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ELIMINATION OF HYDROGEN FLUORIDE FROM FLUORINATED SUCCINIC ACIDS. (III)* KINETICS OF DEHYDROFLUORINATION OF *ERYTHRO*- and *THREO*-α-BROMO-α'-FLUOROSUCCINIC ACIDS

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SUMMARY

Treatment of erythro- and threo-α-bromo-α'-fluorosuccinic acids with aqueous alkali results in the elimination of hydrogen fluoride in preference to hydrogen bromide and gives almost exclusively bromofumaric acid. The elimination of hydrogen fluoride from the two above-mentioned acids is faster by 1-2 orders of magnitude than the elimination of hydrogen fluoride from any fluorinated succinic acids. Kinetic data based on ^{1}H NMR measurements are presented and possible mechanisms and stereochemistry involved are discussed.

INTRODUCTION

Elimination of hydrogen fluoride in preference to hydrogen bromide from vicinal bromofluoro derivatives is very rare. The first example, to the author's knowledge, was reported by A. K. Bose et al. in the reaction of diesters of α-bromo-α'-fluorosuccinic acid with potassium phthalimide [1]. Almost exclusive dehydrofluorination takes place in the treatment of the same esters with sodium azide [2] and with potassium acetate [2]. Preferential elimination of hydrogen fluoride was later observed also when trans-1-bromo-2-fluorocyclohexane was treated with sodium amide and sodium tert-butoxide in tetrahydrofuran [3]. From 1-chloro-2-fluoroacenaphthene hydrogen fluoride was eliminated at a faster rate than hydrogen chloride [4]. All these instances are in sharp contrast to many examples of dehydrohalogenations in which the rate of elimination follows the element trend I > Br > Cl >> F [5,6].

*Part II: Kinetics of Dehydrofluorination of Fluoro-, 2,2-Difluoro-, meso- and DL-2,3-difluoro, and Trifluorosuccinic Acids. Ref. 7.

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A kinetic study of the reaction of dimethyl and diethyl erythro- and threo-α-bromo-α'-fluorosuccinates with potassium acetate in 50% aqueous methanol or ethanol at 35° revealed that hydrogen fluoride was eliminated at a much higher rate than hydrogen bromide. The rate of dehydrofluorination depended on the concentrations of the ester and of the base, was slightly lower with erythro- than with threo-isomers, and gave predominantly esters of bromofumaric acid from both diastereomers [2]. This somewhat surprising finding was explained by syn- rather than anti-elimination from the erythro-isomers [2].

RESULTS

In a hope that more straightforward results would be obtained from elimination of hydrogen fluoride from free acids than from diesters, measurements of the rate of dehydrofluorination were carried out with erythro- and threo-α-bromo-α'-fluorosuccinic acids in aqueous sodium hydroxide using ^{1}H NMR methodology described in the previous paper [7].

Elimination of hydrogen fluoride from the both diasteromeric acids is very rapid and exclusive. No fluorofumaric or fluoromaleic acid was ever found in noticeable amounts. The only product was bromofumaric acid which was formed more rapidly from the erythro than from the threo isomer. The kinetic measurements were carried out only at two temperatures (30° and 45°). At 60° the elimination of hydrogen fluoride was complete within 5 minutes. Because of such rapid reaction the data obtained by the NMR method are not terribly accurate especially since some reaction has taken place during the preparation of the samples. Nevertheless enough data were collected to draw the following conclusions (Table 1).

1 Elimination of hydrogen fluoride follows the second order kinetics as evidenced by a linear course of the plot of ℓn B/A where B is concentration of the base and A concentration of the acid (Fig. 1).

