Mechanism of Addition of Neat Trifluoroacetic Acid to Protoadamantene

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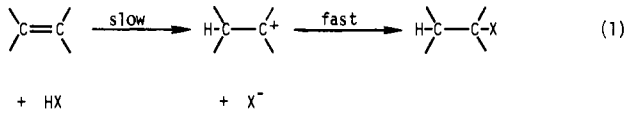
Abstract: Protoadamantene (**1**) reacts smoothly with neat trifluoroacetic acid at 25 °C to give 2-adamantyl trifluoroacetate (**2**-OTFA) and a trace of metastable *exo*-4-protoadamantyl trifluoroacetate (**4**-OTFA), which isomerizes to **2**-OTFA. The rearrangement attending addition was shown to involve a simple Wagner–Meerwein shift only. Protoadamantene is $>10^2$ times more reactive under these conditions than model olefins cyclohexene and cycloheptene. The addition of CF_3CO_2D was found to produce a mixture of the four diastereomeric 2-adamantyl-*4-d* trifluoroacetates, **11**-OTFA–**14**-OTFA, with predominant exo attachment of the electrophilic deuterium. The results are taken to indicate protoadamantene–trifluoroacetic acid complexes as the species from which rearrangement occurs.

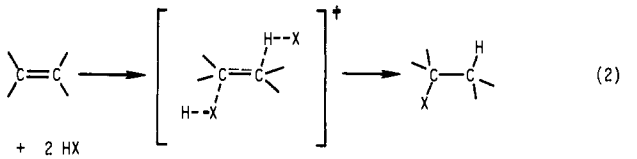
Several mechanisms have been advanced for additions of Brønsted acids to alkenes.[1] The simplest, symbolized Ad_E2 or $A_{SE}2$, involves rate-determining protonation to produce a free intermediate carbenium ion (eq 1). Extensive evidence has been



(1)

adduced by Schubert,[2] Tidwell,[1f,3] Taft, Kresge, Deno, and others[1e-i] for such a pathway in acid-catalyzed additions of water and alcohols. A related possibility is direct formation of an ion pair. Fahey and McPherson[4] have made an exemplary case for this mechanism in the reaction of *tert*-butylethylene with HCl in HOAc. Dewar and Fahey[5] have formulated the stepwise generation of ion pairs in explanation of the predominantly syn course of DBr addition observed with styrenoid olefins.

Representative simple alkenes, in contrast, have been found by Hammond,[6] Fahey,[7] Pocker,[8] and Pasto[9] and co-workers to undergo preferential anti addition of several acids with concomitant third-order kinetics. Both concerted and two-step termolecular processes, Ad_E3, have been proposed[1a,6,7,9,10] for these reactions, eq 2 and 3, respectively. The latter postulates product formation



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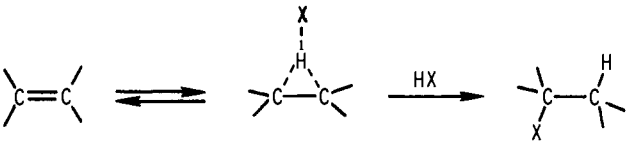
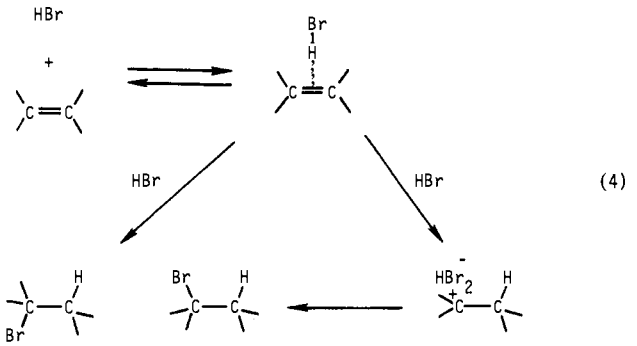


(3)

from a reversibly generated π complex, whose experimental demonstration poses a subtle problem.[11] Staab and co-workers[12] have recently reported parallel medium effects on the syn/anti and rearrangement/addition ratios in HBr reaction with 1,1,4,4-tetramethyl-1,4-dihydronaphthalene as evidence for competitive product-generating reactions of a first-formed π complex (eq 4). A second molecule of HBr is envisioned here as playing either a nucleophilic or electrophilic role, with divergent consequences as outlined.



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(1) Reviews: (a) Dewar, M. J. S.; Fahey, R. C. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 245; (b) de la Mare, P. B. D.; Bolton, R. "Electrophilic Additions to Unsaturated Systems"; Elsevier: New York, 1966; Chapters 3–5; (c) Fahey, R. C. *Top. Stereochem.* **1968**, *3*, 237; (d) Bolton, R. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: London, 1973; Vol. 9, p 1; (e) Schmid, G. H.; Garratt, D. G. In "The Chemistry of Double-bonded Functional Groups"; Patai, S., Ed.; Wiley: New York, 1977; Chapter 9; (f) Nowlan, V. J.; Tidwell, T. T. *Acc. Chem. Res.* **1977**, *10*, 252; (g) March, J. "Advanced Organic Chemistry", 2nd ed., McGraw-Hill: New York, 1977; pp 672–678; (h) Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry", Part A; Plenum Press: New York, 1977; pp 265–272; (i) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: New York, 1976; Chapter 7.

(2) Schubert, W. M.; Lamm, B.; Keeffe, J. R. *J. Am. Chem. Soc.* **1964**, *86*, 4727. Schubert, W. M.; Lamm, B. *Ibid.* **1966**, *88*, 120. Schubert, W. M.; Keeffe, J. R. *Ibid.* **1972**, *94*, 559. Schubert, W. M.; Jensen, J. L. *Ibid.* **1972**, *94*, 566.

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(8) (a) Pocker, Y. *J. Chem. Soc.* **1960**, 1292. (b) Pocker, Y.; Stevens, K. D.; Champoux, J. J. *J. Am. Chem. Soc.* **1969**, *91*, 4199. (c) Pocker, Y.; Stevens, K. D. *Ibid.* **1969**, *91*, 4205. (d) See also: Pocker, Y.; Buchholz, R. F. *Ibid.* **1970**, *92*, 4033.

(9) (a) Pasto, D. J.; Meyer, G. R.; Kang, S. Z. *J. Am. Chem. Soc.* **1969**, *91*, 2163. (b) Pasto, D. J.; Meyer, G. R.; Lepeska, B. *Ibid.* **1974**, *96*, 1858. (c) Pasto, D. J.; Gadberry, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 1469.

(10) In a third view, Pocker[8c] has favored steric effects within a carbenium ion mechanism in explanation of anti addition in such systems.

(11) See Banthorpe, D. V. *Chem. Rev.* **1970**, *70*, 295.

(12) Staab, H. A.; Wittig, C. M.; Naab, P. *Chem. Ber.* **1978**, *111*, 2965. Naab, P.; Staab, H. A. *Ibid.* **1978**, *111*, 2982.

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Concerted molecular HX addition has also been considered,[1c,13] although Brown[14] has presented effective evidence against this mechanism in a leading case.

