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REACTIVITY OF FLUORINE IN FLUORINATED SUCCINIC ESTERS

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SUMMARY

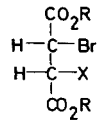
In basic medium, dimethyl and diethyl *erythro-* and *threo*-α-bromo-α′-fluorosuccinate eliminate hydrogen fluoride considerably faster than hydrogen bromide. The reaction rate depends slightly on the concentration of the ester, and strongly on the concentration of the base (acetate). Methyl esters react considerably faster than ethyl esters, *threo* isomers slightly faster than the *erythro* isomers. The negligible difference in the rates of elimination of hydrogen fluoride from the two diastereomeric esters contrasts sharply with the large difference in the rates of elimination of hydrogen bromide from the two corresponding dibromo esters, *meso-* and DL-α,α′-dibromosuccinates. The elimination of hydrogen fluoride from the bromofluoro esters is evidently influenced not only by steric factors but also by attraction between hydrogen and fluorine (possibly hydrogen bonding) which can account for the considerable proportion of *cis* elimination in the case of the *erythro* isomer.

INTRODUCTION

In an attempt to synthesize α′-fluoroaspartic acid, Bose, Das and Funke[1] treated dimethyl *threo*-α-bromo-α′-fluorosuccinate with potassium phthalimide. However, instead of the expected dimethyl α-fluoro-α′-phthalimidosuccinate, a mixture of dimethyl fluoro- and bromo-maleates and -fumarates was obtained. Thus, instead of the expected nucleophilic displacement of bromine, elimination took place with preferential removal of hydrogen fluoride to hydrogen bromide in a ratio of 3 : 2. This finding was somewhat surprising, and it was of interest to find out whether a weaker base than potassium phthalimide would be more selective and would possibly lead to the desirable displacement of bromine rather than to the elimination of hydrogen fluoride.

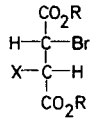
PRESENT WORK

Experiments with sodium azide and dimethyl *erythro*-α-bromo-α′-fluorosuccinate (Ib) showed that displacement indeed took place in addition to the elimination. However, it was again exclusively fluorine which was either replaced by the azido group, or eliminated as hydrogen fluoride. As a result, a mixture of 50% of dimethyl azidomaleate (IIIa) (or dimethyl azidofumarate) (IVa) with 40% of dimethyl bromofumarate (IVb) and 10% dimethyl bromomaleate (IIIb) was obtained. The same unsaturated azido ester ((IIIa) or (IVa)) resulted from a reaction of sodium azide with dimethyl DL-α, α′-dibromosuccinate (IId) with sodium azide (Scheme 1).



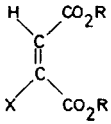
X = F, R = H CH_3 C_2H_5
(Ia) (Ib) (Ic)

X = Br, R = CH_3 C_2H_5
(Id) (Ie)



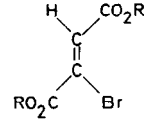
X = F, R = H CH_3 C_2H_5
(IIa) (IIb) (IIc)

X = Br, R = CH_3 C_2H_5
(IId) (IIe)



X = N_3, R = CH_3 (IIIa)

X = Br, R = CH_3 C_2H_5
(IIIb) (IIIc)



X = N_3, R = CH_3 (IVa)

X = Br, R = CH_3 C_2H_5
(IVb) (IVc)

This rather surprising higher reactivity of fluorine as compared to bromine towards both nucleophilic displacement and elimination was worthy of further study. Experiments using free *erythro*- and *threo*-α-bromo-α′-fluorosuccinic acid ((Ia), (IIa)) could not be carried out because they were not available in a pure enough form. In alkaline hydrolysis of the corresponding esters with potassium hydroxide both bromine and fluorine were eliminated at 25° within 30 min. When insufficient amounts of potassium hydroxide were used, elimination of hydrogen fluoride was approximately twice as fast as that of hydrogen bromide, and both reactions took place prior to the hydrolysis of the ester groups. Even so gentle a base as silver oxide eliminated hydrogen fluoride almost quantitatively after 90 h at 35°.

Acidic hydrolysis of dimethyl *erythro*- and *threo*-α-bromo-α′-fluorosuccinate ((Ib), (IIb)) was carried out using 5% sulfuric acid. However the products,

erythro- and *threo*-α-bromo-α′-fluorosuccinic acid ((Ia), (IIa)), were isolated in low yields, and could not be obtained analytically pure.

Kinetic measurements of the rates of elimination of hydrogen fluoride and hydrogen bromide were therefore carried out with the esters, dimethyl *erythro-* and *threo*-α-bromo-α′-fluorosuccinate ((Ib) and (IIb) respectively) and diethyl *erythro-* and *threo*-α-bromo-α′-fluorosuccinate ((Ic) and (IIc) respectively). Potassium acetate was used as a base because it is strong enough to effect the elimination, and, at the same time, does not affect to an appreciable extent the ester groups. In addition to the elimination of hydrogen fluoride, elimination of hydrogen bromide from the above esters and from diethyl *meso-* and DL-α,α′-dibromosuccinate was also followed. The results are shown in Figures 1–5 and Table 2 which appear later in this paper.

All the esters subjected to kinetic experiments gave blue solutions from which a dark blue substance was isolated by evaporation *in vacuo* and extraction with dichloromethane or carbon tetrachloride. This liquid was separated by vacuum distillation, or better still by chromatography on silica gel, into esters of bromomaleic (IIIc) or bromofumaric (IVc) acid or a mixture of both, and a small amount of a dark blue non-crystalline solid soluble both in water and in organic solvents. Whereas the unsaturated esters were readily identified (Table 1) by means of NMR spectroscopy, where the vinylic hydrogen shows a signal at $\delta = 7.38$ ppm (bromomaleate) or $\delta = 6.45$ ppm (bromofumarate), the blue solid remains a puzzle. It shows carbonyl absorption at 5.75–5.8 μ, and no C=C absorption at 6.2 μ. The proton NMR spectrum shows only two broad peaks with the area ratio of 3 : 2 suggesting, both by position and ratio, ester ethyl groups. The compound can be prepared in low yields (up to 4%) from ethyl esters of both diastereomeric bromofluoro- and dibromo-succinic acids as well as from diethyl bromofumarate. It does not contain bromine. Elementary analysis did not give satisfactory data. The approximate empirical formula $C_8H_{10}O_6$ could suggest a carbon or carbon–oxygen polymeric chain with ethyl groups attached.

