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Registry No. 1, 76673-35-3; **2**, 76673-34-2; $^1O_2$, 7782-44-7; $O_2^{-\cdot}$, 11062-77-4; NaN_3, 26628-22-8; *i*-PrOH, 67-63-0; N_2O, 10024-97-2; SOD, 9054-89-1; DPBF, 5471-63-6; NBT, 298-83-9; methylene blue, 61-73-4; imidazole, 288-32-4; *p*-nitroso-*N*,*N*-dimethylaniline, 138-89-6; α-lipoic acid, 62-46-4; ferricytochrome *c*, 9007-43-6; catalase, 9001-05-2; *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenyldiamine, 100-22-1; *N*,*N*,*N*′,*N*′-tetramethyl-*o*-phenylenediamine, 704-01-8; 3,4-dimethoxy-*N*,*N*-dimethylaniline, 2748-79-0; *N*,*N*,*N*′,*N*′-tetramethyl-*m*-phenylenediamine, 22440-93-3; *N*,*N*-dimethyl-*p*-methoxyaniline, 701-56-4; *N*,*N*-dimethyl-*o*-methoxyaniline, 700-75-4; *N*,*N*,2,4,6-pentamethylaniline, 13021-15-3; *N*,*N*,2,4-tetramethylaniline, 769-53-9; *N*,*N*,*p*-trimethylaniline, 99-97-8; *m*-methoxy-*N*,*N*-dimethylaniline, 15799-79-8; *N*,*N*-dimethylaniline, 121-69-7; *p*-chloro-*N*,*N*-dimethylaniline, 698-69-1.

Intermolecular Interactions of the C–F Bond: The Crystallographic Environment of Fluorinated Carboxylic Acids and Related Structures

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Abstract: The structure of the 1:2 complex of a monoethyl ester of (+)-*erythro*-fluorocitrate and (−)-methylbenzylamine was determined by X-ray crystallographic methods and refined to $R = 0.049$. The fluorocitrate portion of the molecule has a similar backbone conformation to that determined in earlier studies by us for two other fluorocitrates, with a gauche arrangement of the F–C–C–OH group. The hydrogen bonding from the carboxyl group to the nitrogen atom of the cation is such that the adjacent fluorine atom also lies near this cation with H··O and H··F distances of 2.00 (2) and 2.29 (1) Å and N–H··O,F angles of 159 and 124°, respectively. Thus, while fluorine does not form a strong hydrogen bond, some interaction appears present. In order to examine the generality of this observation, and also the observation in our earlier paper on rubidium ammonium fluorocitrate that the fluorine took part in the coordination sphere of the metal cation, the Cambridge Crystallographic Data File was searched for similar interactions of C–F bonds. It appears that the C–F bond is capable of significant interactions with alkali metal cations and with proton donors, although these are generally weaker than the corresponding ones involving C–O and C–N groups. The examples found in the data file are discussed in detail.

The biochemistry of fluorine-containing compounds has been studied extensively by Peters,[2] Kun,[3] Walsh[4] and their co-workers. Such studies[5] have mainly centered around the replacement of a C–H bond by a C–F bond and the resulting behavior of the fluorinated substrate analogue in the active site of an enzyme or receptor. Fluorine is small and the C–F bond is slightly shorter than a C–OH bond, but the high electronegativity of fluorine[6] might be expected to cause it to behave differently from hydrogen. For example, it has been shown[4,7] that the electron-withdrawing ability of fluorine is sufficient to cause sodium fluoropyruvate to exist mainly as the *gem*-diol, rather than as the carbonyl form, even in an aqueous environment.

When fluorine is substituted for hydrogen in a C–H bond of a substrate of an enzyme, the resulting behavior of the fluorinated compound in the active site of the enzyme is of interest. Often the fluoro analogue behaves initially as a competitive inhibitor of the enzyme. In some cases this inhibition ultimately becomes irreversible, possibly through the formation of covalent links and/or loss of F^-. Such an inhibition and inactivation can occur in vivo when animals eat plants containing fluoroacetate.[2] Fluoroacetate is converted to fluorocitrate by the enzyme citrate synthase and violently toxic effects result. This toxicity is believed to occur because fluorocitrate, instead of the normal substrate citrate, inhibits and ultimately inactivates the enzyme aconitase.[2,8] This action of a fluorinated substrate is referred to by Peters[2] as a "lethal synthesis" since the fluorocitrate synthesized in vivo is the toxic agent, not the ingested fluoroacetate.

Experiments on the absolute configuration of the biochemically active isomer of fluorocitrate[8-10] have shown that the fluorine atom has been substituted in the area of the citrate molecule that is *not* acted on by the enzyme aconitase (the "aconitase-inactive" end of citrate). As a result of a study of the crystal structure of the rubidium salt containing the active isomer we were able to show that the fluorine atom in fluorocitrate, unlike a carbon-bound hydrogen atom in citrate, takes part in the coordination sphere of the metal. This led us to propose[8] that such metal chelation is the reason that fluorocitrate is a strong inhibitor and inactivator of aconitase, even though the isomer involved has fluorine on the "aconitase-inactive" end of the molecule. We showed that this isomer, when bound to metal with the fluorine atom near the metal, had a free carboxyl group that could project into the active-site area of the enzyme and so could possibly cause inhibition and inactivation. The presence of fluorine (from a C–F bond) in the metal coordination sphere is an integral part of this mechanism, which accounts for the powerful biochemical activity of only one of the four isomers of fluorocitrate.

A general review of the literature on the possible modes of interaction of C–F bonds with other groups has been made. Most effort has been given to the possibility of C–F··H–O bonding, particularly in 2-fluoroethanol, which has been intensively studied.[11-16] This has a gauche conformation in the gas phase with

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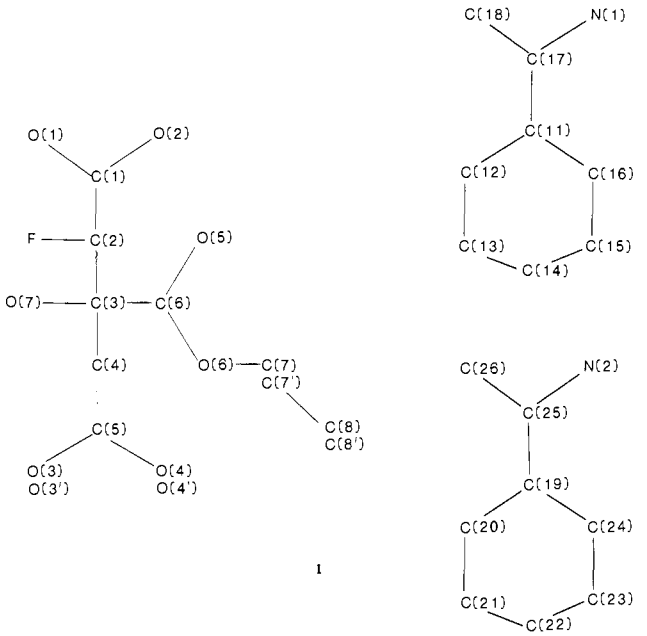
a bent O–H··F arrangement, which some authors interpret as a hydrogen bond. Others point out that similar gauche conformers exist for molecules that cannot form hydrogen bonds and produce alternative explanations. Opinions on the importance of intermolecular C–F··H(O,N) contacts are also divided. Some authors use phrases like "relatively weak interaction" or "possible bond". In discussions of the biological activity of C–F-containing compounds some authors describe C–F··HO bonds as "strong" and apparently assume them to be totally authenticated.[17] The strongest crystallographic identification of an C–F··HO bond was made in 9α-fluorocortisol, where two sets of authors independently described the interaction as such.[18,19] However, in a subsequent discussion of the possible role that fluorine might play in steroids, C–F··H–O bonding was not discussed.[20] The situation with C–F···M (metal) interactions is even less clear. Most of the authors of papers reporting structures with short M··F contacts tabulated the distances, but none made any special comment on them.

