Reaction of Cycloalkyldifluoramines with Acids[1]

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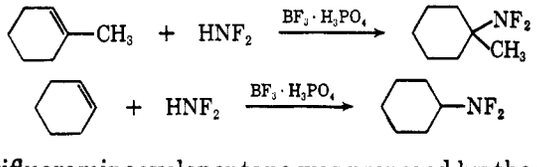
Difluoraminocyclohexane, 1-difluoramino-1-methylcyclohexane, and difluoraminocyclopentane were allowed to react with sulfuric acid to give the N-fluorimonium ions resulting from ring expansion with fluoride leaving. The reaction of 1,2-bis(difluoramino)cyclohexane with fluorosulfonic acid gave the N-fluorimonium ion resulting from migration of the unsubstituted methylene group. Difluoraminocyclohexane, 1-difluoramino-1-methylcyclohexane, and *t*-butyldifluoramine were synthesized by the addition of difluoramine to cyclohexene, 1-methylcyclohexene, and isobutylene, respectively, catalyzed by the boron trifluoride complex of phosphoric acid.

Alkyldifluoramines have been reported to rearrange in the presence of strong acids to give N-fluorimonium ions.[2] The reactions of *t*-butyldifluoramine, 2-difluoraminobutane, and 1-difluoraminobutane resulted in migrations of methyl, ethyl, and propyl groups, respectively, whereas ethyldifluoramine gave only elimination of HF. This study has been extended to cycloalkyl difluoramine derivatives.

Difluoraminocyclohexane and 1-difluoramino-1-methylcyclohexane were synthesized for this work by the acid-catalyzed addition of difluoramine to cyclohexene and to 1-methylcyclohexene. The addition of difluoramine to isobutylene and to 2-methyl-2-butene in the presence of acids has been reported recently.[3] The use of sulfuric acid as a catalyst for this reaction presented difficulties in that the products rearranged rapidly under the reaction conditions. We found, independently, that the boron trifluoride–phosphoric acid complex, commonly used for alkylating aromatic compounds,[4] catalyzes the addition of difluoramine to olefins while allowing convenient isolation of the product. Thus, the addition of 1-methylcyclohexene to a mixture of this complex and refluxing difluoramine gave 1-difluoramine-1-methylcyclohexane in 83% yield. Similarly, cyclohexene gave difluoraminocyclohexane in 34% yield and isobutylene gave *t*-butyldifluoramine in 63% yield. The latter compound, previously prepared by another reaction,[5] was included only to show the generality of the method.

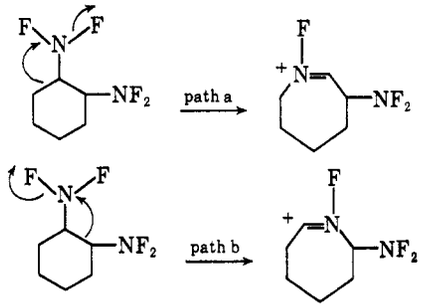


Difluoraminocyclopentane was prepared by the fluorination of ethyl N-cyclopentylcarbamate.[6] A difunctional starting material, 1,2-bis(difluoramino)cyclohexane, a mixture of *cis* and *trans* isomers, was prepared by the addition of tetrafluorohydrazine to cyclohexene.[7]

The reactions of 1-difluoramino-1-methylcyclohexane, difluoraminocyclohexane, and difluoraminocyclopentane with concentrated sulfuric acid all took place cleanly at 0° to give the corresponding cyclic N-fluorimonium ions resulting from ring expansion. The nmr data are given in Table I and no signals inconsistent with these structures were obtained.

It is noteworthy that the coupling constant of the methine to the adjacent methylene hydrogens for the difluoraminocyclohexane product is approximately double that for the difluoraminocyclopentane product. The coupling constants of the vinyl hydrogens of cycloheptene and cyclohexene to the adjacent methylenes are in the same ratio.[8] The coupling constant of fluorine to the adjacent methylene is about four times as large in the difluoraminocyclohexane product as for the difluoraminocyclopentane product. The large changes of the coupling constants with ring size are attributed to changes in the dihedral angles.

In the reaction of 1,2-bis(difluoramino)cyclohexane with acids, either the methylene group (path a) or the difluoraminomethylene group (path b) could take part in migration to the electron-deficient nitrogen. Actu-



ally, the nmr spectra of the solution formed from 1,2-bis(difluoramino)cyclohexane and sulfuric acid were quite complex and relative peak heights changed while the spectrum was being recorded. Apparently, hydrolytic degradation of the rearrangement product took place. This problem was avoided by using fluorosulfonic acid in place of sulfuric acid. Although a violent reaction took place when 1,2-bis(difluoramino)-cyclohexane was added dropwise to this acid at 0°, the reaction proceeded smoothly when the acid was cooled to −78°. The solution formed was stable at room temperature.