EXPERIMENTAL

Bromofluoro esters (Ib and c) and (IIb and c) were prepared according to the literature[1] by adding bromine fluoride (from *N*-bromoacetamide and anhydrous hydrogen fluoride) to dimethyl and diethyl fumarate and maleate, respectively. The n_D^{25} values are 1.4577, 1.4490, 1.4600 and 1.4511, respectively. Their purity was checked by ^1H NMR spectroscopy whose pattern coincided with those of the literature[1].

Dibromo esters (Ie), (IId) and (IIe) were prepared by adding bromine to the corresponding unsaturated esters according to the literature[2]. (IId): m.p. 41–42° (lit.[2] 43°); (Ie): m.p. 54–58.5° (lit.[2] 58°); (IIe): b.p. 87°/0.2 mmHg (lit.[2] 137–138°/11 mmHg), n_D^{30} 1.4559.

Dimethyl azidofumarate (or maleate) ((IIIa) or (IVa))

Method (a)

A solution of 6.0 g (0.02 mole) of dimethyl DL-α,α′-dibromosuccinate (IId) in 10 ml of methanol was refluxed for 12 h with a solution of 2.0 g (0.03 mole) of sodium azide in 90 ml of methanol. After evaporation *in vacuo* the residue was shaken with equal amounts of water and ether, the ether layer was evaporated and the residue was distilled at 85–94° at 0.05–1 mmHg pressure (decomposition) to give 1.4 g of a viscous oil which on re-distillation afforded 0.4 g of a colorless liquid, b.p. 63°/0.1 mmHg, composed, according to elementary analysis, of 80–87% of the azido ester (IIIa) or (IVa) and 13–20% of dimethyl bromofumarate. The IR spectrum showed maxima of $-N_3$ (at 4.7 μ), $-CO_2$ (at 5.8 μ) and C=C (at 6.2 μ). The proton NMR spectrum showed vinylic proton at 6.07 δ and methyl protons (doublet) at 3.77 δ ($J = 11$ cps).

Method (b)

A solution of 1.4 g (0.005 mole) of dimethyl *erythro*-α-bromo-α′-fluorosuccinate (Ib), 0.4 g (0.006 mole) of sodium azide and 0.2 g of sodium iodide in 15 ml of methanol was refluxed for 4.25 h. After similar work-up as above, a mixture composed of 50% of the azide (IIIa) or (IVa), 40% of dimethyl bromofumarate (IVb) and 10% dimethyl bromomaleate (IIIb) (according to proton NMR) was obtained.

Bromofluoro acids (Ia) and (IIa) were prepared from the methyl esters (Ib) and (IIb) as follows:

The ester (4.4 g, 0.018 mole) was refluxed with 10 ml of 5% sulfuric acid at 100–125° (vapor temperature 93–86°) for 30 min. From the cold solution the unreacted ester was separated and repeatedly treated with the proportional amount of 5% sulfuric acid in the same way. The aqueous layer was continuously extracted with ether, combined ether extracts from 3–4 consecutive runs of the hydrolysis were dried with magnesium sulfate and evaporated *in vacuo*. The crystalline residue (approximately 1 g (26%)) was dissolved in approximately 1 ml of hot water. Since no crystals deposited on cooling the solution was evaporated to a small volume, and the semi-solid crystalline residue was spread over a porous plate. The crystals thus obtained (overall yield 3%) could not be recrystallized from any common solvent. The melting points may therefore not be final since small amounts of unknown impurities were still present according to proton NMR spectroscopy using deuterium oxide. The spectrum showed the characteristic pattern of H–F couplings but some of the signals were obscured by the signal of DOH. *erythro*-α-Bromo-α′-fluorosuccinic acid, (Ia), had m.p. 128–133° (sealed capillary); *threo*-α-bromo-α′-fluorosuccinic acid, (IIa), had m.p. 138–142° (sealed capillary) mixed m.p. 105–110°. The melting points lie dangerously close to that of maleic acid (137°) but only traces of this acid could have been present according to the NMR spectra.

Diethyl bromomaleate (IIIc) and diethyl bromofumarate (IVc)

The following procedure is representative of the preparation of the esters (IIIc) or (IVc) (or their mixtures) from the stereoisomeric diethyl α,α′-dibromosuccinates and α-bromo-α′-fluorosuccinates.

A solution of 3.32 g (0.01 mole) of diethyl *meso*-α,α′-dibromosuccinate (Ie) and 10 g (0.1 mole) of potassium acetate in a mixture of 20 ml of water and 10 ml of ethanol was heated at 35° for 38 h. The intensely blue solution was evaporated *in vacuo* at 40° and the viscous dark blue residue was extracted with the same volume of dichloromethane. The extract was evaporated and the dark blue oil (2.5 g) was chromatographed over 33 g of silica gel. Elution with diethyl ether gave 1.3 g of colorless diethyl bromomaleate (IIIc) distilling at 77–90°/0.16 mmHg. IR spectrum: $-CO_2$ 5.8 μ, C=C 6.15 μ. Properties of products obtained from the dibromo and bromofluoro esters are tabulated in Table 1.