In an attempt to clarify the structural evidence for hydrogen bonding to C–F bonds we have recently determined the structures of two RNH_3^+ (R = PhCHMe) salts of fluorocitrate. For the first[9] only poor crystals could be obtained. The second structure determination of such a fluorocitrate is more accurate and is reported here.

In addition, in view of the importance of C–F bonds in biological systems and the confused literature on their interactions, we have carried out a computer analysis of all crystal structures that contain C–F bonds. In light of this we develop a picture of some of the most important features in the interaction of C–F bonds with other molecules. In particular we have concentrated on groups likely to be found in biomacromolecules to assist us in understanding how fluorinated ligands bind to receptors or enzymes.

Experimental Section

Crystals of the 1:2 complex between a monoethyl ester of (+)-*erythro*-fluorocitrate and (–)-methylbenzylamine (I) were isolated, and



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the structure was determined. They were obtained by heating the diethyl ester of (2*S*,3*S*)-fluorocitrate with excess (–)-methylbenzylamine in aqueous ethanol and allowing some evaporation of the solvent. As determined by this study, the hydrolysis occurs at a terminal carboxyl ester linkage, leaving the central carboethoxy group intact. Crystal data and details of the data collection are listed in Table I.

Table I. Crystal Data and Some Details of the Data Collection for the (–)-Methylbenzylamine Complex of Monoethyl Fluorocitrate

formula	$C_8FH_9O_7^{2-}\cdot 2C_8H_{12}N^+$
M_r	480.53
temp, °C	~–110 °C
a, Å	28.019 (8)
b, Å	6.784 (1)
c, Å	14.634 (3)
β, deg	113.95 (2)
V, Å^3	2542 (1)
space group	$C2$
Z	4
D_c g cm^{-3}	1.26
D_o, g cm^{-3}	1.25, measured in benzene–bromobenzene mixture
crystal description	0.1 × 0.15 × 0.4 mm (clear, colorless parallelepiped)
diffractometry	Syntex $P2_1$ with θ–2θ variable scan
no. of reflections measured (excluding those systematically extinct)	6062
(sin θ)/λ range, Å^{-1}	0.06–0.81
radiation	Mo Kα (λ = 0.710 69 Å) no absorption correction: no crystal deterioration during the data collection
criterion for threshold value:	$I_{obsd} = 2.33\sigma(I)$
no. of reflections below threshold value	2874
criterion for $\sigma(I)$	counting statistics
criterion for $\sigma(F)$	$\sigma(F) = (F/2)\{[\sigma^2(I)/I^2] + \delta^2\}^{1/2}$ where δ (instrumental uncertainty) = 0.0352
weights, ω, for reflections in the least-squares calculation	$\sigma^{-2}(F)$; 0 if below threshold value
function minimized in least-squares calculation:	$\Sigma\omega\|\|F_o\| - \|F_c\|\|^2$
scattering factors	ref 68–70
computer programs	ref 71 and 72

Structure Solution and Refinement. The structure was solved by direct methods with the computer program MULTAN[21] and Fourier maps. Non-hydrogen atoms were refined isotropically, and then anisotropically, by full-matrix least-squares techniques. All hydrogen atoms except those of the ethyl group were located in difference Fourier syntheses and were refined isotropically. Both carbon atoms (C(7) and C(8)) of the ethyl ester group are disordered between two principal positions; occupancy refinements indicated that these two positions were approximately equally occupied. Hydrogen atoms bonded to these atoms were placed at idealized positions and included in calculations but not refined. In the final stages of refinement, peaks corresponding to disordered C(5) carboxyl oxygens were noted in a difference Fourier synthesis. Occupancy refinement indicated that this torsional change about the C(4)–C(5) bond occurred with a population of approximately 20%. Disordered atoms O(3) and O(4) were refined only isotropically.

The final crystallographic residual for observed data is 0.049 with a weighted R of 0.058; the R for all data is 0.112. The final difference Fourier had no peak greater than 0.24 e Å^{-3}. Atomic coordinates are listed in Table II. Temperature factors and observed and calculated structure factors are given in Tables A and B, respectively, in the supplementary material.

Discussion of the Fluorocitrate Structure

The conformation of the fluorocitrate ester studied here is shown in Figure 1 and is compared with that of the diester[9] and the simple anion.[8,22] In each case the fluorocitrate is represented with the absolute configuration of the biochemically active isomer (even though its stereoisomer may have been, as is the case here, the

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Table II. Atomic Parameters of the Ethyl Ester of the Noninhibitory Isomer of Fluorocitrate and of the (−)-Methylbenzylammonium[a] Cation

