Solid-state and Solution Structures of Fluorocholine and Some Analogues: Nuclear Magnetic Resonance and *X*-Ray Studies

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The preferred conformation of fluorocholine $(CH_3)_3-N^+-CH_2-CH_2-F$ and several analogues in aqueous solution has been determined by n.m.r. spectroscopic analysis and the crystal structure of $(CH_3CH_2)_3N^+-CH_2-CH_2-F\cdot Br^-$ determined. The preferred conformation of $N^+-C-C-F$ is clearly synclinal. In comparison, that of $N^+-C-C-O-$ has previously been shown also to be synclinal and that of $N^+-C-C-S-$ and $N^+-C-C-Se-$ to be antiplanar.

In the past decade there have been many conformational studies of physiologically and pharmacologically important molecules containing the group $N^+-C-C-X-$.[1-8] It has been clearly shown that the observed conformation both in solution [6] and in crystals,[8] of the $N^+-C-C-O$ group is synclinal and not antiplanar. The present study provides the preferred conformation of the $N^+-C-C-F$ group of some fluorocholine analogues in the crystalline state and in solution.

EXPERIMENTAL

The 100 MHz ^1H n.m.r. spectra were obtained with Varian HA100D and XL-100 spectrometers. The compounds were examined as 20—500mM solutions in deuterium oxide at 30°. Chemical shifts are expressed as p.p.m. downfield from an external hexamethyldisiloxane reference. Except when stated otherwise, the pD (meter reading) of the solutions was 7.0 ± 0.5.

1-Bromo-2-fluoroethane, b.p. 73—74°, was synthesised according to the published procedure.[9] Fluorocholine bromide [(2-fluoroethyl)trimethylammonium bromide] was prepared by a modification of the method of Kubiczek and Neugebauer.[10] 1-Bromo-2-fluoroethane (3.0 g) in 2 : 1 butan-2-one–trimethylamine (10 ml) was left for 16 h at room temperature. The crystals were filtered, well washed with butan-2-one, and dried *in vacuo* to give (2-fluoroethyl)-trimethylammonium bromide as a deliquescent solid (3.0 g), m.p. 257—259° (decomp.) [lit.,[10] 252—253° (decomp.)]. Similar procedures using triethylamine and dimethylamine (10 days reaction time) gave (2-fluoroethyl)triethylammonium bromide, non-deliquescent crystals, m.p. 235—238° (decomp.), and bis-(2-fluoroethyl)dimethylammonium bromide, m.p. 234° (decomp.). Demethylation of fluorocholine bromide (1.05 g) was accomplished by sodium thiophenoxide (3.0 g) in anhydrous refluxing butan-2-one (20 ml) containing AcOH (50 μl) for 2 h. Following acidification with 2M-citric acid (25 ml) and extraction with light petroleum, the aqueous solution was made alkaline (pH 11), and extracted with chloroform. The extract was dried and evaporated to give an oil which was converted into the hydrochloride salt and recrystallised from acetone to give feathery crystals of 2-fluoroethyldimethylammonium chloride (0.3 g), m.p. 165—167° (lit.,[11] 165°).

Preliminary analysis of the ^1H n.m.r. spectra were carried out assuming that the spectra approximate to an AA'MXX' spin system.

The n.m.r. spectrum simulation program SIMEQ (kindly made available by Drs. C. W. Kort and M. J. A. de Bie) was used with a VDM620i computer to simulate spectra using parameters obtained for the approximate analysis. Spectral parameters were adjusted to improve the fit of simulated to observed spectra, thereby removing the approximations.

Crystals recrystallised from an ethanol and ether solution of $(CH_3CH_2)_3N^+CH_2CH_2F\cdot Br^-$ are plates elongated in the *c* direction and show the forms (001), (010). Crystals are fairly deliquescent and one was mounted in a glass capillary tube for *X*-ray analysis. Space group and preliminary cell parameters were determined from precession photographs. Refined cell parameters and standard deviations were obtained by a least squares refinement of the three angular parameters of twelve diffraction maxima accurately aligned on a computer-controlled four-circle diffractometer.