TABLE 1

Starting diethyl dihalosuccinate	Yield(%)	B.p.(°/mmHg)	n_D/temp.*	H^1 NMR vinylic	H^1 NMR proton	Ratio *trans:cis*
erythro-α-Bromo-α′-fluoro (Ic)	20	60–62°/0.05	1.4760/25	7.38	6.42	70:30
threo-α-Bromo-α′-fluoro (IIc)	32	61°/0.05	1.4768/25	7.38	—	100:0
meso-α,α′-Dibromo (Ie)	52	80–81°/0.16	1.4733/30	—	6.45	0:100
DL-α,α′-Dibromo (IIe)	40	80°/0.3	1.4726/30	7.40	6.45	95:5

* $n_D^{14.3}$ of diethyl bromofumarate = 1.4819 by interpolation[3].

The dark blue compound adsorbed on silica gel in the column could not be eluted by ethanol since it decolorized. The blue portion was transferred from the column and digested with water. The resulting blue solution was evaporated to dryness *in vacuo*, the residue was dissolved in carbon tetrachloride and the solution filtered and evaporated to dryness. The respective yields of the blue compound from the esters (Ic), (IIc), (Ie), (IIe) and from diethyl bromofumarate (IVa) were 2.6%, not isolated, 4%, 0.9% and 4%, respectively.

The blue compound is not crystalline, its solution in carbon tetrachloride or water leaving on evaporation a blue film homogeneous under a microscope. It does not melt but decomposes when heated. It shows two maxima in the visible spectrum at 3550 and 5850 Å (in carbon tetrachloride) and at 3150 and 5700 Å (in water), and the following maxima in the IR spectrum (carbon tetrachloride solution between two salt discs): 3.4, 5.8 (vs), 6.05 (sh), 6.95 (s), 7.35 (m), 8.1 (vs, broad), 9.15 (s) and 9.7 (s) μ. The proton NMR spectrum shows two broad signals at

1.2–1.3 δ and 4.1 δ. The positions of the signals coincide with those of ethyl protons in esters but the signals are not split into a triplet and quartet, respectively. The ratio of the areas is 3 : 2.

Isotope exchange experiments

(a) Without added base

Diethyl *erythro*-α-bromo-α′-fluorosuccinate (Ic) (0.375 g, 0.00138 mole) and 0.37 g (0.00112 mole) of CH_3OD were sealed in a tube and heated at 95° for 15 h. The proton NMR spectrum was unchanged.

(b) With sodium methoxide

The ester (Ic) was mixed with 1/8 of its volume of CH_3OD in which a small piece of sodium had been dissolved. A white compound, presumably sodium fluoride, was precipitated immediately. No change in the proton NMR spectrum was noticed.

(c) With potassium acetate

The ester (Ic) (0.3396 g, 0.00125 mole) was added to 0.0368 g (0.00111 mole) of CH_3OD and 0.02 g (0.0002 mole) of potassium acetate, and the mixture was sealed and heated at 35° for 16 h. A crystalline precipitate, presumably potassium fluoride, was deposited. No change in the proton NMR pattern was noticed.

Kinetic measurements

Kinetic measurements were carried out in 50% aqueous methanol or ethanol using 0.00125, 0.000625 and 0.000312 moles of dimethyl or diethyl *erythro*- and *threo*-α-bromo-α′-fluorosuccinates and DL- and *meso*-α,α′-dibromosuccinates, and 0.0025, 0.005 and 0.01 moles of potassium acetate, respectively. The solutions were heated at 35 $\pm$ 0.1° in 25 ml volumetric flasks so that the concentrations of the esters were 0.05, 0.025 and 0.0125 and those of the acetate 0.1, 0.2 and 0.4 molal, respectively. The molal ratios of the esters to the base were 1 : 2, 1 : 4 and 1 : 8.

Because the fluoride selective electrode (Orion) did not give reproducible results when used in solutions containing organic solvents, the Willard–Winter method[4] was used for the determination of fluoride. Bromide was determined according to Fajans[5].

To determine fluoride, a 2 ml aliquot was mixed with 0.2, 0.4 and 0.8 ml of 1 *N* sulfuric acid (for 0.1, 0.2 and 0.4 molal solutions of potassium acetate, respectively), 2 ml of glycine–perchlorate buffer (containing 67 g of glycine, 110 g of sodium perchlorate and 55 ml of 2 *N* perchloric acid in 1 liter) and 10 drops of an indicator prepared from equal volumes of 0.05% aqueous solution of sodium alizarinsulfonate and 0.01% aqueous solution of indigo carmin. The sample was titrated with 0.05 *N* thorium(IV) nitrate until the pink shade did not change. Blanks were 0.05, 0.10 and 0.20 ml of the titrant for titration in aqueous methanol and 0.1, 0.15 and 0.25 ml for ethanolic solutions for 0.1, 0.2 and 0.4 molal concentrations of potassium acetate, respectively, in the samples.

To determine bromide, 2 ml aliquots were acidified with 3 ml of 6 *N* acetic acid and titrated with 0.05 *N* silver nitrate using 10 drops of 0.1% solution of eosin in 70% ethanol as the indicator.

The accuracy of both determinations was ± 2–2.5%.