atom[b]	x	y	z	B	atom[b]	x	y	z	B
F	0.38543 (3)	0.59610 (0)	0.63129 (9)	3.68 (4)	H(2C4)	0.4688 (8)	0.581 (4)	0.622 (2)	4.0 (5)
C(1)	0.34589 (6)	0.9157 (3)	0.6101 (1)	3.02 (5)	H(O7)	0.426 (1)	0.816 (5)	0.489 (2)	5.9 (8)
C(2)	0.39613 (5)	0.7949 (2)	0.6566 (1)	2.55 (5)	H(1N1)	0.1925 (9)	0.837 (4)	0.396 (2)	4.0 (5)
C(3)	0.43856 (5)	0.8604 (2)	0.6212 (1)	2.56 (5)	H(2N1)	0.2018 (8)	1.036 (4)	0.415 (2)	2.9 (4)
C(4)	0.48296 (6)	0.7063 (2)	0.6565 (2)	3.10 (5)	H(3N1)	0.244 (1)	0.898 (5)	0.460 (2)	6.5 (8)
C(5)	0.53158 (6)	0.7678 (3)	0.6400 (2)	3.18 (6)	H(C12)	0.131 (1)	0.823 (5)	0.210 (2)	6.4 (8)
C(6)	0.45979 (6)	1.0622 (3)	0.6676 (2)	2.83 (6)	H(C13)	0.060 (1)	0.955 (7)	0.082 (3)	9.0 (10)
C(7)	0.4921 (2)	1.2316 (8)	0.8253 (4)	4.9 (2)	H(C14)	0.071 (1)	1.264 (6)	0.011 (3)	8.2 (9)
C(7')	0.5108 (2)	1.2311 (8)	0.8121 (5)	4.4 (2)	H(C15)	0.148 (2)	1.428 (8)	0.071 (3)	11.0 (10)
C(8)	0.5487 (3)	1.265 (1)	0.8477 (6)	7.8 (3)	H(C16)	0.218 (1)	1.304 (7)	0.207 (3)	9.0 (10)
C(8')	0.5449 (4)	1.165 (2)	0.9118 (6)	8.2 (4)	H(C17)	0.2527 (9)	1.055 (4)	0.334 (2)	4.9 (6)
O(1)	0.35133 (5)	1.0947 (2)	0.6283 (1)	4.45 (6)	H(1C18)	0.217 (1)	0.672 (6)	0.270 (3)	7.8 (9)
O(2)	0.30442 (5)	0.8239 (2)	0.5616 (1)	3.91 (5)	H(2C18)	0.257 (1)	0.791 (6)	0.235 (3)	7.8 (9)
O(3)	0.55165 (6)	0.9309 (3)	0.6761 (2)	4.51 (6)	H(3C18)	0.275 (2)	0.726 (8)	0.341 (3)	10.0 (10)
O(4)	0.54944 (5)	0.6515 (3)	0.5944 (1)	3.84 (5)	H(1N2)	0.0635 (8)	0.875 (4)	0.593 (2)	3.9 (5)
O(5)	0.46073 (6)	1.2068 (2)	0.6212 (1)	3.97 (5)	H(2N2)	0.0638 (9)	0.718 (4)	0.526 (2)	4.8 (6)
O(6)	0.47698 (5)	1.0562 (2)	0.7663 (1)	3.79 (5)	H(3N2)	0.063 (1)	0.670 (5)	0.623 (2)	6.1 (7)
O(7)	0.41527 (4)	0.8833 (2)	0.5167 (9)	3.38 (4)	H(C20)	0.166 (1)	0.505 (6)	0.793 (3)	7.7 (9)
N(1)	0.21426 (5)	0.9287 (2)	0.4022 (1)	3.26 (5)	H(C21)	0.199 (2)	0.588 (7)	0.955 (3)	9.0 (10)
C(11)	0.18202 (8)	1.0453 (3)	0.2271 (2)	4.23 (7)	H(C22)	0.202 (2)	0.920 (9)	1.020 (4)	12.0 (10)
C(12)	0.1340 (1)	0.9512 (5)	0.1848 (2)	5.5 (1)	H(C23)	0.176 (2)	1.184 (9)	0.914 (4)	12.0 (10)
C(13)	0.0935 (1)	1.0372 (8)	0.1047 (2)	7.4 (2)	H(C24)	0.146 (1)	1.073 (6)	0.737 (3)	7.6 (9)
C(14)	0.0995 (2)	1.2120 (8)	0.0661 (2)	8.3 (2)	H(C25)	0.1401 (8)	0.602 (4)	0.628 (2)	3.3 (4)
C(15)	0.1459 (2)	1.3049 (6)	0.1060 (3)	7.9 (2)	H(1C26)	0.1430 (8)	1.005 (4)	0.575 (2)	3.6 (5)
C(16)	0.1875 (1)	1.2248 (4)	0.1871 (2)	5.8 (1)	H(2C26)	0.196 (1)	0.858 (5)	0.615 (2)	5.9 (6)
C(17)	0.22743 (7)	0.9602 (3)	0.3139 (2)	4.12 (7)	H(3C26)	0.1417 (9)	0.839 (5)	0.508 (2)	5.2 (6)
C(18)	0.2471 (1)	0.7652 (5)	0.2904 (3)	8.1 (1)	H(1C7)*	0.485	1.227	0.890	6.1
N(2)	0.07520 (5)	0.7537 (3)	0.5912 (1)	3.57 (5)	H(2C7)*	0.469	1.360	0.779	6.1
C(19)	0.15321 (7)	0.7880 (4)	0.7506 (2)	4.09 (8)	H(1C7')*	0.488	1.348	0.823	5.4
C(20)	0.1713 (1)	0.6382 (5)	0.8196 (2)	6.2 (1)	H(2C7')*	0.531	1.275	0.769	5.4
C(21)	0.1893 (1)	0.6863 (8)	0.9232 (3)	8.5 (2)	H(1C8)*	0.564	1.396	0.891	9.0
C(22)	0.1885 (2)	0.876 (1)	0.9521 (3)	9.0 (3)	H(2C8)*	0.571	1.140	0.892	9.0
C(23)	0.1704 (2)	1.0230 (7)	0.8848 (3)	8.0 (2)	H(3C8)*	0.555	1.272	0.781	9.0
C(24)	0.1529 (1)	0.9806 (4)	0.7837 (2)	5.4 (1)	H(1C8')*	0.573	1.279	0.948	9.4
C(25)	0.13357 (7)	0.7418 (3)	0.6405 (2)	3.44 (6)	H(2C8')*	0.527	1.113	0.953	9.4
C(26)	0.15544 (7)	0.8724 (4)	0.5825 (2)	4.29 (8)	H(3C8')*	0.570	1.041	0.900	9.4
H(C2)	0.4097 (7)	0.801 (4)	0.728 (2)	3.3 (5)	O(3')	0.5338 (6)	0.939 (3)	0.618 (1)	7.0 (4)
H(1C4)	0.4957 (8)	0.696 (4)	0.730 (2)	3.7 (5)	O(4')	0.5565 (6)	0.635 (3)	0.631 (1)	4.9 (4)

[a] Positional parameters, x, y, and z, expressed as fractions of cell edges, and average equivalent isotropic temperature factors in the form $\exp(-B(\sin^2\theta)/\lambda^2)$ with B values given in Å^2. Atoms were refined anisotropically except for the hydrogen atoms. The numbers in parentheses after each parameter represent the estimated standard deviation with respect to the last digits quoted. Values are given for the structure studied here. To obtain coordinates of the ethyl ester of the isomer of fluorocitrate that is synthesized from fluoroacetate by the enzyme citrate synthase and that inhibits the enzyme aconitase the coordinates x, y, and z, listed here, must be multiplied by −1. [b] An asterisk indicates a calculated position.

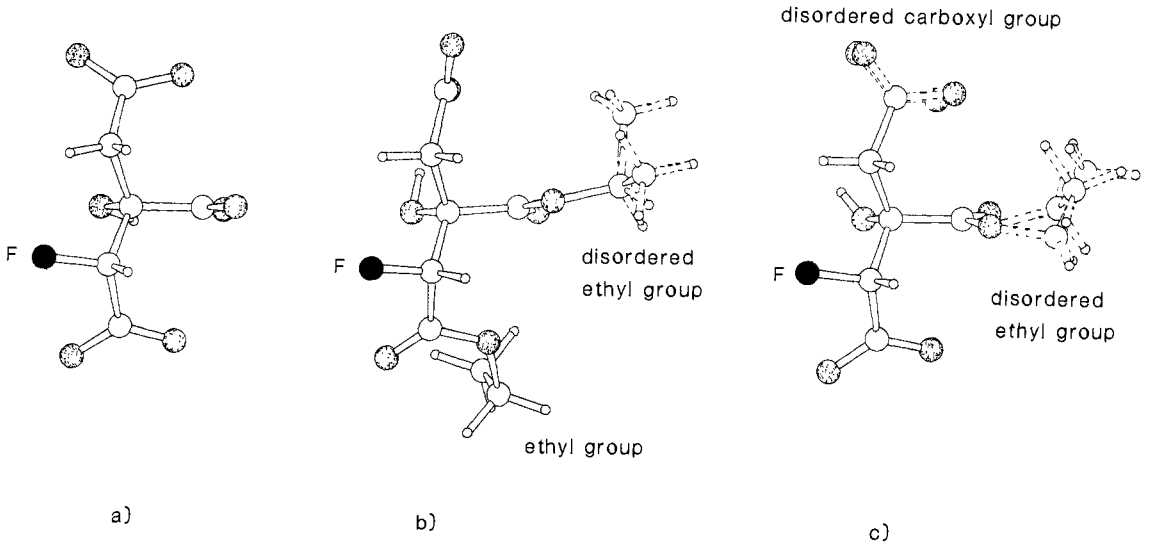

Figure 1. Conformations of the fluorocitrate anion and of the two methylbenzylamine salts of ethyl esters: (a) rubidium ammonium fluorocitrate (ref 8, 22), (b) methylbenzylamine salt of the diethyl ester of fluorocitrate (1:1) (ref 9), and (c) methylbenzylamine salt of the monoethyl ester of fluorocitrate (2:1) (this work). Note the similarities in the backbone conformation. Disordered groups are represented in Figures 1 and 2 by broken lines.

structure actually studied). The C–F bond length is 1.398 (2) Å and the F–C(2)–C(1)–O(2) and F–C(2)–C(3)–O(7) torsion angles are 2.1° and 75.2°, respectively. Thus the fluorine atom lies approximately in the plane of the α-carboxylate group. A comparison of the geometries of these three structures is given as Table C of the supplementary material.

