PREFERENTIAL ELIMINATION OF HYDROGEN FLUORIDE FROM FLUOROHALO COMPOUNDS

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Examples of base-promoted eliminations of hydrogen fluoride in preference to other hydrogen halides from vicinal fluorohalo compounds are quoted, and an explanation of the fairly rare preferential elimination of "poorer halogen leaving group" is offered.

Hydrogen fluoride is eliminated from fluoro, polyfluoro and fluorohalo compounds thermally, catalytically and by means of bases. There are numerous examples of all of the above types. As a rule, elimination of hydrogen fluoride usually requires more energetic conditions and takes place much less readily than that of the other hydrogen halides. However there are a few cases when hydrogen fluoride has been split out under basic conditions in preference to hydrogen chloride and hydrogen bromide (and hydrogen chloride in preference to hydrogen bromide). Such reactions in which "poorer halogen leaving group" is removed preferentially are usually accompanied by special stereochemistry. It is these rather rare examples that will be subject of the present discussion.

A comparison of bond dissociation energies of carbon–halogen bonds (Table I) shows that the carbon–fluorine bond is out of proportion much stronger than the carbon–chlorine, carbon–bromine and carbon–iodine bonds. This makes the E1 mechanism, in which the rate determining step is breaking of the carbon–halogen bond, highly unlikely.

By the same token, in base-promoted E2 dehydrohalogenations the rate of elimination of the halogen as a halide ion is expected to be $I > Br > Cl \gg F$. This "element effect" has indeed been documented in many instances, a few examples of which are listed in Table II.

The ratios of the rates of elimination of hydrogen halides depend evidently on the structure of the halogenated compound and span many orders of magnitude. The rate of dehydrofluorination was always found much slower than that of dehydrochlorination, dehydrobromination and dehydroiodination.

It came therefore as a surprise when, in the reaction of dimethyl and diethyl α-bromo-α′-fluorosuccinates with potassium phthalimide, elimination of hydrogen

fluoride predominated[6] over that of hydrogen bromide in a ratio of 3 : 2. Similar observation was made when the above-mentioned esters were refluxed with sodium azide in methanol giving mainly dialkyl bromofumarates and dialkyl azidofumarates[7]. These rather unexpected results prompted the author to carry out a kinetic study of a base-promoted dehydrohalogenation of dimethyl and diethyl α-bromo-α'-fluorosuccinates, effected by heating with aqueous-methanolic potassium acetate[7]. The study revealed that hydrogen fluoride was eliminated in preference to hydrogen bromide at a rate higher by 1–2 orders of magnitude. Since only dimethyl and diethyl bromomaleates or bromofumarates but not the corresponding fluoromaleates and fluorofumarates were isolated, the elimination of hydrogen bromide took probably place only after most of the hydrogen fluoride has been split out. The rates of elimination of hydrogen fluoride from *erythro*- and from *threo*-α,α'-fluoro esters were only slightly different from each other. In contrast, the rate of elimination of hydrogen bromide from diethyl D,L- and *meso*-α,α'-dibromosuccinates differed considerably. The elimination of hydrogen bromide from the D,L-dibromo ester was faster than the dehydrofluorination of both bromofluoro esters, and that in turn was faster than the dehydrobromination of the *meso*-dibromo ester (Table III).

TABLE I

Bond lengths and bond dissociation energies of carbon–halogen bonds

Carbon–halogen[a]	C–F		C–Cl		C–Br		C–I
Bond length, Å	1·38		1·77		1·94		2·21
Bond dissociation energy, kcal mol^{-1}	108		83·5		70		56
Differences, kcal mol^{-1}		24·5		13·5		14	

[a] Ref.[1].

TABLE II

Relative rates of base-promoted dehydrohalogenations of halogenated compounds

Halogen compound	Base, solvent	Temp. °C	X				Ref.
			F	Cl	Br	I	
$PhCHBrCF_2X$	EtONa, EtOH	25	1	$4 . 10^5$	$3 . 10^7$	—	2
$PhCH_2CH_2X$	EtONa, EtOH	30	1	$6{\cdot}8 . 10^1$	$4{\cdot}1 . 10^3$	$2{\cdot}6 . 10^4$	3, 4
BuCHXMe	MeONa, MeOH	100	1	$7{\cdot}14 . 10^2$	$2{\cdot}72 . 10^4$	$1{\cdot}07 . 10^5$	5

