylcarbinyl, and simple secondary alkyl reactants have closely similar rate-controlling mechanisms, which must therefore be dominated by substrate ionization.[39] If methyl migration in pinacolyl cation is not a substantially higher activation step than gegenion return, then, it is unlikely that Wagner–Meerwein rearrangement in tightly tosylate-paired 4-homoadamantyl cations (even if not exothermic) is significantly slower than collapse to substrate. It follows that most of the return for 4-homoadamantyl tosylate is measured by the 4,3-deuterium rearrangement in recovered reactant; k_i/k_t is only ~3.

5,4-Hydride migration in a tightly ion paired 4-homoadamantyl cation would be expected to be specific for hydrogen trans to the leaving group, **17.** We take the absence of stereoselectivity in hydride shift, therefore, as evidence for the dissociation of tight ion pairs prior to hydride shift, presumably to form solvent-separated ion pairs.[16,40] The results suggest that the intimate ion pairs may possess a relatively rigid geometry, stereoelectronically unfavorable to hydride migration, which relaxes upon tosylate dissociation to allow the rearrangement. Goering's extensive studies[36] have indicated that solvent-separated ion pairs should be expected to lose configurational stability.[41] The success of the quantitative E1 elimination model above, then, dictates that contact ion pair dissociation in the present system must be essentially irreversible.



17

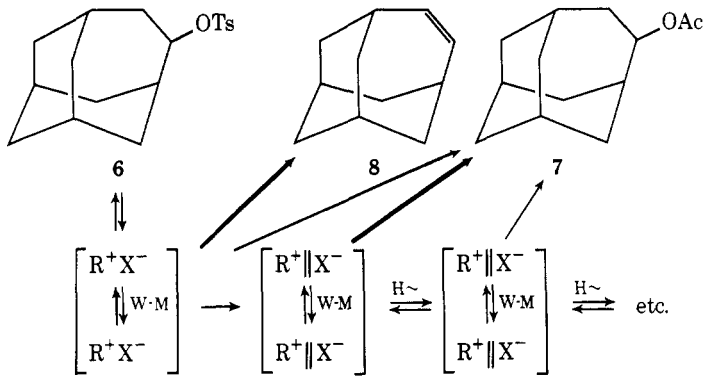
The stereochemistry of substitution has not been ascertained in the present study. In 80% aqueous acetone solvent, however, hydride shift is largely suppressed and substitution has been found to proceed with ca. 70% retention of configuration.[42] This preference should be amplified in the less nucleophilic[43] solvent acetic acid. It may be inferred, then, that the major share of acetate product formation occurs at or beyond the stage of solvent-separated ion pairs.

The assembled mechanistic conclusions are summarized in Scheme IV.

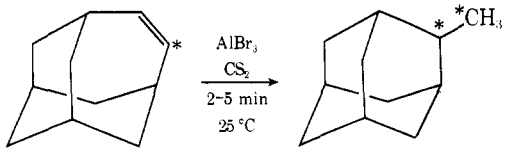
The deductions reached here are similar to suggestions made recently by Goering and co-workers[36,44] for solvolyses of the 1,2-dimethyl-*exo*-2-norbornyl and 1,2-dimethyl-*exo*-2-benzonorbornenyl systems. Less racemization was found to accompany elimination than substitution, over several combinations of leaving group and solvent. It was thus proposed likewise that tight ion pairs were the source of olefin, with the alcohol or ether arising subsequent to tight ion pair dissociation. Such differential origins of E1 and SN1 products in solvolysis of appropriate systems, then, may be an emergent general observation.

4-Homoadamantyl Cation under Other Conditions. Recent work by Majerski and co-workers[5a-d] and Yamaguchi and co-workers[5e] affords a comparison of the present solvolytic chemistry with that of the 4-homoadamantyl cation, **1,** produced under contrasting conditions. When homoadamantene,

