Highly Fluorinated Adamantanols: Synthesis, Acidities, and Reactivities

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Aerosol direct fluorination of 1-adamantyl acetate produces *F*-1-adamantyl trifluoroacetate and 2-hydryl-*F*-1-adamantyl trifluoroacetate in a near 1:1 ratio. Hydrolyses of these two esters give the corresponding alcohols, *F*-adamantan-1-ol and 2-hydryl-*F*-adamantan-1-ol. 2-Hydryl-*F*-adamantan-2-ol is synthesized by $LiAlH_4$ reduction of *F*-adamantanone. The acidities of these alcohols and the rates of their acetylation reactions were measured. A ^{1}H NMR study of their hydrogen bonding with *t*-$BuOCH_3$ is described.

Introduction

The aerosol direct fluorination (AF) method has proved to be very successful in the synthesis of perfluorinated organic compounds. Many functionalized compounds such as alkyl chlorides, ethers, and esters have been successfully perfluorinated using AF.[1] In earlier work with perfluorinated esters in our laboratory, Cherry found that the successful AF of organic esters depended on the structures of the esters.[2] Methyl esters are especially susceptible to loss of the methoxyl group, which decomposes to form carbonyl fluoride. Higher homologs are considerably more stable to cleavage. Furthermore, if a bulky alkyl group is attached to either the acyl side or the alkoxyl side, the cleavage of the ester group is also greatly reduced. Later work showed, however, that careful control of AF conditions can significantly reduce cleavage of methyl esters.[3]

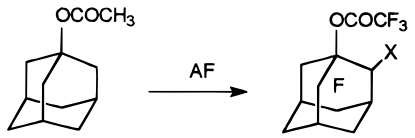
Acetylation of alcohols provides a protecting group for the hydroxyl group during AF of many tertiary alcohols. The AF of 1-adamantanol acetate was described in an earlier report.[4] Perfluorinated esters are highly hygroscopic and are easily hydrolyzed, even by atmospheric moisture, to form perfluorinated acids and alcohols. This facile hydrolysis of perfluorinated esters offers a convenient synthetic route to perfluorinated *tertiary* alcohols. This report describes the syntheses of *F*-adamantan-1-ol and 2-hydryl-*F*-adamantan-1-ol by hydrolyses of the corresponding trifluoroacetates, the acidities of these alcohols, and the rates of their acetylation reactions.

The strong inductive effect of a highly fluorinated alkyl group results in a corresponding increase in acidity of an alcohol bearing these fluoroalkyl groups.[5] The resulting acidities of these alcohols are comparable to carboxylic acids. The acidities of *F*-adamantan-1-ol and 2-hydryl-*F*-adamantan-1-ol were measured potentiometrically during acid−base titration. For comparison, 2-hydryl-*F*-adamantan-2-ol was synthesized and its acidity measured. The nucleophilicities of these alcohols toward acetyl chloride was also investigated.

Fluorinated alcohols are more acidic than the corresponding fluorine-free alcohols, and as a consequence they are stronger hydrogen-bond donors.[6] Fluorinated alcohols have been the subject of many studies involving hydrogen bonds formed by hydroxyl groups with different kinds of hydrogen-bond acceptors.[7] Ladika and coworkers[8] have found that when 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) form hydrogen bonds with *tert*-$BuOCH_3$ molecules, the chemical shifts of the methoxyl groups in *t*-$BuOCH_3$ changed with the molar ratio of alcohol/ether. The $\Delta\delta$ showed a good correlation with the pK_a value of the alcohols. The results of a similar ^{1}H NMR study of hydrogen bonding of *F*-adamantan-1-ol, 2-hydryl-*F*-adamantan-1-ol, and 2-hydryl-*F*-adamantan-2-ol with *t*-$BuOCH_3$ is described in this paper.