The stereochemistry of the dehydrobromination of the diethyl α,α′-dibromosuccinates was in accord with the expectation: the *meso*-compound gave 100% of the *cis*-bromo ester (diethyl bromomaleate), while the D,L-isomer gave 95% of *trans*- and 5% of the *cis*-ester (diethyl bromofumarate and bromomaleate, respectively). In the case of diethyl α-bromo-α′-fluorosuccinates the *threo*-isomer afforded 100% of diethyl bromofumarate, but the *erythro*-isomer gave only 30% of diethyl bromomaleate and 70% of diethyl bromofumarate. Diethyl bromofumarate was not formed by rearrangement of diethyl bromomaleate, for the latter does not rearrange under the conditions used.

The finding shows that, whereas the elimination of hydrogen fluoride from the *threo*-α-bromo-α′-fluoro esters occurred in the *anti*-mode, the dehydrofluorination of the *erythro*-isomer took place both by *anti*- and by *syn*-elimination.[7]

Similar results as with dimethyl and diethyl α-bromo-α′-fluorosuccinates were obtained when the free acids – *erythro*- and *threo*-α-bromo-α′-fluorosuccinic acids – were treated with aqueous alkalies. Because the kinetic measurements were carried out using ^{1}H NMR, sodium deuteroxide in deuterium oxide were used as the basic medium[8].

Under these conditions hydrogen fluoride was eliminated exclusively in preference to hydrogen bromide giving predominantly or exclusively bromofumaric acid from both diastereomers. The reaction was very fast and followed second order kinetics. Two series of measurements were made, at 30° and at 45°. The *erythro*-isomer eliminated hydrogen fluoride faster than the *threo*-isomer. Activation energy for the *erythro*-compound calculated from the Arrhenius plot was found to be lower by 2 kcal than that of the *threo*-compound. The same difference was between the enthalpies of activation, while the entropy of activation of the *erythro*-acid was more negative by 6 e.u. than that of the *threo*-acid[8] (Table IV).

TABLE III

Rates of dehydrobromination of D,L- and *meso*-α,α′-dibromosuccinates and of dehydrofluorination of *erythro*- and *threo*-α-bromo-α′-fluorosuccinates (k_2 in mol l^{-1} s^{-1}) by aqueous-methanolic potassium acetate (concentrations of the esters were 0·05 mol l^{-1} and of the base 0·20 mol . l^{-1}) at 35°C

Ester	$k_2 . 10^5$,[a]
D,L-$EtO_2CCHBrCHBrCO_2Et$	126 (±22)
meso-$EtO_2CCHBrCHBrCO_2Et$	29 (±3·6)
threo-$EtO_2CCHBrCHFCO_2Et$	73 (±7·8)
erythro-$EtO_2CCHBrCHFCO_2Et$	59 (±9·6)

[a] Ref.[7]; the accuracy of the rate determinations in % is given in parentheses.

Preferential elimination of hydrogen fluoride from vicinal halofluoro compounds was also observed in the cyclohexane series[9], acenaphthene series[10] and dihydrofuran series[11].

While the preferential *cis*-elimination of hydrogen fluoride from *trans*-1-bromo--2-fluorocyclohexane was achieved only when a "complex base", sodamide in tert--butyl alcohol and tetrahydrofuran, was used[9], potassium tert-butoxide alone caused similar elimination of hydrogen fluoride in preference to hydrogen chloride or hydrogen bromide in 1-chloro- or 1-bromo-2-fluoroacenaphthenes[10] and in 2,3--dihalo-2,3-dihydrobenzofurans[11].

In order to find how justified was Bartsch's assumption that only a complex base, sodamide in tert-butyl alcohol and tetrahydrofuran, causes the preferential elimination of hydrogen fluoride, the author carried out elimination of hydrogen halides from *trans*-1-bromo-2-fluorocyclohexane and found, that sodamide alone was capable of achieving *syn*-elimination of hydrogen fluoride. Sodium methoxide and potassium tert-butoxide caused elimination of hydrogen bromide only. The results[12] are shown in Table V.

