Electronic structure and reactivity of organofluorine compounds
6.* The effect of the position of the CF_3 group on the basicity of aliphatic amines

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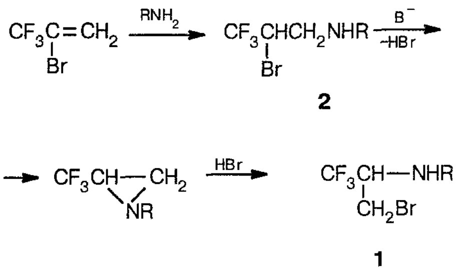
The basicity of isomeric bromoethylamines having a CF_3 substituent in the α- and β-positions with respect to the amino group was studied. According to potentiometric titration in H_2O, CH_3NO_2, and CH_3CN, the basicity of α-trifluoromethylamines is 4—5 orders of magnitude lower than that of β-trifluoromethyl isomers. Quantum-chemical calculations (AM1) showed that the decrease in the basicity of α-trifluoromethylamines does not correlate with the change in the electron density at the nitrogen atom.

Key words: basicity of bromo(trifluoromethyl)amines, potentiometric titration, quantum-chemical calculations, electronic structure.

Isomeric $CH_2BrCH(CF_3)NHR$ (**1**) and $CF_3CHBrCH_2NHR$ (**2**) differ noticeably in their reactivity in nucleophilic addition reactions. Amines **2** readily react with CS_2 at 20 °C to give thiazolidinthiones, whereas amines **1** do not add CS_2 under these conditions.[1] One may assume that this results from differences in the decrease in the electron density at the nitrogen atom due to the α- and β-CF_3 groups. In this connection we studied the basicity of amines **1** and **2** by potentiometric titration and the quantum-chemical method.

Amines **1** were prepared by ring-opening of the corresponding aziridines, which had in turn been synthesized by cyclization of 2-bromo-3,3,3-trifluoropropylamines **2**. The synthesis of amines **2** was carried out by the addition of alkylamines to 2-bromo-3,3,3-trifluoropropene:[2,3]



Potentiometric titration was carried out in water and nitromethane using a glass electrode. pK_a of the corresponding protonated forms of the amines $BH^+ \rightleftharpoons B + H^+$ were determined. For comparison, we also determined the pK_a values for protonated tertiary amines $CF_3CHBrCH_2NR^1R^2$ (**3**).

The data given in Table 1 indicate that the dissociation constants of the protonated forms of α-trifluoromethylamines are 4—5 orders of magnitude higher than those of amines containing the CF_3 group in the β-position. Correspondingly, the basicity of α-trifluoromethylamines is lower than the basicity of β-trifluoromethyl isomers by 4—5 orders or magnitudes. This dependence of pK_a on the position of the CF_3 group is

Table 1. Dissociation constants (pK_a) of the protonated forms of amines $CH_2BrCH(CF_3)NHR$ (**1**), $CF_3CHBrCH_2NHR$ (**2**), and $CF_3CHBrCH_2NR^1R^2$ (**3**) according to the data of potentiometry in H_2O and CH_3NO_2 (298 K)

Compound			pK_a	
			H_2O	CH_3NO_2
1a	R =	Me*	3.21	5.6
1b		Et	3.22	5.6
1c		Bn	3.31	3.8
2a	R =	Me**	8.10	10.0
2b		Et	8.11	9.8
2c		Bn	7.78	8.2
2d		H	7.02	9.0
3a	R^1R^2 =	$-(CH_2)_4-$	8.11	10.0
3b		$-(CH_2)_5-$	8.12	10.6
3c		$-C_2H_4OC_2H_4-$	6.09	7.6

* For **1a** pK_a (CH_3CN) = 9.7.
** For **2a** pK_a (CH_3CN) = 13.8.

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observed in both solvents (H_2O and CH_3NO_2). The relative increase in the basicity in CH_3NO_2 is due to the known lower proton-acceptor ability of this solvent. A similar effect of the CF_3 group on the basicity of amines in H_2O has been observed previously for trifluoroethyl- and trifluoropropylamine.[4]

It is known that, along with the direct solvation of ions and dipoles, polar solvents may affect the equilibrium of ionic reactions by the specific solvation of induced intramolecular dipoles. To evaluate the contribution from this specific solvation to the basicity of **1** and **2** we determined pK_a for a pair of isomeric amines in CH_3CN, whose solvating properties differ from those of H_2O and CH_3NO_2. It turned out that the role of specific solvation is modest, and that the distinction between the basicities of amines **1a** and **2a** in CH_3CN remains: $\Delta pK_a = 4.1$.