Scheme IV



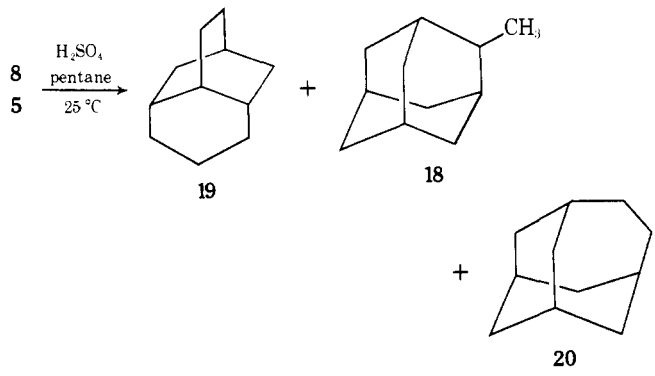
8, was treated briefly with aluminum bromide in carbon disulfide at 25 °C the major tractable product was found[5a] to be 2-methyladamantane, (**18**), a transformation abruptly different from those seen in solvolysis but one for which **1** is a reasonable intermediate. The course of this reductive rearrangement was shown by ^{13}C labeling, moreover, to involve for the most part only the original two-carbon bridge, [5c] **8**-*4*-^{13}C → **18**-*2*,CH_3-^{13}C. Wagner–Meerwein rearrangement,



8-*4*-^{13}C (* = ^{13}C) 18-*2*,CH_3-^{13}C

therefore, which rapidly achieves equilibrium under solvolysis, is essentially suppressed in the ring-contraction process. It is evident that the carbocations between **8** and **18** are severely encumbered.

Reaction of either homoadamantene (**8**) or 4-homoadamantanol (**5**) with concentrated sulfuric acid in the presence of pentane, on the other hand, gave rise to 4-homoisotwistane (**19**), 2-methyladamantane (**18**), and homoadamantane (**20**)

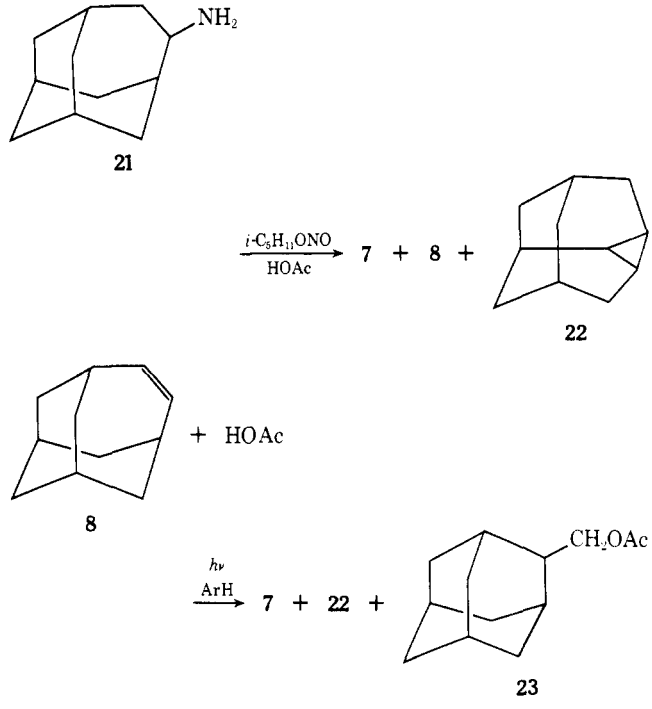


19 18 20

in 2:1:1 ratio, respectively.[5b] In this case the label in 4-homoadamantanol-*5*-^{13}C reactant was distributed over all the carbon atoms in each product,[5d] revealing the operation of multiple 1,2-carbon shifts, 1,2-hydride shifts, and 1,3-hydride shifts in relatively long-lived intermediate cations.

Further distinctive reactivity has been observed in the deamination of 4-homoadamantylamine (**21**) in acetic acid.[5e] Here in addition to the expected 4-homoadamantyl acetate (**7**) and homoadamantene (**8**), the products include 2,4-dehydroadamantane (**22**). The latter hydrocarbon is generated as well in the photosensitized addition of acetic acid to homoadamantene (**8**), along with 4-homoadamantyl acetate (**7**) and 2-adamantylcarbinyl acetate (**23**).[5e]

The collective results demonstrate a variety of pathways open to 4-homoadamantyl cation, under the decisive influence of counterion, solvent, and perhaps vibrational state.[5e] We shall present shortly detailed rearrangement data obtained from the trifluoroacetolysis and aqueous acetone hydrolysis of tosylate



6, which cast additional light on the behavior of this informative system.