Crystal Data.—(2-Fluoroethyl)triethylammonium bromide, $C_8H_{19}BrFN$, $M = 228.19$, $a = 8.791(5)$, $b = 8.126(4)$, $c = 15.125(5)$ Å, $\beta = 92.3(6)°$, $U = 1\,080$ Å^3, $D_m = 1.440$ g cm^{-3}, $D_c = 1.403$ g cm^{-3} (by flotation), $Z = 4$. Systematic absences: $h0l$ for $l = 2n + 1$, $0k0$ for $k = 2n + 1$, space group $P2_1/c$.

Data, Structure, and Refinement.—Radiation: Mo-K_α, 40 kV, 18 mα, graphite (002) monochromator. Instrument: PDP8/S controlled four circle diffractometer;[12] θ–2θ step scan 1.6°; $\Delta 2\theta = 0.04°$; step time = 5s/step; range $2\theta = 5$—45°. 992 diffraction maxima [$I < 3\sigma(I)$] observed out of 1 719 possible in 1/4 reciprocal space; corrected only for Lorentz and polarisation effects. Patterson function: Br^- observed. Br^- phased Fourier synthesis: all non-hydrogen atoms observed. Full matrix least squares analysis non-hydrogen atoms: (a) isotropic thermal parameters, $R = 0.136$; (b) anisotropic thermal parameters, $R = 0.080$. Difference synthesis: all hydrogen atoms observed. Full matrix least squares analysis: non-hydrogen anisotropic, hydrogen isotropic in fixed observed positions, $U_{iso.} = 0.063$ Å^2 until $\Delta x_i < 0.1\sigma(x_i)$; $R = 0.067$. Function minimised $\Sigma\omega(|F_o| - |F_c|)^2\omega = I/x^2$; $x = \sigma(I) + 0.05I$. Atomic transforms: C, N, F, Br^-;[13] H.[14]

Fractional co-ordinates, thermal motion parameters, and the interatomic distances and angles are given in Tables 1—3. Table 3 includes two sets of co-ordinates for the hydrogen atoms. The first set (a) is that observed in the difference synthesis; the second set (b) is of calculated co-ordinates using standard bond lengths and angles, and are possibly more reliable than the observed co-ordinates, which were used in the least squares refinement.

Observed and calculated structure factors for (2-fluoroethyl)triethylammonium bromide are given in Supplementary Publication No. SUP 22817 (10 pp.).*

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Table 1

Fractional co-ordinates and thermal motion parameters (× 10^4) * derived from least-squares refinement, with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br(1)	2 366(1)	3(1)	1 567(1)	130(2)	120(2)	46(1)	0(2)	13(1)	−12(1)
N(1)	2 583(8)	3 901(9)	3 630(5)	74(12)	69(14)	31(4)	−7(10)	9(5)	−12(6)
C(1)	3 020(14)	4 066(13)	2 681(6)	180(20)	89(19)	35(5)	−15(16)	14(8)	6(8)
C(2)	2 078(14)	5 519(13)	4 011(8)	115(16)	72(17)	45(6)	−4(14)	16(9)	−4(8)
C(3)	3 944(13)	3 279(13)	4 174(7)	98(17)	95(19)	42(5)	2(14)	−3(8)	−1(9)
C(4)	1 269(13)	2 686(13)	3 672(7)	134(17)	93(19)	45(6)	−20(15)	27(8)	1(8)
C(5)	821(16)	2 132(15)	4 563(8)	174(24)	125(23)	51(7)	−47(20)	27(10)	−4(10)
F(1)	1 711(10)	800(9)	4 839(5)	315(17)	162(13)	67(4)	−2(13)	37(7)	38(7)
C(6)	1 779(16)	4 802(15)	2 061(9)	160(21)	193(28)	52(6)	8(23)	1(9)	21(12)
C(7)	3 150(25)	6 969(19)	3 842(10)	287(35)	98(21)	59(9)	−68(22)	6(15)	−13(12)
C(8)	4 624(18)	1 694(16)	3 837(9)	184(24)	120(21)	66(8)	58(19)	23(11)	3(11)