Despite the low temperature of the data collection, it appears that the molecules pack in such a way that space is available in

Table III. Hydrogen Bonding[a]

D–H···A			D···A	D–H	H···A	angle D–H···A, deg	symmetry operation
N(1)	H(1N1)	O(1)	2.837 (2)	0.85 (2)	1.99 (3)	170	I
	H(2N1)	O(2)	2.822 (2)	0.86 (2)	2.00 (2)	159	II
		F	2.867 (1)		2.29 (1)	124	II
	H(3N1)	O(2)	2.747 (2)	0.94 (3)	1.81 (3)	174	III
N(2)	H(1N2)	O(4)	2.799 (2)	0.89 (3)	1.92 (3)	170	IV
		O(4')	2.748 (14)		1.89 (3)	163	IV
	H(2N2)	O(5)	2.870 (2)	0.91 (3)	1.98 (3)	166	I
	H(3N2)	O(3)	2.728 (2)	0.88 (3)	1.88 (3)	160	V
		O(3')	2.536 (15)		1.76 (4)	145	V
O(7)	H(O7)	O(4)	2.719 (2)	0.75 (3)	1.97 (3)	175	VI
		O(4')	3.081 (15)		2.35 (3)	167	VI
		O(3)	3.323 (2)		2.84 (3)	124	VI
		O(3')	2.896 (13)		2.43 (3)	122	VI

occupancies		distances		symmetry	
C7, C7'	50%	C7–C7'	0.629 (5)	I	$1/2 - x, y - 1/2, 1 - z$
C8, C8'	50%	C8-C8'	1.20 (1)	II	$1/2 - x, 1/2 + y, 1 - z$
O3', O4'	20%			III	x, y, z
				IV	$x - 1/2, 1/2 + y, z$
				V	$x - 1/2, y - 1/2, z$
				VI	$1 - x, y, 1 - z$

[a] Distances are given in Å and angles in degrees.

the crystal to accommodate the observed disorders. For the carboxyl group at C(5), there is 80% and 20% occupancy, respectively for the unprimed and primed groups, with the internal hydrogen bond from O(7) involving either O(4) or O(3'). For the ethyl group each position is equally occupied. There is no apparent specific interaction with the ester oxygen atom O(6).

In view of the fact that the formation of O–H···F hydrogen bonds has been the subject of much theoretical discussion, we were interested in the hydrogen bonding observed in the structure described here. The hydrogen atom H(2N1) of one benzylamine cation forms a hydrogen bond to O(2), as shown in Figure 2 and listed in Table III, with an O··H distance of 2.00 (2) Å. This hydrogen atom is also near the fluorine atom with a F··H distance of 2.29 (1) Å. Thus the hydrogen bonding appears to be of the type N–H··O, but the fluorine atom seems to interact with the N–H group as well, although less successfully. This finding prompted us to analyze other C–F-containing compounds to determine if this is a common type of phenomenon.

Analysis of the Crystal Structures of Compounds with C–F Bonds

We have now determined the structure of several fluorinated carboxylate salts and have noticed some recurrent features in the environment of the C–F bond. These suggest that this group may be involved in intermolecular interactions that may be important in its biological action. Specifically we have determined two structures where the covalently bonded fluorine appears to act as a ligand to alkali metals[7,8] and two structures (Figure 2) that suggest that C–F bonds can act as weak proton acceptors in forming hydrogen bonds.[9]

Although one or other of these interactions is consistently present, we have so far been reluctant to emphasize them because of the small number of structures containing them. Until recently, a search of the crystallographic literature for confirmatory examples (or counterexamples) has been extremely difficult, often because the original authors have not specifically described the coordination of the fluorine. The availability of the Cambridge Crystallographic Data Files[23] and associated programs now makes it possible to search rapidly and reliably for any desired molecular fragment and to tabulate and analyze its geometry, including intermolecular contacts. We and others[24-28] have previously described how it is possible to deduce intermolecular interactions by surveying the environment of a given group in a large number of different crystal structures; here we apply this method to the C–F bond.

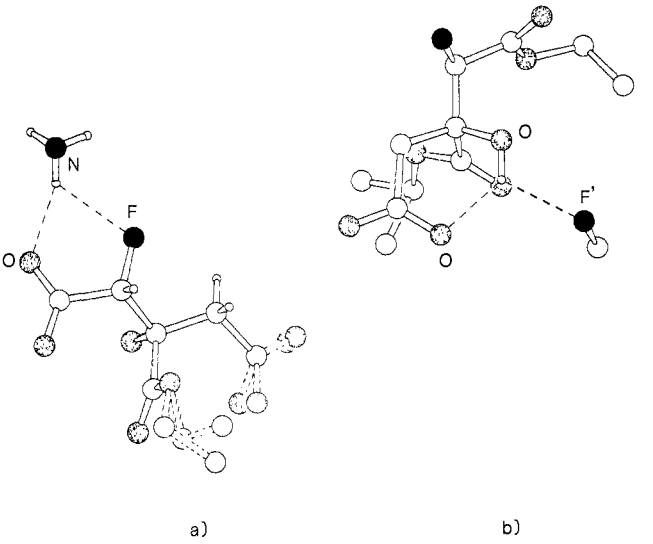

Figure 2. Partial fluorine participation in hydrogen bonding in two fluorocitrate esters: (a) fluorocitrate monoester (this work) and (b) fluorocitrate diester (ref 9).

The different ways in which replacement of C–H by C–F *might* affect intermolecular interactions are now considered.

(1) Coordination to a Metal. Although halide ions are very common ligands, covalently bound halogen (C–X, X = halogen) is not normally considered a good donor.[29] If this effect is present

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(25) (a) Rosenfield, R. E., Jr.; Parthasarathy, R.; Dunitz, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 4860. (b) Guru Row, T. N.; Parthasarathy, R. *Ibid.* **1981**, *103*, 477.

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(27) (a) Britton, D.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 1068. (b) Britton, D.; Dunitz, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 2971.

(28) Einspahr, H.; Bugg, C. E. *Acta Crystallogr., Sect. B*, **1980**, *B36*, 264.