Experimental Section

General. Melting points were obtained using capillary tubes (sealed just above the sample in the case of volatile compounds) in a Thomas-Hoover apparatus. Infrared spectra were recorded, unless otherwise indicated, on a Beckman IR-8 spectrophotometer using ca. 2% solutions in carbon tetrachloride (0.50-mm sodium chloride cells) or neat liquid film samples (sodium chloride plates). Nuclear magnetic resonance spectra were recorded on a Varian A-60-A instrument using samples ca. 10 wt % in carbon tetrachloride, deuteriochloroform, or carbon disulfide, with tetramethylsilane as internal reference. Gas chromatographic (GC) analyses were performed with a Varian Aerograph Model 600-D chromatograph, using columns of di-*n*-nonyl phthalate and Carbowax 1540, 5% on 90–100 mesh Anakrom ABS. Preparative gas chromatography utilized diethylene glycol succinate 20% on 60–80 mesh Chromosorb W as stationary phase in a 14-ft × ¼-in. o.d. copper column at 120–150 °C in a Barber-Colman Model 5340 instrument. Quantitative elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

4-Homoadamantanone (4). Homologation of adamantanone (Aldrich) was carried out initially by a Tiffeneau-Demjanov sequence.[1a,6] Later, direct conversion by reaction with methanolic diazomethane was employed,[1b,7a] details for which have been reported by Black and Gill.[7b] Following vacuum sublimation (1.5 mm, 125 °C) 4-homoadamantanone (85% yield) had mp 269.0–270.0 °C (sealed cap-

illary) (lit. 270.0–271.5,[1b] 258–260,[6b] 269.5–270.5 °C[7b]) and NMR spectral features matching those subsequently reported.[7b,45] Careful measurement of the ir spectrum of a sample 2.0 wt % in carbon tetrachloride using a Beckman IR-12 instrument and 0.50-mm sodium chloride cells gave $\nu_{C=O}$ 1698 cm^{-1} (center of doublet fine structure)[46] [lit. 1697 (CCl_4),[1b] 1695 (CCl_4),[7b] 1700 cm^{-1} (KBr)[6b]].

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.60; H, 9.92.

4-Homoadamantanol (5). Reduction of 4-homoadamantanone with lithium aluminum hydride in ether, essentially as described by Black and Gill,[7b] gave the alcohol, **5**, in 92% yield after vacuum sublimation (1.5 mm, 140 °C) mp 267.0–268.0 °C (lit. 269.5–270.5,[1b] 269.5–270.0 °C[7b]) and NMR and ir spectral characteristics in accord with those later reported.[7b] *p*-Nitrobenzoate, mp 127.5–128.5 °C (from pentane).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.60; H, 10.92.

4-Homoadamantyl Tosylate (6). The tosylate was prepared from 4-homoadamantanol and *p*-toluenesulfonyl chloride in dry pyridine in the usual manner.[47] It was recrystallized between room temperature and −70 °C from 95% ethanol and again from pentane to produce a 60% yield of white crystalline compound, mp 73.0–73.5 °C (lit. 71.5–72.5,[1a] 71–73 °C[1b]).

Anal. Calcd for $C_{18}H_{24}SO_3$: C, 67.47; H, 7.55. Found: C, 67.69; H, 7.61.

The tosylates of the deuterated 4-homoadamantanols, below, were prepared likewise.

4-Homoadamantyl Acetate (7). In a 25-ml round-bottomed flask equipped with a reflux condenser and drying tube to the atmosphere a solution of 0.415 g (2.50 mmol) of 4-homoadamantanol and 1.02 g (10.0 mmol) of acetic anhydride in 7 ml of dry pyridine was heated on a steam bath for 5.5 h. The cooled mixture was added to 300 ml of 10% sulfuric acid and extracted with 200 ml of ether. The ether solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated in a 100-ml round-bottomed flask by rotary evaporation. The residual liquid was distilled under vacuum (1.0 mm, 120 °C bath) into a small glass cup at the bottom of a cold-finger condenser extending into the center of the flask. The colorless liquid product, 0.416 g (2.00 mmol, 80% yield), was homogeneous by GC. Ir (CCl_4) 1740 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.72; H, 9.52.