RESULTS

The following observations were made during the kinetic measurements of elimination of hydrogen fluoride and hydrogen bromide from α,α′-dihalosuccinates:

(1) Dialkyl α-bromo-α′-fluorosuccinates eliminated hydrogen fluoride preferentially to hydrogen bromide. The rate of elimination of hydrogen bromide was found to be lower by 1–2 orders of magnitude than that of hydrogen fluoride (Fig. 1). Since the product of elimination of hydrogen fluoride—the unsaturated

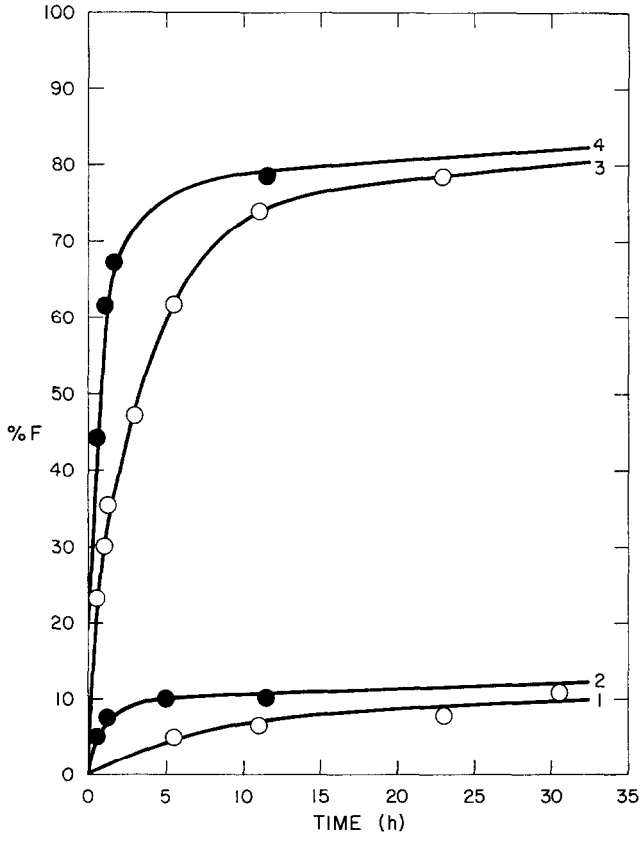


Fig. 1. Elimination of hydrogen bromide and hydrogen fluoride from diethyl *erythro*-α-bromo-α′-fluorosuccinate using 2 and 8 equivalents of potassium acetate.
Curve 1: Elimination of Br, 2 equiv. of AcOK.
Curve 2: Elimination of Br, 8 equiv. of AcOK.
Curve 3: Elimination of F, 2 equiv. of AcOK.
Curve 4: Elimination of F, 8 equiv. of AcOK.

bromo ester—was isolated, whereas no unsaturated fluoro ester was ever noticed, it is likely that the elimination of hydrogen bromide occurs only when all hydrogen fluoride has been split off. Possibly the measured rate of elimination of hydrogen bromide corresponds to that of vinylic bromine.

(2) The rate of elimination of hydrogen fluoride depends strongly on the concentration of potassium acetate. Data in Figure 2 show, at the same time, considerable difference in the rate of elimination of hydrogen fluoride from methyl and ethyl esters, the latter reacting more slowly.

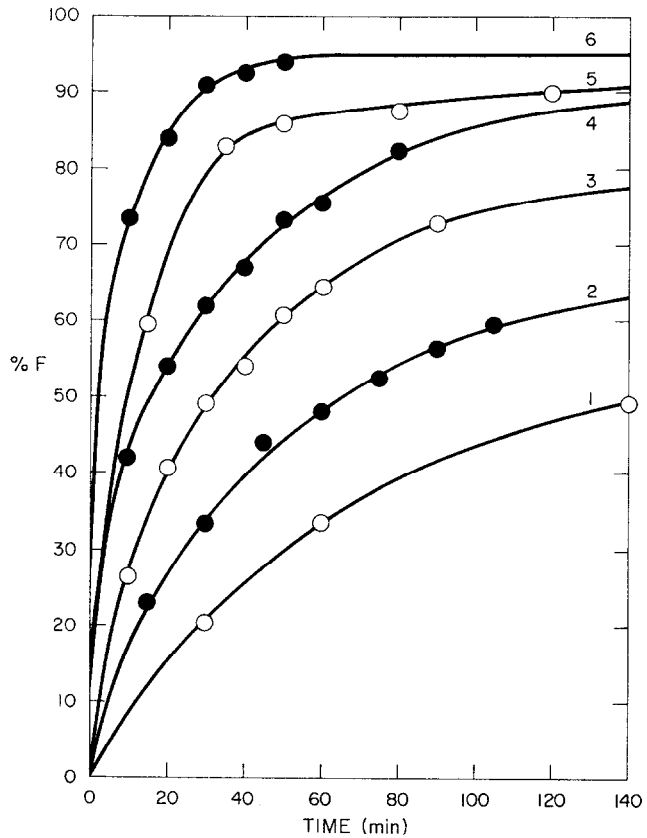


Fig. 2. Elimination of hydrogen fluoride from dimethyl and diethyl *threo*-α-bromo-α'-fluorosuccinate ((IIb) and (IIc) respectively) using 2, 4 and 8 equivalents of potassium acetate, respectively.
Curve 1: Diethyl ester (IIc), 2 equiv. of AcOK.
Curve 2: Diethyl ester (IIc), 4 equiv. of AcOK.
Curve 3: Diethyl ester (IIc), 8 equiv. of AcOK.
Curve 4: Dimethyl ester (IIb), 2 equiv. of AcOK.
Curve 5: Dimethyl ester (IIb), 4 equiv. of AcOK.
Curve 6: Dimethyl ester (IIb), 8 equiv. of AcOK.

(3) The rate of elimination of hydrogen fluoride depends on the concentration

of the ester. Surprisingly (at first glance), decreasing concentration of the ester shows higher reaction rate (Fig. 3). However, it must be considered that with concentration of potassium acetate kept constant, decreased concentration of the ester means larger relative excess of the base which, as shown in Figure 2, increases the rate of elimination of hydrogen fluoride drastically. But even if the ester-to-base ratio is kept constant, a slight change of the reaction rate with the change of concentration of the ester was observed (Fig. 4).