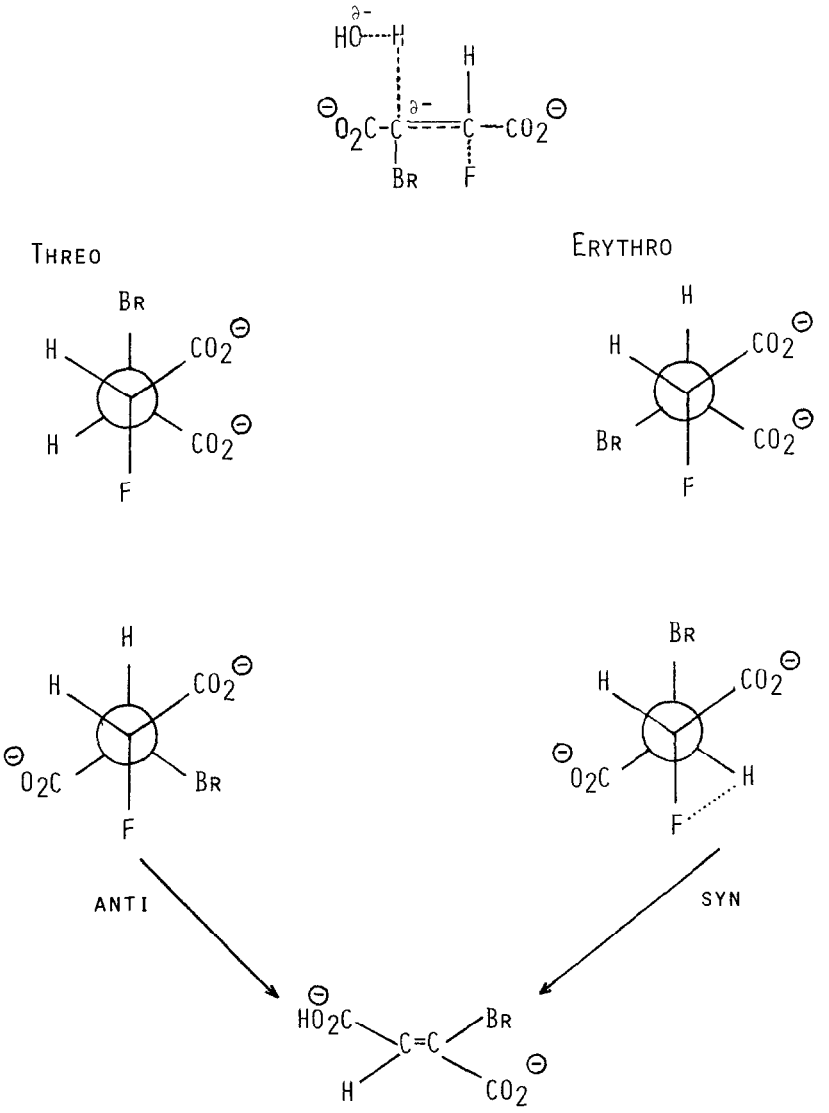
2 Arrhenius plot of the log k versus reciprocal absolute temperature gives activation energies of 12.8 and 14.8 kcal/mol for the erythro- and threo-α-bromo-α'-fluorosuccinic acids, respectively [Fig. 2].

3 Both the erythro and the threo isomers afford the same product of dehydrofluorination, i.e. bromofumaric acid. This finding implies that, while the elimination of hydrogen fluoride from the threo isomer takes place in the usual anti (trans) mode, that from the erythro acid occurs in the less common syn (cis) mode.

TABLE 1

DEHYDROFLUORINATION OF α-BROMO-α-FLUOROSUCCINIC ACIDS

$HO_2CCHBr-CHFCO_2H$	CONCN. OF ACID	CONCN. OF BASE	TEMP. °C	HALF-LIFE TIME, MIN.	K_2 MOL ℓ^{-1} SEC^{-1}	E_{ACT} KCAL	ΔH‡ KCAL	ΔG‡ KCAL	ΔS‡ CAL/°
ERYTHRO	0.05M	0.2M	30	9.25	0.00405 ±15.3%	12.8	12.2	21.1	-29.4
ERYTHRO	0.05M	0.2M	45	3.0	0.01133 ±12.0%			21.5	
THREO	0.05M	0.2M	30	18.75	0.00307 ±4.9%	14.8	14.2	21.2	-23.3
THREO	0.05M	0.2M	45	4.8	0.01010 ±4.0%			21.6	