4-Homoadamantyl Ethyl Carbonate (18). To a solution, maintained at 0–5 °C, of 7.00 g (42 mmol) of 4-homoadamantanol in 140 ml of dry pyridiine in a 500-ml, three-necked, round-bottomed flask fitted with an overhead stirrer, addition funnel, and reflux condenser with drying tube to the atmosphere was added dropwise 20 ml (22.7 g, 210 mmol) of freshly distilled ethyl chloroformate (Eastman). After overnight reaction, 50 ml of water was cautiously added, and the mixture was poured into 500 ml of 10% hydrochloric acid and extracted with four 200-ml portions of ether. The ether solution was washed with 10% hydrochloric acid, water, 5% sodium bicarbonate, and water and was dried over anhydrous magnesium sulfate. Solvent removal by rotary evaporation and short-path vacuum distillation of the residue gave 8.54 g (36 mmol, 86%) of the desired ester, bp 134–135 °C (1.5 mm), homogeneous by GC. Ir (CCl_4) 1740, 1450, 1370, 1260, 990, 952, 792 cm^{-1}; NMR (CCl_4) τ 5.20 (septet, >CHO-), 5.92 (quartet, $-CH_2O-$), 7.2–8.9 (broad band, ring β-ω H's), 8.64 (triplet, CH_3-).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.42; H, 9.37.

Homoadamantene (8). Homoadamantene was synthesized by treatment of 3.10 g (9.69 mmol) of 4-homoadamantyl tosylate with 1.63 g (14.6 mmol) of potassium *tert*-butoxide (City Chemical Corp.) in 60 ml of *tert*-butyl alcohol for 8 h with magnetic stirring. The mixture was added to 1.0 l. of water and the product extracted six times into pentane. The pentane solution was washed with 10% sulfuric acid, then water, and was dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent left a white solid, which was purified by vacuum sublimation, yielding 0.69 g (4.7 mmol) of olefin, mp 237.5–238.5 °C (sealed capillary) (lit. 237–238,[1b] 237.0–237.5 °C[7b]).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 88.89; H, 11.09.

Homoadamantene was also prepared by the pyrolysis of 4-homoadamantyl ethyl carbonate (see below), by pyrolysis of the borate[48] of 4-homoadamantanol (64% yield), and by attempted chromatography of 4-homoadamantyl tosylate over basic alumina (Woelm, activity grade I) in pentane (45% yield). More recently the method of choice in our laboratory has become the dehydration of 4-homoadamantanol in boiling hexamethylphosphoramide, as reported by Yamaguchi et al.[49] Using a workup of pentane extraction, several brine washings, and chromatography of the dried solution over silica gel, pure homoadamantene has been obtained in 93% yield.

Hydrogenation at 40 psig of 100 mg (0.67 mmol) of homoadamantene in 25 ml of 95% ethanol over 10 mg of platinum oxide for 5 h, followed by standard workup and vacuum sublimation yielded 33 mg (0.22 mmol, 33%) of homoadamantane (**20**), mp 256–257 °C (lit. 258–259,[50a] 259–260 °C[50b]), identical spectrally with the product of reduction[5] of 3-bromohomoadamantane[11] with lithium and *tert*-butyl alcohol in tetrahydrofuran,[51] and with an authentic sample kindly supplied by Dr. B. R. Vogt.

Homoadamantene Oxide (10). Homoadamantene (2.0 g, 13.5 mmol) was epoxidized with 3.0 g (14.0 mmol) of *m*-chloroperbenzoic acid (Aldrich) in methylene chloride under standard conditions,[52] yielding after vacuum sublimation 2.0 g (12.2 mmol, 90%) of pure product, mp 299.0–300.0 °C (lit.[1b] 300–301 °C) and NMR spectral properties the same as those published by Schleyer et al.[1b]

4-Homoadamantyl Trimethylsilyl Ether (11). In a 50-ml round-bottomed flask with reflux condenser and drying tube to the atmosphere a solution of 400 mg (2.41 mmol) of 4-homoadamantanol and 2.5 g (23 mmol) of distilled trimethylchlorosilane in 15 ml of dried pyridine was boiled under reflux for 24 h. The cooled solution was poured into 300 ml of 10% hydrochloric acid and extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate, and water and was dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. Vacuum distillation of the crude product as described above for 4-homoadamantyl acetate (**7**) gave 343 mg (1.45 mmol, 60%) of the silyl ether as a colorless liquid, shown by its ir spectrum to be alcohol-free, homogeneous by GC, and of correct molecular weight (238) by mass spectrometry.

The silyl ether was subsequently found to be more readily formed using *N,O*-bis(trimethylsilyl)acetamide ("BSA", Pierce Chemical Co.), 1.0 ml per 50 mg of 4-homoadamantanol in 1.0 ml of pyridine at 50 °C for 4 h. The product in this case was purified by preparative GC as needed. This method was used for the deuterium-content analyses, below.