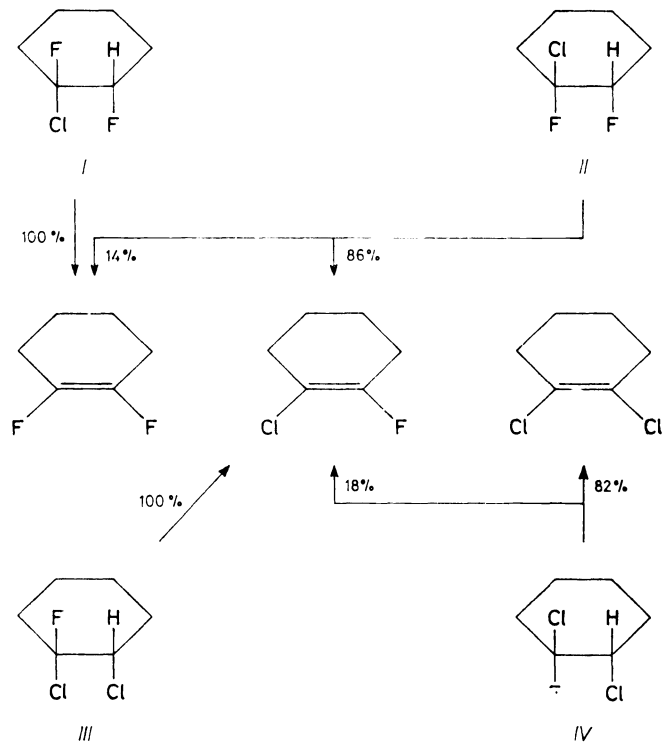
Preferential elimination of hydrogen fluoride was also observed[13] in 1*H*-2-chlorodecafluorocyclohexanes *I*, *II* and in 1*H*-1,2-dichlorononafluorocyclohexanes *III*, *IV*. It took place predominantly but not exclusively only in those isomers where hydrogen and fluorine were in antiperiplanar conformation. When hydrogen and fluorine were in synperiplanar positions, only hydrogen chloride was eliminated on treatment with 18 M potassium hydroxide at room temperature for 14 h (ref.[13]) (Scheme 1).

TABLE IV

Dehydrofluorination of *erythro*- and *threo*-α-bromo-α'-fluorosuccinic acids by sodium deuteroxide in deuterium oxide (concentrations of the disodium salts of the acids were 0·05 mol l^{-1} and of the base 0·20 mol l^{-1})

$HO_2CCHBrCHFCO_2H$	Temp. °C	$t_{1/2}$[a] min	$k_2 \cdot 10^3$[b] mol l^{-1} s^{-1}	E_{act} kcal	ΔH kcal	ΔS e.u.
erythro-	30	9·25	4·05 (±12·3)	12·8	12·2	−29·4
	45	3·00	11·33 (±12·0)			
threo-	30	18·75	3·07 (±4·9)	14·8	14·2	−23·3
	45	4·80	10·10 (±4·0)			

[a] Ref.[8], $t_{1/2}$ half-life time; [b] the accuracy of k_2 determination in % is given in parentheses.



SCHEME 1

TABLE V

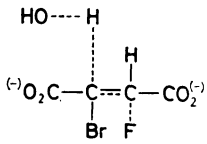
Results of dehydrohalogenation of *trans*-1-bromo-2-fluorocyclohexane (yields of the products in per cent)

Base	Reaction conditions[a]	Cyclohexene			1,3-CHD[b]
		1-bromo	3-fluoro	3-methoxy	
MeONa	MeOH, reflux, 9 h		92·5[c]	7·5[c]	
t-BuOK	t-BuOH, reflux, 75 min		89		11
$NaNH_2$	THF, room temp., 12 h	60[d]			
	t-BuOH-THF, room temp., 24 h	47			

[a] Ref.[12]; [b] 1,3-CHD 1,3-cyclohexadiene; [c] the yields are based on the consumed starting material of which 32·5% was recovered; [d] the product still contained some tetrahydrofuran.

DISCUSSION

The results obtained from the kinetic measurements of dehydrofluorination of *erythro-* and *threo*-α-bromo-α'-fluorosuccinic acid and their esters were interpreted in the previous papers[7,8]. It may be assumed that the reaction proceeds by way of a variable transition state with a "carbanion-like" character[14] (cf. structure *A*). A clean-cut Elcb mechanism is unlikely since under several attempted conditions it was not possible to achieve any hydrogen–deuterium exchange[7].

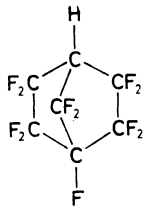


A

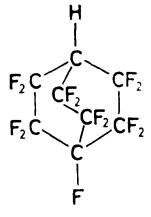
Factors contributing to the elongation of the carbon–hydrogen bond in the transition state are: (i) "acidifying" effect of fluorine which stabilizes the partial negative charge on β-carbon, and (ii) "acidifying" effect of bromine in α-position to the hydrogen.