To estimate the effect of solvation on the protonation equilibrium and the effect of the dielectric constant of the medium on the intramolecular interactions of dipoles, the values of the proton affinity (PA) for amines **1** and **2** in the gas phase were calculated by the AM1 semiempirical method. The calculations for the molecules were carried out with full optimization of the geometry, and PA was determined as the difference between the heats of formation of the final reaction products and the starting compounds. The results obtained for the gas phase qualitatively coincide with the experimental data obtained by potentiometric titration for H_2O and CH_3NO_2 solutions: the PA of amine **1** (R = H) turned out to be 14 kcal mol^{-1} higher than that of its isomer **2d**.

$$CH_2BrCH(CF_3)NH_2 + H^+ \rightarrow CH_2BrCH(CF_3)NH_3^+$$

$$PA = 142.96 \text{ kcal mol}^{-1}$$

$$CF_3CHBrCH_2NH_2 + H^+ \rightarrow CF_3CHBrCH_2NH_3^+$$

$$PA = 157.03 \text{ kcal mol}^{-1}$$

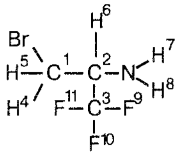
The decrease in the basicity and nucleophilicity of trifluoromethyl substituted amines may be associated with the decrease in the electron density of the lone electron pair at the nitrogen atom owing to the displacement of the electrons caused by the electron-withdrawing CF_3 group.[5]

However, the quantum-chemical calculations performed showed that the substantial decrease in the basicity of amines **1** is not associated with the change in the electron density at the nitrogen atom (Table 2). Actually, the total formal charges at nitrogen (according to Malliken) in isomers **1** and **2** turned out to be practically equal, −0.339 and −0.345, respectively.

Previously no correlation between the electron density at the nitrogen atom and the basicity (proton affinity) of amines has been observed in the series NH_3—methylamine—dimethylamine—trimethylamine.[6,7]

The results obtained are in agreement with the data from the "separate molecules" method (in the OST-3 GF basis set). It was shown that the inductive effect of the CH_2F group on the change in the basicity of amines is caused by the energetic stabilization of the system owing to direct electrostatic interaction of the C—F bond dipole with the amino group.[8—10]

Table 2. Heats of formation (ΔH_f), dipole moments (μ), energy levels of boundary orbitals (HOMO and LUMO), and the distribution of formal charges (q) at the atoms in isomeric amines **1** and **2** (AM1 calculations with full optimization of the geometry)



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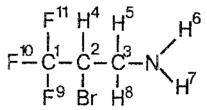

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Atom	q(**1***)	q(**2****)
C(1)	−0.276	0.423
C(2)	−0.045	−0.227
C(3)	0.420	−0.078
H(4)	0.115	0.162
H(5)	0.124	0.077
H(6)	0.134	0.154
H(7)	0.165	0.162
H(8)	0.170	0.117
F(9)	−0.159	−0.158
F(10)	−0.165	−0.157
F(11)	−0.151	−0.154
Br	0.007	0.024
N	−0.339	−0.345

* ΔH_f = −152.5 kcal mol^{-1}, μ = 3.87 D, HOMO = −10.72 eV, LUMO = 0.15 eV. ** ΔH_f = −158.0 kcal mol^{-1}, μ = 2.00 D, HOMO = −10.3 eV, LUMO = −0.36 eV.

Experimental

^1H NMR spectra were recorded on a Bruker WP-200 SY (200 MHz) spectrophotometer with HMDS as the internal standard.

***N*-(1-Bromomethyl-2,2,2-trifluoroethyl)-*N*-methylamine (1a).** 15 mL (0.11 mol) of 40 % aqueous HBr was gradually added with stirring to 6.25 g (0.05 mol) of 1-methyl-2-trifluoromethylaziridine at 5 °C. After 10 min, an excess of a 10 % aqueous solution of $NaHCO_3$ was added to the reaction mixture until the organic layer entirely sedimented. The organic layer was separated, dried with $MgSO_4$, and distilled. Yield 9.3 g (90 %), b.p. 115—117 °C. Found (%): C, 23.55; H, 3.42. $C_4H_7BrF_3N$. Calculated (%): C, 23.30; H, 3.39. ^1H NMR (C_6D_6), δ: 0.9 (br.s, 1 H, NH); 2.2 (s, 3 H, CH_3); 2.7 (d d q, H_C, CH); 2.9 (d d, H_B, CH_2); 3.1 (d d, H_A, CH_2); J_{HC,CF_3} = 7.5 Hz; J_{H_A,H_B} = 12.9 Hz; J_{H_A,H_C} = 4.5 Hz; J_{H_B,H_C} = 7.1 Hz.