4,5-Adamantanedione (12). A magnetically stirred mixture of 300 mg (1.83 mmol) of 4-homoadamantanone, 224 mg (2.01 mmol) of selenium dioxide, and 6 ml of 70 vol % aqueous acetic acid was boiled under reflux for 24 h, cooled, and gravity filtered to remove the black precipitate of selenium. The filtrate was added to 300 ml of water and extracted with three 100-ml portions of ether. The ether solution was washed with water, 10% sodium bicarbonate solution, and water and dried over anhydrous magnesium sulfate. After rotary evaporation of the solvent, the crude product was vacuum sublimed and recrystallized from carbon tetrachloride (ether may alternatively be used, with chilling), yielding 240 mg (1.35 mmol, 74%) of the dione as bright yellow needles: mp 277–278 °C (sealed capillary) (lit.[6b] 287 °C dec); ir (CCl_4) 1720 cm^{-1} [lit. (KBr)[6b] 1725, 1710 cm^{-1}]; MS *m/e* 178 (M, base peak), 150 (M − CO); and NMR as subsequently reported.[6b] Quinoxaline derivative,[6b] from reaction with *o*-phenylenediamine in 10% aqueous acetic acid plus benzene, mp 178–180 °C [neutral alumina chromatography (benzene) and vacuum sublimation] (lit.[6b] 177–178 °C).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.91; H, 7.83.

4-Homoadamantanol-*4-d* (5-*4-d*). Using essentially the same procedure as that cited for the preparation of **5**, 3.30 g (20 mmol) of 4-homoadamantanone was reduced with 1.0 g (24 mmol) of lithium aluminum deuteride (Ventron, stated isotopic purity ≥99%) to give 3.00 g (18 mmol, 90%) of chemically pure 4-homoadamantanol-*4-d*. The NMR spectrum showed no signal for >CH-O. The deuterium contents of two separately prepared products as determined from the mass spectra (see below) of the trimethylsilyl ethers (see above) were 99.2 and 98.7% d_1.

4-Homoadamantanol-*trans-5-d* (5-*t-5-d*). In a 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, and reflux condenser with drying tube was placed 200 ml of di-*n*-butyl ether, 1.0 g (24 mmol) of lithium aluminum deuteride (Ventron), and 2.50 g (15.2 mmol) of homoadamantene oxide. The stirred suspension was boiled under reflux (solvent bp 142 °C) for 20

h, changing from white to gray. (Lithium aluminum hydride is known to decompose to lithium hydride, aluminum, and hydrogen at 150 °C[53].) The excess deuteride was decomposed by cautious addition to the cooled mixture of 10 ml of water and 60 ml of 1.5 N sodium hydroxide, and 30 ml of water was then added.[54] The product was extracted into four 200-ml portions of ether, and the ether solution was washed twice with 100-ml portions of water and dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent and vacuum sublimation of the residue gave 1.80 g (10.8 mmol, 70%) of labeled alcohol, **5-*t*-5-*d***. The deuterium incorporation was measured by MS of the trimethylsilyl ether to be 95.8%; for two subsequent identical preparations the corresponding values were 97.4 and 97.6%.

The constitution of the labeled alcohol was established by oxidation of 100 mg (0.60 mmol) with 1.0 ml (1.22 mequiv) of Jones reagent[55] in 10 ml of acetone at 0–5 °C to give 4-homoadamantanone (65 mg, 0.39 mmol, 65%) 94.2% d_1 by MS, and oxidation of this ketone with selenium dioxide, as described above, to produce 4,5-homoadamantanedione of 0.7% d_1 content (considered negligible) by MS.

For the determination of diastereomeric purity, 700 mg (4.2 mmol) of the alcohol was converted as described above to the ethyl carbonate ester, which was pyrolyzed to olefin[56] by passage dropwise in a slow nitrogen stream through a vertical 12-in. × 1-in. o.d. Pyrex tube packed with glass helices and heated to 325 °C. The products were collected in an ice-cooled receiver, to which was added the material washed by ether from the column after cooling to room temperature. Rotary evaporation of the solvent and chromatography of the residue over silica gel in pentane gave 0.20 g (1.34 mmol, 32%) of pure homoadamantene, shown by MS to be 94.4% d_1.

