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A Superstable Nitrogen Pyramid: Stereodirected *N*-Halogenation of Methyl 2-Aziridinecarboxylate

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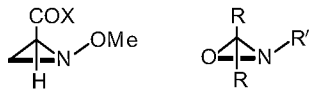
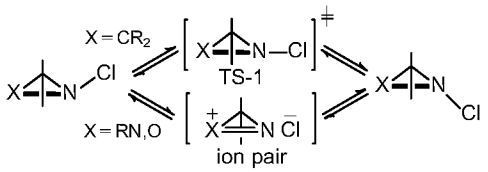
Partial *cis*-*N*-halogenation of methyl 2-aziridinecarboxylate (Azy–OMe) takes place only under conditions of intramolecular hydrogen bond breaking under the action of F_2 in the presence of Et_3N, and also under the action of KOCl in the presence of H_2O; for the *N*-fluoro derivative, a record high nitrogen inversion barrier was found ($\Delta G^{\neq}$ 35 kcal mol^{-1}).

Until recently the highest configurational stability was observed in three-membered nitrogen heterocycles containing an *exo*- or *endo*-N–O bond **1**–**4** (in brackets, $\Delta G^{\neq}_{inv}$/kcal mol^{-1}).



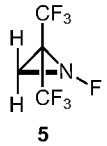
1 X = Me_2N (32.9)[1] **3** R = Ph, R′ = Me (34.1)[2]
2 X = MeO (32.1)[1] **4** R + R = $(CH_2)_5$, R′ = Pr^i (31.1)[3]

The possibility of increasing the nitrogen inversion barrier by introducing one more σ-electronegative *N*-substituent led to the following observation: when the *N*-alkyl substituent is changed to Cl in oxaziridine **4**, $\Delta G^{\neq}_{inv}$ remains practically the same,[4] and considerably decreases in diaziridines.[5] This is explained by the dissociative mechanism of inversion through a solvate-unseparated ion pair. The ionization of the N–Cl bond is caused by $n_x \rightarrow \sigma^*_{NCl}$ hyperconjugation, whereas in *N*-chloroaziridines the inversion of nitrogen atom occurs by a normal mechanism through planar transition state TS-1.[5,6]



Thus, the point of interest is aziridines containing the maximally σ-electron-accepting *N*-substituent – the fluorine atom. For two series of compounds $Bu^tN(CH_2Ph)X$[7] and $MeO_2CCH_2CMe_2N(OMe)X$[8] it is known that when X = Me is changed to X = F, $\Delta G^{\neq}_{inv}$ increases by 9 and 14.3

kcal mol^{-1}, and when X = Cl changes to X = F it increases by 6.2 and 7.3 kcal mol^{-1}, respectively. So in *N*-fluoroaziridines the barrier to inversion must be 30 kcal mol^{-1} higher. The first *N*-fluoroaziridine **5** was synthesized in our laboratory.[9,10]



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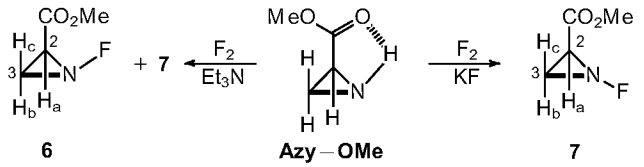
Later, *N*-fluoroaziridines were obtained under the action of CF_3OF and characterized only in solution.[11] However, nitrogen inversion barriers in these compounds have not been measured.

In the present work *cis*-**6** and *trans*-**7** N–F derivatives of Azy–OMe were first obtained under the action of F_2/N_2 (1:40) in Freon-113 at −35 °C (Scheme 1).



Scheme 1

In the presence of Et_3N a mixture of **6** and **7** was obtained in the ratio ~1:1.4, whereas in the presence of powdered KF only *trans*-isomer **7** was formed. This is explained by the fact that the *cis*-isomer of Azy–OMe is stabilized by an intramolecular hydrogen bond.[12] When the bond breaks under the action of Et_3N the opportunity arises both for *cis*- and *trans*-attack by F_2 at the nitrogen atom. In the presence of powdered KF, the hydrogen bond remains and only *trans*-attack by F_2 occurs. The structure of the products was confirmed by NMR spectroscopy† (Figure 1) and the configuration by spin coupling constants values by comparison with *N*-fluoroaziridine **5**.[10] The configuration assignment is also confirmed by thermal transformation of *cis*-**6** into *trans*-**7**. From the kinetics of this isomerization a record high nitrogen inversion barrier was found: $\Delta G^{\neq}_{inv} \sim 35$ kcal mol^{-1} at 120 °C (Figure 1).

Corresponding to the above fluorination, chlorination of Azy–OMe under conditions of hydrogen bond breaking under the action of KOCl in a toluene–H_2O mixture gives a mixture of *cis*-**8** and *trans*-**9** *N*-chloro-derivatives of Azy–OMe in the ratio 1:5. Chlorination by Bu^{t}OCl,[12–14], Cl_2 or *N*-chlorosuccinimide in aprotic solvents gives only *trans*-**9** (Scheme 2).