RESULTS AND DISCUSSION

N.m.r. Spectra.—Figure 1 shows the $N^+-CH_2-CH_2-F$ region of the ^1H n.m.r. spectrum of fluorocholine bromide in D_2O. The FCH_2 and $\overset{+}{N}CH_2$ resonances exhibit large two- and three-bond H–F coupling constants of 48.1 and 28.7 Hz, respectively. Similarly, the $^3J_{^{14}N-H}$ spin–spin coupling constant (2.9 Hz) is measured as a first-order splitting on the FCH_2 resonance. The vicinal proton–proton spin-coupling constants can be estimated initially according to the procedure of Culvenor and Ham [1,2] from the values of N and L (see Figure 1) which are the sum and the difference respectively of the vicinal coupling constants in an AA′BB′ spin system. The estimates were refined by simulation, and the spectral parameters for the best-fit simulations of the spectrum are collected in Table 4. There is essentially no variation in $^2J_{HF}$ and $^3J_{HF}$, and little variation in the other coupling constants between the fluorocholine analogues.

Table 2

Fractional co-ordinates (× 10^3) for hydrogen atoms derived from difference Fourier synthesis [column (a)] and by calculation [column (b)]

	x		*y*		*z*	
Atom	(a)	(b)	(a)	(b)	(a)	(b)
H(1)	383	404	480	485	263	268
H(2)	368	331	265	283	250	245
H(3)	185	199	534	534	459	473
H(4)	120	94	576	579	387	371
H(5)	455	481	415	426	425	418
H(6)	350	357	323	309	479	485
H(7)	91	30	341	330	346	333
H(8)	153	162	183	161	329	328
H(9)	105	98	295	315	488	504
H(10)	−12	−38	158	177	462	453
H(11)	82	83	409	392	201	198
H(12)	131	136	567	595	211	235
H(13)	234	225	479	506	143	141
H(14)	403	430	620	667	355	410
H(15)	340	274	731	807	411	418
H(16)	288	317	747	721	332	313
H(17)	508	545	131	121	423	434
H(18)	495	520	172	194	332	322
H(19)	388	371	64	79	398	371

Conformational Analysis.—The value of vicinal coupling constants depends on the dihedral angle between the two nuclei concerned. This fact has been used to interpret vicinal coupling constants in terms of rotamer preferences. The observed vicinal coupling constants are the time-averaged values for the values in the component rotamers. Since the equilibrium conformations for the individual rotamers are likely to be close to staggered conformations (see Figure 2) the approach of Abraham and Gatti [15] may be used to describe the time-averaged observed coupling constants in terms of the

Table 3

Interatomic distances (Å) and angles (°) for non-hydrogen atoms with estimated standard deviations in parentheses

(*a*) Distances

C(1)–N(1)	1.51(1)	F(1)–C(5)	1.39(2)
C(2)–N(1)	1.51(1)	C(6)–C(1)	1.53(2)
C(3)–N(1)	1.51(1)	C(7)–C(2)	1.54(2)
C(4)–N(1)	1.52(1)	C(8)–C(3)	1.52(2)
C(5)–C(4)	1.49(2)		

(*b*) Angles

C(2)–N(1)–C(1)	112.1(9)	C(5)–C(4)–N(1)	117.6(11)
C(3)–N(1)–C(1)	108.8(9)	F(1)–C(5)–N(1)	110.0(11)
C(3)–N(1)–C(2)	108.8(9)	C(6)–C(1)–N(1)	114.5(11)
C(4)–N(1)–C(1)	108.7(9)	C(7)–C(2)–N(1)	114.4(13)
C(4)–N(1)–C(2)	108.3(9)	C(8)–C(3)–N(1)	114.5(12)
C(4)–N(1)–C(3)	110.2(9)		

