Rearrangement of a Homoallylic Alcohol via an Acid-Catalyzed 1,4-Hydride Shift Yields a Saturated Ketone

Doug T. H. Chou, Xicai Huang, Raymond J. Batchelor, Frederick W. B. Einstein, and Andrew J. Bennet*

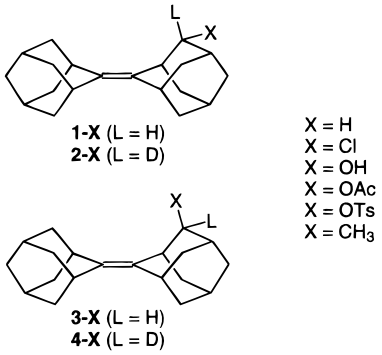
Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia V5A 1S6, Canada

Received August 6, 1997

The homoallylically substituted alcohols (**1-OH** and **3-OH**) of the sterically congested alkene adamanylideneadamantane (**1-H**) react with acid catalysis in a solvent of 50% v/v acetic acid:50% v/v aqueous sulfuric acid at 110 °C to give a saturated ketone **5**, the structure of which has been characterized by ^{1}H and ^{13}C NMR spectroscopy and by single-crystal X-ray diffraction. Isotopic labeling studies demonstrate that the reaction involves a stereospecific protonation of the double bond and an intramolecular 1,4-hydride transfer from the secondary alcohol C−H to the other carbon of the olefin. The rearrangement reaction exhibits a kinetic isotope effect (KIE) of 2.34 ± 0.17 for the intramolecular hydride transfer reaction and a competitive isotope effect of 1.2 for protonation of the olefin. These results are consistent with a two-step reaction in which the protonation of the double bond, a potentially reversible process, is followed by the rate-determining, intramolecular 1,4-hydride transfer.

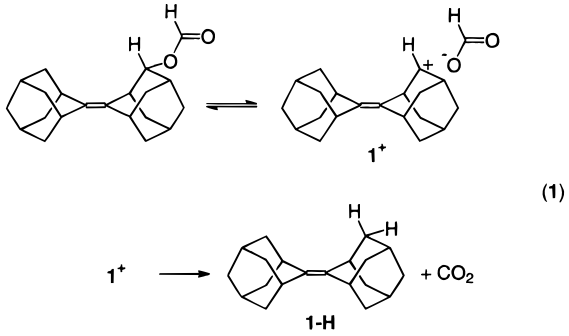
Introduction

For many years, it has been known that sterically congested alkenes such as adamantylideneadamantane (**1-H**) can react with electrophilic chlorinating reagents including benzenesulfenyl chloride,[1,2] *N*-chlorosuccinimide,[3] and benzeneselenyl chloride[2,4] to give the homoallylically substituted product **1-Cl**.



The mechanism for this unusual substitution reaction with benzenesulfenyl chloride has been investigated recently using the methyl-substituted alkene **3-CH$_3$** as the sterically congested reactant.[2] Synthesis of an alkene that is stereospecifically labeled with deuterium (**4-H**) would allow measurement of the primary kinetic isotope effect (k_H/k_D) for this reaction using an intermolecular competition experiment between **1-H** and **4-H**, an experiment that could contribute to the characterization of the mechanism for this homoallylic chlorination reaction.

A promising synthetic route for this compound would involve the formation of ion pairs between the homoallylic carbenium ion **1**$^+$ and formate.[5] It is expected that ion pairs such as these would collapse, giving the formate ester as the major reaction product. However, reversible formation of the ion pairs could generate the reduced product **1-H** and CO_2 through an inherently minor side reaction involving disproportionation (eq 1).



Prolonged heating of the alcohol **1-OH** in 88% formic acid containing a few drops of sulfuric acid as a catalyst yields an isomeric saturated ketone as the product.[6] The present paper focuses on the structure of the saturated ketone product and on the mechanism of this acid-catalyzed hydride transfer.

Materials and Methods

NMR spectra were acquired using C_6D_6 or $CDCl_3$ as the solvent and as the internal reference (*J* values are given in Hz). Melting points are reported as corrected values. Electron

* To whom correspondence should be addressed. Tel.: (604) 291-3532. FAX: (604) 291-3765. E-mail: bennet@sfu.ca.

(1) Bolster, J.; Kellogg, R. M.; Meijer, E. W.; Wynberg, H. *Tetrahedron Lett.* **1979**, 285−286.

(2) Huang, X.; Batchelor, R. J.; Einstein, F. W. B.; Bennet, A. J. *J. Org. Chem.* **1994**, *59*, 7108−7116.

(3) Meijer, E. W.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1982**, *47*, 2005−2009.

(4) Lopez, L.; Troisi, L.; Mele, G. *Tetrahedron Lett.* **1991**, *32*, 117−120.

(5) (a) Huang, X.; Bennet, A. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1279−1284. (b) Huang, X.; Tanaka, K. S. E.; Bennet, A. J. *J. Am. Chem. Soc.*, in press.

(6) Boelema, E.; Wieringa, J. H.; Wynberg, H.; Strating, J. *Tetrahedron Lett.* **1973**, 2377−2380.

S0022-3263(97)01465-5 CCC: $15.00
Published on Web 01/22/1998

impact mass spectra were recorded using an ionizing voltage of 70 eV. The standard GC conditions used for all analyses were as follows: DB-1 column (35 m), initial temperature 150 °C, final temperature 250 °C, and a thermal gradient of 20 °C min^{-1}. The percentages of each isotopomer present in a mixture were calculated by the least-squares method of Brauman[7] using the molecular ion isotopic peak distribution measured in the mass spectrum.

(1*R**,2*R**)-2-Hydroxy-4-tricyclo[3.3.1.1^{3,7}]dec-2-ylidenetricyclo[3.3.1.1^{3,7}]decane (**1-OH**; GC retention time 13.78 min),[2] the 2-*deuterio* isotopomer (**2-OH**),[8] and the epimeric alcohol (**3-OH**; GC retention time 13.28 min)[8] and its 2-*deuterio* isotopomer (**4-OH**)[8] were synthesized by literature procedures.