The nmr spectra of the fluorosulfonic acid solution (Table I) showed that path a was followed. The only extraneous signals were a broad weak proton band at δ 3.0 and a fluorine doublet at −112.6 ppm (J = 20 cps) and small signals at 87 and 90 ppm. It is noteworthy that the fluorines of the difluoroamino group,

(1) This work was supported by the Office of Naval Research and the Advanced Research Projects Agency.

(2) K. Baum and H. M. Nelson, *J. Am. Chem. Soc.*, **88**, 4459 (1966).

(3) W. H. Graham and J. P. Freeman, *ibid.*, **89**, 716 (1967).

(4) A. V. Topchiev, *et al.*, "Boron Trifluoride and Its Compounds as Catalysts in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p 125.

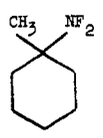
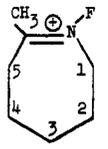
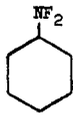
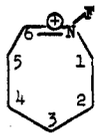
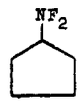
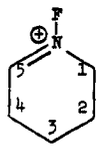
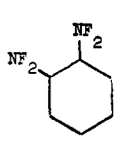
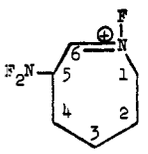
(5) R. C. Petry and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 3912 (1961).

(6) V. Grakauskas, private communication.

(7) A. J. Kijkstra, Ph.D. Thesis, Leiden, Holland, 1965.

(8) G. V. Smith and H. Kriloff, *J. Am. Chem. Soc.*, **85**, 2016 (1963); K. B. Wiberg and B. J. Nist, *ibid.*, **83**, 1226 (1961).

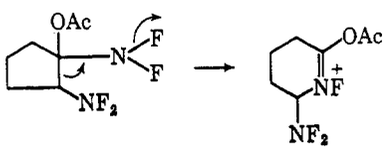
TABLE I
NMR DATA[a]

Starting Material[b]	Product	Fluorine[c]	Proton
		-151.6 ppm (t), $J_{CH_2-F} \cong 16$ cps	H_1: 4.57 δ (d,m), J_{H-F} = 18 cps H_5: 2.95 δ (m) Methyl: 2.66 δ (d), J_{H-F} = 5 cps H_2, H_3, H_4: 1.91 δ [d]
		-173.8 ppm (d,t), J_{CH_2-F} = 12 cps, J_{CH-F} = 24 cps	H_1: 4.63 δ (d), J_{HF} = 11.8 cps H_6: 8.88 δ (d,t), J_{HF} = 27.4 cps, J_{HH} = 6.0 cps H_5: 3.03 δ (m) H_2, H_3, H_4: 1.98 δ [d]
		-157.53 ppm (d), J_{HF} = 24.1 cps	H_1: 4.28 δ (d), J_{HF} = 2.8 cps H_5: 8.83 δ (d,t), J_{HF} = 25.2 cps, J_{HH} = 2-3 cps H_4: 3.13 δ (m) H_2, H_3: 2.43 δ (m), 2.06 δ (m)
		NF_2: -132.5 and -119.0 ppm (d, AB quartet), J_{F-F} = 611 cps, J_{HF} = 11.8 and 3.31[e] NF: -179.4 ppm[d]	H_1: 4.7 δ (d), J_{HF} = 18 cps H_6: 9.4 δ (d,d), J_{HF} = 25.6 cps, J_{HH} = 3.7 cps H_5: 5.3 δ (m) H_2, H_3, H_4: 2.2 δ [d]

[a] Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet. [b] Solvent was concentrated sulfuric acid for the first three examples and fluorosulfonic acid for the last. [c] External trifluoroacetic acid reference. All spectra also showed an HF signal at −117 ppm. [d] Broad unresolved bond. [e] For the −132.5 and −119.0 ppm legs, respectively.

attached to an asymmetrically substituted carbon atom, possessed different chemical shifts and different coupling constants to the adjacent hydrogen. This general phenomenon has recently been discussed by Johnson, Haney, and Stevens.[9]