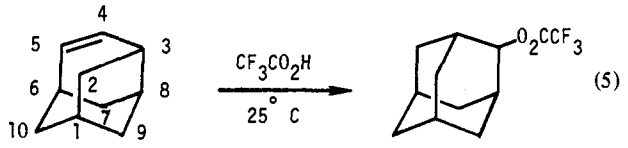
We report here new insights into the addition of Brønsted acids to olefins gained through an investigation of regiochemistry, stereochemistry, and relative reactivity for the addition of neat trifluoroacetic acid to the distinctively constituted olefin protoadamantene (4-tricyclo[4.3.1.$0^{3,8}$]decene) (**1**).

Protoadamantene is an elaborated cyclohexene (or cycloheptene from another perspective) in which the more exposed exo face of the double bond (away from the viewer in formula **1**) is relatively normal. The structure on the endo side, however, is one of potential Wagner–Meerwein rearrangement; by C(2)–C(3) bond shift a 4-protoadamantyl cation is convertible to the more stable 2-adamantyl isomer. This migration in fact characterizes the reactions previously published[15] between protoadamantene and Brønsted acids. The driving force for protoadamantyl to 2-adamantyl rearrangement thus makes the C(2)–C(3) bond in **1** an effective intramolecular nucleophile toward carbenium ion development at C(4). Adamantane has recently been directly measured to be more stable than protoadamantane by 11.22 kcal/mol.[16]

Trifluoroacetic acid was chosen as addend for the present study because of its high reactivity among acids whose adducts with olefins are conveniently converted to alcohols for analysis. Peterson and co-workers[17] have reported extensive characterization of the addition of trifluoroacetic acid to a variety of alkenes.[18]

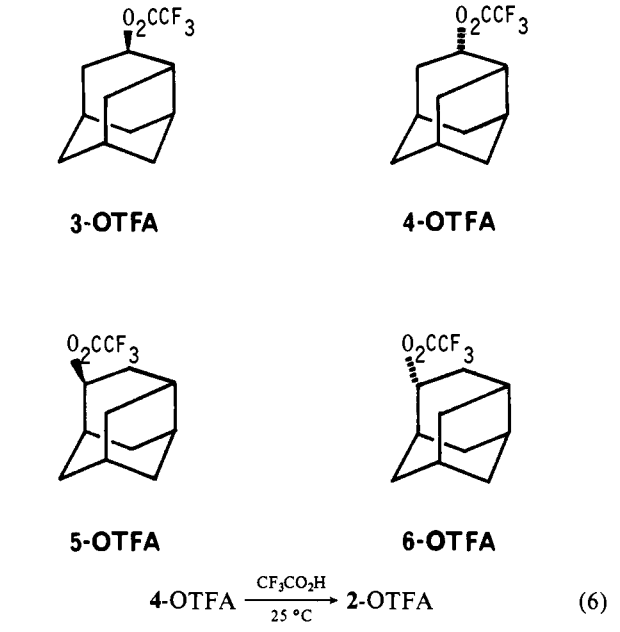
Results

Products from CF_3CO_2H. Protoadamantene was found to react smoothly with a large excess of neat trifluoroacetic acid (0.075 m solution) at room temperature over 6 h to produce exclusively 2-adamantyl trifluoroacetate (**2**-OTFA) isolated in 93% yield (eq

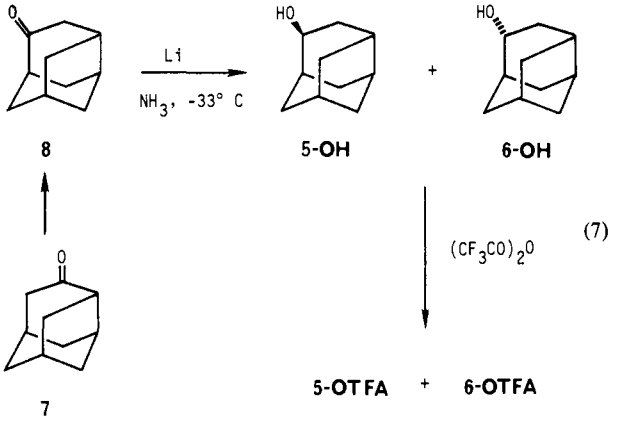


1 **2-OTFA** (5)

5). The possible presence of *endo*- or *exo*-4- or -5-protoadamantyl trifluoroacetates (**3**-OTFA–**6**-OTFA, respectively) in the crude product was securely excluded (<0.2%) by gas chromatography together with ^1H and ^{19}F NMR. Independently prepared esters **3**-OTFA, **5**-OTFA, and **6**-OTFA were shown to be stable to trifluoroacetic acid under the conditions employed for addition to **1**. *exo*-4-Protoadamantyl trifluoroacetate (**4**-OTFA) was found to rearrange in this medium quantitatively to 2-adamantyl trifluoroacetate (**2**-OTFA) (eq 6) but at a rate (see below) sufficiently slower than that of addition of the acid to **1** to allow **4**-OTFA to be rejected as a significant precursor to **2**-OTFA in the olefin addition process. 4-Protoadamantyl trifluoroacetates **3**-OTFA and **4**-OTFA were made from the respective alcohols synthesized as described by Schleyer and co-workers.[15] For the preparation of the 5-protoadamantyl esters, 5-protoadamantanone (**8**)[19] was generated from 4-protoadamantanone (**7**) by the ketone transposition sequence recently reported by Nakai and Mimura.[20] Reduction of **8** with lithium in liquid ammonia[21] yielded the epimeric alcohol mixture **5**-OH + **6**-OH, which was trifluoroacetylated to **5**-OTFA + **6**-OTFA (eq 7). These two esters exhibited ^{19}F NMR signals distinctly separated from each other and from that of **2**-OTFA, and the determination of their stabilities was based on this property.



$$\text{4-OTFA} \xrightarrow[25\,^\circ C]{CF_3CO_2H} \text{2-OTFA} \qquad (6)$$



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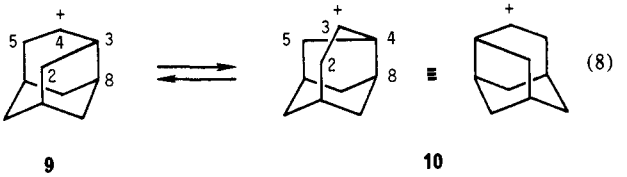
While the rearrangement in conversion of **1** to **2**-OTFA is apparently a simple methylene shift, a further control experiment was conducted against possible preliminary degenerate rearrangement equivalent to **9** ⇄ **10** (eq 8), a process identified by



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(13) Cristol, S. J.; Seifert, W. K.; Johnson, D. W.; Jurale, J. B. *J. Am. Chem. Soc.* **1962**, *84*, 3918. Cristol, S. J.; Sullivan, J. M. *Ibid.*, **1971**, *93*, 1967. Morrill, T. C.; Greenwald, B. E. *J. Org. Chem.* **1971**, *36*, 2769. Stille, J. K.; Sonnenberg, F. M.; Kinstle, T. H. *J. Am. Chem. Soc.* **1966**, *88*, 4922.

(14) Brown, H. C.; Kawakami, J. H.; Liu, K.-T. *J. Am. Chem. Soc.* **1970**, *92*, 3816. Brown, H. C.; Liu, K.-T. *Ibid.* **1971**, *93*, 7335.