Results and Discussion

Perfluorinated esters are generally produced in synthetically useful yield during AF of hydrocarbon esters bearing a bulky alkyl group attached to either the acyl side or the alkoxyl side of the ester. 1-Adamantyl acetate is therefore a good precursor for *F*-1-adamantanol (**3**).[4] During the workup of the reaction mixture, two major products, 1-*F*-adamantyl trifluoroacetate (**1**) and 1-[2-hydryl-*F*-adamantyl] trifluoroacetate (**2**), were collected as shown in eq 1. Depending on the hydrogen and



(1)

1 : X = F

2 : X = H

fluorine ratios that are used in the reactor, the ratio of **1** and **2** varied between 30:70 and 50:50. Under the conditions used the perfluorinated compound would normally be more than 90% of the products that are collected. This unusual result is attributed to formation of an intramolecular hydrogen bond between the carbonyl group on the trifluoroacetate and one of the α-hydrogen

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(1) Adcock, J. L.; Cherry, M. R. *Ind. Eng. Chem. Res.* **1987**, *26*, 208.
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(3) Brenuan, M. Master Thesis, The University of Tennessee at Knoxville, 1987.
(4) Adcock, J. L.; Zhang, H. *J. Org. Chem.* **1995**, *60*, 1999.
(5) Chambers, R. D. *Fluorine in Organic Chemistry*; John Wiley and Sons: New York, 1973.
(6) Middleton, W. J.; Lindsey, R. V. *J. Am. Chem. Soc.* **1964**, *86*, 4948.
(7) Mentel, T. F.; Luck, W. A. *J. Phys. Chem.* **1991**, *95*, 68. Schriver, L.; Schriver, A.; Peil, S.; Schrems, O. *Can. J. Chem.* **1991**, *69*, 1520. Luck, W. A. P.; Peil, S. *J. Mol. Struct.* **1990**, *224*, 175.
(8) Jursic, B; Ladika, M.; Sunko, D. E. *Tetrahedron Lett.* **1985**, *26*, 5323.

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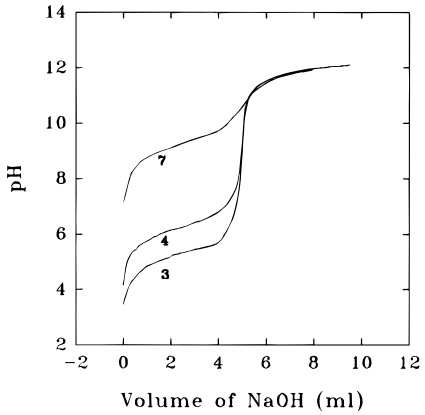
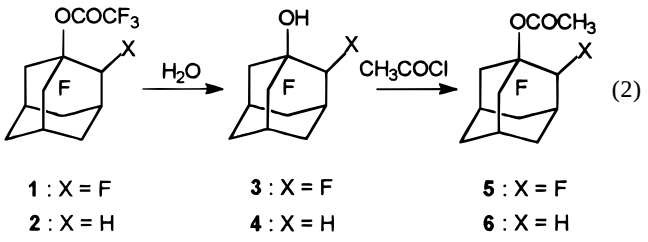


Figure 1. Titration curve of compounds **3**, **4**, and **7**.

atoms polarized during fluorination of the rest of the adamantyl group. As a consequence, the trifluoroacetyl group blocks fluorine attack and prevents fluorine substitution of the last hydrogen atom, resulting in an anomalously high yield of compound **2**.[4]

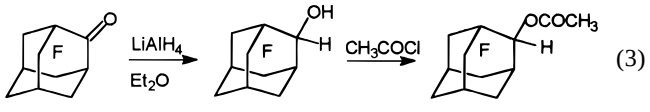
The $-CF_3$ and F-adamantyl groups in **1** and **2** strongly activate the ester group to nucleophilic attack. Consequently, these esters are easily hydrolyzed. The moisture in the atmosphere is sufficient to completely hydrolyze these esters on leaving the product container open to the atmosphere overnight. The yields for hydrolysis of these esters are quantitative. The hydrolysis products are **3** and **4** (eq 2).



(2)

1 : X = F **3** : X = F **5** : X = F
2 : X = H **4** : X = H **6** : X = H

F-Adamantanone was synthesized in this laboratory in 1992.[9] The carbonyl group is made strongly electron deficient by the highly fluorinated adamantyl residue. Reduction of this carbonyl group was easily achieved by stirring *F*-adamantanone with a $LiAlH_4$−ether solution at room temperature overnight (eq 3). The yield is 93%.



(3)

7 **8**

When the highly fluorinated adamantyl residues are attached to the hydroxyl group, alcohols **3**, **4**, and **7** are expected to have relatively high acidities. Actually, all three alcohols dissolved in a methanol/water solution (1:1 by volume) can be titrated by aqueous NaOH. The titration curves are shown in Figure 1. The acidities of compounds **3**, **4**, and **7** greatly depend on their structures. There are six β fluorine atoms to stabilize the conjugated base species of compound **3**. It is the strongest acid among the three compounds.