The migratory aptitudes observed in the previously reported examples of acid-catalyzed alkyldifluoramine rearrangements[2] suggested that positive charge in the transition state was carried by the migrating group. The observed ring expansion in the rearrangement of 1-difluoramino-1-methylcyclohexane, difluoraminocyclohexane, and difluoraminocyclopentane, rather than methyl or hydrogen migration, can also be rationalized on this basis. The difluoramino group has been shown to be electron-withdrawing in nitrogen trifluoride, difluoramine, and difluoraminoethane, with a group electronegativity of about 3.25.[10] On the other hand, the unshared pair of electrons on nitrogen is available to stabilize cations, such as NF_2O^+ [11] and $NF_2{=}NF^+$.[12] Small changes in structure might thus result in reversals of relative migratory aptitude between an unsubstituted migrating group and a similar one containing a difluoramino group. The recently reported reaction[13] of 1,2-bis(difluoramino)-1-acetoxycyclopentane with acids to give 3-difluoramino-2-fluoro-2-azacyclohexanone indicated preferential migration of the NF_2-substituted methylene. In the reaction of 1,2-bis-



(difluoramino)cyclohexane, the reverse occurred. The difluoramino group is thus similar to halogens in its diversity of electronic responses.

Experimental Section

Difluoramine.—Difluoramine was prepared by the method reported by Grakausakas.[14] Difluorourea solution was prepared by bubbling 8 moles of fluorine diluted twofold with nitrogen into a stirred solution of 240 g (4 moles) of urea in 3.6 l. of water at 0–5°. The solution was stable for several months at −20°. The difluoramine generator consisted of a three-necked flask fitted with a dropping funnel, a nitrogen inlet, a magnetic stirrer, and a water-cooled reflux condenser.

(9) F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, **32**, 466 (1967).
(10) R. Ettinger, *J. Phys. Chem.*, **67**, 1558 (1963).
(11) W. B. Fox, *et al.*, *J. Am. Chem. Soc.*, **88**, 2604 (1966).
(12) A. R. Young and D. Moy, *Inorg. Chem.*, **6**, 178 (1967).
(13) T. E. Stevens and W. H. Graham, *J. Am. Chem. Soc.*, **89**, 182 (1966).
(14) V. Grakauskas, Abstracts, 140th National Meeting of the American Chemical Society, Chicago, Ill., 1961, p 23M.

The top of the condenser was connected in series to a 0° trap, a U-tube filled with calcium sulfate, and a three-necked reaction flask fitted with a magnetic stirrer, an addition funnel, and a Dry Ice cooled reflux condenser which was vented to the atmosphere through a trap filled with aqueous potassium iodide. A stream of nitrogen was continually passed through the system.

Difluorourea solution was placed in the generator flask and concentrated sulfuric acid (20 ml/100 ml of difluorourea solution) was added from the dropping funnel. The solution was heated to 90° to liberate difluoramine, which was swept by the nitrogen stream to the reaction flask, where it refluxed. The yield of difluoramine was 4.5–5 g/100 ml of difluorourea solution. The system must be flushed thoroughly with nitrogen before difluoramine is generated. Difluoramine is a very sensitive explosive and adequate barriers must be used.

Difluoraminocyclohexane.—Cyclohexene (4.12 g, 0.05 mole) was placed in the reactor flask and difluoramine generated from 200 ml of difluorourea solution was refluxed over it. Boron trifluoride complex of phosphric acid[4] (2 ml) was added dropwise and the mixture was stirred for 2 hr. The excess difluoroamine was flushed out of the reactor by allowing the Dry Ice condenser to warm to room temperature. The mixture was poured onto 50 ml of crushed ice and the product was extracted with two 15-ml portions of pentane. The pentane solution was dried over sodium sulfate and distilled to give 2.3 g (34% yield) of difluoraminocyclohexane, bp 34° (11–12 mm).

Anal. Calcd for $C_6H_{11}NF_2$: C, 53.33; H, 8.15; N, 10.37. Found: C, 53.03; H, 7.90; N, 10.40.

The infrared spectrum consisted of peaks at 3.55 (s), 3.45 (m), 6.83 (m), 7.3 (w), 9.5 (w), 10.3 (s), 10.6 (m), 10.85 (m), 11.3 (m), 11.8 (s), 12.0 (m), 12.7 (w), 13.8 (w), and 14.7 μ (w).

1-Difluoramino-1-methylcyclohexane.—To a mixture of difluoramine (generated from 400 ml of difluorourea solution) and 2 ml of the boron trifluoride complex of phosphoric acid, 20 g (0.209 mole) of 1-methyl-1-cyclohexene was added dropwise, with stirring. Stirring was continued for 3 hr and then 200 ml of pentane was added and unreacted difluoramine was vented off. The insoluble catalyst layer was discarded and the pentane layer was dried over sodium sulfate and was distilled. After the solvent was removed, the residue was vacuum distilled to yield 25.8 g (83% yield) of 1-difluoramino-1-methylcyclohexane, bp 44° (14 mm).