(1*R,4*S**)-4-(Tricyclo[3.3.1.1^{3,7}]dec-2-yl)-2-tricyclo[3.3.1.1^{3,7}]decanone (5).** Fifty percent v/v aqueous sulfuric acid (10 mL) was added to a solution of the alcohol **1-OH** (100 mg, 0.35 mmol) in glacial acetic acid (20 mL). The resulting mixture was heated with stirring to 140 °C for 3 h, and then the reaction mixture was quenched by pouring it into ice-cold water. The reaction product was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O, saturated aqueous $NaHCO_3$, and brine. The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white precipitate (95 mg, 95%). Purification of the crude product by flash column chromatography (silica; eluant hexane, followed by 5% EtOAc in hexane) yielded a white solid (89 mg, 89%), which was recrystallized in methanol to give colorless crystals: mp = 186.5−187.5 °C (lit.[6] mp 187.6−187.9 °C); GC retention time 14.51 min; ^{1}H NMR (400 MHz; C_6D_6) δ 1.43 (m, 1 H, H-4′), 1.47 (m, 1 H, H-9′a), 1.55−1.58 (m, 2 H, H-9a, H-2′), 1.58−1.90 (m, 19 H), 1.90−1.95 (m, 1 H, H-9b), 2.11 (bs, 1 H, H-1′), 2.16 (bd, 1 H, H-4), 2.48 (bs, 1 H, H-1), 2.70 (bs, 1 H, H-3); ^{13}C NMR (150 MHz, C_6D_6) δ 27.48 (C-7), 27.63 (C-5), 27.67 (C-3′), 27.93 (C-5′), 28.04 (C-1′), 28.12 (C-7′), 31.48 (C-4′), 31.65 (C-9′), 33.85 (C-9), 38.13 (C-6), 38.27 (C-6′), 39.08 (C-10′), 39.09 (C-8′), 39.28 (C-8), 39.76 (C-10), 43.42 (C-2′), 46.68 (C-1), 47.47 (C-4), 48.53 (C-3), 214.75 (C-2); MS (EI, 70 eV) *m*/*z* (relative intensity) 284 (M^+, 100), 285 ($M^+ + 1$, 21.3), 286 ($M^+ + 2$, 2.3). Anal. Calcd for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.14; H, 10.09.

(1*R,2*R**)-2-Acetoxy-4-(tricyclo[3.3.1.1^{3,7}]dec-2-ylidene)tricyclo[3.3.1.1^{3,7}]decane (1-OAc).** Acetic anhydride (0.5 mL) was added to a solution of the alcohol **1-OH**[2] (50 mg; 0.18 mmol) in pyridine (8 mL), and this solution was stirred at 40−50 °C for 24 h. The resulting solution was concentrated at aspirator pressure to give a syrupy residue that was then dissolved in CH_2Cl_2. The resulting organic layer was washed with 10% v/v H_2SO_4, saturated aqueous $NaHCO_3$, and brine. This solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light brown syrup. Subsequent purification of the crude product by flash column chromatography (silica; eluant hexane, followed by 5% EtOAc in hexane) gave a colorless oil, which was then crystallized from 50% aqueous methanol to give colorless crystals (47 mg, 81%): mp = 110−111 °C; GC retention time 14.75 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45−1.51 (m, 1 H), 1.57−1.74 (m, 7 H), 1.77−1.94 (m, 11 H), 2.03−2.07 (m, 2 H), 2.08 (s, 3 H), 2.09−2.15 (m, 1 H), 2.84−2.91 (m, 3 H), 2.99 (bs, 1 H), 4.73 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 27.6, 28.5, 28.6, 30.8, 31.4, 31.9, 32.4, 32.6, 33.4, 35.9, 36.9, 37.3, 39.2, 39.6, 39.6$_5$, 39.7, 39.7$_2$, 77.3, 130.0, 137.0, 170.4. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.70; H, 9.02.

(1*R,2*S**)-2-Acetoxy-4-(tricyclo[3.3.1.1^{3,7}]dec-2-ylidene)tricyclo[3.3.1.1^{3,7}]decane (3-OAc).** Acetic anhydride (0.5 mL) was added to a solution of the alcohol **3-OH**[8] (50 mg; 0.18 mmol) in pyridine (8 mL), and this was stirred at 40−50 °C for 48 h. The resulting solution was concentrated at aspirator pressure to give a syrupy residue that was then dissolved in CH_2Cl_2. The organic layer was washed with 10% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, and the washed solution was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a light brown syrup. This crude product was purified by flash column chromatography (silica; eluant hexane, followed by 5% EtOAc in hexane) to give a colorless oil, which was then crystallized from methanol to give colorless crystals (42 mg, 72%): mp = 121−122 °C; GC retention time 14.94 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.78 (m, 8 H), 1.80−1.97 (m, 14 H), 2.01 (s, 3 H), 2.79 (bs, 1 H), 2.86 (bs, 1 H), 2.92 (bs, 1 H), 3.10 (bs, 1 H), 4.93 (m, 1 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 21.5, 27.4, 28.6 (2C), 31.2, 32.1, 32.3, 32.3$_3$, 33.8, 35.7, 36.2, 37.3, 38.1, 39.1, 39.6 (2C), 39.7, 39.7$_2$, 78.6, 128.4, 137.0, 170.6. Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 80.95; H, 9.21.

Stereochemical Assignment. The C−C connectivity of both the adamantyl ring systems in the ketone product was assigned using standard 2D INADEQUATE, 2D NOESY, and 2D heteroCOSY experiments. Ketone **5** (120 mg) in C_6D_6 (1.5 mL) was filtered through a glass wool plug into a 10 mm NMR tube, and the 2D INADEQUATE spectrum was acquired at an operating frequency of 150 MHz using a 10 mm broad-band probe. Acquisition parameters were set so that crosspeaks were observed between alkyl carbon atoms but were not detected between the carbonyl carbon (C-2) and the two adjacent alkyl carbon atoms (C-1 and C-3). The 2D NOESY and 2D heteroCOSY experiments were used to assign fully the unsubstituted adamantyl ring system.