The pK_a value is 5.2, which is in the same range of that of aliphatic acids. Compound **4** has five fluorine

(9) Adcock, J. L.; Luo, H. *J. Org. Chem.* **1992**, *57*, 4297.

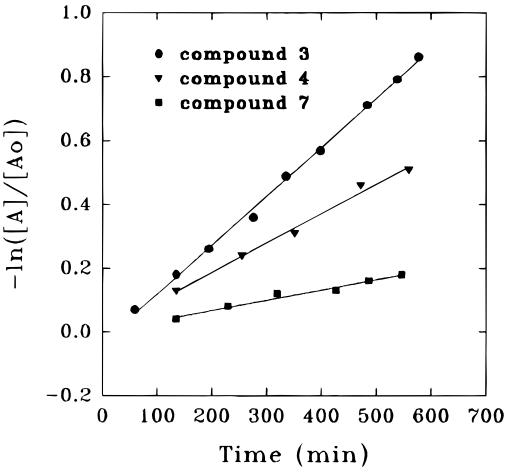


Figure 2. Rate measurement of compounds **3**, **4**, and **7** at 56 °C.

Table 1. pK_a and Rate Constant at 56 °C of Compounds 3, 4, and 7

compd	pK_a	$k_{obsd} \times 10^4$ (min^{-1})
3	5.2	15.4
4	6.3	8.9
7	9.4	3.1

atoms β to the hydroxyl group. The pK_a of 6.3 for **4** is, as expected, relatively higher than that of **3**. Compound **7**, a secondary alcohol, has one α-hydrogen atom and only two β-fluorine atoms. The acidity of **7** with a pK_a value of 9.4, similar to the acidities of phenols, is much lower than that of **3** and **4**. However, it is still a much stronger acid than a fluorine-free aliphatic alcohol. The acidities of these alcohols mostly depend on the numbers of β-fluorine atoms. Neglecting the α-hydrogen atom, there is an inverse relationship betweeen pK_a and the number of β-fluorine atoms over the range observed.

The difference in acidities among these alcohols led us to investigate the nucleophilicities of these compounds. These alcohols react with acetyl chloride to form the corresponding acetates. ^{19}F NMR kinetic studies of the pseudo-first-order acetylation reactions for all three compounds were conducted in acetyl chloride solution at 56 °C. With the products and reactants ratio measured by ^{19}F NMR, a plot of $-\ln [A]/[A_o]$ versus time (min) for each compound is shown in Figure 2.[10] The rate constants, k_{obsd}, derived from the plot are listed in Table 1. Compound **3** has the fastest rate (largest rate constant) followed by **4** and then **7**.

These results indicate that under the pseudo-first-order reaction conditions employed the k_{obsd} depends principally on the ease of formation of the alkoxide anion in the nucleophile attacking acetyl chloride. Compound **3** is the strongest acid among these three compounds; its conjugate base is therefore the most stable and easily formed species, although the least basic. This is apparently the deciding factor in determining the rate of reaction of the fluorinated alcohols with acetyl chloride.

These alcohols easily form hydrogen bonds with hydrogen-bond acceptors. According to Ladika,[8] adding any of these alcohols to a solution of *t*-$BuOCH_3$ in CCl_4 will allow hydrogen bonds to form with *t*-$BuOCH_3$, which can be detected by measuring the chemical shift change of

(10) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; p 195.

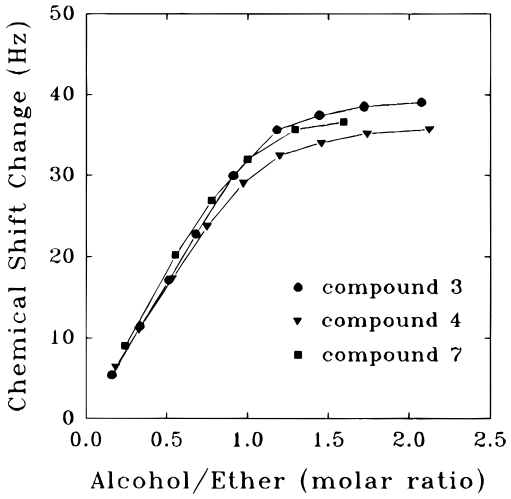


Figure 3. Correlation of chemical shift changes and molar ratio of alcohol/ether.