The results correspond to a virtually exclusive syn elimination mechanism for the carbonate pyrolysis, with essentially all of the 5-d label trans to the hydroxyl group in the alcohol, as intended. In application of this reaction to configurational analysis of the cis-5-d labeled alcohol, below, there is evidence for appreciable anti elimination, but this pathway evidently accounts for no more than 1.4% of the reaction in the present instance. The diminution of label between the lithium aluminum deuteride (stated isotopic purity ≥99%) and alcohol (average d_1 incorporation 96.9%) points to the incursion of some slight exchange process under the forcing conditions necessary to open the hindered epoxide. In addition, SN2 ring opening of the epoxide is apparently complicated by a 1.6− competitive pathway delivering deuterium to the 4 position (most reasonably isomerization of the epoxide to ketone, then reduction).

4-Homoadamantanol-*cis*-5-*d* (5-*c*-5-*d*). The hydroboration technique of Sondheimer and Wolfe[57] was applied to the deuteroboration of homoadamantene. In a 500-ml, three-necked, round-bottomed flask equipped with a magnetic stirrer, addition funnel, reflux condenser, and nitrogen atmosphere was placed 100 ml of anhydrous ether, 3.0 g (20 mmol) of homoadamantene, and 4.5 g (3.17 mmol) of freshly distilled boron trifluoride etherate. To the stirred solution was added a slurry of 1.00 g (23.8 mmol) of lithium aluminum deuteride (Ventron, isotopic purity ≥99%) in 150 ml of ether. The reaction mixture was stirred at room temperature for 2.0 h, and then 200 ml of acetone was added, followed by 50 ml of saturated sodium sulfate solution and 75 g of anhydrous sodium sulfate. The ether solution was filtered under vacuum and transferred to a 500-ml round-bottomed flask. To it was added 100 ml of 90% aqueous ethanol containing 2.4 g (0.060 mol) of sodium hydroxide, followed by 30 ml of 30% hydrogen peroxide. After an initial exothermic reaction the mixture was heated in an oil bath at 50–70 °C for 1.0 h, cooled to room temperature, poured into 100 ml of water, and extracted with three 100-ml portions of ether. The ether solution was washed with 100 ml of saturated sodium bicarbonate solution and 100 ml of saturated sodium chloride solution, and was dried over anhydrous magnesium sulfate. Rotary evaporation of the solvent and chromatography of the solid residue over 30 g of silica gel gave 0.50 g (3.3 mmol, 17% recovery) of homoadamantene (pentane elution), followed by 2.0 g (12 mmol, 71% yield based on unrecovered olefin) of *cis*-5-deuterio-4-homoadamantanol (ether elution).

Mass spectrometry of the derived trimethylsilyl ether (see above and below) showed an isotopic content of 96.9% d_1 and 3.1% d_0. (Subsequent preparations gave products of 98.1 and 97.8% d_1 content.)

The invariant syn stereochemistry of hydroboration–oxidations in the literature[58] provides assurance of high diastereomeric purity for this product. To test the self-consistency of the diastereomeric analysis by carbonate pyrolysis used for the trans-5-d alcohol, above, 75 mg of the present alcohol (96.9% d_1, 3.1% d_0) was converted to the ethyl carbonate and pyrolyzed under the conditions described. The isotopic content of the homoadamantene product by MS was 4.7% d_1 and 95.3% d_0. The appreciable retention of deuterium is probably best explained as the result of a small fraction of pyrolysis occurring in the liquid phase by a stepwise and nonstereospecific pathway. This complication is more evident here where syn elimination encounters a primary deuterium isotope effect than with the trans-5-d isomer, where this effect reinforces the syn elimination preference.

