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THE MECHANISM OF SERINE FLUORODEHYDROXYLATION: ^{13}C AND ^{19}F NMR STUDIES

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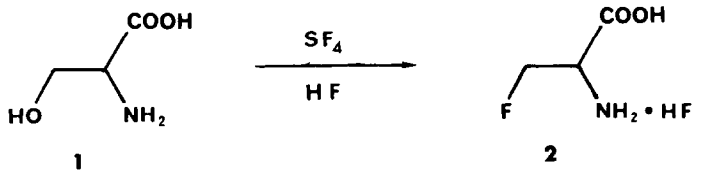
Summary: Competitive reaction pathways responsible for the incomplete fluorination of serine by SF_4 were elucidated and inhibited.

Among the methods for conversion of a primary hydroxyl to an alkyl fluoride[1] only the use of sulfur tetrafluoride is suitable for serine fluorination.[2] The product is β-fluoroalanine 2 whose S-isomer is a broad spectrum antimicrobial.[3] In investigating the reaction



1 2

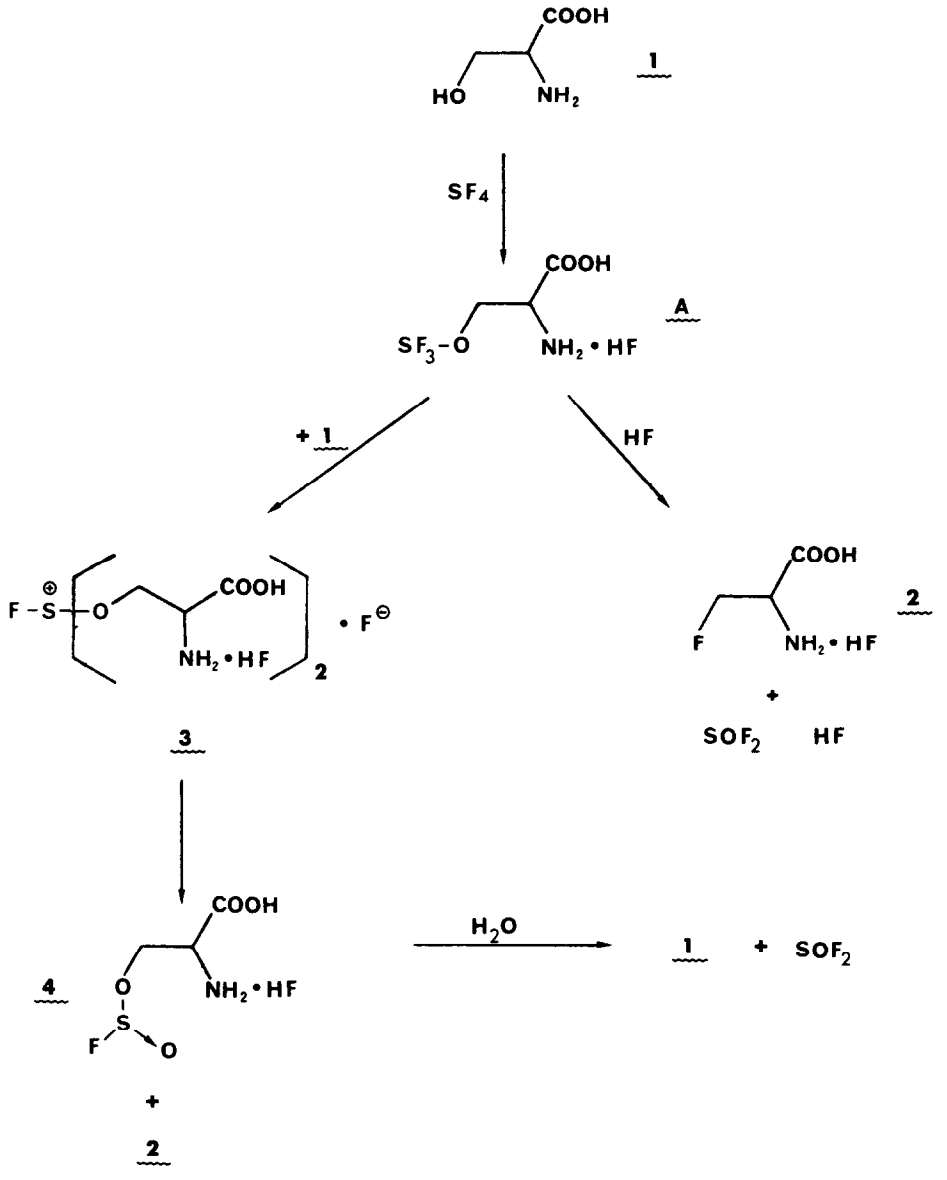
using HF as solvent we were surprised to find as much as 40% "unreacted" serine 1, even with large excesses of SF_4. Difficulty in separating amino-acids 1 and 2 made complete conversion imperative. Suspecting serine to be held up as an O-blocked species and regenerated upon aqueous work-up, we turned to in situ ^{19}F and ^{13}C NMR examination of the reaction. A pathway involving coupling of two serines to one SF_4 was found.