Kinetics. The alcohol **1-OH** (90 mg) was dissolved in acetic acid (30 mL), 50% v/v aqueous H_2SO_4 (30 mL) was then added, and the resulting solution was divided and sealed into 60 ampules (ca. 1 mL per ampule). In a typical kinetic run, 10 such ampules were placed in a "boiler" that was designed to hold ampules suspended in the vapor of a refluxing solvent. The ampules were removed from the solvent vapor at various time intervals, and the reaction was quenched by pouring the mixture from the ampules into ice-cold water. The organic material was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and with brine. The washed solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white precipitate that was dried under vacuum (0.1 mmHg) for at least 24 h. The resulting solid was dissolved in $CDCl_3$ (0.6 mL) and filtered through a glass wool plug, and the fraction of starting material remaining in the mixture was calculated from the integrated intensities of the proton resonances observed for both the product and equilibrating starting materials, in the ^{1}H NMR (400 MHz) spectrum. First-order rate constants for the rearrangement were determined by a nonlinear least-squares fit to a standard first-order equation of the fraction of starting material remaining versus time. All kinetic runs exhibited clean first-order behavior for at least 3 half-lives of the reaction.

Isotopic Labeling Experiments. Using conditions identical to those used for the protiated alcohol (**1-OH**), the analagous deuterated alcohol **2-OH** was rearranged to give the specifically-labeled product **6**: MS (EI, 70 eV) *m*/*z* (relative intensity) 285 (M^+, 100), 286 ($M^+ + 1$, 21.5), 287 ($M^+ + 2$, 2.4). Analysis of the isotopic distribution showed the presence of 0.01% dideuteration. The ^{13}C NMR spectrum (100 MHz; C_6D_6) was identical to that for **5** except that the ^{13}C singlet corresponding to C-2′ was replaced by a low intensity triplet at δ 43.2 ($^1J_{C,D}$ = 19 Hz), and the ^{1}H NMR spectrum (400 MHz; C_6D_6) showed the following changes from the spectrum acquired on the fully protiated compound **5**: (a) the broad doublet at 2.16 ppm is replaced by a broad singlet and (b) the two sets of multiplets at 1.55−1.58 and 1.90−1.95 were simplified.

In a separate experiment using the epimeric deuterated alcohol **4-OH** and reaction conditions identical to those used for the deuterated alcohol **2-OH**, the ^{13}C NMR spectrum (100 MHz; C_6D_6) of the isolated product was indistinguishable from that of the product formed from **2-OH**. When the reaction of the alcohol **1-OH** was performed using deuterated solvent the specifically deuterated product **7** was formed: MS (EI, 70 eV) *m*/*z* (relative intensity) 285 (M^+, 100), 286 ($M^+ + 1$, 25.5), 287 ($M^+ + 2$, 3.7), 288 ($M^+ + 3$, 0.5), and analysis of the isotopic distribution showed the presence of about 4% dideuterated and 96% monodeuterated product. The ^{13}C NMR spectrum (100

(7) Brauman, J. I. *Anal. Chem.* **1966**, *38*, 607−610.

(8) Huang, X.; Bennet, A. J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1027−1033.

MHz; C_6D_6) was identical to that of **5** except that the ^{13}C singlet corresponding to C-4 was replaced by a low intensity triplet at δ 47.3 ($^1J_{C,D}$ = 20 Hz), and the ^1H NMR spectrum (400 MHz; C_6D_6) showed the following changes from the spectrum acquired on the fully protiated compound **5**: (a) the broad doublet at 2.16 ppm disappears; (b) the multiplet at 1.55−1.58 simplifies; and (c) the pattern from 1.58−1.90 changes.

Isotopic Exchange in the Ketone Product. A solution of the ketone **5** (10 mg) in acetic acid-*d* (1.5 mL) and 50% D_2SO_4 in D_2O (1.5 mL) was sealed in an ampule and heated at 110 °C for a time corresponding to 5 half-times for rearrangement of **1-OH**. After cooling, the organic material was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and with brine. The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white precipitate that was dried under vacuum (0.1 mmHg) for at least 24 h. The resulting residue was analyzed by mass spectrometry (MS (EI, 70 eV) *m*/*z* (relative intensity) 284 (M^+, 100), 285 ($M^+ + 1$, 21.7), 286 ($M^+ + 2$, 2.5)) and least-squares analysis of the isotopic distribution showed the presence of approximately 0.2% deuterated ketone.

Primary Kinetic Isotope Effect. A solution containing a mixture of **1-OH** and **2-OH** (30 mg; isotopic ratio 49.5:50.5)[9] in acetic acid (6 mL) and 50% v/v aqueous H_2SO_4 (6 mL) was divided and sealed into 6 ampules (ca. 2 mL per ampule) that were heated at 110 °C for either 20, 30, or 45 min. The isomerization reaction was subsequently quenched by rapid cooling. The combined organic material from two ampules was extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and with brine. The solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white precipitate that was dried under vacuum (0.1 mmHg) for at least 24 h. The residue was analyzed by GCMS to obtain the isotopic compositions of all of the equilibrating starting materials and the final ketone product. The fraction of the deuterated starting material that had reacted was estimated by integration of all peaks at a chemical shift $\delta \geq 3.60$ relative to the peak of the ketone product at δ 1.30 in the ^2H NMR (61.4 MHz; $CHCl_3$) spectrum.