***N*-(1-Bromomethyl-2,2,2-trifluoroethyl)-*N*-ethylamine (1b)** was prepared from 1-ethyl-2-trifluoromethylaziridine in 85 % yield in a similar way, b.p. 50 °C (60 Torr). Found (%): C, 27.11; H, 4.15. $C_5H_9BrF_3N$. Calculated (%): C, 27.27; H, 4.09. ^1H NMR (C_6D_6), δ: 0.9 (t, 3 H, CH_3); 1.1 (s, 1 H, NH); 2.5 (m, 2 H, $C\underline{H}_2CH_3$); 2.9 (m, H_C, CH); 3.0 (d d, H_B, CH_2); 3.2 (d d, H_A, CH_2); J_{HC,CF_3} = 7.5 Hz;

J_{H_A,H_B} = 12.9 Hz; J_{H_A,H_C} = 4.5 Hz; J_{H_B,H_C} = 6.4 Hz; $J_{CH_2-CH_3}$ = 6.5 Hz.

***N*-(1-Bromomethyl-2,2,2-trifluoroethyl)-*N*-benzylamine (1c)** was prepared from 1-benzyl-2-trifluoromethylaziridine in 90 % yield in a similar way, b.p. 120—122 °C (10 Torr). Found (%): C, 42.99; H, 3.92; F, 20.34. $C_{10}H_{11}BrF_3N$. Calculated (%): C, 42.55; H, 3.90; F, 20.21. ^{1}H NMR ($CDCl_3$), δ: 1.3 (s, NH); 2.6 (s, H_C, CH); 2.75 (d, H_A, CH_2); 2.85 (d, H_C CH_2); 3.4 (s, 2 H, CH_2Ph); 6.95 (m, 5H, C_6H_5); J_{HC,CF_3} = 7.4 Hz; J_{H_A,H_B} = 12.7 Hz.

***N*-(1-Bromo-3,3,3-trifluoropropyl)pyrrolidine (3a).** At 5—10 °C, 4.8 g (0.67 mol) of pyrrolidine was slowly added to 8.0 g (0.45 mol) of 3,3,3-trifluoro-2-bromopropene. The reaction mixture was warmed to room temperature and left for 24 h. Then it was diluted with 20 mL of water and extracted with ether (3 • 20 mL). The ethereal extract was washed with 20 mL of water and dried with $MgSO_4$; the ether was evaporated and the product was distilled. Yield 9.6 g (87 %), b.p. 61—63 °C (10 Torr). Found (%): C, 33.80; H, 4.46. $C_7H_{11}BrF_3N$. Calculated (%): C, 34.14; H, 4.46. ^{1}H NMR (C_6D_6), δ: 1.05 (m, 4 H, $-CH_2CH_2-$); 2.25 (m, 4 H, $-CH_2NCH_2-$); 2.75 (d d, H_B, CH_2); 2.8 (d d, H_A, CH_2); 4.0 (m, H_C, CH); $J_{HC,CF3}$ = 7.4; J_{H_A,H_B} = 12.9; J_{H_A,H_C} = 3.0; J_{H_B,H_C} = 3.5.

***N*-(2-Bromo-3,3,3-trifluoropropyl)morpholine (3c)** was prepared in a similar way from 3,3,3-trifluoro-2-bromopropene and morpholine over a period of 4 days. Yield 90 %, b.p. 85—87 °C (15 Torr). Found (%): C, 31.88; H, 4.31; F, 22.08. $C_7H_{11}BrF_3NO$. Calculated (%): C, 32.06; H, 4.19; F, 21.75. ^{1}H NMR (CD_3OD), δ: 2.5 (m, 4 H, $-CH_2NCH_2-$); 2.85 (d d, H_B, CH_2); 2.9 (d d, H_A, CH_2); 3.7 (m, 4 H, $-CH_2OCH_2-$); 4.6 (m, H_C, CH); J_{HC,CF_3} = 7.5 Hz; J_{H_A,H_B} = 12.9 Hz; J_{H_A,H_C} = 4.5 Hz; J_{H_B,H_C} = 3.2 Hz.

Potentiometric titration was carried out at 298±0.1 K according to the known procedure[11] using a Radelkis OP-211/1 pH meter, a Radiometer G202C glass electrode, and a Radiometer K 401 calomel electrode with the contact through a porous ceramic. Freshly distilled amines **1—3** were used in the investigations.

The electrode pair was calibrated with buffer solutions in the corresponding solvent. The concentration of the solution of the amine under study was 10^{-3} *M*, a 0.02 *M* solution of $HClO_4$ in the corresponding solvent was used as the titrant. The purification of reference compounds and solvents has been described previously.[11—13]

The accuracy of the determination of pK_a in water was 0.03—0.06 units; that in nitromethane and acetonitrile was within 0.1 unit (the reproducibility was 0.02—0.05 units).

Quantum-chemical calculations were carried out on an ES-1061 computer by the AM1 semiempirical method.[14] Geometric parameters were optimized on the basis of the total energy minimum with superimposition of the conditions for «local symmetry» of the CF_3 group.

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