The structure of the products was confirmed by NMR spectroscopy† and the configuration by comparison with **9** (^{15}N)[12] and thermal transformation **8** → **9**.

† *Spectral data*: **6**, ^{1}H NMR ($CDCl_3$): δ 2.48 ddd (H_c), 2.98 ddd (H_b), 3.17 ddd (H_a), 3.82 s (MeO), $^3J_{ab}$ = 7.9, $^3J_{ac}$ = 5.2, $^2J_{bc}$ = −7.9, $^3J_{aF}$ = 40.9, $^3J_{bF}$ = 16.8, $^3J_{cF}$ = 26.9; ^{13}C NMR ($CDCl_3$): δ 37.7 (3-C, $^1J_{CH}$ = 175.1 and 176.6, $^2J_{CF}$ = 4.4), 41.8 (2-C, $^1J_{CH}$ = 175.8, $^2J_{CF}$ = 8.7), 53.0 (Me, $^1J_{CH}$ = 146.8), 163.7 (CO, $^3J_{CF}$ = 8.6); ^{19}F NMR ($CDCl_3$, from CF_3CO_2H): δ 11.4 ppm.

7, ^{1}H NMR ($CDCl_3$): δ 2.64 ddd (H_c), 2.84 ddd (H_b), 3.22 ddd (H_a), 3.76 s (MeO), $^3J_{ab}$ = 10.1, $^3J_{ac}$ = 7.6, $^2J_{bc}$ = −4.9, $^3J_{aF}$ = 29.3, $^3J_{bF}$ = 38.8, $^3J_{cF}$ = 28.7; ^{13}C NMR ($CDCl_3$): δ 39.2 (3-C, $^1J_{CH}$ = 177.3 and 178.8, $^2J_{CF}$ = 2.9), 41.5 (2-C, $^1J_{CH}$ = 181.7, $^2J_{CF}$ = 8.7), 52.7 (Me, $^1J_{CH}$ = 148.2), 167.0 (CO, $^3J_{CF}$ = 7.2); ^{19}F NMR ($CDCl_3$, from CF_3CO_2H): δ 43.1 ppm.

8, ^{1}H NMR ([$^2H_8$]toluene): δ 1.78 dd (H_b), 2.35 dd (H_c), 2.47 dd (H_a), 3.35 s (MeO), $^3J_{ab}$ = 6.1, $^3J_{ac}$ = 5.8, $^2J_{bc}$ = -2.8.

9, ^{1}H NMR ([$^2H_8$]toluene): 1.8 dd (H_b), 2.2 dd (H_c), 2.57 dd (H_a), 3.21 s (MeO), $^3J_{ab}$ = 7.9, $^3J_{ac}$ = 5.5, $^2J_{bc}$ = −2.8; ^{13}C NMR ($CDCl_3$): δ 41.6 (3-C, $^1J_{CH}$ = 175.1 and 178.8, $^2J_{CH}$ = 1.5), 43.8 (2-C, $^1J_{CH}$ = 180.2, $^2J_{CH}$ = 1.6 and 2.9), 52.1 (Me, $^1J_{CH}$ = 148.2), 167.6 (CO, $^2J_{CH}$ = 1.5, $^3J_{CH}$ = 3.6).

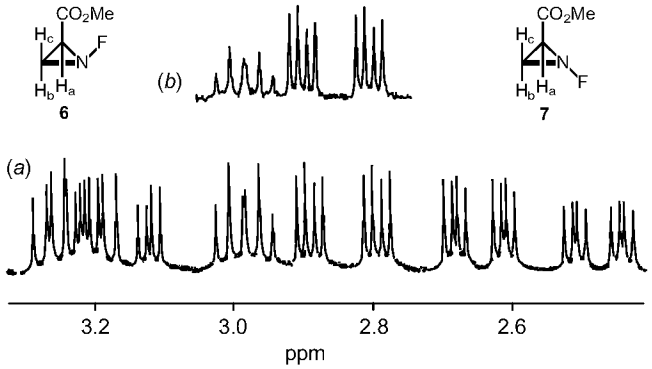


Figure 1 (*a*) ^{1}H NMR spectrum of ring protons of the mixture **6** (42%) + **7** (58%); (*b*) after heating for 10 h at 100 °C, 4 h at 120 °C, and 8 h at 150 °C: **6** (22%) + **7** (78%).

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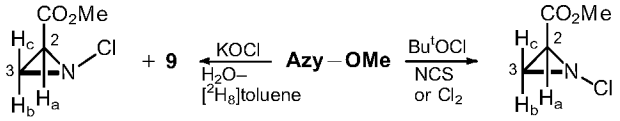

Scheme 2

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