Solvent Kinetic Isotope Effect. A solution of the alcohol **1-OH** (20 mg) in acetic acid (4 mL), acetic acid-*d* (4 mL), 50% v/v aqueous H_2SO_4 (4 mL), and 50% v/v D_2SO_4 in D_2O (4 mL) was sealed in an ampule and heated at 110 °C for a period of time that corresponded to 5 half-lives for the rearrangement of **1-OH**. The rearranged ketone was isolated as described above, and least-squares analysis of the isotopic distribution of the molecular ion region as determined by mass spectroscopy gave the following isotopic distribution for the product: $^2H_0$, 54.7%; $^2H_1$, 44.9%; $^2H_2$, 0.4%.[9]

Rearrangement of Alcohol 4-OH. A solution of the deuterated "pseudoaxial" alcohol **4-OH** (100 mg) in acetic acid (10 mL) and 50% v/v aqueous H_2SO_4 (10 mL) was heated at 110 °C for 6 h. Using the separation protocol detailed previously for ketone **5**, a product was isolated from the rearrangement of alcohol **4-OH** that was identified as the deuterated ketone **6** (yield after recrystallization 80 mg, 80%).

Rearrangement Reactions of Glycol 11. A solution of 2,2′-dihydroxy-2,2′-diadamantane (**11**)[10] (100 mg, 0.33 mmol) in acetic acid (10 mL) and 50% v/v aqueous H_2SO_4 (10 mL) was heated at 110 °C for 6 h. The separation procedures described for ketone **5** were utilized here to obtain a product that was identified as spiroketone **13** (79 mg, 84%), mp = 177−178 °C (lit.[10] mp 178−179 °C). The ^1H-NMR spectrum (400 MHz; $CDCl_3$) of this product was identical to a previously reported spectrum for this compound.[10] However, when a solution of 2,2′-dihydroxy-2,2′-diadamantane (**11**)[10] (150 mg, 0.50 mmol) in acetic acid (10 mL) and 50% v/v aqueous H_2SO_4 (10 mL) was heated at 140 °C for 96 h, the product isolated from the reaction was identified as ketone **5** (124 mg, 88%).

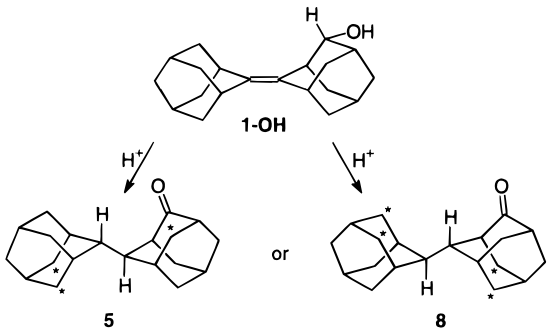
(9) Estimated standard error ± 0.2−0.3%.

(10) Clark, T.; Teasley, M. F.; Nelsen, S. F.; Wynberg, H. *J. Am. Chem. Soc.* **1987**, *109*, 5719−5724.

X-ray Structure Determination. Crystals of **5** suitable for structural analysis were obtained by slow evaporation of a solution of **5** in dichloromethane. The selected crystal of **5** was mounted on a glass fiber using epoxy as adhesive. Data were recorded at 295 K with an Enraf-Nonius CAD4F diffractometer using graphite-monochromatized Mo Kα radiation. Data reduction included corrections for Lorentz and polarization effects. The molecule is disordered and centered on an inversion center. In the asymetric unit ($C_{10}H_{14}O_{0.5}$), the oxygen atom has partial occupancy in two independent sites of 0.364(4) and 0.136. The coordinate and occupancy shifts of the complementarily disordered hydrogen atom sites and the lower occupancy oxygen site were linked appropriately. Two isotropic thermal parameters were refined for these fractional sites. Anisotropic thermal parameters were refined for all carbon atoms and for the higher occupancy oxygen site. Coordinates and isotropic thermal parameters were refined for the remaining (full occupancy) hydrogen atoms. Final full-matrix least-squares refinement of 148 parameters for 964 data ($I_o \geq 2.5\sigma(I_o)$) converged at $R = 0.042$. The final maximum |shift/error| was 0.01. The programs used for absorption corrections, data reduction, structure solution, refinement, and plot generation were from the *NRCVAX* Crystal Structure System.[11] Final refinement was made using CRYSTALS.[12] Complex scattering factors for neutral atoms[13] were used in the calculation of structure factors. Computations were carried out on a Pentium computer.

Results and Discussion

The major product isolated from the isomerization reaction of **1-OH** in 88% formic acid that contains concentrated sulfuric acid (5% v/v) was identified by ^{13}C NMR spectroscopy to be a saturated ketone that displayed 20 separate ^{13}C resonances.[14] The stereochemistry of this product was initially assigned to be **5** rather than **8**, a designation that was based on the γ-gauche effect.[15] Three shielded (upfield) CH_2 groups were observed in the ^{13}C-NMR spectrum of the reaction product, a result that is consistent with stereoisomer **5**, whereas the epimeric ketone **8** would be expected to show four shielded CH_2 groups. The respective shielded CH_2 groups are indicated with asterisks on structures **5** and **8**. On



the basis of the NMR data, this reaction was tentatively assigned to be an acid-catalyzed, 1,4-hydride shift. However, a careful search of the literature revealed a report by Wynberg and co-workers in which the reaction of

(11) Gabe, E. J.; LePage, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *NRCVAX*−An Interactive Program System for Structure Analysis. *J. Appl.Crystallogr.* **1989**, *22*, 384−387.

(12) Watkin, D. J.; Carruthers, J. R.; Betteridge, P. W. *CRYSTALS*; Chemical Crystallography Laboratory, University of Oxford: Oxford, England,1984.

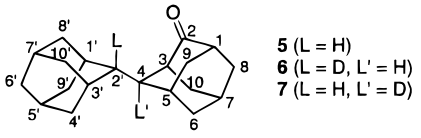
(13) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1975, Vol. IV, p 99.

(14) In the absence of sulfuric acid no rearrangement was observed.

(15) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5315−5318.