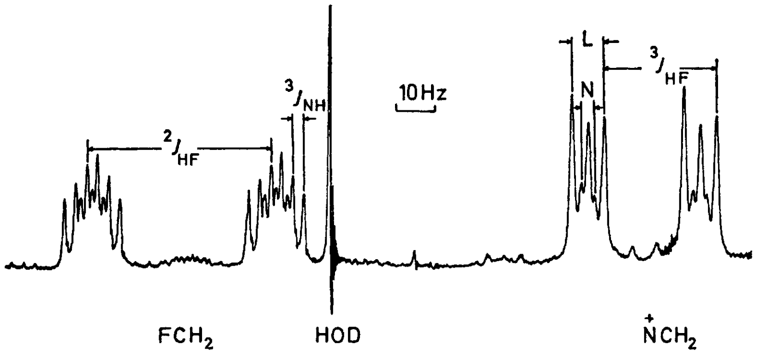

Figure 1 100 MHz ^1H N.m.r. spectrum of the $F-CH_2CH_2-N^+$ moiety of fluorocholine bromide in D_2O

TABLE 4

^{1}H Chemical shifts and coupling constants for fluorocholine and fluorocholine analogues

	Chemical shift [a]			Coupling constants (Hz)				
	CH_2F	CH_2N	N-R	$^2J_{H-F}$	$^3J_{H-F}$	$^3J_{N-H}$	$^3J_{1.4}$	$^3J_{1.3}$
Fluorocholine	5.34	4.15	3.59 $(CH_3)_3$	47.1	28.7	2.9	6.15	2.45
(2-Fluoroethyl)dimethylammonium [b]	5.23	3.94	3.59 $(CH_3)_2H$	46.8	27.9	*f*	5.65	3.45
(2-Fluoroethyl)dimethylamine [c]	4.93	3.01	2.59 $(CH_3)_2$	47.0	30.8	*f*	5.50	4.10
(2-Fluoroethyl)triethylammonium	5.21	3.97	3.68 [d] 1.59 [e] $(CH_3CH_2)_3$	47.0	28.2	2.6	5.75	2.95
Bis-(2-fluoroethyl)dimethylammonium	5.43	4.19	4.73 $(CH_3)_2$	47.4	29.1	2.8	5.90	2.70

[a] P.p.m. downfield from an external hexamethyldisiloxane reference. [b] pH 3. [c] pH 10.5. [d] 'Quartet', J 7.4 Hz. [e] Triplet J 7.4 Hz. [f] No coupling detected because of efficient quadrupolar relaxation

population-weighted component coupling constants, $J_{1.3}$ and $J_{1.4}$ [equations (1)]. Rearrangement leads to an expression for the fractional populations [equation (2)]. For $J_{1.4}$ a similar equation can be obtained, but it is less sensitive to changes in a and b since J_t^g is similar in magnitude to $\frac{1}{2}(J_g^t + J_g^{g'})$. Values for the component coupling constants may be obtained from the work of Abraham and Gatti[15] using equations of the form (3)

$$J_{1.3} = aJ_g^g + aJ_g^g + bJ_t^t \qquad (1)$$
$$J_{1.4} = aJ_g^t + aJ_g^{g'} + bJ_t^g$$

$$a = (J_t^t - J_{1.3})/2(J_t^t - J_g^g) \qquad (2)$$

$$J = K_1 + K_2(E_X + E_Y) \qquad (3)$$

where E_X and E_Y are the Huggins electronegativities for the substituents X and Y in XCH_2CH_2Y. For fluorine and nitrogen ($E_F + E_N = 6.95$) the component coupling constants, defined in Figure 2 are J_t^t 11.95, J_g^g 2.41, J_t^g 5.73, and $J_g^t + J_g^{g'}$ 12.81 Hz.

Using these values the populations of the synclinal O/N^+ and the antiplanar O/N^+ rotamers have been evaluated. The results are collected in Table 5.

An alternative method of calculating fractional populations is provided by the three bond $^{14}N-H$ coupling constants which can be treated similarly to the vicinal H–H coupling constants. The suggested component values[6] are J^g_{NH} 0.7 and J^t_{NH} 4.9 Hz. Hence compounds with measured $^3J_{NH}$ values of 2.6—2.9 exist predominantly in the synclinal conformation (*cf.* Table 4).