the methoxy proton of *t*-BuOCH$_3$. According to Ladika's results,[8] acidities correlate with the chemical shift changes. A stronger acid will cause a higher chemical shift change than a weaker acid. Figure 3 shows a plot of the molar ratio (alcohol/ether) against the chemical shift change. For compounds **3** and **4**, the *t*-BuOCH$_3$ methoxy proton chemical shift changes correlate with the acidities. Compound **7** would be expected to cause a curve lower than either compound **3** or **4** due to its lower acidity. However, compound **7** exhibits chemical shift changes that indicate a stronger interaction than its acidity would suggest. In compounds **3** and **4**, the hydroxyl groups are located on the bridgehead carbon atoms. In compound **7**, the hydroxyl group is located on a bridge carbon and may experience less steric hindrance allowing compound **7** to form a stronger hydrogen bond than either compounds **3** or **4**.

Conclusion

The pK_a values of *F*-adamantan-1-ol (**3**), 2-hydryl-*F*-adamantan-1-ol (**4**), and 2-hydryl-*F*-adamantan-2-ol (**7**) are 5.2, 6.3, and 9.4, respectively. As the number of β-fluorine atoms decrease, the acidities decrease logrithimically. The acetylation rate constants of the three fluorinated alcohols correlate with their anion-forming abilities and inversely with their acidities. The ability of the alcohols to form hydrogen bonds with *t*-BuOCH$_3$ weakly correlate with their acidities as possibly modified by the steric hindrance around the hydroxyl groups of these compounds.

Experimental Section

pH values were measured in a methanol/water, 1:1, mixed solvent using a semimicro-combination electrode and are uncorrected. ^{19}F NMR spectra were recorded at 84.7 MHz using $CFCl_3$ as the solvent and the internal standard. ^{1}H NMR spectra were recorded at 250 MHz using $CFCl_3/CDCl_3$ mixture (1:3, v/v) as the solvent. Mass spectra were recorded in positive ion EI mode at 70 eV. All gas chromatographic separations were carried out with a 7 m × 3/8 in. column packed with 60−80 mesh, acid-washed chromosorb P with 13% fluorosilicone QF-1 (Analabs) stationary phase conditioned at 225 °C (12 h). Transfers were made by vacuum line. The perfluorinated alcohols were degassed under vacuum to eliminate acidic gases.

Synthesis. The detailed procedure for the synthesis of compounds **1**, **2** and perfluorinated adamantanone are described elsewhere.[4,9]

***F*-Adamantan-1-ol (3).** 1-*F*-Adamantyl trifluoroacetate (**1**) (0.54 g, 1.0 mmol) was dissolved in 1 mL of $CFCl_3$. The bottle lid was opened to the atmosphere overnight. **3** (0.45 g, 1.0 mmol) was obtained as a white solid. The product was further purified by GC (column temperature, 180 °C; retention time, 11.5 min) followed by vacuum line transfer to remove volatile acids. Characterization of **3**: MS (EI) *m*/*z* (intens, ident) 422 (17, M^+), 403 (24, $M^+ - F$), 203 (100, C_6F_6OH); ^{19}F NMR ($CFCl_3$) δ −123.0 (narrow unresolved multiplet, 12F), −224.3 (narrow unresolved multiplet, 3F).[4]

2-Hydryl-*F*-adamantan-1-ol (4). 1-(2-hydryl-*F*-adamantyl) trifluoroacetate (**2**) (0.47 g, 0.94 mmol) was dissolved in 1 mL of $CFCl_3$. The bottle lid was opened to the atmosphere overnight. **4** (0.37 g, 0.79 mmol) was obtained as a white solid. The product was further purified by GC (column temperature, 180 °C; retention time, 14.8 min). Characterization of **4**: MS (EI) *m*/*z* (intens, ident) 404 (63, M^+), 385 (30, $M^+ - F$), 203 (100, C_6F_6OH); ^{19}F NMR ($CFCl_3$) δ −116.4 to −127.1 (m, 10F), −213.7 (narrow unresolved multiplet, 1F), −222.5 (narrow unresolved multiplet, 1F), −223.5 (narrow unresolved multiplet, 1F), −224.5 to −226.3 (m, *gem*HF, 1F); ^{1}H NMR ($CDCl_3$) δ 5.23 (d-quartet, ^2J = 48.2Hz, J_{obs} = 6.2 Hz); IR (film) 3379.0 (broad), 2993.5 (w) cm^{-1}.[4]