(15) Lenoir, D.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1974**, *96*, 2138. See also: Kropp, P. J.; Gibson, J. R.; Synder, J. J.; Poindexter, G. S. *Tetrahedron Lett.* **1978**, 207.

(16) Clark, T.; Knox, T. McO.; McKervey, M. A.; Mackle, H.; Rooney, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 2404.

(17) (a) Peterson, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 5834. (b) Peterson, P. E.; Allen, G. *J. Org. Chem.* **1962**, *27*, 1505. (c) Peterson, P. E.; Allen, G. *Ibid.* **1962**, *27*, 2290. (d) Peterson, P. E.; Casey, C.; *Tetrahedron Lett.* **1963**, 1569. (e) Peterson, P. E.; Allen, G. *J. Am. Chem. Soc.* **1963**, *85*, 3608. (f) Peterson, P. E.; Tao, E. V. P. *J. Org. Chem.* **1964**, *29*, 2322. (g) Peterson, P. E.; Casey, C. *Ibid.* **1964**, *29*, 2325. (h) Peterson, P. E.; Tao, E. V. P. *J. Am. Chem. Soc.* **1964**, *86*, 4503. (i) Peterson, P. E.; Casey, C.; Tao, E. V. P.; Agtarap, A.; Thompson, G. *Ibid.* **1965**, *87*, 5163. (j) Peterson, P. E.; Bopp, R. J. *Ibid.* **1967**, *89*, 1283. (k) Peterson, P. E.; Chevli, D. M.; Sipp, K. A. *J. Org. Chem.* **1968**, *33*, 972.

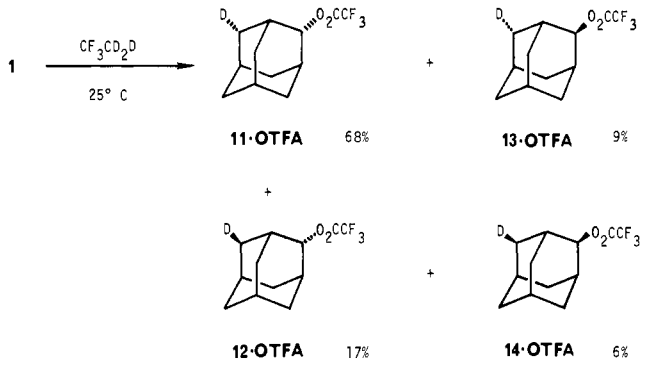
(18) See also: Latrêmouille, G. A.; Eastham, A. M. *Can. J. Chem.* **1967**, *45*, 11; Weisleder, D.; Friedman, M. *J. Org. Chem.* **1968**, *33*, 3542; Roberts, R. M. G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1374.

(19) Fărcasiu, M.; Fărcasiu, D.; Slutzky, J.; Schleyer, P. v. R. *Tetrahedron Lett.* **1974**, 4059. Whitlock, H. W.; Siefken, M. W. *J. Am. Chem. Soc.* **1968**, *90*, 4929.

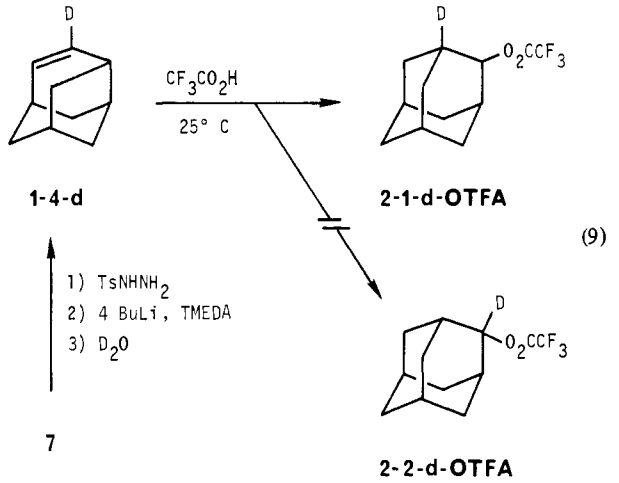
(20) Nakai, T.; Mimura, T. *Tetrahedron Lett.* **1979**, 531.

(21) Boyd, J.; Overton, K. H. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2533; *J. Chem. Soc., Chem. Commun.* **1971**, 211.

Scheme I



Lenoir, Hall, and Schleyer[15] in the solvolysis of *endo*-4-protoadamantyl tosylate. Thus trifluoroacetic acid was added to 4-deuterated olefin, **1**-*4-d*, and the product ester and derived ketone were examined by ^2H NMR and mass spectrometry, respectively. Both methods evidenced the formation of 2-adamantyl-*1-d* trifluoroacetate (**2**-*1-d*-OTFA) only (eq 9). In particular the 2-



(9)

labeled isomer, **2**-*2-d*-OTFA, which would have been formed in 50% yield following equilibration of type **9** ⇄ **10**, was found to be absent. **1** and **2**-OTFA are therefore connected by a simple Wagner–Meerwein rearrangement.

Products from CF_3CO_2D. Deuteriotrifluoroacetic acid was added to protoadamantene under standard conditions to determine the reaction stereochemistry. Saponification of the 2-adamantyl trifluoroacetates followed by ^2H NMR analysis with added Pr(fod)$_3$, as described separately,[22] revealed the formation of all four diastereomeric alcohols, **11**-OH–**14**-OH. The quantitative data are presented in terms of the addition reaction in Scheme I. The results were found to be invariant with reaction duration from 1 to 6 h, showing the esters to be stable. Oxidation to the corresponding adamantanones and mass spectrometry demonstrated the incorporation of one deuterium atom only (96% d_1 + 4% d_0).

The products of exo attachment of deuterium, **11**-OTFA + **13**-OTFA, are seen to predominate, with cis (ax) location of the trifluoroacetate (**11**-OTFA) being favored over trans (eq) (**13**-OTFA). In the products from endo attachment of deuterium the trans (again ax) orientation of trifluoroacetate (**12**-OTFA) is preferred over the cis (eq) (**14**-OTFA).

Reaction Rates. Measurements were made to compare the rates of addition of trifluoroacetic acid to protoadamantene and model olefins cyclohexene and cycloheptene. The relatively fast reaction of **1** was followed by quenching aliquots at 10-s intervals and determining residual reactant by gas chromatographic analysis against a small quantity of decane as internal standard. The reactions of the monocycloalkenes were monitored by real-time ^1H NMR with reference to 0.09 M added chloroform. Good

Table I. Rates of Addition of Trifluoroacetic Acid to Protoadamantene and Cycloalkenes at 25.0 °C

substrate	initial concn, M	$10^4 k_1$, s^{-1}	$t_{1/2}$, s	rel k_1
1	0.107	527	13.1	1
cyclohexene	0.423	1.29	5370	408^{-1}
cycloheptene	0.367	4.87	1420	108^{-1}

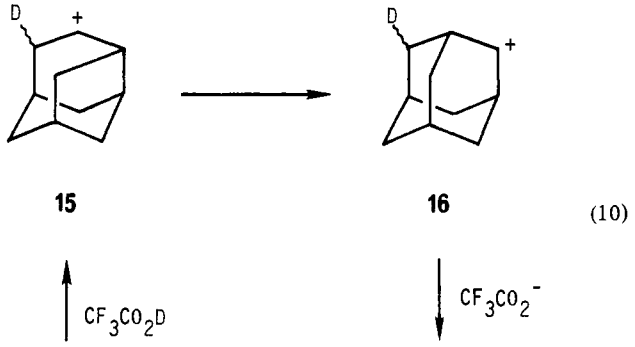
first-order rate behavior was observed in each case. The results are presented in Table I. The addition to protoadamantene at 25 °C is seen to be faster than that to cyclohexene and cycloheptene by factors of 410 and 110, respectively.[23]

A kinetic study was also made of the isomerization of *exo*-4-protoadamantyl trifluoroacetate (**4**-OTFA) to 2-adamantyl trifluoroacetate (**2**-OTFA) in trifluoroacetic acid to assess the possible importance of this unrearranged ester as an intermediate in the conversion of protoadamantene to **2**-OTFA. Rearrangement was followed by ^{19}F NMR on samples from quenched and extracted aliquots. This reaction of **4**-OTFA was thus found to proceed at 25 °C with $k_1 = 7.40 \times 10^{-4}$ s^{-1}, $t_{1/2} = 936$ s.