Scheme. TRANSITION STATES OF DEHYDROFLUORINATION OF α-BROMO-α'-FLUOROSUCCINIC ACIDS

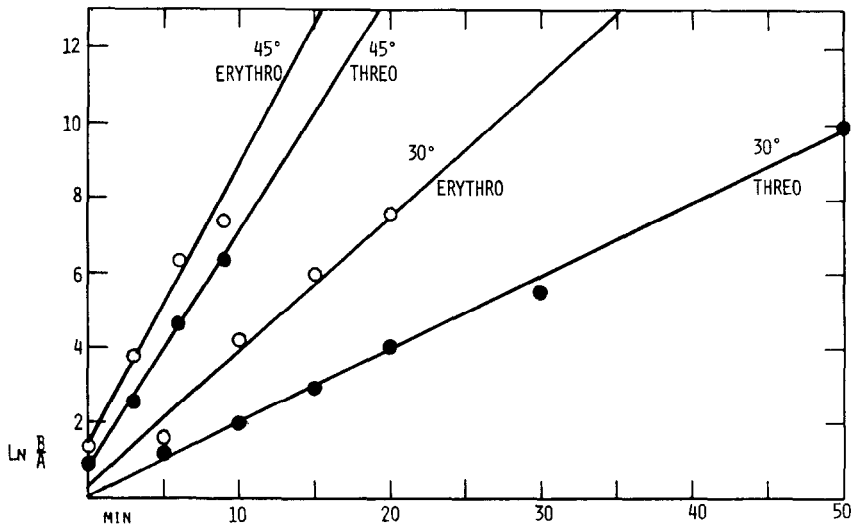


Fig. 1. Plot of ln [B]/[A] *versus* time, *erythro*- and *threo*-α-bromo-α'-fluorosuccinic acid at 30° and 45°.

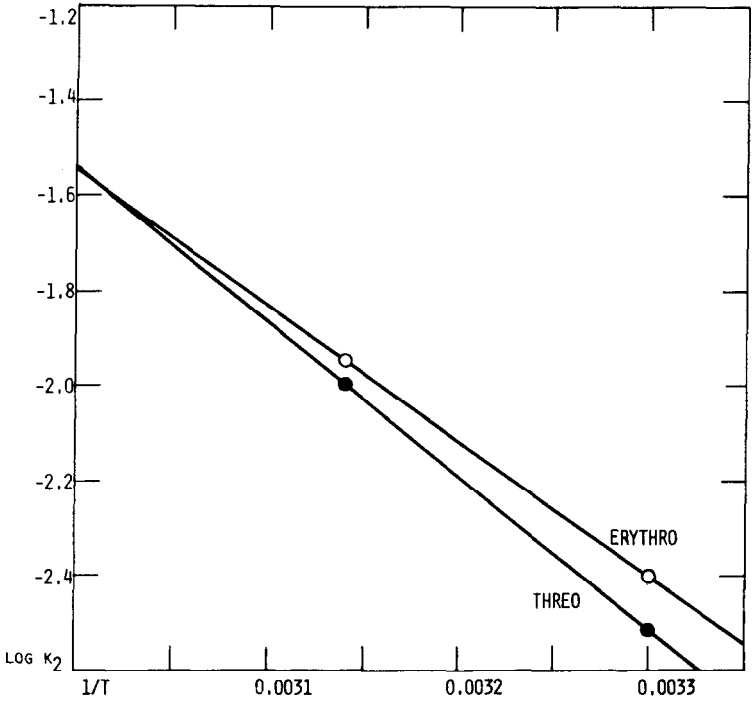


Fig. 2. Arrhenius plot of log K *versus* 1/T, *erythro*- and *threo*-α-bromo-α'-fluorosuccinic acid.

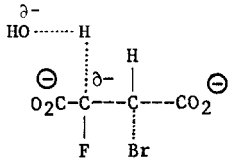
DISCUSSION

The present study reveals two interesting features, one kinetic and the other stereochemical.

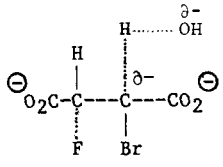
Preferential elimination of hydrogen fluoride from α-bromo-α'-fluorosuccinic acids excludes the E1 and E2 mechanisms since in both the transition state involves breaking of the carbon fluorine bond which is considerably stronger than carbon-bromine bond (the respective values being 107-116 kcal versus 66 kcal).

Clear-cut carbanion mechanism (E1cb) can also be ruled out since no hydrogen-deuterium exchange was observed on treatment of the acids or their salts with deuterated solvents (deuterium oxide and deuteromethanol). The esters of α-bromo-α'-fluorosuccinic acids did not exchange hydrogens for deuterium in deuteromethanol in the absence of a base at 95°. In the presence of base an immediate precipitation of fluoride took place [2].

Preferential elimination of hydrogen fluoride can be best explained using the concept of variable transition state with "nearly carbanion' character [6,8]. Such a mechanism is in agreement with the second order kinetics. Two carbanion-like species can be visualized as transition states for the dehydrohalogenation.



A



B

While in the transition state A the partial negative charge on carbon is α to fluorine and β to bromine, in the transition state B the charge is on the carbon α- to bromine and β- to fluorine.