Synthesis of 2-Hydryl-*F*-adamantan-2-ol (7). *F*-Adamantanone (0.30 g, 0.74 mmol, GC purified) was dissolved in 5 mL of dry Et_2O. The solution was dropped into a solution of 0.10 g of $LiAlH_4$ in 10 mL of dry Et_2O at 0 °C within 10 min and stirred at 0 °C for 2 h then at room temperature overnight. Two mL of absolute EtOH was added, and the mixture was poured into a solution of 5 g of concentrated H_2SO_4 in 10 mL of H_2O. The mixture was extracted with Et_2O and then dried over Na_2SO_4. After the Et_2O solvent was evaporated, **7** (0.28 g, 0.69 mmol, 93%) was obtained as a white solid. If *F*-adamantanone was used directly from the aerosol direct fluorination reaction without GC purification, the final purification for **7** could be accomplished by dissolving the reaction mixture in 0.5 M NaOH solution, extracting the aqueous solution with ethyl ether, and neutralizing the aqueous layer with 70% H_2SO_4 followed by extraction of **7** into $CF_2ClCFCl_2$ solvent. Characterization of **7**: MS (EI) *m*/*z* (intens, ident) 404 (1, M^+), 402 (13, $M^+ - 2H$), 383 (7, $M^+ - 2H - F$), 205 (100, C_6F_7); ^{19}F NMR ($CFCl_3$) δ −115.0 to −126.3 (m, 10F), −214.4 (narrow unresolved multiplet, 2F), −223.4 (narrow unresolved multiplet, 1F), −224.6 (narrow unresolved multiplet, 1F); ^{1}H NMR ($CDCl_3$) δ 4.90 (pentet, J_{obs} = 6.0 Hz), δ_{OH} 3.3−3.6 var; IR (film) 3500.0 (broad), 2998.6 (w) cm^{-1}.[11]

General Procedure for Acetylation of Alcohols 3, 4, and 7. The alcohols (0.050 g) were dissolved in 3 mL of acetyl chloride and refluxed for 3 days. The acetyl chloride was evaporated, and the residue was dissolved in 0.5 mL of $CF_2ClCFCl_2$ and purified by GC.

Characterization of **5**: ^{19}F NMR ($CFCl_3$) δ −114.7 (s, 6F), −121.3 (s, 6F), −221.8 (s, 3F); ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H).

Characterization of **6**: ^{19}F NMR ($CFCl_3$) δ −111.8 to −126.6 (m, 10F), −212.5 (narrow unresolved multiplet, 1F), −222.3 to −223.1 (m, 3F); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 6.69 (d-quartet, 1H, ^2J = 45.9 Hz, $J_{obs} \cong$ 6.6 Hz); IR (film) 3024.5 (w), 2965.6 (w), 2931.8 (w), 2870.1 (w), 1799.8 (s) cm^{-1}.

Characterization of **8**: ^{19}F NMR ($CFCl_3$) δ −116.6 to −126.7 (m, 10F), −213.9 (narrow unresolved multiplet, 2F), −223.3 (narrow unresolved multiplet, 1F), −224.7 (narrow unresolved multiplet, 1F); ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 6.29 (pentet, $J_{obs} \cong$ 5.6 Hz, 1H); IR (film) 2970.4 (m), 2866.2 (w), 1797.6 (s) cm^{-1}.

Titrations. Distilled water used to prepare the solutions was boiled for 1 h to eliminate CO_2 gas. In each titration, about 0.1000 g of alcohol was dissolved in 4.00 mL of MeOH

(11) Mira, K.; Adcock, J. L.; Luo, H; Zhang, H.; Li, H.; LeNoble, W. J., *J. Am. Chem. Soc.* **1995**, *117*, 7088.

and 4.00 mL of H_2O and titrated with 0.0459 M NaOH. Duplicate titrations were run for each alcohol with virtually identical results.

Rate Measurements. Each of the alcohols (0.027 g) was dissolved in about 1.000 g of acetyl chloride in a 5 mm NMR tube. The NMR tube was connected to a drying tube through a rubber septum and was submerged in a water bath to the solvent level. Water temperature was controlled at 56.0 ± 0.1 °C. The ratio of reactant to product was calculated from the integration values.

Acknowledgment. We acknowledge the very helpful discussions and suggestions of Professor Richard M. Pagni of this department.

Supporting Information Available: Rate measurements for compounds **3**, **4**, and **7** (1 page). 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 mashead page for ordering information.

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