With these data in hand, the addition of CF_3CO_2H to **1** was conducted again for a duration of 5.0 min, 23 half-lives for addition and 0.32 half-life for **4**-OTFA → **2**-OTFA rearrangement, in order to preserve any unrearranged ester. ^{19}F NMR analysis showed the presence this time of 1% of **4**-OTFA along with 99% **2**-OTFA. A trace of *exo*-4-protoadamantyl trifluoroacetate is thus indicated to be a primary product in the addition reaction. The stereochemical results with CF_3CO_2D, however, cannot be significantly affected by this pathway.

Discussion

Ad_E2 Mechanism. The simplest explanation to be considered for the results in Scheme I is rate-determining deuteronation of protoadamantene (**1**) both exo and endo at C(5) to produce the diastereomeric 4-protoadamantyl-*5-d* cations, **15**, followed by isomerization to the corresponding 2-adamantyl species, **16**, and trifluoroacetate attachment preferentially but not exclusively at the side opposite the migrating bond (eq 10). With extension to incorporate the rearrangement this is the familiar Ad_E2 mechanism[1] (eq 1).

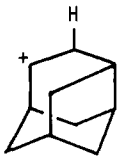


(10)

We disfavor this pathway on the basis of its inability to explain the nonformation of 5-protoadamantyl products, which have been strictly excluded here and undetected also in earlier addition reactions.[15] If discrete formation of unrearranged carbenium ions were to occur, we would expect the 5-protoadamantyl species, **17**, to be produced competitively with the 4-protoadamantyl, **18**, leading to a measurable quantity of 5-protoadamantyl ester. Cations **17** and **18** should be similar in stability, and comparable accessibility of the two olefinic carbons in **1** is both apparent from models and indicated experimentally by hydroboration to give 58% 4-protoadamantanols plus 42% 5-protoadamantanols[21] and by $LiAlH_4$ ring openings of *exo*- and *endo*-4,5-epoxyprotoadamantane, which proceed with 80% displacement at C(5) and

(22) Nordlander, J. E.; Haky, J. E. *J. Org. Chem.* **1980**, *45*, 4780.

(23) For cycloalkene data at 35 °C see ref 17b.



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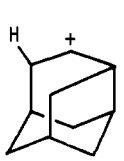

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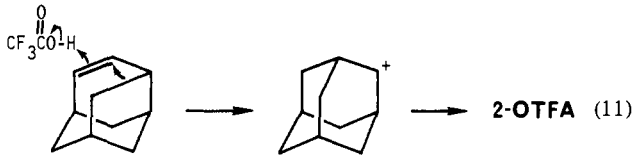
95% displacement at C(4), respectively.[21,24] There is furthermore no evident explanation in terms of simple protonation for the substantial acceleration of **1** over the monocycloalkenes ($>10^2$), which points more reasonably to involvement of the skeletal rearrangement in rate determination.

Intramolecular Ad_E3 Mechanism. An alternative course is reaction initiated by protonation of **1** at C(5) assisted by C(2)–C(3) bond migration to generate the 2-adamantyl cation (**19**) directly and essentially exclusively (eq 11). This mechanism is the intramolecular counterpart of a concerted Ad_E3 process (eq 2). It is attractive in providing a rationale for both the rate acceleration and the regiospecificity of this and other HX additions to **1**.



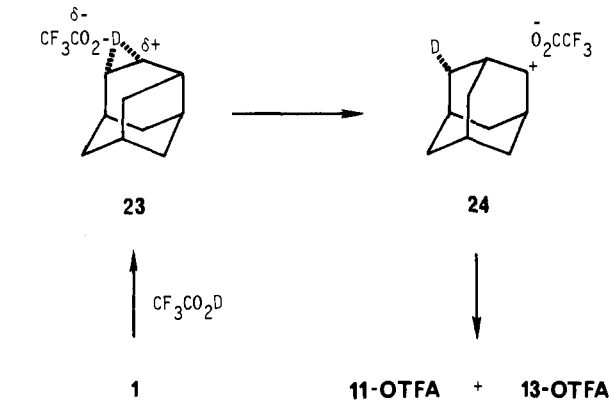
2-OTFA (11)

1 19

We take the stereochemical evidence to argue against this pathway, however. Assisted protonation would be expected to exhibit a markedly higher preference for exo attachment of the electrophile than that found experimentally. Models show that concurrent exo protonation and rearrangement could take place with a H–C(5)–C(4)–(C(3)–C(2)) torsional angle equal or close to 180°. Under endo protonation, on the other hand, a corresponding angle of ~30° is indicated. Taking this addition-rearrangement to be a retrograde analogue of E2 elimination, one would predict from experimental and theoretical precedents[26-28] a stereoelectronic optimum for the antiperiplanar (180°) geometry and a major relative disadvantage in orbital overlap and thus rate ($>10^2$) for a 30° alignment. The modest exo/endo preference of 3.3:1 measured for C(5) deuteronation, Scheme I, is instead readily explicable as the result of moderate steric effects that render the endo side of the protoadamantene double bond somewhat more hindered than the exo face. This bias is exemplified with respect to small reagents in hydroboration (exo:endo = 2.0:1)[21] and epoxidation (6.0:1).[21,29,30]

Analogous behavior has been observed in the addition of acids[31,32] to 1-methylnorbornene (**20**). Proton attachment at C(3) in **20** offers the potential benefit of concerted Wagner–Meerwein rearrangement (manifest in the solvolysis of 1-methyl-*exo*-2-norbornyl derivatives[31,33]) to produce directly the tertiary carbenium ion and subsequently the corresponding covalent product, e.g., chloride **22**. In fact, however, under several conditions[31,32] tertiary chloride production is favored only slightly over the regiochemically alternative 1,2-addition to give **21** (eq 12). Similar results have been observed with formic acid.[31] The driving force for carbenium ion rearrangement operative in the formation of **22** is not reflected in site selectivity for electrophilic attack. Thus **20** is a second bridged cyclic olefin well constituted for σ-assisted protonation which fails to take advantage of this possibility.