It has been demonstrated on many examples that fluorine stabilizes the negative charge not on α-carbon but on β-carbon. In this way the high acidity of hydrogens on carbons β- to fluorine is accounted for [9]. In contrast, bromine (and also chlorine and iodine) stabilizes the negative charge on α-carbon as shown in high acidities and hydrogen-deuterium exchanges in the case of haloforms [10] and their homologs [11,12] and analogs [13].

The transition state B with the partial negative charge on carbon α- to bromine and β- to fluorine is therefore preferred. Its collapse to water, fluoride ion and the unsaturated bromo acid is enhanced by high resonance energy of the α,β-conjugated system and by solvation of the fluoride anion.

The other surprising feature of the action of alkalies on α-bromo-α'-fluorosuccinic acids, the exclusive syn elimination of hydrogen fluoride from the erythro acid, can be accounted for by the following argument.

In the dianions of α-bromo-α'-fluorosuccinic acid the most favored conformation is undoubtedly the one in which the two negatively charged carboxylate groups are as far apart as possible, i.e. anti to each other, regardless of the stereoisomer involved. In the case of the threo-diasteromer such conformation has the hydrogen and the fluorine anti to each other, and therefore placed properly for the anti-elimination.

Such mutual position of the hydrogen and fluorine in the erythro-compound would require the two carboxylate groups to occupy a gauche position which is both sterically and electronically less advantageous. It is therefore not surprising that the elimination of hydrogen fluoride takes place in a syn-mode as energetically more favorable. This interpretation is also corroborated by the fact that the activation energy for the syn-dehydrofluorination of the erythro-acid was found smaller by 2 kcal than that of the anti-dehydrofluorination of the threo-acid (Table 1).

Syn-stereochemistry in eliminations of hydrogen halides takes place quite frequently and is usually attributed to special bases and solvents which tend to complex with the substrates in the transition states [14,15]. Syn-elimination of hydrogen fluoride from 1-deutero-1-fluoro-1-phenylsulfonyl-2-phenylthioethane was accomplished by triethylamine [14], and syn-eliminations of hydrogen fluoride from trans-1-bromo-2-fluorocyclohexane by a mixture of sodium amide and sodium tert-butoxide in tetrahydrofuran [3]. Treatment of trans-1-chloro-2-fluoroacenaphthene with solutions of potassium tert-butoxide in tert-butyl alcohol and/or sodium ethoxide in ethanol resulted also in syn-elimination of hydrogen fluoride (rather than hydrogen chloride) [4].

EXPERIMENTAL

Apparatus

The measurements were carried out in 5 mm NMR tubes using JEOL FX-200 Fourier Transform NMR Spectrometer with a super-conducting magnet.

Chemicals

Both, erythro- and threo-α-bromo-α'-fluorosuccinic acids were obtained by hydrolysis of their dimethyl esters in a way described in a special paper and were purified by crystallization. The erythro- compound had mp. of 146-147°, the threo-compound mp. of 145.5-146.5°. The mixed mp. was 116-122°, [16].

Sodium deuteroxide (98% D), deuterium oxide (99.8%), deutero-acetone (99.0%) and other chemicals were of commerical grade.

Measurements

The methodology of the kinetic measurements was the same as described in the second communication of this series [7].

The bromofluoro acid (0.0322g, 0.00015 mol) was dissolved in a 3 ml volumetric flask in deuterium oxide, 0.90 ml of 1.0 N sodium deuteroxide (0.0009 mol) was added while the flask was immersed in an ice-water bath, the contents of the flask were stirred while cooled, and deuterium oxide was added to the mark (with a correction for the temperature of filling and that of the calibration of the flask). An aliquot - 0.5 ml - was transferred into a 5 mm NMR tube immediately after the preparation of the sample and the ^1H NMR spectra were recorded at preset intervals at given temperatures.

With six equivalents of the base (two needed for the neutralization of the acid) the concentration of the acid (in form of its disodium salt) was $[A]_o$ = 0.05M and the starting concentration of the base $[B]_o$ = 0.20M.

CONCLUSIONS

The loss of 'poorer' halogen leaving group was claimed by some authors to be associated with syn-elimination and with special 'complex bases' [3,15]. However, in cis-1-chloro-2-fluoroacenaphthene where syn-elimination is impossible hydrogen fluoride was removed preferentially to hydrogen chloride even in the anti-elimination process [4], and in the present work the dehydrofluorination was achieved by aqueous alkali. The reasoning of the preferential elimination of 'poorer' halogen leaving group and its stereochemistry as offered in the above discussion may not be entirely general but accounts for the present findings in a simple and understandable way.

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