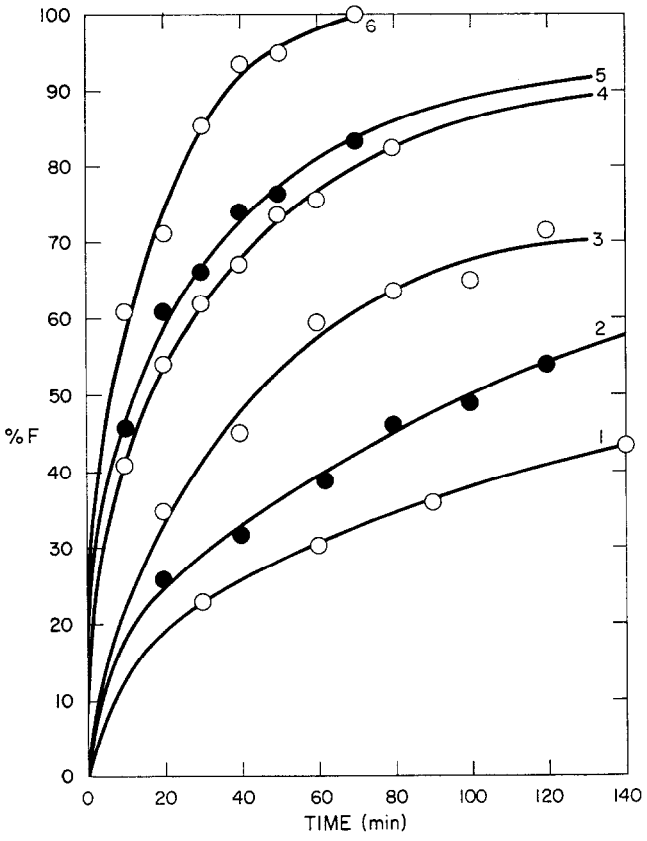


Fig. 3. Elimination of hydrogen fluoride from diethyl *erythro*-α-bromo-α′-fluorosuccinate (Ic) (curves 1–3) and from dimethyl *threo*-α-bromo-α′-fluorosuccinate (IIb) (curves 4–6) using constant (0.1 molal) concentration of potassium acetate and varying concentration of the esters.
Curves 1 and 4: Concn. of ester 0.050 molal, 2 equiv. AcOK.
Curves 2 and 5: Concn. of ester 0.025 molal, 4 equiv. AcOK.
Curves 3 and 6: Concn. of ester 0.0125 molal, 8 equiv. AcOK.

(4) There is a negligible difference between the rates of elimination of hydrogen fluoride from the two diastereomeric bromofluoro esters. On the other hand,

the rate of elimination of hydrogen bromide from the racemic dibromosuccinate is approximately one order of magnitude higher than that of the *meso* compound (Fig. 5).

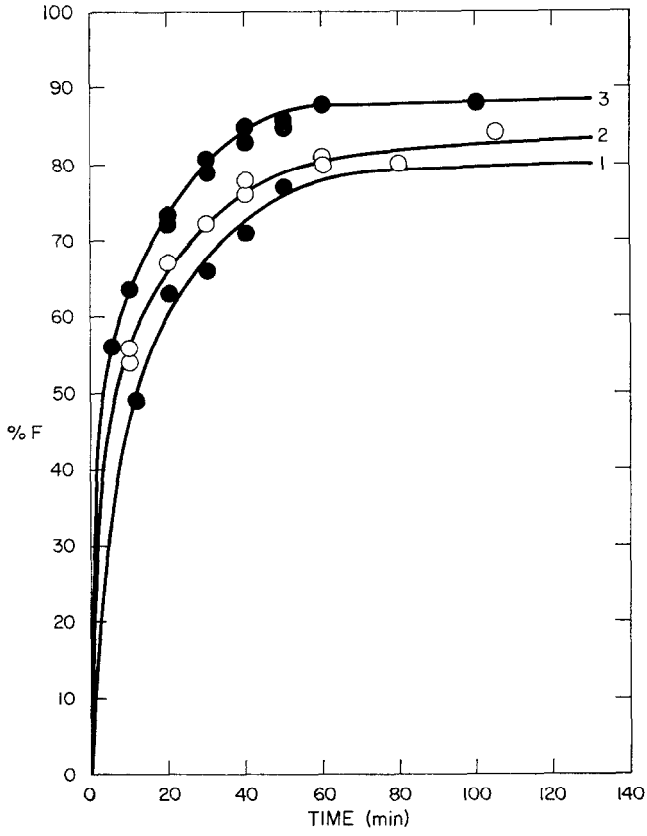


Fig. 4. Elimination of hydrogen fluoride from dimethyl *erythro*-α-bromo-α'-fluorosuccinate at constant ester-to-base ratio of 1:8.
Curve 1: Concn. of ester 0.0125 molal, concn. of AcOK 0.1 molal.
Curve 2: Concn. of ester 0.0250 molal, concn. of AcOK 0.2 molal.
Curve 3: Concn. of ester 0.0500 molal, concn. of AcOK 0.4 molal.

The kinetics of elimination of hydrogen fluoride from bromofluorosuccinates or of hydrogen bromide from dibromosuccinates are not straightforward. Neither first-order kinetics (simple E1 or E1cb mechanism) nor second-order kinetics were obtained under any of the conditions explored in this study.

In order to compare the relative rates of elimination of hydrogen halides from the halogenated succinates, the percentage elimination of the hydrogen halides after 20, 40, 60 and 80 min are listed in Table 2 as obtained by graphical interpolation of the measured values.