1-OH with aqueous sulfuric acid, at elevated temperatures and under heterogeneous conditions, was reported to yield **8**, and this rearrangement was proposed to involve a 1,3-hydride migration.[6]

Given the critical difference between the two structures and the possible rearrangement mechanisms that would generate these structures, a thorough investigation of the isomerization reaction was required. For this type of study, accurate measurements of rate constants, kinetic isotope effects, and activation parameters are necessary, and these measurements are best made using homogeneous reaction solutions rather than heterogeneous reaction conditions. Therefore, the reaction conditions used for the rearrangement reaction were modified as follows: (1) formic acid was excluded from the reaction medium because it decomposes with acid catalysis to give H_2O and CO,[16] and (2) acetic acid was added to the aqueous sulfuric acid solution in order to attain homogeneous reaction conditions. After several trials, a solvent system of 50% v/v AcOH:50% v/v aqueous H_2SO_4 was selected for use in the kinetic studies. The product isolated from the reaction, at elevated temperatures, of **1-OH** in aqueous sulfuric/acetic acid solutions was shown to be identical to that isolated from the formic acid-based solutions. Several 2-D NMR spectroscopic techniques were utilized to confirm the structural assignment of the rearranged product as **5**. Structural information derived from the 2-D INADEQUATE spectrum, a $^{13}C-^{13}C$ correlation experiment, showed that one of the three upfield CH_2 groups (relative to the remaining six CH_2 groups) is unambiguously assigned as carbon atom 9, while the other two are assigned as carbon atoms 4′ and 9′.[17] This result provides confirmation that the reaction product is **5**.



5 (L = H)
6 (L = D, L' = H)
7 (L = H, L' = D)

Further evidence that the rearrangement involves a 1,4-hydride migration is provided by NMR analysis of the ketone product generated from the deuterated alcohol **2-OH**, which after rearrangement, gives a low intensity triplet associated with carbon C-2′ in the ^{13}C NMR spectrum of the ketone product, a result that is consistent with structure **6**. Subsequent to the NMR analysis, suitable crystals of **5** were obtained for an X-ray diffraction study. Figure S1 (Supporting Information) presents an ORTEP diagram of the crystal structure that was ascertained for the ketone. This structural information confirms that the stereoisomer is **5**, not **8**. Given in Tables S1−S4 (Supporting Information) are the full crystallographic details for the structure determination of **5**, including fractional atomic coordinates, anisotropic displacement parameters and selected intramolecular distances and angles.

In addition, when the rearrangement of **1-OH** was conducted in deuterated solvent (see the Experimental Section), the isolated product exhibited the incorporation of a single deuterium that is bonded to carbon atom C-4 (**7**).

Species Present in Solution. The rearrangement of **1-OH** in aqueous sulfuric/acetic acid solutions gives rise to the ester **1-OAc**, a product that is derived from the reversible formation of a carbenium ion ($\mathbf{1}^+$) that can react with either H_2O to give **1-OH** or acetic acid to give **1-OAc**.[5a] Furthermore, reaction of the epimeric, deuterated alcohol **4-OH** using the standard conditions for rearrangement produces the deuterated ketone **6** as the major product. This observation is in contrast to the report by Boelema *et al.* that states that the "pseudo-axial" alcohol remains unchanged upon heating a mixture of the epimeric alcohols (**1-OH** and **3-OH**) in aqueous sulfuric acid.[6] Moreover, another minor component that is detected in the material isolated during the rearrangement reaction of the 50:50 mixture of **1-OH** and **2-OH** displays a broad singlet in both the ^1H NMR and ^2H NMR spectra at approximately δ 3.6, a retention time of 13.58 min in the gas chromatogram, and molecular ion peak at 284/285 in the mass spectrum (see the Experimental Section). Although, this compound has not been positively identified, the most probable structure is **9** (Scheme 1).

The minimum reaction framework for the rearrangement of **1-OH** in the aqueous sulfuric/acetic acid solution is given in Scheme 1. On the basis of the known solvolytic rearrangement of **3-OTs** to give **10-OH** and **10-OEt**,[8] it is presumed that the acid-catalyzed reactions of the alcohol **3-OH** in acetic acid will yield **10-OH** and **10-OAc**. Accordingly, the allylic protoadamantyl compounds **10** are included in Scheme 1. Upon prolonged heating in aqueous acidic media, **10-OH** rearranges back to **3-OH**.[8] Therefore, under these strongly acidic and elevated temperatures conditions, both classes of compound (**3** and **10**) would be expected to be at equilibrium, although the equilibrium certainly lies to the side of the thermodynamically more stable adamantyl (**3**), rather than to that of the protoadamantyl derivatives (**10**).[18,19]

Reaction Kinetics. The complexity of the free energy surface for the rearrangement of **1** negates the possibility of measuring absolute rate constants for each possible interconversion, such as the isomerization of **1-OH** into **5**. Therefore, global rate constants (k_{glob}) were measured for the rearrangement of a complex mixture of adamantylidene compounds to yield mainly **5** and a small quantity of **9** (vide infra). However, the measured values of k_{glob} obtained from separate runs varied markedly (up to 20%) when different batches of reaction media were employed. This observation indicates that slight alterations in the solvent composition result in significant variations in k_{glob}. Hence, in order to obtain reproducible rate constants, all of the measurements were performed by heating sealed ampules, each of which contained a solution of the alcohol (**1-OH**) in the reaction media. Following the reaction, **1-OH**, **1-OAc**, **3-OH**, **3-OAc**, **5**, and **9** were isolated from the medium, and subsequent integration of the ^1H NMR spectral peaks corresponding to the four homoallylic protons in the four unsaturated compounds (δ range 2.78−3.12) as well as the signal for the H-1 proton in the product ketone at δ 2.45 lead to an estimate of the relative proportions of **1-OH**, **1-OAc**, **3-OH**, and **3-OAc** to be approximately 0.14:0.52:0.17:1.00. These ratios were shown to be independent of time.