(29) A preliminary report has recently been made of a very interesting structure,[30] $[IrH_2(C_6H_4I_2)L_2]BF_4$, where 1,2-diiodobenzene seems to act as a bidentate ligand to the iridium ion (L = large ligand).

we expect it to be strongest when X = F because of the large polarity of the C–F bond. Fluoride is a hard base,[31,32] and we might expect C–F to be hard also, so that the strongest coordination should be to hard acids. Both our structure determinations are of alkali metal salts of fluoroacids where the M··F distances are impressively short (Na··F–C fluoropyruvate[7] = 2.470 (1) Å and Rb··F–C in fluorocitrate[22] = 2.979 (5) and 3.095 (4) Å). Our criteria for assessing the strength of such interactions are given later.

(2) Hydrogen Bonding. As mentioned already, despite the polarity of the C–F bond, its ability to act as a proton acceptor is unclear. At first sight, since data on about 260 structures with C–F bonds are available for analysis from the Cambridge Crystallographic Data File, this seems surprising. However, the packing in a molecular crystal is a compromise among many different intermolecular forces and is likely to be most influenced by the strongest. Most proton donors (–OH, –NHR, $-NH_2$) are also proton acceptors and, if they are better acceptors than C–F, will generally be used as acceptors in preference to the fluorine. Besides their greater proton-accepting ability these groups can also form chains in which additional energy is derived from the cooperative effect.[33,34] Fluorine in a C–F bond can only act as a proton acceptor and hence could interrupt a cooperative sequence of hydrogen bonds.

Thus even though C–F··H–X interactions may be appreciably attractive, they will normally only be found in crystals if they can coexist in a packing scheme predominantly determined by the stronger interactions. This is a generalization, of course, and is conceptually based on the approximation of separable intermolecular interactions (e.g., the atom–atom potential approach[35]). It is exemplified by the crystal structure of fluoroacetic acid[36] where, although packing schemes involving C–OH··F–C may be possible, the (presumably much stronger) standard carboxylic acid dimer is in fact found. However, in structures with an excess of proton donors over acceptors (e.g., involving RNH_3^+, NH_4^+, etc.), or where bifurcated bonds are efficiently formed, we might expect CF···H bonding to be observed in the crystal packing.

(3) Dipolar Interactions. With its high dipole moment (1.81 D in CH_3–F)[37] the C–F bond may form important dipole–dipole interactions in crystals. Thus in fluoroacetic acid the C–F bond lies, in an antiparallel manner, over a C–F bond in another molecule related by a center of symmetry such that the distance between the centers of the bonds is 3.25 Å and the F···F distance is 3.17 Å. This type of interaction presumably is energetically important but is a difficult one to investigate in a quantitative manner.

(4) van der Waals Interactions. Relative to effects 1–3 we expect these to be weaker and essentially isotropic around much of the fluorine atom. We do not expect them to be obviously manifested by particular geometrical arrangements. At present the most we may hope to do is to find the effective van der Waals envelope of the bound C–F group.

(5) Secondary Interactions. Many of the heavier nonmetallic elements show strong "secondary" interactions with neighboring nucleophiles. Thus the pattern of nucleophiles around C–I and C–S bonds is strongly anisotropic[24,25] and can be represented by resonance contributors such as C–I^-–O^+< that involve a formal decet around the central atom. These are important factors in intermolecular interactions and may be important in the transport and action of thyroid hormones.[38] Because of the high dipole of C–F and the very high energy of decet resonance structures

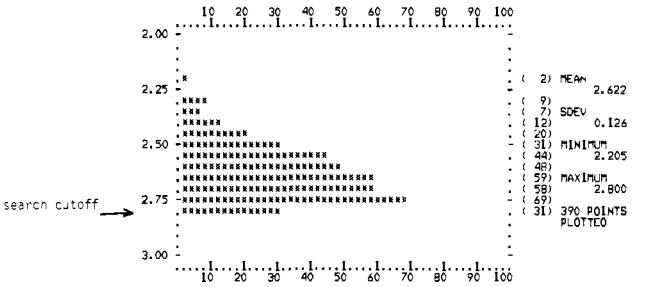

Figure 3. Histogram (produced by GEOSTAT) of r (F··H) (r < 2.8 Å) in CF··H contacts. (The bars represent points lying within ±0.5 unit from the internal values: e.g., there are 69 points in the range 2.725–2.774.) This diagram shows a minimum of ~2.2–2.3 Å for F··H distances.

for fluorine we do not expect this effect, which is found in heavier elements, to be relevant to our study of fluorine compounds, and this is confirmed below.

(6) Inductive and Other Effects on Neighboring Groups. The very strong inductive effect of fluorine may influence the properties of nearby groups in the molecule and hence their ability to interact with other molecules. Thus 2-fluoroethanol is more acidic than ethanol, and this has been suggested as one reason why 9α-fluoro corticosteroids often show enhanced activity.[20] It was also suggested[20] there that the fluorine might, through "conformational electronic transmission", affect quite distant parts of the steroid molecule (e.g., the charges on the 4-en-3-one group). These effects will be highly dependent on the chemical nature of the neighborhood of the C–F bond and cannot be examined in a general study.

Use of the Cambridge Files for Studying Intermolecular Interactions

The use of the Cambridge Crystallographic Data Files to study interactions of molecules is fairly new, and a brief outline of the method is provided here. For this study we used the January 1982 version of the Cambridge Files, the CONNSER[23] search program, our own modification of RETRIEVE,[39] and GEOSTAT[40] (our enhancement of the GEOM78 program, which includes extra features for molecular geometry and several statistical routines). When considering intermolecular geometry, we can (1a) calculate INTERmolecular distances between a given pair of atom types in different residues or symmetry-related molecules; (1b) using the EXT[41] and LAB[40] option, investigate the chemical environment of both atoms of the pair; (1c) select, using TESTs in FRAG or SELECT, only those intermolecular contacts that fulfill user-defined geometrical criteria; (1d) if necessary, using the EXact option

(30) Crabtree, R. H. Abstracts, 65th Canadian Chemical Conference, Toronto, Canada, May 30–June 2, 1982, Abstract No. IN5-1.
(31) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.
(32) Pearson, R. G. *Science (Washington, D.C.)* **1966**, *151*, 172.
(33) Del Bene, J. E.; Pople, J. A. *J. Chem. Phys.* **1970**, *52*, 4858.
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(38) Cody, V. *Endocr. Rev.* **1980**, *1*, 140.

(39) RETRIEVE has been rewritten by R. K. Stodola (ICR) in Fortran 77 and adapted to use indexed sequential files on disk for fast retrieval of BIB, CON, and DAT entries. In addition we have added a routine that allows preliminary screening of the DAT file entries. Any or all of the following entries can be rejected: those with no atomic coordinates; without H atomic coordinates; with ERRor flag (Cambridge); with unlocated atoms; with disorder flags; with RFActor or AS (the esd's of a typical C–C bond) greater than a certain value; and with one or more heavy atoms (defined by atomic number). The program can also format/unformat files, update them or remove entries with specified REFCODEs. AND, OR, and NOT operations can thus be carried out on two files of REFCODEs. We intend to make this program available to the CCDC for distribution to National Centers. Capital letters signify programs or keywords available in CONNSER/BIBSER/GEOM/GEOSTAT/RETRIEVE.