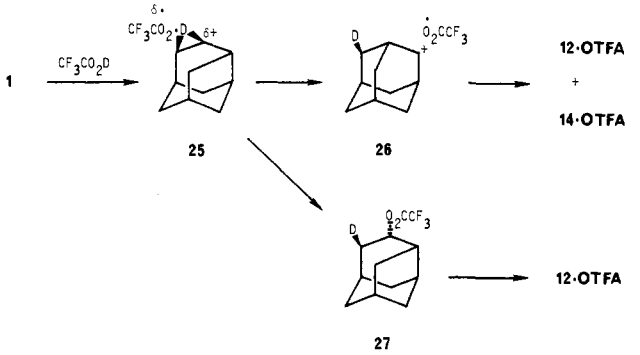
Scheme II



23 24

1 **11-OTFA** + **13-OTFA**

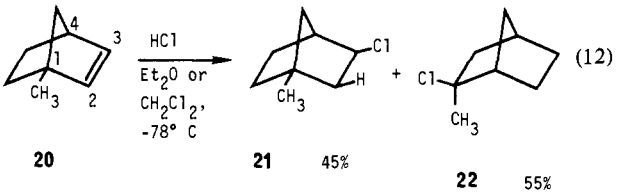
Scheme III



25 26 27

12-OTFA + **14-OTFA**

12-OTFA



20 21 45% 22 55%

(12)

Rearrangement within Olefin–Acid Complexes. We consider the present results best rationalized by the formation not of carbenium ions but of diastereomeric olefin–trifluoroacetic acid complexes as first and key intermediates. The formation of π complexes between Brønsted acids and alkenes (and aromatics) is well established on physical grounds,[11,34] and the presence of intermediates of this type in addition processes has been considered by a number of authors.[1,5-7,9,11,12,35] Of principal significance has

(24) Higher regio- and stereoselectivity is observed in reaction of protoadamantene with the comparatively large reagent in oxymercuration.[15,21,25]

(25) Cuddy, B. D.; Grant, D.; McKervey, M. A. *J. Chem. Soc. C* **1971**, 3173; *J. Chem. Soc., Chem. Commun.* **1971**, 27.

(26) Saunders, W. H., Jr.; Cockerill, A. F. "Mechanisms of Elimination Reactions"; Wiley: New York, 1973; Chapter 3.

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(30) Higher preferences for exo attack have been observed in osmylation,[29] bromination,[25,29] and reaction with *N*-bromosuccinimide.[25]

(31) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 3901.

(32) Brown, H. C.; Liu, K.-T. *J. Am. Chem. Soc.* **1975**, *97*, 600. These authors have observed the same behavior in the addition of HCl to bornylene (1,7,7-trimethylnorbornene).

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been the possibility that product formation may take place directly from such an intermediate, as in eq 3. A π-complex mechanism is consistent with the present data and distinctively strengthened by the evidence developed against alternative carbenium ion pathways. Further support is found in the recent interpretation of kinetic data for a variety of simpler proton-transfer reactions, both in solution[36] and in the gas phase,[37] in terms of the preformation of a hydrogen-bonded encounter complex, a proposal first made by Eigen.[38]

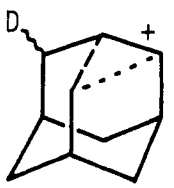
We postulate sterically preferred formation of exo complex **23** and rearrangement of this species to the 2-adamantyl-*ax-4-d* cation (**24**) as its exclusive forward reaction. Combination of **24** with trifluoroacetate then produces epimeric esters **11**-OTFA + **13**-OTFA (Scheme II).

Concurrent attack of acid at the comparatively hindered endo face of **1** should generate a lesser quantity of epimeric complex **25**. We envision predominant rearrangement of this intermediate likewise to the corresponding 2-adamantyl ion, **26**, and combination of the latter with trifluoroacetate to give the *eq-4-d* esters **12**-OTFA + **14**-OTFA. The rearrangement here need not be as rapid as the isomeric **23** → **24** process, however, a point to be amplified below. Both rearrangements would be expected to involve electrophilic assistance from one or more additional molecules of trifluoroacetic acid.[5,8,12] We see **25** also as the most reasonable precursor to the metastable *exo*-4-protoadamantyl trifluoroacetate (**4**-OTFA) detected at trace level, now hypothesized as having its *5-d* label endo, **27** (Scheme III). This route to **27** by anti-1,2-addition is in accord with stereochemical precedents for ordinary olefins (above)[6-9] and the regiochemistry of *endo*-epoxide opening (above).[21]

The proposed mechanism provides an explanation of the enhanced rate for addition to **1** over cyclohexene and cycloheptene in terms of comparative rates of π-complex decomposition. Peterson's extensive studies of neat trifluoroacetic acid additions to alkenes[17] have revealed marked, solvent-amplified rate retardations by electron-withdrawing substituents,[17c-e,i,k] suppressed hydride shifts relative to solvolysis,[17a,b] and rate-enhancing participation by 5-positioned halogen and methoxy substituents.[17e,h,i] These observations point to a mechanism for simple olefins involving π-complex formation followed principally by fully or nearly rate-limiting carbenium ion production, with possible competition from direct product formation or hydride shift.[39,40] The accelerations effected by *n*-electron neighboring groups are more attractively explained, in our view, by interception of a π complex than by anchimerically assisted protonation,[17h,l] which would require occupancy of a highly eclipsed conformation at the moment of acid attack. The rate enhancement evident for protoadamantene can likewise be understood as the result of exceptionally favorable forward reaction of complexes **23** and **25** by rearrangement to **24** and **26**.

Of the two rearrangements one would expect that of the exo complex, **23** → **24**, to be distinctly advantaged stereoelectronically and correspondingly faster than that of the endo counterpart, **25** → **26**. If both proceed as postulated over low activation barriers, however, their rates will be comparable.[41] At the limit, both could be rapid enough effectively to preempt reversion of the complexes to reactants, in which case the product ratio (**11**-OTFA + **13**-OTFA)/(**12**-OTFA + **14**-OTFA) would be determined by the relative rates of formation of **23** and **25**. The magnitude of this ratio, 3.3, is congruent with first-step steric effects, as already noted.

Additional mechanistic information is embodied in the ratios of product formation by axial and equatorial nucleophilic attachments, **11**-OTFA/**13**-OTFA = 7.6 and **12**-OTFA/**14**-OTFA = 2.9. In both cases trifluoroacetate incorporation occurs with a modest preference for axial orientation, i.e., on the side opposite the shifted C–C bond. One hypothesis to accommodate these results is protoadamantyl-to-adamantyl rearrangement partially induced by backside nucleophilic attack at C(3) (C(2) in the product). An alternative possibility is weak bridging in the 2-adamantyl cation formed on rearrangement, **28** in place of **24** and



28

26. This property has earlier been suggested for the 2-adamantyl ion by Whiting[42] and by Schleyer[15] to account for solvolysis with preferred retention of configuration and the confirmed formation of a slight quantity of *exo*-4-protoadamantyl acetate in the acetolysis of 2-adamantyl tosylate. A broad pattern of evidence for strong bridging in the cation from 1-methyl-2-adamantyl or 4-methyl-4-protoadamantyl reactants has also been assembled by Lenoir, Schleyer, and Majerski and co-workers.[43] One would expect carbocation stabilization by β,γ-bond delocalization to favor opposite-side nucleophilic attack increasingly along the structural scale[44] from minimal hyperconjugation to symmetrical bridging.