(16) Liler, M. *Reaction Mechanisms in Sulphuric and Other Strong Acid Solutions*; Academic Press, Inc.: New York, 1971; pp 254−259.
(17) Although the assignment as C-8' and C-10' is consistent with the INADEQUATE spectrum.
(18) Fort, R. C., Jr. *Adamantane: The Chemistry of Diamond Molecules*; Marcel Dekkar, Inc.: New York, 1976; pp 35−66.
(19) No evidence for a significant fraction of the protoadamantyl derivatives was found.

Scheme 1

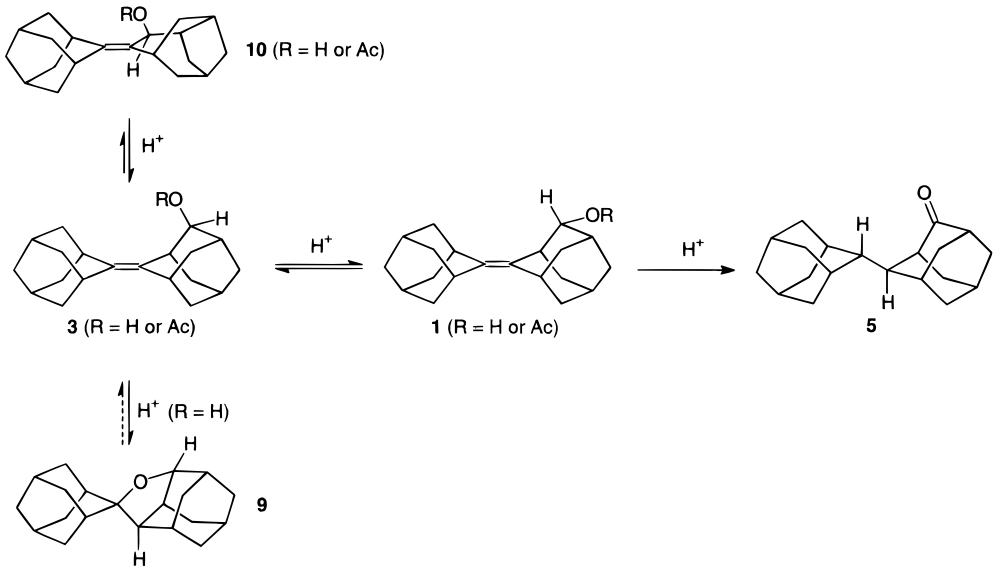


Table 1. Calculated Global Rate Constants for the Rearrangement of 1-OH in 50/50 v/v CH_3CO_2H:50% H_2SO_4 in H_2O as a Function of Temperature

T (°C)	$10^5 \times k_{glob}$[a] (s^{-1})	T (°C)	$10^5 \times k_{glob}$[a] (s^{-1})
117.7[b]	37.5 ± 1.8	100.0[e]	8.10 ± 0.13
110.6[c]	21.9 ± 1.6[d]	81.6[f]	1.24 ± 0.11

[a] Single kinetic determination. [b] 1-Butanol used in "boiler". [c] Toluene used in "boiler". [d] Repeat measurement (21.0 ± 1.0) × 10^{-5} s^{-1}. [e] Water used in "boiler". [f] Acetonitrile used in "boiler".

Thus, the four species are in rapid equilibrium relative to the rate of the rearrangement reaction. Although the proportion of **9** slowly increased during the isomerization reaction, the percentage (as determined by ^{1}H NMR spectroscopy) of this isomer never exceeded 13% of the total material present. Since the fraction of reaction ([starting materials]$_{total}$ / ([starting materials]$_{total}$ + [product])) versus time data gave good agreement to a standard first-order rate equation, no other kinetic analysis was attempted. Table 1 lists the calculated global rate constants (k_{glob}) for the rearrangement reaction.

Since the reaction yields two products, one major and one minor, the observed pseudo-first-order rate constant k_{glob} is comprised of the two rate constants k_{ket} and k_{eth}, the pseudo-first-order rate constants for formation of ketone **5** and ether **9**, respectively. Nevertheless, changes in the rate constant for ketone formation (k_{ket}; such as in a KIE experiment) will be responsible for the bulk of the observed effect seen in the global rate constant k_{glob}.

Activation Parameters. Using the Eyring equation and the data given in Table 1, the activation parameters calculated for the global rearrangement constant (k_{glob}) in the standard acidic aqueous sulfuric/acetic acid solvent were $\Delta H^{\ddagger} = 25.4 \pm 0.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = -9.5 \pm 1.0$ cal K^{-1} mol^{-1}. The resulting Eyring plot is shown in Figure 1.

Mechanism of Acid Catalyzed 1,4-Hydride Shift. Implicit in the following analysis is the assumption, which is supported by the labeling studies reported above, that the pseudo-axial compounds (**3-OH** and **3-OAc**) cannot rearrange directly to the ketone (Scheme 1). The two most plausible mechanisms for the acid-catalyzed 1,4-hydride shift are as follows: (1) the reaction occurs in a stepwise fashion, with either the protonation or the subsequent hydride transfer acting as the rate-determining step or (2) the reaction is concerted, with both protonation and hydride transfer occurring simultaneously. Kinetic isotope effect (KIE) measurements on both the protonation and the hydride-transfer steps were undertaken in order to narrow down the number of possible mechanisms for this reaction.

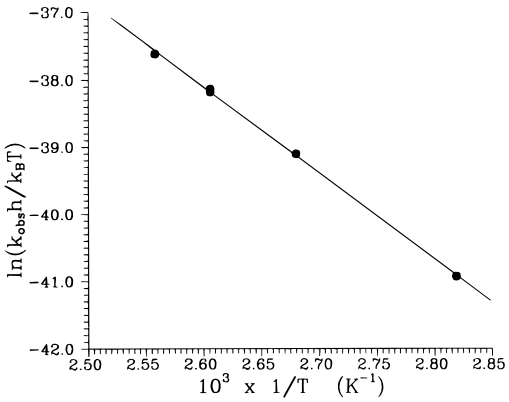


Figure 1. Correlation of $\ln(k_{obs}h/k_BT)$ with $1/T$ for the rearrangement of **1-OH** to give **5**. The displayed line is the calculated fit to the Eyring equation.