Anal. Calcd for $C_7H_{13}NF_2$: C, 56.37; H, 8.72; N, 9.40; F, 25.5. Found: C, 55.93; H, 9.10; N, 9.15; F, 25.2.

The proton nmr spectrum of a carbon tetrachloride solution of the compound consisted of a triplet (J = 1.9 cps) at δ 1.26 for the methyl group and a broad multiplet at δ 1.59 for the methylenes. The F^{19} spectrum contained only a broadened singlet at ϕ −22.17. The infrared spectrum consisted of peaks at 3.38 (s), 3.48 (m), 6.8 (sh), 6.9 (m), 7.23 (m), 7.4 (m), 8.65 (w), 10.15 (w), 10.5 (s), 10.97 (w), and 11.5–11.9 μ (s).

***t*-Butyldifluoramine.**—To a refluxing mixture of 13 g of isobutylene (0.232 mole) and difluoramine (from 600 ml of difluorourea solution), 1 ml of the boron trifluoride complex of phosphoric acid was added. An additional 1 ml of the catalyst was added after 1 hr and the mixture was allowed to reflux for an additional 3-hr period. *n*-Decane (100 ml) was then added and the excess difluoramine was removed. Distillation of the decane solution gave 15.9 g (0.146 mole, 63% yield) of *t*-butyldifluoramine, bp 54°.[5]

Reaction of Alkyldifluoramines with Acids.—Sulfuric acid solutions for the nmr spectra were prepared as described previously.[2] The product from fluorosulfonic acid and 1,2-bis(difluoramino)cyclohexane was prepared by adding 0.2 ml of the NF compound to 1 ml of the acid, cooled in a Dry Ice bath. The mixture was agitated until a homogeneous solution was formed. This solution was stable at room temperature. When the addition was conducted with the acid at 0°, a fume-off occurred when the first drop was added.

Registry No.—Difluoraminocyclohexane, 14182-78-6; 1-difluoramino-1-methylcyclohexane, 14182-79-7; difluoraminocyclopentane, 14182-80-0; *cis*-1,2-bis(difluoramino)cyclohexane, 14182-81-1; *trans*-1,2-bis(difluoramino)cyclohexane, 14182-82-2; N-fluoroimonium ion from 1-difluoramino-1-methylcyclohexane, 14182-83-3; N-fluoroimonium ion from difluoraminocyclohexane, 14182-84-4; N-fluoroimonium ion from difluoroaminocyclopentane, 14182-85-5; N-fluoroimonium ion from 1,2-bis(difluoramino)cyclohexane, 14182-86-6.

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The Conversion of Acylic Carbohydrates to Tetrahydrofuran Derivatives. The Acid-Catalyzed Dehydration of Tetritols and Pentitols[1]

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The acid-catalyzed dehydration of tetritols and pentitols leads primarily to the formation of tetrahydrofuran derivates without inversion of configuration. The process appears to involve the intramolecular displacement of water. The rate of cyclization is strongly influenced by the inductive effects of groups adjacent to the leaving group and to the entering group. The rate is also influenced by changes in the configuration of hydroxyl groups not directly involved in the reaction. This effect is attributed to interactions of the C–O dipoles. There is a strong interaction possible between a hydroxyl group adjacent to the leaving group and the leaving group which strongly influences the rate of cyclization. When these groups are *gauche*, the leaving group is effectively restrained from leaving by hydrogen bonding to the adjacent hydroxyl group.

The acid-catalyzed conversion of alditols to anhydroalditols has been the subject of numerous investigations,[2–5] none of which has been primarily concerned with the mechanism of the reaction or with the effect of configuration and substitution on its rate and course.

The acid-catalyzed ring closure of alditols, such as ribitol, has been proposed to be a nucleophilic displacement from C-1 of a protonated leaving group by a suitably situated hydroxyl group, usually at C-4[5,6] (Scheme I, route 2). Similar displacement reactions

(1) This investigation was supported in part by a Public Health Service Research Grant (GM 11,963) and by a Public Health Service Research Career Program Award (GM 24,808) to R. B. from the Institute of General Medical Sciences.

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(6) F. Shafizadeh, *Advan. Carbohydrate Chem.*, **13**, 59 (1958).