Acetolysis of 4-Homoadamantyl tosylate (6). In a 500-ml round-bottomed flask equipped with a magnetic stirrer and a reflux condenser with a drying tube to the atmosphere was placed 350 ml of a solution of 2.29 g (16.8 mmol, 0.048 M, 20% excess) of sodium acetate trihydrate and 8.67 g of distilled acetic anhydride (5.14 g, 50.4 mmol, for reaction with the water of hydration of the salt plus 33.53 g to constitute a 1.0 wt % excess) in distilled acetic acid. To the stirred medium maintained at 40 ± 1 °C (using a Thermowatch, Instruments for Research and Industry, Cheltenham, Pa.,) was added 4.50 g (14.0 mmol, 0.040 M) of 4-homoadamantyl tosylate, and reaction was conducted for 50 h (20 half-lives). The cooled solution was poured into 700 ml of water, and the products were extracted with four 300-ml portions of ether, which were combined and washed with two 600-ml portions of water, excess 10% sodium bicarbonate solution, and 200 ml of water and dried over anhydrous magnesium sulfate. The ether was removed, leaving a viscous liquid, which was first subjected to gas chromatography (di-*n*-nonyl phthalate column) and then separated by column chromatography over silica gel, yielding 0.477 g (3.22 mmol, 23%) of 4-homoadamantene on pentane elution, followed by 2.01 g (9.65 mmol, 69%) of 4-homoadamantyl acetate on ether elution. After calibration of the GC detector[6a] the product mixture was established to be 25.0% of the olefin and 75.0% of the acetate. The product composition was shown to be that of kinetic control by subjection of the acetate and olefin separately without change to the buffered reaction medium at 40 °C for 50 h and by solvolysis of the tosylate in unbuffered acetic acid with essentially the same results[6a] as those from the buffered solvent.

Mass Spectrometry. Mass spectra were obtained with a Varian M-66 cycloidal mass spectrometer, operated generally at an electron energy of 70 eV. All peaks were sharp and cleanly resolved, and intensities were taken as proportional to heights. Intensity data for analysis were obtained as averages of ten scans of the pertinent spectral region. Precision was consistently better than 0.5%.

The spectra of 4-homoadamantanone and 4,5-homoadamantanedione showed no detectable (<0.5%) M − 1 complication (hydrogen loss). For these compounds mixtures of deuterium-labeled and unlabeled material were analyzed as follows, illustrated for 4-homoadamantanone (MW 164).

$$I_{164} = k\mathrm{d}_0^{164}$$

$$I_{165} = k(\mathrm{d}_1^{165} + \mathrm{d}_0^{165})$$

$$= k(\mathrm{d}_1^{165} + 0.1218\mathrm{d}_0^{164})$$

where I_i = peak intensity at $m/e = i$, k = instrumental proportionality constant, d_1^i and d_0^i = concentrations of monodeuterated and undeuterated species, respectively, of mass i, and 0.1218 = the natural-abundance isotopic (M + 1) factor[59] for $C_{11}H_{16}O$ (due predominantly to ^{13}C), as a fraction of M. By simultaneous solution, the percentage of deuterated compound, % d_1, is given by

$$\%\,\mathrm{d}_1 = 100 \times \frac{I_{165} - 0.1218I_{164}}{I_{165} + 0.8782I_{164}}$$

For 4,5-homoadamantanedione (MW 168) the correspondingly derived expression is

$$\%\,\mathrm{d}_1 = 100 \times \frac{I_{179} - 0.1219I_{178}}{I_{179} + 0.8781I_{178}}$$

Homoadamantene exhibited a small but measurable M − 1 peak, of intensity 0.009 relative to that of M, invariant over the accessible electron-energy range of 70 to 20 eV. This hydrogen loss is markedly less than that characteristic of model cycloalkenes,[59] reflecting the stereoelectronic unfavorability of allylic cleavage in homoadamantene. Inclusion of M − 1 fragmentation in the deuterium-content analyses of homoadamantene solvolysis products requires assumptions concerning primary isotope effects and the mechanism of hydrogen loss. We have elected to treat the phenomenon under the rough but rea-

sonable overall approximation that hydrogen cleavage is due 80% to protium (20% deuterium). Derivation through equations for the peak intensities at *m/e* 148 and 149 thus leads to the following expression[60] for percentage of deuterated olefin:

$$\% d_1 = 100 \times \frac{1.138I_{149} - 0.1380I_{148}}{1.131I_{149} + I_{148}}$$

Results by this approach differ from those in which M − 1 loss is ignored by ca. 0.5%.

Labeled homoadamantanol starting materials were analyzed as the trimethylsilyl ethers[61] (dehydration precluded observation of the alcohol molecular ions). As observed for other such derivatives,[61] 4-homoadamantyl trimethylsilyl ether loses CH_3 as a major fate of the molecular ion, generating the (M − 15) ≡ M′ cation (nominal mass 223) as the species most suitable for analysis. The natural isotopic M′ + 1 factor was calculated from those[59] for $C_{13}H_{23}O$ and Si as follows:

$$(M' + 1) = 0.8648(0.0471)\ [\text{for } C_{13}H_{23}O^{195}, Si^{29}] + 0.1251(0.9217)\ [\text{for } C_{13}H_{23}O^{196}, Si^{28}] = 0.1560$$

relative to the sum of the isotopic variants, or 0.1560/0.8648(0.9217) = 0.1957 as a fraction of the M′ peak.