A typical NMR experiment (Varian XL-100A, Fourier transform operation) had 505 mg (5 mmol) L-serine dissolved in anhydrous HF (1.0 mL) in a specially constructed Kel-F® cell, treated at -78°C with SF_4 (540 mg, 5 mmol). Spectra were obtained between -60 and -30°C (^{13}C at 25.159 Mhz; ^{19}F at 94.128 or 94.150 Mhz).

Using ^{13}C we found virtually complete disappearance of serine with formation of fluoroalanine 2 and a novel species 3 in 1:2 ratio. With time 3 vanished, producing more fluoroalanine and another novel compound 4 in a final 60:40 ratio. Aqueous work-up produced a 60:40 mixture of fluoroalanine:serine (^1H, ^{13}C NMR, HPLC[4]).

A companion ^{19}F study revealed slow conversion of a ϕ = -19.0 ppm singlet to a -53.8 ppm doublet ($t_{1/2}$ = 1.5 hr, -40°C). Integration showed the doublet intensity growth exactly matching the singlet's decrease. We ascribe the doublet to diastereomers of fluorosulfite 4 and propose the following scheme:

SCHEME


COOH
HO
NH2
1
SF4
COOH
SF3-O
NH2 • HF
A
+ 1
HF
F-S
O
COOH
NH2 • HF
2
• F⊖
3
COOH
F
NH2 • HF
2
+
SOF2
HF
COOH
4
O
NH2 • HF
F
S
O
+
2
H2O
1
+
SOF2

Racemic serine results support 3. When the two serines in 3 are both R- or both S- the tetrahedral sulfur is achiral; the single ^{19}F resonance at -19.0 ppm appears. With R,S- or S,R- combinations, sulfur becomes chiral and two diastereotopic resonances at -18.0 and -20.3 are seen. The statistical 1:2:1 pattern we observed with racemic serine is consistent with structure 3.[5]

The unusually large ^{13}C-H spin coupling at C_β (Table), indicative of potent electron withdrawal,[7] fits 3. In addition, C_β appears as doublet with full proton decoupling, due to either ^{13}C shielding inequivalence or a resolvable spin splitting by a single ^{19}F.[8]

Diastereotopically paired signals are expected for 4.[9] All carbons and the fluorine exhibited doubled signals. The fluorine pattern was identical whether L-serine or its racemate was employed. The ^{19}F shift at -54 ppm is within a 10 ppm range reported for some simple analogs.[10,11]

The identification of 3, which presumably arises from the bimolecular reaction of serine with an intermediate oxosulfur trifluoride A (scheme),[12] led us to perform the fluorination at higher dilution. Consequently, 99:1 ratios of fluoroalanine to serine were obtained.

TABLE

Low Temperature NMR Data on Liquid HF

	C_α [a]			C_β [a]			^{19}F [b]	
Cpd.	δ_c	Pattern	$^1J_{CH}$	δ_c	Pattern	$^1J_{CH}$	ø	Pattern
Ser. 1	56.0	s	149.2	61.1	s	154.1	--	--
F-Ala 2	55.7	d, 20 hz	149.2	81.0	d, 172 hz	161.3	+231.2	t of d; 45.5, 30 hz
3	54.0	s[c]	148.5	77.0	d, 6 hz[c]	167.3 ± 1.7	-19.0	s
4	54.2	d, 3½ hz	d)	60.0	t, ~3 hz[c]	~157.	-54.0	d, 0.27 ppm

NOTES: a) ^{13}C @ approx. -50°C, external TMS (in acetone-d_6) reference.

b) ^{19}F @ approx. -40°C, internal C_6F_6 (ø ≡ +163.0) reference.

c) Broad signal

d) Obscured

References

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4. HPLC - ion pairing conditions: EM RP-18 (10 μm) column, 250 mm (L) x 4.6 mm (D); mobile phase: aqueous sodium heptanesulfonate; pH 2.2.
5. A neutral $(RO)_2SF_2$ alternate for 3 might be expected to show fluorine spin splitting in the RS and SR products. Also, the shielding region near -20 ppm is distant from the reported $(ArO)_2SF_2$ examples (-70 ppm).[6]
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8. The alternate mentioned in footnote 5 should present a singlet or a triplet, depending on ^{13}C-^{19}F splitting, assuming axial placement of fluorines in the expected trigonal bipyramid.[6]
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11. A triplet appearing for C_β is ascribed to ^{19}F splitting superimposed on a small shielding inequivalence.
12. NMR evidence was not found for this likely intermediate A (see scheme).

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