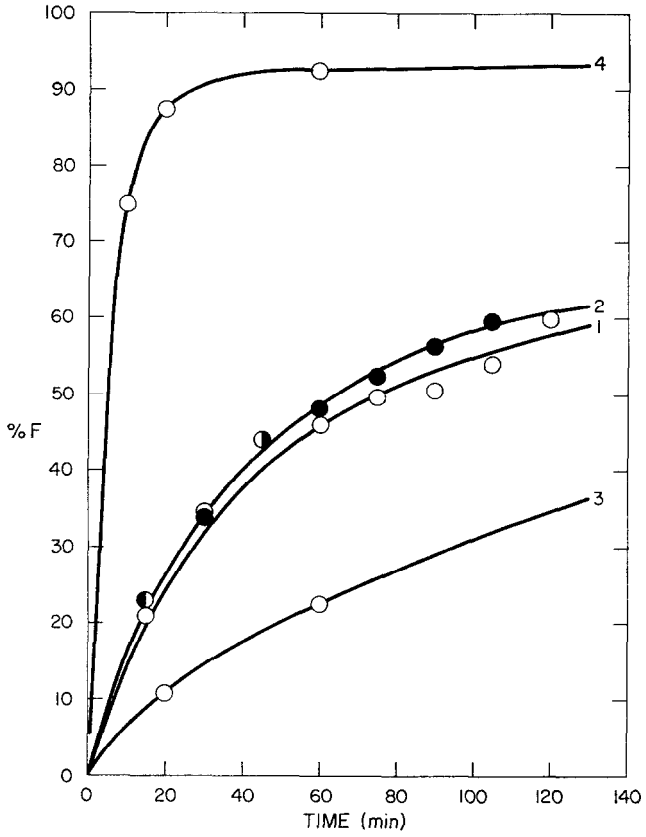


Fig. 5. Elimination of hydrogen fluoride from diethyl *erythro*- and *threo*-α-bromo-α'-fluorosuccinate ((Ic) and (IIc) respectively), and of hydrogen bromide from diethyl *meso*- and DL-α,α'-dibromosuccinate ((Ie) and (IIe) respectively) using 4 equivalents of potassium acetate.
Curve 1: *erythro*-Bromofluorosuccinate (Ic).
Curve 2: *threo*-Bromofluorosuccinate (IIc).
Curve 3: *meso*-Dibromosuccinate (Ie).
Curve 4: DL-Dibromosuccinate (IIe).

DISCUSSION

In general, fluorine in aliphatic compounds is both displaced and eliminated less readily than the other halogens. There are, however, numerous exceptions to this rule. This discussion will be limited only to the most pertinent examples.

One of the oldest reported instances of the ready displacement and elimination of fluorine is the conversion of 1,2-difluoroethane and 1,2-difluorocyclohexane to the corresponding diols in contact with water at room temperature, and the spontaneous conversion to 1,3-butadiene and 1,3-cyclohexadiene, respectively, at room temperature[6]. However, since no experimental evidence accompanied this paper, and none of the reactions had been reported in Beilstein until the end of

TABLE 2

ELIMINATION OF HYDROGEN FLUORIDE FROM FLUOROBROMOSUCCINATES AND OF HYDROGEN BROMIDE FROM DIBROMOSUCCINATES USING AcOK AT 35°*

Ester (succinate)	Formula	Configuration	Concentration (molal)		% Elimination of HX after:			
			ester	AcOK	20 min	40 min	60 min	80 min
Dimethyl α-bromo-α′-fluoro	(Ib)	*erythro*	0.050	0.100	53.5	68.0	77.0	83.5
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.050	0.100	53.5	68.0	77.0	83.5
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.025	0.100	59.5	73.0	81.0	86.0[e]
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.0125	0.100	73.5	92.0	98.0	100
Dimethyl α-bromo-α′-fluoro	(Ib)	*erythro*	0.050	0.200	61.0	78.0	84.5	86.5
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.050	0.200	70.0	84.5	87.5	89.0[e]
Dimethyl α-bromo-α′-fluoro	(Ib)	*erythro*	0.050	0.400	72.5	84.5	87.5	89.0[e]
Dimethyl α-bromo-α′-fluoro	(Ib)	*erythro*	0.025	0.200	65.5	76.5	80.5	83.0
Dimethyl α-bromo-α′-fluoro	(Ib)	*erythro*	0.0125	0.100	60.0	72.0	78.0[e]	79.5[e]
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.050	0.400	82.0	91.5	94.5[e]	95.5[e]
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.025	0.200	73.5	86.5	91.5	93.0
Dimethyl α-bromo-α′-fluoro	(IIb)	*threo*	0.0125	0.100	69.5	80.0	85.5[e]	87.5[e]
Diethyl α-bromo-α′-fluoro	(Ic)	*erythro*	0.050	0.100	17.5	25.0	30.5	34.5
Diethyl α-bromo-α′-fluoro	(Ic)	*erythro*	0.025	0.100	25.0	33.0	39.5	45.0
Diethyl α-bromo-α′-fluoro	(Ic)	*erythro*	0.0125	0.100	33.0	48.0	57.5	63.5
Diethyl α-bromo-α′-fluoro	(IIc)	*threo*	0.050	0.100	17.5	26.5	33.5	38.5
Diethyl α-bromo-α′-fluoro	(Ic)	*erythro*	0.050	0.200	26.5	38.0	45.5	50.0
Diethyl α-bromo-α′-fluoro	(IIc)	*threo*	0.050	0.200	27.5	40.5	49.0	54.5
Diethyl α-bromo-α′-fluoro	(Ic)	*erythro*	0.050	0.400	34.0	51.0	60.5	66.5
Diethyl α-bromo-α′-fluoro	(IIc)	*threo*	0.050	0.400	40.0	55.5	65.0	71.0
Diethyl α,α′-dibromo	(IIe)	DL-	0.050	0.100	69.0	84.0	89.5	93.0
Diethyl α,α′-dibromo	(Ie)	*meso*	0.050	0.200	11.0	17.5	22.5	27.0
Diethyl α,α′-dibromo	(IIe)	DL-	0.050	0.200	87.5	92.0	93.0	94.0
Diethyl α,α′-dibromo	(Ie)	*meso*	0.050	0.400	16.0	25.5	33.0	39.0

* The values obtained by graphical interpolation except where marked e (for extrapolation).