Minor but consistent hydrogen loss from M′ was observed, (M′ − 1) = 0.005 M′. This occurs in all likelihood from a methyl group[61] and was included in our calculations. From equations for the peak intensities at *m/e* 223 and 224, the percentage of deuterium-labeled homoadamantanol is derived[59,60] to be

$$\% d_1 = 100 \times \frac{1.243I_{224} - 0.2435I_{223}}{1.237I_{224} + I_{223}}$$

Kinetics. The acetolyses of 4-homoadamantyl tosylate were followed titrimetrically using standard aliquot and ampule methods,[11] with initial substrate concentrations ca. 0.069 M. The acetic acid was dried with acetic anhydride, carefully distilled, and protected against moisture by the addition of 1.0 wt % acetic anhydride.

Measurements of the faster trifluoroacetolysis rates required special techniques, described elsewhere.[62,63] The reaction medium was purified[64] trifluoroacetic acid containing 1.0 wt % trifluoroacetic anhydride and 0.060 M sodium trifluoroacetate. Initial substrate concentrations were ca. 0.050 M.

Acknowledgments. Partial support of this work by National Science Foundation Grants GP-6074, GP-8421, and MPS 75-04284 and the provision of a research fellowship to R.R.G. by Texaco, Inc., are gratefully acknowledged. We appreciate helpful comments by Professor P. v. R. Schleyer.

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Interaction of α-L-Aspartyl-L-phenylalanine Methyl Ester with the Receptor Site of the Sweet Taste Bud

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Received December 24, 1975

Abstract: The sweetening agent, α-L-aspartyl-L-phenylalanine methyl ester, has been studied in aqueous solutions in the pH range 3.5–11.7. The combination of NMR methods and potential energy calculations gives a very accurate description of the preferred conformations in solution. The results of this analysis have been used to select a conformation as the interacting species with the receptor site of the sweet taste bud. Comparison with known sweet molecules shows the consistency of all the features of the chosen conformation with the models proposed by current theories on sweet taste. The receptor site can be described as a narrow cleft with two interacting parts, one for locking the sweet molecule and another for triggering the nerve impulse.

It has been known for a long time that, besides sugars, many apparently unrelated molecules (with a large spectrum of chemical groups and stereochemical features) can elicit a sweet taste response in man and other animals.[2] The identification of the essential features that impart the sweet taste to these molecules may lead to a satisfactory description of the geometric and chemical aspects of the receptor site and, in turn, provide a sound basis for the design of new potentially useful sweet tastants. In fact, it goes without saying that this problem is quite relevant not only for its biochemical and physicochemical aspects but also from a nutritional point of view.

A major step in the search for common features of sweet agents was made by Shallenberger and Acree[2] who recognized that all sweet compounds possess a bifunctional entity consisting of an acidic (AH) and a basic (B) moiety with a proton to B distance of about 0.3 nm.

Further insight in the nature and geometry of the receptor site was afforded by the observation that the D isomers of most bifunctional amino acids are sweet whereas the corresponding L isomers are bitter.[3] This difference can be explained with the hypothesis of a "spatial barrier" probably apolar in character, placed at about 0.3–0.4 nm from the AH–B entity of the receptor site.

An independent theory by Kier[4] postulates, on the basis of less cogent evidence, the existence of a third binding side that involves a "dispersion bonding" at the receptor. A weak point of both theories is that they are not able to explain the large differences in relative sweetness among known tastants. The complex aspects of a new class of powerful sweet agents[5] may now provide useful clues to an understanding of these differences and, in general of the factors controlling structure–activity relationship in all sweet molecules. The accidental discovery[6] that the dipeptide α-L-Asp-L-PheOMe is at least 150 times as sweet as sucrose has stimulated, during the last few years, the search for other sweetening agents of peptide nature. Many dipeptide derivatives of the type α-L-Asp-X were found to be as sweet or sweeter than α-L-Asp-L-PheOMe.[4,6-9] The X moiety can be an esterified amino acid residue stereo-