Primary Kinetic Isotope Effect. For the 1,4-hydride transfer reaction, the KIE (k_H/k_D) measurement involves an intermolecular competition experiment in which a mixture of the protiated and deuterated starting alcohols (**1-OH** vs **2-OH**) is subjected for various time intervals to the rearrangement conditions. Estimates of the KIE can then be made using either eq 2 or eq 3,[20] where F_D is the fraction of the deuterated compound that has reacted and R_0, R_R, and R_P are the ratios of protiated to deuterated starting material, remaining reactant, and product, respectively. Table 2 lists the calculated per-

$$\frac{k_H}{k_D} = \frac{\log((1 - F_D)R_R/R_0)}{\log(1 - F_D)} \quad (2)$$

$$\frac{k_H}{k_D} = \frac{\log(1 - (F_D R_P/R_0))}{\log(1 - F_D)} \quad (3)$$

Table 2. Measured Percentage of Unlabeled Isotopomers ($^2H_0$) Isolated from the Rearrangement of a Mixture of 1-OH and 2-OH in 50/50 v/v CH_3CO_2H:50% H_2SO_4 in H_2O at 110.6 °C[a]

time (min)	n[b]	**5**[c]	**1-OAc**[c]	**3-OAc**[c]
20	0.363	63.6	35.4	39.0
30	0.444	63.5	29.9	31.6
45	0.586	59.6	21.2	24.0

[a] Toluene used in "boiler". [b] Fraction of reaction of the deuterated starting materials. [c] Percentage of deuterated isomers = 100 − value in the table.

Table 3. Calculated KIEs (k_H/k_D) using the Data from Table 2

time (min)	fraction D reacted	**5**	**1-OAc**	**3-OAc**
20	0.363	2.3	2.3	2.0
30	0.444	2.6	2.4	2.3
45	0.586	2.4	2.5	2.3

centages of nondeuterated materials that were isolated following the rearrangement of an approximately 50:50 mixture of **1-OH** and **2-OH** in 50/50 v/v CH_3CO_2H:50% H_2SO_4 in H_2O at 110.6 °C. Also included in Table 2 is the calculated fraction of reaction for the deuterated compounds, a result that was estimated from the integrated intensities in the ^2H NMR spectrum.

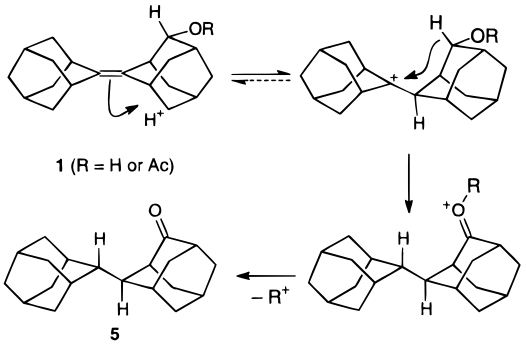
Table 3 presents the calculated primary KIEs (k_H/k_D) that were obtained using eq 2 for the two homoallylic acetates and eq 3 for the ketone product. The formation of biproduct **9** complicated the estimation of F_D for the isomerization reaction due to the ^2H NMR spectrum signal overlap of **9** with the signals of **1-OH** and **3-OH**. As a result, the magnitude of F_D is slightly underestimated, thereby leading to an overestimation of the KIE (k_H/k_D) calculated using eq 2 and an underestimation of the KIE calculated using eq 3. Nonetheless, given that all of the calculated KIEs (k_H/k_D) are in the range of 2.0−2.6 and the average of the KIE values tabulated in Table 3 is 2.34 ± 0.17, the necessary correction to these values must be much smaller than the values themselves. The KIE value obtained herein for an intramolecular, nonlinear, hydride transfer from an secondary alcohol to a positively-charged carbon atom is comparable to the reported value of between 1.8−2.6 for the intermolecular hydride transfer from 2-propanol to triphenylcarbenium ion in sulfuric acid solution.[21] Consequently, it can be concluded that the 1,4-hydride transfer occurs as a part of the rate-limiting step.

Solvent Isotope Effect. Evaluation by KIEs of the mechanism for formation of **5** requires the use of competition experiments that, when performed on mixed, isotopically-labeled solvents, generate an estimate of the competitive isotope effect (k_H/k_D)[22] rather than the solvent KIE (k_{H_2O}/k_{D_2O}). As shown in eq 4, the competitive

$$k_H/k_D = (RH/RD)_{prod}(D/H)_{solv} \quad (4)$$

isotope effect (CIE) is calculated from the ratio of isotopic labels found in the product to that present in the initial solvent mixture. Calculation of reliable CIE values requires that the solvent hydrogen is transferred to a nonexchangeable position in the product.[22]