(40) GEOSTAT is a modification and extension (Raftery, J.; Murray-Rust, P., to be published) of GEOM 78 to allow for more accurate fragment definition (including cyclic/acyclic bonds, exact coordination of atoms, testing of chirality), approximate identification of hybridization types of (first row) elements and bond order, calculation of statistics for C–H bond lengths, identification and LABelling of substituents on a fragment, TRAnsformation of parameters by Fortran-like instruction cards, SELection of fragments on any geometrical or derived parameters, rejection of outlying fragments by iterative or noniterative CHI-square tests, HISTograms and SCATtergrams of parameters, FACtor analysis of selected parameters or of Cartesian coordinates, OUTPUT of COORDINATES with respect to INErtial axes or with least-squares fitting to a given geometry, immediate output of BIBLiographic information for codes that survive the FRAGment matching, SELECT, and CHI-square tests. We intend to make this program (in Fortran 77) available to the CCDC for distribution to national centers.

Table IV. Coordination Geometries of Cations with One or More Organofluorine Ligands and the Bond-Valence Sums[a]

REFCODE	M	R(M-O)	R(M-F)	s(M–O)	s(M-F)	Σs
FPYRVH	Na^+	2.426		0.18		
		2.681		0.12		
		2.306		0.22		
		2.611		0.13		
		2.385		0.19		
		2.407		0.18		
			2.470		0.13	
				1.02	0.13	1.15
NAFLAC20	Na^+	2.430		0.18		
		2.503		0.16		
		2.409		0.18		
		2.607		0.13		
		2.351		0.20		
		2.988		0.07		
			2.562		0.11	
				0.92	0.11	1.03
KHDFMA	K^+	2.896		0.11		
		2.951		0.09		
		2.885		0.12		
		2.951		0.09		
		2.885		0.12		
		2.896		0.11		
		2.963		0.09		
		2.965		0.09		
			3.144		0.05	
			3.144		0.05	
				0.82	0.10	0.92
KHDFMB	K^+	2.898		0.11		
		2.898		0.11		
		2.901		0.11		
		2.901		0.11		
		2.784		0.16		
		2.784		0.16		
			3.213		0.04	
			3.213		0.04	
			2.992		0.08	
			2.992		0.08	
				0.76	0.24	1.00
KTFPHT	K^+	2.747		0.18		
		2.772		0.17		
		2.937		0.10		
		2.735		0.19		
		2.702		0.21		
		2.842		0.13		
			2.871		0.09	
				0.98	0.09	1.07
FLUCIT10	Rb^+	2.826		0.18		
		2.862		0.17		
		3.155		0.08		
		3.073		0.10		
		2.902		0.15		
		2.975		0.13		
		3.348		0.06		
			3.095		0.07	
			2.979		0.09	
				0.87	0.16	1.03
RBFORM	Rb^+	2.874		0.16		
		2.981		0.13		
		3.003		0.12		
		3.080		0.10		
		3.099		0.10		
		2.934		0.14		
		3.178		0.08		
			3.215		0.05	
			2.880		0.11	
				0.83	0.16	0.99

[a] For each compound is given the cation (M); the coordination distances of oxygen R(M–O); the coordinate distances of fluorine R(M–F); the bond valences s(M-O) with their sum; the bond valences s(M–F) and sum and the total bond valence sum (Σs(M-O) + Σs(M–F)). The formula for the bond valences is given by $s = (R/R_0)^{-N}$ from ref 49 with constants R_0 = 1.622, 2.276, and 2.220 Å and N = 4.290, 9.1, and 7.0 for Na^+, K^+ and Rb^+, respectively, for oxygen coordination (R_0 = 1.539 Å, N = 4.29 for F^- coordination to Na^+).

in GEOSTAT, select groups that make, say, exactly one (two, etc.) contact(s) of a given type; *or* (2) calculate, using COORD, the INTRA + INTERmolecular contacts that a given atom makes within a specified radius; (3) save coordinates for data sets that show (or do not show) a given intermolecular geometry and transmit them to an interactive graphics terminal (in our case a Vector General VG3 running programs DOCK and VIEW[42]). All programs were run on a VAX 11/780 since we regard interactive operation as almost essential for this type of study.

Results of the Data File Analysis of Interatomic Contacts Involving C–F Bonds

We first retrieved *all* data file entries for compounds with at least one *isolated* C–F bond (i.e., not part of a CF_2 or CF_3 group) and where coordinates were available. Then, to get a picture of the shortest contacts that might occur, we identified all INTERmolecular C–F··X contacts (EXCLuding hydrogen atoms). The only contacts less than about 2.7 Å were to Na^+ (see below). At and above 2.8 Å we find, inter alia, C, O, N, F, and the larger alkali metals. To assist with identifying hydrogen bonds (if any) of the type C–F··H–X, we also calculated INTERmolecular contacts (INCLuding C, H, and F) for C–F··H for which a histogram is given (Figure 3). The apparent minimum F···H contact appears to be about 2.3 Å (but it must be remembered that because almost all observations come from X-ray diffraction, this might be in error by up to 0.1 Å). The shortest C–F··H–X contacts all occur when X = C.

The analysis was then split into three parts.

(a) Contacts to Metals. Many of the metals in organofluorine compounds are in low oxidation states (and do not seem to form short M···F contacts). Of the more ionic complexes only alkali metals seem to have been studied to any extent. It is worth noting that no complexes of first row M(II) and M(III) ions with monofluorinated carboxylic acids have been reported; their structures should be very interesting.

On the data file we found seven compounds[43] (with reported coordinates) with both C–F bonds and alkali metals: ammonium rubidium hydrogen fluorocitrate (FLUCIT10),[22] sodium fluoropyruvate (FPYRVH),[7] rubidium fluoroorotate (RBFORM),[44]

(41) EXT, available in GEOM 78 but not documented, builds a connectivity array relating to several molecules and thus allows analysis of fragments where atoms belong to different molecules.

(42) Programs DOCK and VIEW were written by H. L. Carrell, W. Wood, and N. Badler at the Institute for Cancer Research, Philadelphia, PA 19111.

(43) The six-letter REFCODES are the Cambridge Crystallographic Data Center (CCDC) identification codes for structures. An occasional two-digit suffix indicates one of two or more references to the same compound.

sodium fluoroacetate (NAFLAC20),[45] dipotassium tetrafluorophthalate (KTFPHT),[46] potassium hydrogen difluoromaleate (KHDFMA),[47] and potassium hydrogen difluorofumarate (KHDFMB).[47] There are three geometrical criteria that we can use for asking whether a C–F··M contact is important: the length of F··M; the C–F··M angle; and the coordination geometry around the metal. *All* seven structures have one or more M··F contacts similar in length to M^+··F^- contacts in ionic compounds (Table IV). In six of these structures the C–F bond can be thought of as part of a chelate ring (II), while only in KTFPHT is the C–F

II

group a monodentate ligand. (This may be because the two CO_2^- groups in the $C_6F_4(CO_2^-)_2$ dianion are at 90° to the benzene ring and hence the ligand has a poor chelating geometry.) Of the nonalkali elements, only (*o*-$(FC_6H_4)N(HgPh)SO_2Ph$) (PHGFAN), an organomercurial, provides a contact less than 3.2 Å.[48] In this the fluorine atom of a neighboring molecule makes an almost perpendicular approach of 2.96 Å to the (linear) C–Hg–N system.

Further support for significance of the C–F··M contact comes from an analysis of the rest of the M coordination geometry. For ionic compounds a general rule holds that, despite widely varying coordination geometries, the sum of the bond valences to the central ion is roughly constant. Taking the Brown–Shannon formula[49] for bond valence ($S = (R/R_0)^{-N}$) and their values for R_0 and N [for (Na, K, Rb)–(O, F)] we have calculated the bond valence sums[49-51] for the cations in the five compounds (Table IV). Since no values exist for covalently bound fluorine we have approximated this by using values for F^-. The bond valence sum, which should be near unity for an alkali metal cation, comes closer to this value, in general, when fluorine is included. Also, in several cases there are M··O distances considerably longer than the M···F distances. Six of the structures have C–F··M angles in the range 108–120°, consistent with bonding through conventional sp^3 lone pairs on the fluorine. In KTFPHT, which is a monodentate ligand, this angle is 161°.