The conclusion of a π-complex mechanism for the present reaction lends support to the analogous more ramified mechanism proposed recently by Staab and co-workers[12] (eq 4). These views accord also with a unifying scheme for electrophilic additions to olefins set forth earlier by Dolbier.[45,46]

The results here prompt comment on the correlation of Wagner–Meerwein rearrangement in electrophilic addition reactions with prior production of a fully formed carbenium ion intermediate. While the two have frequently been associated,[47] any requirement that rearrangement proceed solely from a discrete carbocation has been arbitrary. Rearrangement more reasonably can occur toward carbon centers of varying degrees of electron deficiency, depending on the overall structural driving force.

Experimental Section

General Data. Boiling points and melting points (volatile samples in sealed capillary tubes) are uncorrected. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer by using neat liquid films or Nujol mulls of solid compounds between KCl plates. ^{1}H NMR spectra were obtained with a Varian A-60-A, HA-100, or XL-100 instrument, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{2}H NMR spectra were obtained at 15.4 MHz with the Varian XL-100-15 system in the Fourier-transform mode with modulated proton decoupling; chemical shifts were measured relative to $CDCl_3$ and are expressed with

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(39) Small quantities of added water were found to accelerate the addition of trifluoroacetic acid to 1-hexene, although added sodium trifluoroacetate had little rate effect.[17b]

(40) Latrémouille and Eastham[18] and Roberts[18] have reported second-order dependence on acid in additions of trifluoroacetic acid to isobutene and limonene in weakly polar solvents, evidence against an alternative Ad_E2 mechanism at least under these conditions.

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(46) See also Schleyer, P. v. R. In Brown, H. C. "The Nonclassical Ion Problem"; Plenum Press: New York, 1977; pp 233–235.

(47) See, for example: ref 8c; Ecke, G. G.; Cook, N. C.; Whitmore, F. C. *J. Am. Chem. Soc.* **1950**, *72*, 1511; Gould, E. S. "Mechanism and Structure in Organic Chemistry"; Holt, Rinehart, and Winston: New York, 1959; p 517.

reference to internal $(CD_3)_4Si$.[48] ^{19}F NMR spectra were recorded at 94.1 MHz on the XL-100-15 instrument, using $(CD_3)_2CO$ as solvent; chemical shifts are expressed relative to external CF_3CO_2H. Overlapping signals in the ^2H and ^{19}F spectra were quantitatively deconvoluted by means of a Du Pont Model 310 Curve Resolver, assuming Lorentzian line shapes. Mass spectra were obtained on a Du Pont Model 21-490 spectrometer. Isotopic compositions were calculated from the spectra as described by Biemann.[49] GLC analyses and preparative separations were performed on a Varian Model 920 gas chromatograph employing the following columns: (A) 20 ft × $^1/_4$ in. 20% SE-30 on acid-washed DMCS-treated Chromosorb W, (B) 6 ft × $^1/_8$ in. Carbowax 20M on acid-washed DMCS-treated Chromosorb W.

Trifluoroacetic Acid. Commercial acid was dried over P_2O_5 and distilled under N_2 immediately before use ($(CF_3CO)_2O$ forerun).

Trifluoroacetic acid-*d*. The labeled acid was prepared immediately before use from equimolar amounts of trifluoroacetic anhydride and D_2O according to the method of DePuy et al.[50]

Protoadamantene (1). Treatment of the tosylhydrazone of 4-protoadamantanone[51] with excess methyllithium as described by Cuddy, Grant, and McKervey[25] produced the olefin in 70% yield: mp (sealed tube) 174–177 °C (lit.[25] mp 174–177 °C).

2-Adamantyl Trifluoroacetate (2-OTFA). To a stirred solution of 1.0 g (6.6 mmol) of 2-adamantanol (Aldrich) in 10 mL of dry pyridine and 50 mL of methylene chloride at 0 °C was added in one portion 3.0 g (14.3 mmol) of trifluoroacetic anhydride. After 10 h the mixture was added to 200 mL of 10% hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was washed successively with 10% hydrochloric acid and saturated sodium bicarbonate solution. After the solution was dried ($MgSO_4$), the methylene chloride was removed by rotary evaporation, leaving a yellow oil which was distilled to give 1.4 g (5.6 mmol, 83%) of **2**-OTFA: bp 72–74 °C (0.5 mmHg); ^1H NMR δ 1.4–2.4 (m, 14 H), 5.20 (m, 1 H, >CHO–); ^{19}F NMR δ 0.55.

Anal. Calcd for $C_{12}H_{15}F_3O_2$: C, 58.07; H, 6.09. Found: C, 58.00; H, 6.06 (Galbraith Laboratories, Inc., Knoxville, Tenn.).

***exo*-4-Protoadamantyl Trifluoroacetate (4-OTFA).** *exo*-4-Protoadamantanol (**4**-OH) was prepared in 70% yield by the oxymercuration/reduction of protoadamantene according to the method of Schleyer and co-workers.[15] The alcohol was then trifluoroacetylated according to the procedure used above for 2-adamantyl trifluoroacetate and was purified by distillation, giving the ester as a colorless liquid: bp 72–74 °C (0.5 mmHg); ^1H NMR δ 1.1–2.9 (m, 12 H), 5.45 (m, 1 H); ^{19}F NMR δ 0.25 (s); IR 1728 cm^{-1} ($\nu_{C=O}$).

***exo*- and *endo*-4-Protoadamantyl Trifluoroacetates (3-OTFA + 4-OTFA).** A 2:1 mixture of *endo*- and *exo*-4-protoadamantanol (**3**-OH + **4**-OH) was prepared in 90% yield by $LiAlH_4$ reduction of 4-protoadamantanone (**7**) as reported by Schleyer and co-workers.[15] The resulting mixture was trifluoroacetylated by the same procedure used above for 2-adamantyl trifluoroacetate (**2**-OTFA) and distilled to give a colorless liquid: bp 72–76 °C (0.5 mmHg); ^{19}F NMR δ 0.25 (relative area 1, **4**-OTFA), 0.49 (relative area 2.0, **3**-OTFA).

5-Protoadamantanone (8). To 3.2 g (10 mmol) of the tosylhydrazone[25] of 4-protoadamantanone (**7**) dissolved in 25 mL of dry tetrahydrofuran and 25 mL of dry tetramethylethylenediamine and cooled to −40 °C in a flame-dried 250-mL three-necked flask equipped with a dry-ice condenser, pressure-equalizing addition funnel, dry N_2 atmosphere, and magnetic stirrer was added dropwise over 15 min 10 mL of 2.0 M *n*-butyllithium (20 mmol) in hexane (Ventron).[20] The deep red cold solution was stirred for an additional 10 min, treated by syringe with 0.90 mL (0.94 g, 10 mmol) of dimethyl disulfide (Aldrich), stirred 20 min longer at −40 °C, and treated dropwise over 10 min with another 15 mL (15 mmol) of butyllithium solution. After being stirred for 14 h at room temperature, the mixture was cooled to 0 °C and quenched cautiously with 35 mL of saturated aqueous NH_4Cl. The resulting solution was poured into 200 mL of water and extracted with ether. The combined ether extract was washed with saturated $CuSO_4$ solution and saturated NaCl solution. After the solution was dried ($MgSO_4$), the ether was removed under vacuum, leaving a yellow oil which was purified by preparative GLC on column A to give 1.09 g (61 mmol, 61%) of yellow liquid of bp 82–83 °C (0.5 mmHg) whose ^1H NMR spectrum was consistent with presumed intermediate[20] 5-methylthioprotoadamantene. Reaction of 180 mg (1.0 mmol) of this material with 543 mg (2.0 mmol) of $HgCl_2$ in 10 mL of 3:1 acetonitrile–water with stirring for 12 h at room temperature produced a white precipitate, which was removed by vacuum filtration. The filtrate was combined with 100 mL of ether (first used to wash the separated solid), washed with saturated $NaHCO_3$ solution and saturated brine, and dried over anhydrous $MgSO_4$. Rotary evaporation of the solvent left a white solid, which was recrystallized from hexane at −78 °C to give 130 mg (0.86 mmol, 86%) of pure **8**: mp 222–224 °C (lit.[21] mp 222–225 °C); IR 1728 cm^{-1} ($\nu_{C=O}$) (lit.[21] 1727 cm^{-1}); ^1H NMR δ 0.31–2.76 (m).