The vicinal coupling constant, $^3J_{H-F}$, has been shown to have a Karplus type relationship with the dihedral angle.[16] Approximate values of the component coupling constants (Figure 2) are[16] J_g^F *ca.* 8 and J_t^F *ca.* 44 Hz and hence, for the synclinal conformer, $^3J_{H-F}$ *ca.* 26 Hz and for the antiplanar conformer, $^3J_{H-F}$ *ca.* 8 Hz (*cf.* Table 4).

TABLE 5

Solution conformation of fluorocholine and choline analogues

	Synclinal (%) [a]	Antiplanar (%)
Fluorocholine	100	0
Chlorocholine [(2-chloroethyl)trimethylammonium]	64 [b]	36 [b]
Choline	89 [b]	11 [b]
Choline methyl ether	88 [b]	12 [b]
(2-Methylthioethyl)trimethylammonium	17 [b]	83 [b]
(2-Fluorethyl)triethylammonium	94	6
Bis-(2-fluoroethyl)dimethylammonium	97	3
(2-Fluoroethyl)dimethylammonium	90	10
(2-Hydroxyethyl)dimethylammonium	85 [b]	15 [b]
(2-Fluoroethyl)dimethylamine	82	18
(2-Hydroxyethyl)dimethylamine	64 [b]	36 [b]

[a] Determined from $J_{1.3}$. [b] Data from ref. 6.

Whether the conformational populations are characterised from the H–H, the N–H, or H–F coupling constants, it is clear that the fluorocholines strongly prefer the synclinal conformation. Even the tertiary compound, (2-fluoroethyl)dimethylamine, shows this preference whereas (2-hydroxyethyl)dimethylamine has

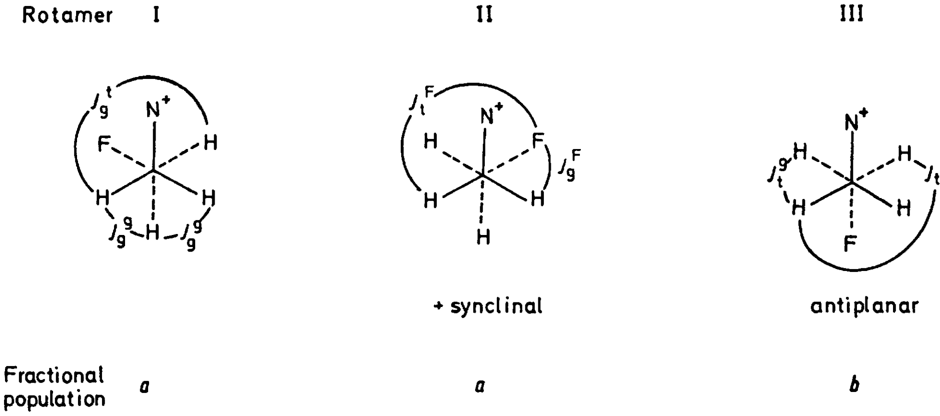

FIGURE 2 Rotamers of the $F-CH_2CH_2-N^+$ moiety

TABLE 6

Torsion angles for non-hydrogen atoms

C(5)–C(4)–N(1)–C(1)	170(1)	C(7)–C(2)–N(1)–C(1)	−48(1)
C(5)–C(4)–N(1)–C(2)	−68(1)	C(7)–C(2)–N(1)–C(3)	−72(1)
C(5)–C(4)–N(1)–C(3)	51(1)	C(7)–C(2)–N(1)–C(4)	−168(1)
C(1)–C(5)–C(4)–N(1)	−86(1)	C(8)–C(3)–N(1)–C(1)	−55(1)
C(6)–C(1)–N(1)–C(2)	−56(1)	C(8)–C(3)–N(1)–C(2)	−177(1)
C(6)–C(1)–N(1)–C(3)	−176(1)	C(8)–C(3)–N(1)–C(4)	64(1)
C(6)–C(1)–N(1)–C(4)	64(1)		

These torsion angles correspond to the co-ordinates of Table 1. As the space group is centrosymmetric, the opposite conformation also exists in the crystal, and the torsion angle values of the latter (the negatives of the above) are considered in the text.

the 2 : 1 ratio expected when there is no conformational preference (Table 5).