Although the data set is very limited we feel there is strong evidence that C–F bonds coordinate to alkali metals. The interactions often seem to be as strong as many of the M··O bonds in these compounds. After the data on the January 1982 Cambridge data base had been analyzed we searched the very recent literature (i.e., 1981 onward) for fluorinated compounds. Although this could not be analyzed automatically we retrieved one structure of a fluorinated compound with a metal, potassium fluoromalonate,[52] and were gratified to see that it contains a K··F contact of 2.80 Å, the second shortest in a coordination sphere of seven oxygen atoms and one fluorine atom.

INTRAmolecular contacts are much less useful in evaluating the importance of M··F interactions because of the constraints of the covalent bonds. There is, however, one structure[53] with an M··F contact less than 3 Å (PFTPCO, which contains Co–S–C_6F_5)[52] where C–F··Co^{II} = 2.445 Å. The original authors felt that this was due to torsional constraints about the S–C bond rather than to an M··F attractive force. On examination of the

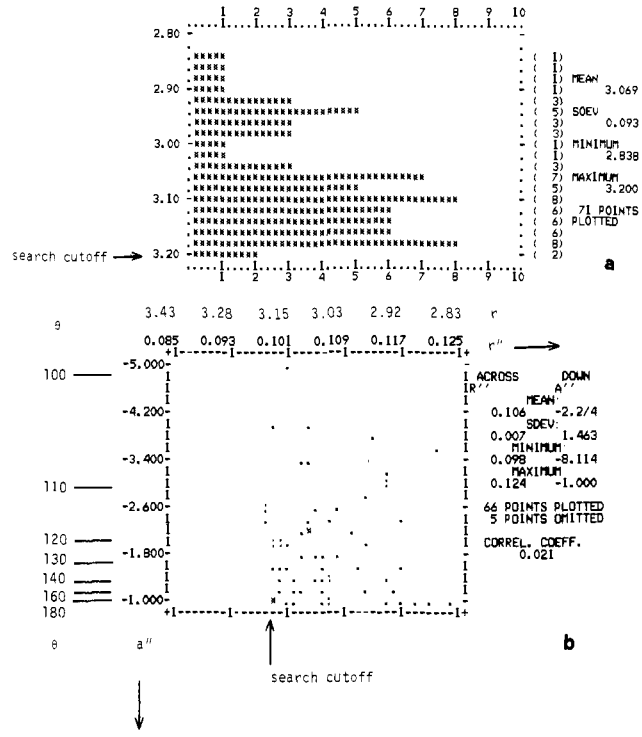

Figure 4. (a) Histogram (GEOSTAT) of r(F··O) in C–F··O contacts <3.2 Å. The literature references on C–F··O and C–F··N contacts are given in supplementary Tables D and E, respectively. No correlation of the value of r(F··O) with the presence or absence of hydrogen on the oxygen atom or with the sp^2 or sp^3 nature of the carbon atom attached to the oxygen atom could be made. (b) Dependence of r(CF··O) on angle θ(C–F··O). The scattergram (GEOSTAT) uses the same scale conventions as the histogram (Figure 3); three or more points falling in the same cell are represented by *. A uniform density of points in three-dimensional space around a polar axis transforms to uniform density on a two-dimensional scattergram of $r'' = 1/r^2$ against $a'' = 1/\cos\theta$ (see ref 26). The scattergram is linear in these quantities with cutoffs at $r'' = 0.098$ (r = 3.2 Å) and $a'' = -5.0$ ($\theta = \sim 95°$). In the region $180 > \theta > 110$ and $3.2 > r > 1.94$ the distribution can be seen to be essentially isotropic.

geometry around the cobalt we feel that the fluorine is an important part of this coordination sphere.

(b) C–F··O and C–F··N Contacts. In deciding whether F··(O,N) intermolecular contacts involve hydrogen bonding it is useful to know the distribution of all F··(O,N) contacts. All entries were searched for C–F··O contacts <3.2 Å; 71 such contacts were found in 37 data entries. A histogram (Figure 4a) shows that these have a minimum value at about 2.85 Å, which may be compared with the conventional sum of the van der Waals radii, 2.75 Å,[54,55] As Figure 4b shows, the distribution of O contacts to F is of roughly uniform density per unit volume beyond this minimum, with no evidence of anisotropy (preferential angle of approach). A similar analysis of the entries with C–F and nitrogen showed that nine CF··N contacts less than 3.2 Å occurred in eight entries. The minimum distance was about 2.95–3.00 Å and, again, there was no evidence of anisotropy. These results suggest that there is no C–F··O or C–F··N interaction analogous to the nucleophilic C–X··O (X = Cl, Br, I) ones we have reported earlier.[24]

(c) C–F··H(O,N) Hydrogen Bonds. Three nonindependent geometrical tests are normally used, whether an X··HY contact is a hydrogen bond or not, to determine the shortness of X··H, the shortness of the X··Y distance, and the linearity of the X··H–Y fragment. Unfortunately the weaker the interaction, the harder these criteria are to apply. If the minimum van der Waals F··H contact is taken as ~2.3 Å (see above) and the O–H distance (as *measured* by X-rays) is ~0.9 Å, then a linear F··H–O contact

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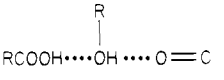
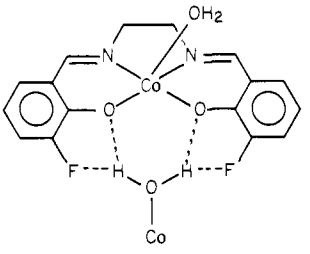
with F··O = 3.2 Å *could* represent a van der Waals contact. Meaningful hydrogen bonds would be expected to show a closer O··F distance. Of the 20 shortest C–F··O contacts described in (b) in only one was the oxygen atom part of an O–H group.

Of the total of 71 C–F··O contacts <3.2 Å derived from the data files in (b), the 20 that involved an O–H group were then examined on the interactive graphics system. For all except one of these cases the authors had reported hydrogen atom positions. In only one case (9α-fluorocortisol[18,19]) was there a classic isolated C–F··H–O contact (F··O = 3.00 Å). In most cases the OH group formed nearly linear contacts with neighboring oxygen atoms and O–H··F angles were around 90°. For example, carboxylic acids formed the well-known dimers (FACETC01,[36] FMALON20,[56] and FPYRVH)[7] or formed chains, e.g.

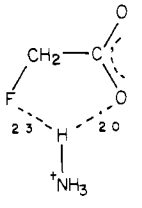




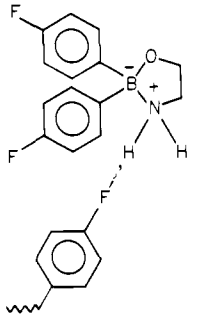
AFSACO

In one case (AFSACO[57]), however, there was evidence for a bifurcated arrangement with the proton effectively chelated. Clearly, therefore, hydroxyl and other groups in these compounds are stronger proton acceptors than C–F. In general there will usually be enough other stronger acceptors around so that there would be a loss of packing energy in forming C–F··OH bonds. Only in the case of bifurcated bonds can the fluorine be involved without seriously diminishing other OH··O bonds. We suggest that CF··HO bonds are energetically favorable, but that other stronger interactions are usually formed in preference.