1949, and further since 1,2-difluoroethane was later prepared in a high yield at a rather high temperature with only a trace of an olefin being observed[7], the easy elimination of fluorine claimed in Reference 6 must be regarded as questionable.

Elimination of hydrogen fluoride from 2-fluoropentane and 2-fluoro-2-methylbutane was accomplished in 18–48% yields by heating the fluorides with methanolic sodium methoxide at 100° and 70–80° respectively[8]. The analogous chlorides, bromides and iodides reacted at considerably lower temperatures.

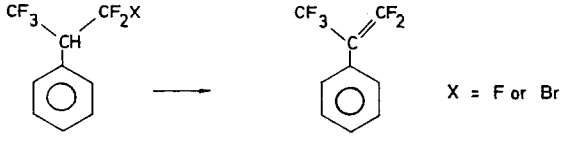
Elimination of hydrogen fluoride from some highly fluorinated alkanes such as 1*H*, 2*H*-hexafluoropropane[9] or 1*H*, 2*H*-hexafluorocyclobutane is relatively easy[10]. Here the reaction occurs spontaneously at room temperature in the presence of aqueous base[10]. The elimination of hydrogen fluoride from 1*H*, 2*H*-hexafluoropropane occurs predominantly (70%) in such a way that hydrogen is eliminated from the carbon carrying less fluorine[11,12].

$$CF_3CHFCHF_2 \rightarrow \underset{30\%}{CF_3CH{=}CF_2} + \underset{70\%\ (cis\ 53\%,\ trans\ 17\%)}{CF_3CF{=}CHF}$$

This hydrogen is supposedly more acidic because the "acidification" of hydrogen is caused more by β-fluorine than by α-fluorine. In this respect fluorine affects the hydrogen much more strongly than chlorine as evidenced by 50 times faster hydrogen–deuterium exchange in 1,1-dichloro-2,2,2-trifluoroethane as compared with 1,1,2-trichloro-2,2-difluoroethane[13]. Direct evidence that β-fluorine "acidifies" hydrogen in fluorinated compounds much more than α-fluorine was provided by isotope exchange in polyfluorinated hydrocarbons. The hydrogen atom in fluoroform with three α-fluorine atoms is 10^9 less acidic than that in tris-trifluoromethylmethane with nine β-fluorine atoms[14]. The acidity of hydrogen atoms α to trifluoromethyl groups in 1,1,1-trifluorodihaloethanes is so high that deuterium exchange occurs in the presence of a base[15] and elimination of hydrogen fluoride takes place by an E1cb mechanism[16].

In the aromatic series, elimination of hydrogen fluoride from fluorinated side-chains is facilitated when a conjugated double bond is formed. The elimination of hydrogen fluoride from β-fluoroethylbenzene proceeds by the conventional E2 mechanism. The alternative E1cb mechanism was ruled out since no deuterium–hydrogen exchange was observed[17].

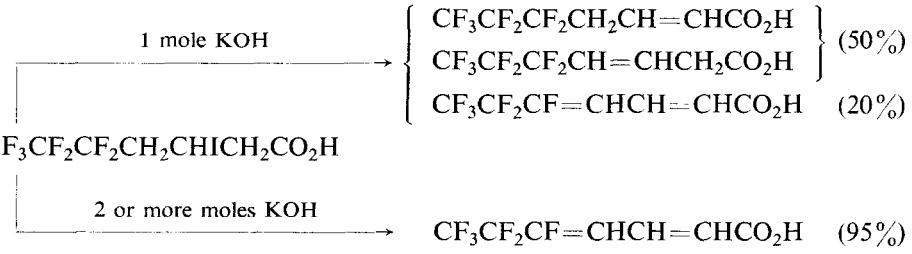
On the other hand, elimination of hydrogen fluoride from (1,1,1,3,3,3-hexafluoro-2-propyl)benzene is 5–10 times slower than the isotope exchange, showing the carbanion mechanism as a potential path[18].



The elimination of hydrogen fluoride from this compound is 10^5 times slower than the elimination of hydrogen bromide from (1-bromo-1,1,3,3,3-pentafluoro-2-propyl)benzene[18].

Easy, sometimes spontaneous, elimination of hydrogen fluoride occurs in fluorinated carboxylic acids where α,β-unsaturated acids are formed. Here, too, conjugation of the double bond with the carboxylic group is the driving force for the reaction. β,β,β-Trifluoropropionic acid[19], α,β-difluorobutyric acid[20] and ethyl β,β-difluorobutyrate[21] gave the corresponding α,β-unsaturated fluoro acids. Elimination of hydrogen fluoride occurs during heating of α,α-difluoro- and trifluoro-succinic acids with aqueous alkali[22]. α,α'-Difluorosuccinic acid is even claimed to give acetylene dicarboxylic acid by mere contact with water at room temperature[23].

An example closest to the situation described in this paper is elimination of hydrogen iodide and hydrogen fluoride from β-iodo-γ-heptafluoropropylbutyric acid[24]. Hydrogen iodide is eliminated preferentially to hydrogen fluoride since no iodine-containing unsaturated acid was ever isolated.



The reaction of esters of α-bromo-α'-fluorosuccinic acids with bases is therefore an unusual and perhaps unique example of the elimination of hydrogen fluoride in preference to the elimination of other hydrogen halides. In these esters hydrogen atoms are α to carboxylic groups and therefore activated for elimination as protons, but since both of them are affected in the same way the influence of the carboxylic groups on the properties of the hydrogen atoms cancels out. The only difference is that one hydrogen atom is β to fluorine and α to bromine whereas the other one is the other way around. As discussed previously and supported by much evidence, fluorine "acidifies" a β-hydrogen atom more strongly than the α-hydrogen[14]. At the same time, bromine "acidifies" α-hydrogen more than fluorine as found by measurements of acidity of hydrogen atoms in haloforms where the hydrogen in fluoroform is the least acidic[25]. Both influences superimpose here and make the hydrogen β to fluorine and α to bromine much more likely to eliminate than the other one. In other words, a carbanion having the negative charge on the carbon β to fluorine and α to bromine is more stable.