The Crystal Structure.—The observed bonded interatomic distances and angles are within 3σ of expected values. Table 6 gives the non-hydrogen torsion angles of the molecule. The N(1)–C(4)–C(5)–F torsion angle is 86° (the space group is centrosymmetric), in agreement with the solution analysis of all the N^+–C–C–F compounds.

Analogues of choline of the form N^+–C–C–O– are almost universally similarly nearly synclinal both in solution [6] and in crystals,[8] with an average torsion angle of *ca.* 85°. Thio- and seleno-analogues, N^+–C–C–S– and N^+–C–C–Se–, however, are observed to be antiplanar both in solution [6] and in crystals.[8] Since in the electronegativity sequence F (4.0), O (3.5), Cl (3.0), S (2.5), and Se (2.4) [17] there is a clear change in preferred conformation from synclinal to antiplanar (Table 5), we infer that the synclinal conformation is stabilised by an electrostatic interaction between the positive charge on the 'onium group and the partial negative charge on X with equilibrium at an electronegativity of *ca.* 3.0. Size alone would not account for the change, although in the compounds with bulky 'onium groups considered, steric hindrance causes the N–C–C–O or F torsion angle to be 78—86°.[8]

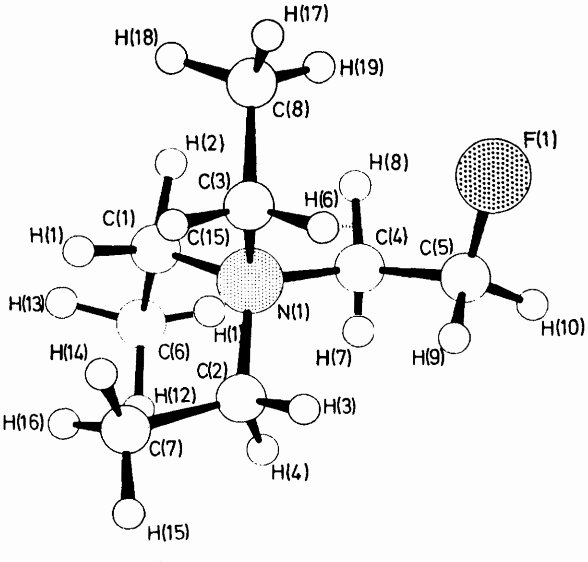

FIGURE 3 View of the ion $(C_2H_5)_3N^+CH_2CH_2F$, with observed hydrogen atom positions

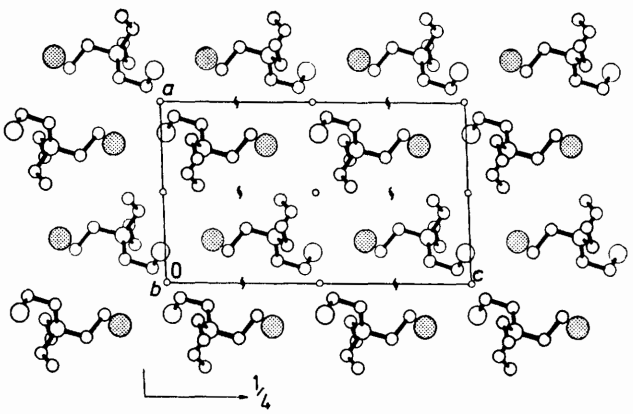

FIGURE 4 Molecular packing viewed down the −*b* axis

The triethylammonium group is rotated 10° from the staggered conformation with respect to the ethyl chain, in a direction away from the synclinal F atom [N^+–C–C–F −86°; C(5)–C(4)–N(1)–C(3) 51° (Table 6)]. Of the three triethylammonium ethyl chains, only one is antiplanar, the one closest to F, the other two are synclinal. This is presumably due to a combination of intramolecular and intermolecular (crystal packing) forces.

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