Both these effects can be documented from the literature. The relative acidities of hydrogen in polyfluoro compounds show that it is β-(and not α-) fluorine that is responsible for the acidifying effect[15]:

CHF_3	$CHF_2(CF_2)_5CF_3$	$CHF(CF_3)_2$	$CH(CF_3)_3$	*V*	*VI*
1	6	$2 . 10^5$	$1 . 10^9$	$5 . 10^9$	$5 . 10^{11}$



V



VI

Based on extensive work of Streitwieser and coworkers[15,16], the "acidification" of the hydrogens β- to fluorine is ascribed to the inductive effect rather than to the "negative hyperconjugation". However, the fact, that in 1,1,1-trifluoroethyl carbanion the C—C bond was found shortened by 0·10 Å and the C—F bond antiparallel to the lone electron pair elongated by 0·13 Å, indicates the possibility that the fluorine

hyperconjugation may also play role in the "near-carbanion" transition state[17].

In contrast to fluorine, other halogens stabilize the negative charge in α-positions, thus "acidifying" hydrogens on the same carbon to which they are bonded. This effect has been demonstrated and explained in papers of Hine and coworkers[18–21] and of Koch and coworkers[2,22]. Based on deuterium exchange reactions, "acidification" of hydrogen α to halogen decreases in the series I ~ Br ≳ Cl ≫ F. A nice example of the acidifying effect of chlorine on α-hydrogen is evident from rates of dehydrofluorination of 1-phenyl-2,2,2-trifluoroethane and 1-chloro-1-phenyl-2,2,2-trifluoroethane (ref.[22], the rates measured in EtONa/EtOH at 50°C):

Compound	$PhCH_2CF_3$	$PhCHClCF_3$
$k_2 . 10^7$, mol l^{-1} s^{-1}	3·45	256
Relative rate	1	85·3

The dehydrofluorination of α-bromo-α′-fluorosuccinic acids is faster by about two orders of magnitude than the dehydrofluorination of mono-, di- and trifluorosuccinic acids[23,24]. This demonstrates the effect of bromine on the acidification of the α--hydrogen. Compared with the rate of dehydrofluorination of monofluorosuccinic acid, the *threo*- and *erythro*-bromofluorosuccinic acids eliminate hydrogen fluoride 77 and 86 times faster, respectively[8,23,24] (Table VI).

Any further speculations as to the effect of numbers of fluorine atoms and their mutual positions on the rate of dehydrofluorination of fluorinated succinic acids

TABLE VI

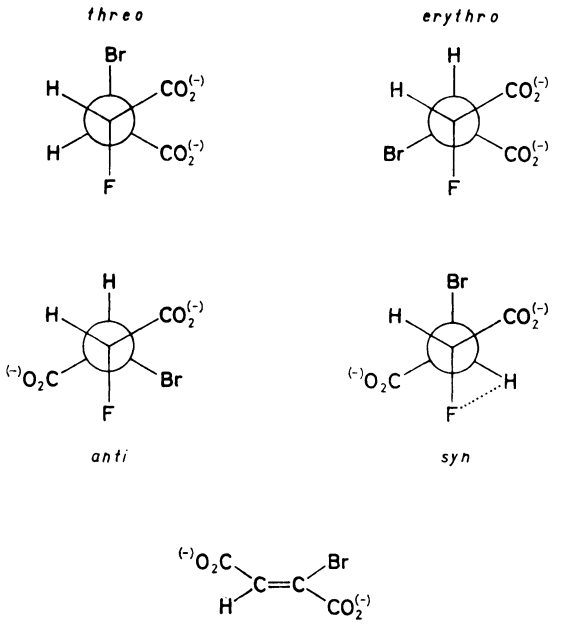
Relative rates of dehydrofluorination of α-bromo-α′-fluorosuccinic acids compared with fluorinated succinic acids using 0·05 molar concentrations of the disodium salts of the acids in 0·20 molar solutions of NaOD in D_2O at 60°C