Scheme 2

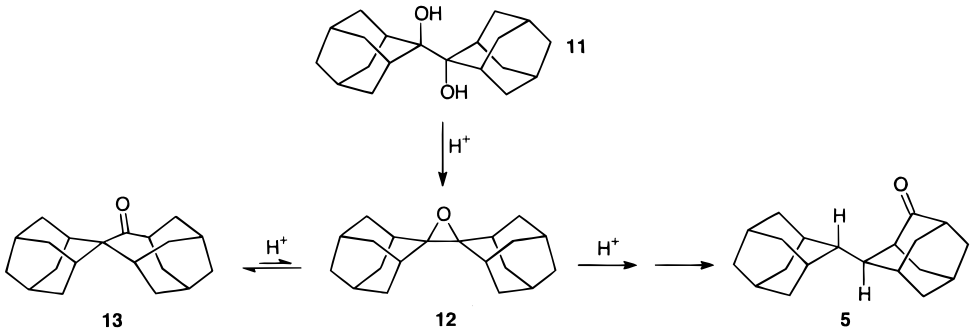


In the present case, heating the ketone **5** in deuterated solvent for a time corresponding to 10 half-times for the rearrangement of **1-OH** results in exchange of less than 0.2% deuterium into each molecule of unlabeled **5**. Similarly, reaction of the unlabeled alcohol **1-OH** in deuterated solvent gives a ketone product that contains about 4% dideuterated material. As a consequence, the majority of deuterium labeling observed in the ketone product arises from label incorporation that occurs during the rearrangement reaction and should allow reliable estimates for the CIE to be obtained from eq 4. An isotopic distribution of $^2H_0$, 54.7%, $^2H_1$, 44.9%, and $^2H_2$, 0.4%, was displayed by the ketone product that was isolated from the acid-catalyzed rearrangement of **1-OH** in 50:50 v/v protiated:deuterated solvent. Since the molar volume of protiated solvents is generally less than 1% greater than the corresponding deuterated solvents, a value of ≈1.01 was used for the $(D/H)_{solv}$ ratio (eq 4),[23] and this results in an estimated value for the CIE (k_H/k_D) of 1.20 (= 54.7/44.9 × 49.7/50.3).

The competitive isotope effect (k_H/k_D) in hydrogen-transfer reactions is substantially larger than the solvent isotope effect (k_{H_2O}/k_{D_2O}), a difference that originates from the preclusion of secondary solvent isotope effects, which are generated by the nontransferring protons, in the CIE (k_H/k_D).[22c,24] A further contributing factor to the larger CIE measurement is that, unlike the SIE value (k_{H_2O}/k_{D_2O}), the CIE does not include isotopic fractionation between protium and deuterium in the protonating acid. Consequently, CIE values (k_H/k_D) are generally larger than 3.0 for general-acid proton transfers. For example, in the acid-catalyzed hydration of 2-methylpropene the measured value for the CIE (k_H/k_D) and the SIE (k_{H_2O}/k_{D_2O}) are 3.9 and 1.4, respectively.[25] The observed value for the CIE of 1.2 measured in the present study is consistent with an essentially complete proton transfer at the rearrangement transition state, although no information is available as to whether the proton transfer is reversible or irreversible. Therefore, the mechanistic picture that emerges from the present study is of a two-step reaction in which the protonation of the double bond,

(20) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: Chichester, 1980; pp 95−102.
(21) Bartlett, P. D.; McCollum, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 1441−1450.
(22) (a) Gold, V.; Kessick, M. A. *Diss. Faraday Soc.* **1965**, *39*, 84−93. (b) Williams, J. M., Jr.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1968**, *6*, 63−101. (c) Kreevoy, M. M.; Eliason, R. *J. Phys. Chem.* **1968**, *72*, 1313−1316.
(23) Schowen, R. L. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: Baltimore, 1977; pp 64−99.
(24) Kresge, A. J.; More-O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177−274.
(25) Gold, V.; Kessick, M. A. *J. Chem. Soc.* **1965**, 6718−6729.

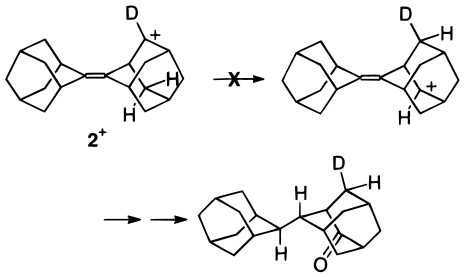
Scheme 3



a possible reversible step, is followed by the rate-determining intramolecular 1,4-hydride transfer (Scheme 2).

Other Mechanistic Deductions. Boelema *et al.*[6] also reported that glycol **11**, epoxide **12** and spiroketone **13** rearrange in acidic solutions to generate **8**. Moreover, previous work has shown that the acid-catalyzed dehydration of glycol (**11**) generates an equilibrium mixture, of oxirane (**12**) and spiro-ketone (**13**), that favors the spiro ketone.[26] In the present study, heating glycol **11** in the identical medium utilized during the study of the rearrangement reactions of **1-OH** readily generates spiroketone **13** as the major dehydration product. Furthermore, isomerization of spiroketone **13** to give ketone **5** requires higher temperatures (140 °C) and longer reaction times (96 h) than the conditions that were necessary for the complete rearrangement of **1-OH** into ketone **5**. In combination, the above information indicates that the spiroketone (**13**) cannot be an intermediate in the acid-catalyzed isomerization reactions of **1-OH** since accumulation of this product would have occurred under the reaction conditions. Scheme 3 displays the minimum mechanistic pathway for the dehydration of glycol **11** to yield the saturated ketone.[27]

Another important inference can be drawn, from the observation in the present study that labeled alcohol **2-OH** isomerized to give ketone (**6**) exclusively, is that during the isomerization reaction any carbenium ion formed ($\mathbf{2}^+$) in the aqueous sulfuric/acetic acid solutions cannot undergo a degenerate 1,3-hydride shift to yield another homoallylic carbenium ion (eq 5).



(5)

Conclusions

The unusual isomerization reaction of the sterically-congested adamantylideneadamantyl alcohols (**1-OH** and **3-OH**) proceeds via a two-step mechanism in which protonation of the double bond by an external acid is followed by a rate-determining, intramolecular 1,4-hydride transfer.

Acknowledgment. We gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada and Simon Fraser University for financial support of this work. We also thank Dr. T. E. Kitos for editorial assistance with this manuscript.

Supporting Information Available: Crystallographic acquisition data, fractional atomic coordinates, anisotropic displacement parameters, selected bond distances and angles, and an ORTEP drawing for ketone **5** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971465J

(26) (a) Wynberg, H.; Boelema, E.; Wieringa, J. H.; Strating, J. *Tetrahedron Lett.* **1970**, 3613−3614. (b) Gill, G. B.; Hands, D. *Tetrahedron Lett.* **1971**, 181−184.

(27) The formation of **5** from **13** probably involves the reaction of protonated **12** to give **1-OH** and **1-OAc** via a mechanism similar to that reported for the homoallylic chlorination of **1-H** via an epithiiranium ion.[2]