Such an activation of a hydrogen atom could easily suggest that the elimination of hydrogen fluoride takes place by an E1cb mechanism. If this were the case, the hydrogen atom β to fluorine should be easily exchanged for deuterium.

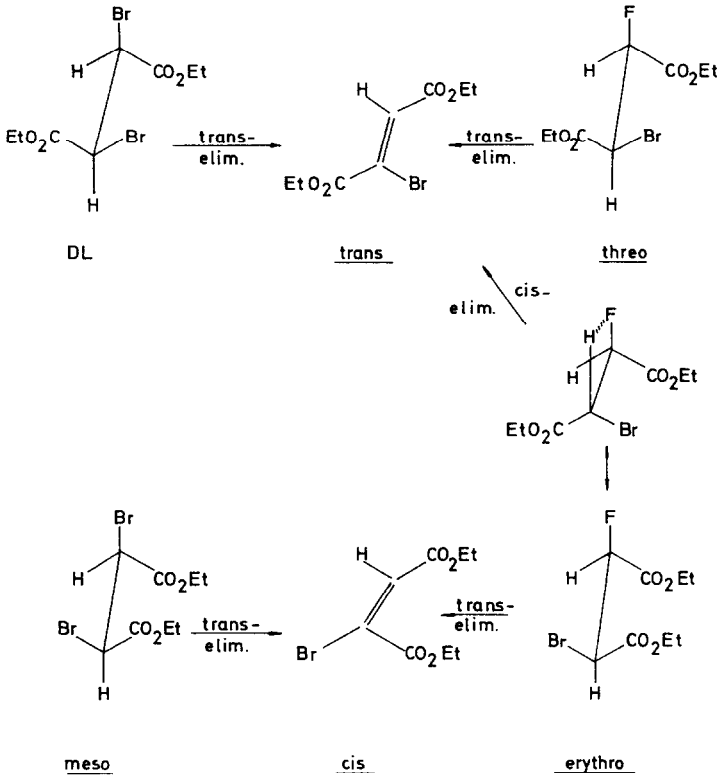
However, in the presence of a base (sodium methoxide or potassium acetate), ready elimination of hydrogen fluoride took place, the expulsion of fluorine evidently being faster than the formation of the carbanion. No hydrogen–deuterium exchange was therefore observed. In the absence of a base the exchange did not take place either, which is in accord with previous experience[15].

The surprisingly fast elimination of fluorine as fluoride ion, and the absence of any observable deuterium exchange, tends to suggest an E2 pathway rather than an E1cb pathway for this reaction, with the stability of the resultant double bond conjugated with two carboxylic groups providing the driving force for concerted elimination of hydrogen fluoride. However, the failure of the reaction to give rise to straightforward second-order kinetics may mean that the reaction mechanism is more complex than the E2 label ordinarily implies.

A comparison of the rate of elimination of hydrogen fluoride from α-bromo-α′-fluorosuccinate with the rate of elimination of hydrogen bromide from the same compound is not very useful since the two hydrogen atoms present in the molecule have different "acidities" and therefore react with the base at different rates. It is more informative to carry out a comparison of the rates of elimination of hydrogen fluoride from α-bromo-α′-fluorosuccinates with the rates of elimination of hydrogen bromide from α,α′-dibromosuccinates. Figure 5 shows that the DL-dibromo ester eliminates hydrogen bromide much faster than the corresponding *threo*-bromofluoro ester eliminates hydrogen fluoride. On the other hand, the *meso* compound loses hydrogen bromide much more slowly than the corresponding *erythro*-bromofluoro ester loses hydrogen fluoride.

The large difference in the rates of elimination of hydrogen bromide from the two dibromo esters is accounted for by steric arguments. In the transition state for the elimination of hydrogen bromide from DL-dibromosuccinate the *anti* conformation of hydrogen and bromine necessary for *trans* elimination places the two carboxylic groups *anti* to each other (Scheme 2). The elimination of hydrogen bromide leads to bromofumarate, more stable because of the *trans* position of the two bulky carboxylic groups. In the case of *meso*-dibromosuccinate, the transition state has the two carboxylic groups in a *gauche* conformation and leads to the less stable bromomaleate in which the two carboxylic groups are *cis* to each other. This accounts for much lower rate of elimination of hydrogen bromide from the *meso* compound[26].

From *threo*-bromofluorosuccinate, bromofumarate is formed analogously by *trans* elimination of hydrogen fluoride. In the case of the *erythro*-bromofluoro ester, *trans* elimination of hydrogen fluoride gives bromomaleate. However, because of the possibility of intramolecular attractive forces between hydrogen and fluorine a transition state may be reached, which leads to the more stable bromofumarate by *cis* elimination. This elimination seems to prevail over the *trans* elimination as bromofumarate always predominated in the product of elimination of hydrogen fluoride from the *erythro* diastereomer.



From the comparison of the reactions of the corresponding stereoisomers of dibromo- and bromofluoro-succinates, it follows that when the same mechanism, *trans* elimination, is operating hydrogen fluoride is removed less readily than hydrogen bromide. Faster elimination of hydrogen fluoride from the *erythro* compounds than that of hydrogen bromide from the *meso* compound is evidently caused by the difference in the mechanisms, mixed *trans* and *cis* elimination of hydrogen fluoride as opposed to pure *trans* elimination of hydrogen bromide.

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