Acid	$k_2 . 10^{4a}$ mol l^{-1} s^{-1}	Relative rates				
$HO_2CCF_2CHFCO_2H$	1·3	1				
D,L-$HO_2CCHFCHFCO_2H$	1·6	1·23			1	
meso-$HO_2CCHFCHFCO_2H$	3·1	2·38				1
$HO_2CCHFCH_2CO_2H$	4·3	3·31	1			
$HO_2CCF_2CH_2CO_2H$	11·5	8·85		1		
threo-$HO_2CCHBrCHFCO_2H$	330[b]	254	77	29	206	106
erythro-$HO_2CCHBrCHFCO_2H$	370[b]	285	86	32	231	119

[a] Taken from refs[8,23]; [b] estimate made by extrapolation.

are difficult. The rates of dehydrofluorinations of the fluorinated succinic acids lie within one order of magnitude and the minor differences defy any rationale. It is only the presence of the bromine which increases dramatically the rate of dehydrofluorination.

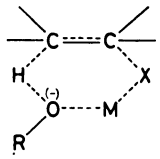
As far as the stereochemistry of the dehydrofluorination of both diastereomeric α-bromo-α′-fluorosuccinic acid is concerned, the somewhat surprising fact that both diastereomers give exclusively bromofumaric acid was rationalized in the following way[7,8]: The most probable conformation is such in which the two bulky and negatively charged carboxylate groups are as far apart as possible, i.e. *anti* to each other. In such a conformation the *threo*-acid eliminates hydrogen fluoride by the common *anti*-elimination, whereas the *erythro*-isomer undergoes *syn*-elimination. The *syn*-elimination may even be assisted by intramolecular hydrogen bonding to fluorine (Scheme 2).



SCHEME 2

Examples of *syn*-elimination in base-promoted dehydrohalogenations are very numerous and have been thoroughly reviewed[25]. *syn*-Eliminations are claimed to be the only course in the cases when a base promoted dehydrohalogenation of vicinal dihalogen compounds ejects the "poorer leaving group", e.g. fluoride rather than

chloride or bromide ion from *trans*-1-fluoro-2-chloro- or 1-fluoro-2-bromocyclohexane, respectively, and chloride rather than bromide from *trans*-1-chloro-2-bromocyclohexane[9]. Since such eliminations were achieved when "complex bases" such as sodamide and sodium tert-butoxide in tetrahydrofuran were used[9], the authors suggest a special six-membered transition state (structure *B*) involving the metal of



B

M = Na, K
X = F, Cl, Br

the base which complexes preferentially with the more negative halogen, e.g. fluorine. However such an explanation may not be entirely correct since similar eliminations of "poorer halogen leaving groups" were also achieved using potassium tert-butoxide in tert-butyl alcohol or potassium ethoxide in ethanol[10,11], and even aqueous-methanolic potassium acetate[7] or aqueous sodium hydroxide[8] or sodium deuteroxide in deuterium oxide[8,24].

Moreover in the case of *cis*- and *trans*-1,2-dihaloacenaphthenes, the preferential elimination of "poorer halogen leaving group" achieved by potassium tert-butoxide in tert-butyl alcohol or by potassium ethoxide in ethanol occurred both in *syn*- as well as *anti*-mode[10]. Similar results were obtained in the series of 2,3-dihalo-2,3-dihydrobenzofurans[11].

CONCLUSIONS

The clue to the preferential elimination of "poorer halogen leaving groups" in base-promoted dehydrohalogenations of vicinal fluorobromo, fluorochloro and chlorobromo compounds is believed to be the acidity of the hydrogen in β-position to the more negative halogen. The acidifying effect of halogens on the α-hydrogen increases in the series: F $\ll$ Cl $<$ Br $\sim$ I while the effect on the β-hydrogen is minimal with the exception of fluorine which strongly enhances the acidity of the β-hydrogen. Thus in α-fluoro-β-halo compounds the β-hydrogen is acidified both by fluorine and by the other halogen. Therefore the preferential elimination of "poorer halogen leaving group" is most distinct in vicinal fluorobromo and fluorochloro compounds and not as strong in the case of chlorobromo compounds[9].

The claims that such preferential eliminations of "poorer halogen leaving groups" are contingent upon the use of "complex bases"[9] does not seem to be fully justified,

since the same effects were achieved by simple alkoxides[10,11], and even by aqueous alkalies[7,8,12,23,24]. Likewise, the arguments that the preferential eliminations occur exclusively via *syn*-elimination[25] are weakened by cases of *anti*-eliminations recorded in similar instances[7,8,10,11].

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