***exo*- and *endo*-5-Protoadamantyl Trifluoroacetates (5-OTFA + 6-OTFA).** A mixture of 70% *exo*- and 30% *endo*-5-protoadamantanol was prepared in 75% yield by lithium–ammonia reduction of 5-protoadamantanone (**8**) as reported by Boyd and Overton.[21] The resulting mixture was trifluoroacetylated by the same procedure used above for 2-adamantyl trifluoroacetate (**2**-OTFA) and distilled to give the esters as a colorless liquid: bp 73–75 °C (0.5 mmHg); ^{19}F NMR δ 0.48 (relative area 7.0, **5**-OTFA), 0.49 (relative area 3.0, **6**-OTFA), integrations aided by curve resolution (see above).

Protoadamantene-*4-d* (1-*4-d*). A three-necked 250-mL flask was fitted with a dry ice condenser, a pressure-equalizing addition funnel, dry nitrogen atmosphere, and a magnetic stirrer. After being flame-dried and cooled, the flask was charged with 3.2 g (10 mmol) of 4-protoadamantanone tosylhydrazone,[25] 25 mL of dry tetramethylethylenediamine, and 25 mL of dry tetrahydrofuran. The solution was stirred until homogeneous and then cooled to −40 °C with a dry ice–acetone bath. A 40-mL (40 mmol) portion of a 2 M solution of *n*-butyllithium (Ventron) was then added dropwise over a 15-min period. The deep red solution was stirred at −40 °C for an additional 10 min and then at room temperature for 2 h. The mixture was cooled to 0 °C in an ice bath, and 44.3 g (2.21 mol) of deuterium oxide was added over a 40-min period. The mixture was poured into water and extracted with pentane. The extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated by careful distillation through a Vigreux column. The residue was passed down a column of silica gel (100 g) by using pentane as eluant, yielding deuterated olefin **1-*4-d***: mp 175–177 °C. Mass spectral analysis (M^+s at *m/e* 135 and 134) showed the material to consist of 85.9% monodeuterated and 14.1% undeuterated compound.

2-Adamantanol-2-*d* (2-*2-d*-OH). Adamantanone (250 mg, 1.64 mmol) was reduced with 50 mg (1.19 mmol) of lithium aluminum deuteride (Merck, Sharp, & Dohme) in 20 mL of absolute ether. After the usual workup[52] 232 mg (1.54 mmol, 94%) of **2-*2-d*-OH** was obtained: mp (sealed tube) 256–260 °C. The ^1H NMR spectrum showed no signal at δ 3.9, while the ^2H NMR showed a single peak at δ 3.9 in the absence of shift reagent and at δ −20.3 with added $Pr(fod)_3$ (15 mg of substrate + 70 mg of shift reagent in 400 μL of $CHCl_3$).

Reaction of Protoadamantene (1) with Trifluoroacetic Acid. Protoadamantene (**1**) (100 mg, 0.75 mmol) was stirred in 10.0 g of trifluoroacetic acid at 25 °C for 6 h. The solution was then poured into water and extracted with methylene chloride. The combined extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The methylene chloride was removed by rotary evaporation, leaving a yellow liquid. GLC of the crude product on column A at 150 °C showed one peak, identified as 2-adamantyl trifluoroacetate (**2**-OTFA) by coinjection with authentic material. The crude product was then purified by distillation, giving 173 mg (0.70 mmol, 93%) of **2**-OTFA: bp 72–73 °C (0.5 mmHg), identical by GLC and NMR with authentic material.

Trifluoroacetolysis of *exo*- and *endo*-4-Protoadamantyl Trifluoroacetates (3-OTFA + 4-OTFA). A 150-mg (0.60 mmol) sample of the twofold trifluoroacetate mixture **3**-OTFA + **4**-OTFA (above) was stirred in 10 g of trifluoroacetic acid at 25 °C for 6 h. The mixture was worked up by the procedure described for the reaction of trifluoroacetic acid with protoadamantene, giving 130 mg (52 mmol, 87%) of a yellow liquid whose ^{19}F NMR spectrum consisted of two signals in the ratio of 2.0:1. While the signal at δ 0.49 corresponding to **3**-OTFA remained, the peak for **4**-OTFA at δ 0.25 was gone, replaced by a signal corresponding to 2-adamantyl trifluoroacetate (**2**-OTFA) at δ 0.55.

Trifluoroacetolysis of *exo*- and *endo*-5-Protoadamantyl Trifluoroacetates (5-OTFA + 6-OTFA). A 150 mg (0.60 mmol) sample of the twofold trifluoroacetate mixture **5**-OTFA and **6**-OTFA (above) was stirred in 10.0 g of trifluoroacetic acid at 25 °C for 6 h. The mixture was worked up as in the preceding reaction, giving 132 mg (52 mmol, 87%) of a yellow liquid whose ^{19}F NMR spectrum consisted only of signals at δ 0.48 and 0.49, corresponding to **5**-OTFA and **6**-OTFA in the original ratio. No signal at δ 0.55 was present, indicating the absence of 2-adamantyl trifluoroacetate.

(48) ^1H and ^2H NMR chemical shifts are parallel. Jensen, H.; Schaumberg, K. *Acta Chem. Scand.* **1971**, *25*, 663. Diehl, P. In "Nuclear Magnetic Resonance Spectroscopy of Nuclei Other than Protons"; Axenrod, T.; Webb, G. A., Eds.; Wiley: New York, 1974, Chapter 18.

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(51) Majerski, Z.; Hameršak, Z. *Org. Synth.* **1979**, *59*, 147.