An examination of the interaction of C–F with NH groups may be more rewarding, since protonated groups (e.g., NH_4^+, RNH_3^+, etc.) are good proton donors and cannot act as acceptors. The eight entries with C–F··N contacts <3.2 Å were examined on the computer graphics system. Two of these (AMMFAC[58] (NH_4^+-$FCH_2CO_2^-$) and FPBXZL[59]) contained shortish, fairly linear



AMMFAC



FPBXZL

N–H··F arrangements. In AMMFAC, the angle NH··F = 141°, N··F = 3.13 Å, and F··H = 2.3 Å. There is a chelate-like arrangement of the fluoroacetate group around this NH bond so that there is a bifurcated bond with N··O = 2.89 Å, H··O = 2.0 Å, and the angle N–H··O = 143°. In FPBXZL the situation is similar, with N–H··F = 155°, N··F 3.01 = Å, and H··F = 2.36 Å. (A fourth structure UFACCU10[60] contains a coordinated urea group with a short N···F contact of 3.01 Å; but the N–H··F angles (102°, 90°) and distances (2.6, 2.8 Å) are not very favorable.) To these structures we can add the present study. These all show N–H··F contacts that resemble the geometry in AMMFAC.

Although we have found relatively few structures with possible (O, N)–N··F interactions, there are enough for us to propose that C–F can act as a weak proton acceptor. Where there is an excess of proton donors over acceptors it seems that CF··HX hydrogen bonds, albeit very weak ones, will be formed. With so few structures it is difficult to estimate the F··H distances (in F··H–O or F··H–N interactions) corresponding to the potential energy minimum, but we suggest that they are in the range 2.3–2.4 Å (comparable to the sum of the van der Waals radii, which lies between 2.35 and 2.55 Å).

Conclusions

We believe that the C–F bond is capable of significant, if not prominent, interactions with both alkali metal cations and proton donors. These interactions seem to be similar in character to, though usually weaker than, the corresponding ones involving C–O– and C–N< groups. Presumably other cations, particularly hard acids such as alkaline earth or some first-row transition-metal ions, can also form complexes. (The only transition-metal complexes of fluoroalkanecarboxylic acids are between Cu(II) and fluoroacetate (FACCUQ (+ quinoline)[61] and UFACCU10[60] (+ urea)), which contain the well-known dimeric copper acetate structure. The quinoline and urea, respectively, fill the sixth coordination position and are presumably stronger ligands than C–F.) By careful choice of solvent (e.g., one with poor coordinating power) it might be possible to form fluorocarboxylate complexes of, say, Fe(III). Our general conclusions are supported by the results of theoretical studies.[62,63]

A comparison of the above results with those for B–F bonds is useful. These form well-authenticated B–F··M interactions (particularly in BF_4^- complexes) where the length of the M··F contact can vary considerably, sometimes playing an important role in the coordination sphere of transition metals. Thus in ENFBNI[64] ($[Ni(en)_2(aq)\cdot BF_4]BF_4$), Ni··$FBF_3$ = 2.12 Å, while in TTCDNI[65] ($[Ni(1,4,8,11\text{-tetrathiacyclotetradecane})](BF_4)_2$), Ni··$FBF_3$ = 2.89 Å. A classic example of a B–F··HN hydrogen bond (3.01 ± 0.03 Å) is found in H_3NBF_3.[66] We therefore carried out a similar survey of the environment of B–F bonds and found the same type of interactions as for C–F, but, as might be expected from the greater bond polarity, occurring with greater frequency.

The unusual biological activity of certain fluorinated compounds may be due to several causes not yet understood. The high strength of the C–F bond may hinder metabolism, thus increasing the effective lifetime of the active molecule. In some cases the C–F bond (particularly when activated) may undergo fission, leaving a covalently bound ligand. In a number of cases, however, it seems

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that binding (presumably initially reversible) to macromolecules is important, resulting in, for instance, triggering of a receptor or inhibition of an enzyme (as happens when fluorocitrate is added to the aconitase system). Geometrical constraints for ligand/macromolecule interactions are presumably much more stringent than the constraints on the crystal packing of small molecules, so that the weaker C-F··X interactions may become very significant.

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Supplementary Material Available: Tables containing atomic parameters and anisotropic temperature factors, observed and calculated structure factors, fluorocitrate dimensions, literature on C-F··O contacts, and literature on C-F··N contacts (33 pages). Ordering information is given on any current masthead page.

Regioselective Functionalization of Bicyclic Piperazinedione Bridgehead Carbanions

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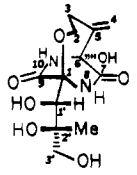
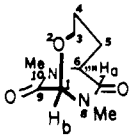
Abstract: Generation of the bridgehead carbanions of bicyclic piperazinediones **2** and **3** with LDA in THF at −78 °C (kinetic conditions) followed by quenching with various electrophiles results in mixtures of the two monosubstitution products **12** and **13** with relatively poor regiochemical control. Addition of HMPA to **2** and **3** followed by LDA treatment and addition of an electrophile significantly favors functionalization of the carbanion adjacent to the bridging methylene (product **12**). HMPA facilitates the interconversion of bridgehead anions **15** and **16** to produce a preponderance of the thermodynamically more stable carbanion **15**. This methodology provides a highly regioselective and efficient synthesis of the unsymmetrically substituted bicyclic piperazinediones.

As part of a program directed toward the total synthesis of the novel antibiotic bicyclomycin[1,2] (**1**) and the synthesis of analogues,



1



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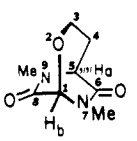


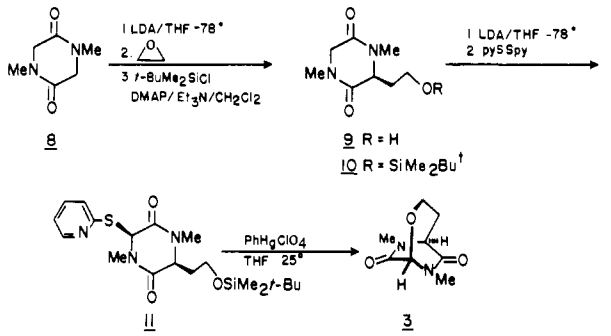
3

we have had the opportunity to study the interesting behavior of the bridgehead carbanions derived from bicyclic piperazinediones **2**[3] and **3**.

Our primary objectives in this area were to develop a rapid and efficient entry to the general bicyclomycin ring system with an inherently high degree of flexibility to allow the preparation of a wide variety of bicyclomycin analogues that would be valuable in elucidating the apparently unique mechanism of action of the natural product.

Several synthetic approaches to the bicyclomycin ring system have appeared,[3,4] yet no total synthesis has been achieved. Recently we reported[5] a short and efficient synthesis of bicyclic piperazinedione **2** and the regio- and stereocontrolled conversion of **2** into *N,N'*-dimethyl-4-desmethylenebicyclomycin via functionalization of the corresponding bridgehead carbanions. We have examined the reactivity of the bridgehead carbanions derived from model compounds **2** and **3** for several reasons. First, we

Scheme I



8 **9** R = H **10** R = $SiMe_2Bu^t$ **11** **3**

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