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Reaction of Protoadamantene-*4-d* (1·*4-d*) with Trifluoroacetic Acid. Protoadamantene-4-*d* (**1**-*4-d*) (100 mg, 0.75 mmol) was stirred in 10 g of trifluoroacetic acid at 25 °C for 6 h. The solution was then poured into 200 mL of 20% methanolic potassium hydroxide and stirred for 12 h. The bulk of the methanol was removed by rotary evaporation, and the residue was poured into 1 L of water and extracted with ether. The ether extracts were combined, washed with water, and dried ($MgSO_4$). Rotary evaporation of the ether left a white solid. GLC of the crude product on column B at 150 °C showed one peak, identified as 2-adamantanol by coinjection with authentic material. The crude product was then purified by recrystallization from hexane at −78 °C, giving 108 mg (0.71 mmol, 95%) of 2-adamantanol: mp (sealed tube) 258–260 °C. The shift-enhanced ^2H NMR spectrum (15 mg of substrate + 70 mg of $Pr(fod)_3$ in 400 μL of $CHCl_3$) consisted of a single signal at δ −8.7, distinct from and intermediate between the chemical shifts established for 2-adamantanol-2-*d* (δ −20.3) and the four 2-adamantanols-*4-d* (δ −2.0 to −7.3)[22] under these conditions. Oxidation of this product with Jones reagent[22] and mass spectral analysis of the ketone (M^+s at *m/e* 151 and 150) showed the material to consist of 85.8% monodeuterated and 14.2% undeuterated compound, corresponding to the isotopic composition of the starting olefin (**1**-*4-d*).

Reaction of Protoadamantene (1) with Trifluoroacetic Acid-*d*. A 100 mg (0.75 mmol) sample of protoadamantene (**1**) was stirred in 10 g of trifluoroacetic acid-*d* at 25 °C for 1 h. The solution was then poured into 200 mL of 20% methanolic KOH and stirred for 12 h. Workup as described above for the addition of trifluoroacetic acid to protoadamantene-*4-d* furnished 110 mg (0.72 mmol, 96%) of 2-adamantanol-*4-d*: mp (sealed tube) 258–260 °C. The ^2H NMR spectrum (15 mg of substrate + 70 mg of $Pr(fod)_3$ in 400 μL of $CHCl_3$) showed 4 signals corresponding[22] to the following product composition: **11**-OH (δ −7.27), 68%; **12**-OH (δ −4.13), 17%; **13**-OH (δ −2.70), 9%; **14**-OH (δ −1.95), 6%. Jones oxidation[22] of this product and mass spectral analysis of the ketone (M^+s at *m/e* 151 and 150) showed the material to consist of 96% monodeuterated and 4% undeuterated compound.

Repetition of the addition reaction over 6 h and identical analysis gave the same results.

Kinetics of the Addition of Trifluoroacetic Acid to Protoadamantene (1). Protoadamantene (100 mg, 0.75 mmol) was dissolved in 100 μL of dry methylene chloride and 10 μL of decane in a stoppered 20-mL test tube. This solution was placed in a constant temperature bath at 25 °C, and after 0.5 h 10 g of trifluoroacetic acid (preequilibrated at 25 °C) was added and the solution was shaken for 10 s. Five samples of approximately 1 mL were then withdrawn from the solution at approximately 10-s intervals and quenched by injection into 150-mL portions of ice water. The reaction time for each sample was carefully noted. Each of the product mixtures was then extracted with ether (3 × 50 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The dried extracts were analyzed for remaining protoadamantene by GLC on column A by using the decane peak as internal integration standard. Each analysis was run at least in triplicate. Linear least-squares first-order kinetic analysis gave a rate constant $k_1 = 5.3 \times 10^{-2}$ s^{-1}, correlation coefficient 0.997.

Kinetics of the Addition of Trifluoroacetic Acid to Cyclohexene and Cycloheptene. Cyclohexene (300 μL, 0.243 g, 2.9 mmol) was dissolved in 50 μL of chloroform in a 20-mL test tube in a constant-temperature bath at 25.2 °C. After 30 min 10.0 g of trifluoroacetic acid (preequilibrated to the same temperature) was added, and the solution was shaken for 10 s. A 0.5-mL sample of this solution was transferred to a 5-mm NMR tube, and the ^1H NMR spectrum was recorded at 6 measured times over a 90-min duration on the A-60A spectrometer with the sample temperature maintained at 25.2 °C. The progress of the reaction was followed by comparative integration of the vinylic proton and chloroform peaks. Linear least-squares first-order kinetic treatment gave $k_1 = 1.29 \times 10^{-4}$ s^{-1}, correlation coefficient 0.996.

The same measurements with cycloheptene yielded $k_1 = 4.87 \times 10^{-4}$ s^{-1}, correlation coefficient 0.997.

Kinetics of the Trifluoroacetolysis of *exo*-4-Protoadamantyl Trifluoroacetate (4-OTFA). *exo*-4-Protoadamantyl trifluoroacetate (151 mg, 0.61 mmol) was dissolved in a solution of 50 mg of 1-adamantyl trifluoroacetate (internal integration reference) in 100 μL of methylene chloride. This solution was brought to 25.2 °C in a constant temperature bath, 10 g of trifluoroacetic acid was added, and the solution was shaken for 10 s. Six samples of approximately 1 mL were then withdrawn from the solution at approximately 2-min intervals (including a zero-time sample) and quenched at measured times by injection into 150 mL of ice water. Each of the quenched samples was extracted with methylene chloride (3 × 10 mL), and the extracts were washed with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). The bulk of the methylene chloride was then removed from each solution by careful distillation through a fractionating column down to a volume of ca. 0.5 mL. The residual solution was dissolved in acetone-d_6 and analyzed by ^{19}F NMR, integrating the *exo*-4-protoadamantyl trifluoroacetate peak at δ 0.25 against the 1-adamantyl trifluoroacetate peak at δ 0.01. First-order kinetic analysis gave $k_1 = 7.40 \times 10^{-4}$ s^{-1}, correlation coefficient 0.979.

Short-Term Reaction of Protoadamantene (1) with Trifluoroacetic Acid. Protoadamantene (100 mg, 0.75 mmol) was stirred in 10 g of trifluoroacetic acid at 25 °C for 5.0 min. The solution was then poured into 300 mL of ice water and worked up in the same manner as in the longer term reaction above, giving 108 mg of a yellow oil as crude product. The ^{19}F NMR spectrum of this material consisted of two signals in the ratio of 99:1, the major signal at δ 0.55 having the chemical shift of 2-adamantyl trifluoroacetate, with the minor signal at δ 0.25 having that of *exo*-4-protoadamantyl trifluoroacetate.

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Structure and Biosynthesis of Setomimycin. A Novel 9,9′-Bianthryl Antibiotic

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Abstract: The structure of an antibacterial and antitumor antibiotic setomimycin, produced by *Streptomyces pseudovenezuelae* AM-2947, was determined to be a unique substituted 9,9′-bianthryl **1** by means of various new ^{13}C NMR techniques including ^{13}C $\{^1H\}$ selective decoupling, ^{13}C $\{^1H\}$ selective population transfer, and ^{13}C $\{^1H\}$ NOE experiments. The biosynthetic studies were also carried out by labeling with [1-^{13}C]- and [1,2-$^{13}C_2$]sodium acetates. The labeling pattern was determined by the ^{13}C–^{13}C coupling constants with the aid of ^{13}C $\{^{13}C\}$ homonuclear decoupling experiments, which allowed for the elucidation that **1** is derived from two nonaketide metabolites via decarboxylation at the terminals.

Setomimycin, produced by *Streptomyces pseudovenezuelae* AM-2947, shows antimicrobial activities against Gram positive bacteria including *Mycobacteria* as well as antitumor activity against solid Sarcoma 180 in mice.[2] Described in this paper are

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