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ELIMINATION OF HYDROGEN FLUORIDE FROM FLUORINATED SUCCINIC ACIDS. (II)*
KINETICS OF DEHYDROFLUORINATION OF FLUORO-, 2,2-DIFLUORO-, MESO- AND DL-2,3-DIFLUORO-, AND TRIFLUOROSUCCINIC ACIDS

M. HUDLICKY and T. E. GLASS

Department of Chemistry, Virginia Polytechnic Institute and State
University, Blacksburg, Virginia 24061 (U.S.A.)

SUMMARY

Elimination of hydrogen fluoride from fluorosuccinic acid gave fumaric acid, from 2,2-difluorosuccinic acid, meso- and DL-2,3-difluorosuccinic acid fluorofumaric acid, and dehydrofluorination of trifluorosuccinic acid afforded difluoromaleic acid. Kinetic data based on ^1H NMR measurements are presented for temperatures of 60°, 75° and 90°. All the dehydrofluorinations follow second order kinetics. Activation energies for the dehydrofluorination of the above acids were found to be: 19.3, 17.3, 18.8, 17.9 and 18.3 kcal, respectively. Since both diastereomeric 2,3-difluorosuccinic acids give fluorofumaric acid as the only product of dehydrofluorination, one of them (DL) undergoes trans elimination while the other (meso) must undergo cis elimination.

INTRODUCTION

The discovery of elimination of hydrogen fluoride in preference to hydrogen bromide from dimethyl and diethyl 2-bromo-3-fluorosuccinates [1] triggered off a study of kinetics of elimination of hydrogen fluoride from fluorinated succinic acids. The first part of this study [2] was carried out by titrimetric determination of fluoride ion using fluoride selective electrode. This somewhat time consuming technique required working with fairly large volumes and consequently relatively large amounts of fluorinated acids.

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*Part I: Kinetics of Dehydrofluorination of 2,2-Difluorosuccinic Acid, see reference 2.

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In order to cut down on the amounts of the fluorinated materials used in the kinetic measurements, and even on the amount of work involved, we attempted to utilize NMR spectroscopy as the analytical tool. Because of the relatively low concentrations of the fluorinated acids used in our experiments simple NMR instruments were not sensitive enough, and FFT arrangement had to be used.

Initially ^{19}F NMR was attempted for the determination of the unsaturated products in aqueous solutions. Unfortunately integration of signals at certain chemical shifts was impossible for interference by polytetrafluoroethylene parts in the instrument. Therefore we had to resort to the use of ^{1}H NMR which required work with deuterated base and solvent. We used semimicroscale volumetric technique and consequently the accuracy of our measurements by the NMR method was only about one half of that of the titrimetric determination of fluoride ion [2]. Also the reproducibility of the NMR measurements was worse than that of titration experiments mainly because integration of the NMR signals of some measurements suffered from occasional variations of the signal to noise ratio of the instrument. As a trade-off the NMR technique reduced the amount of samples as all the measurements at one temperature were carried out in the same NMR tube.

All in all, the NMR method although less accurate than titration provided enough data for the evaluation of the dehydrofluorination process. As can be seen in Fig. 1, all the starting materials as well as the products give spectra easily distinguishable from each other. In addition, with the exception of the product of dehydrofluorination of trifluorosuccinic acid - difluoromaleic acid - the ^{1}H NMR spectra reveal the stereochemistry of the dehydrofluorination since the signals of cis and trans-products are distinctly different. Identification of difluoromaleic acid was made by ^{19}F NMR in a separate sample.

EXPERIMENTAL

Apparatus

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

Chemicals

2,2-Difluorosuccinic acid was the commercial product of PCR and found to be 100% ± 0.2% pure by alkalimetric titration [2]. The other fluorinated succinic acids were prepared according to the literature and purified by crystallization.

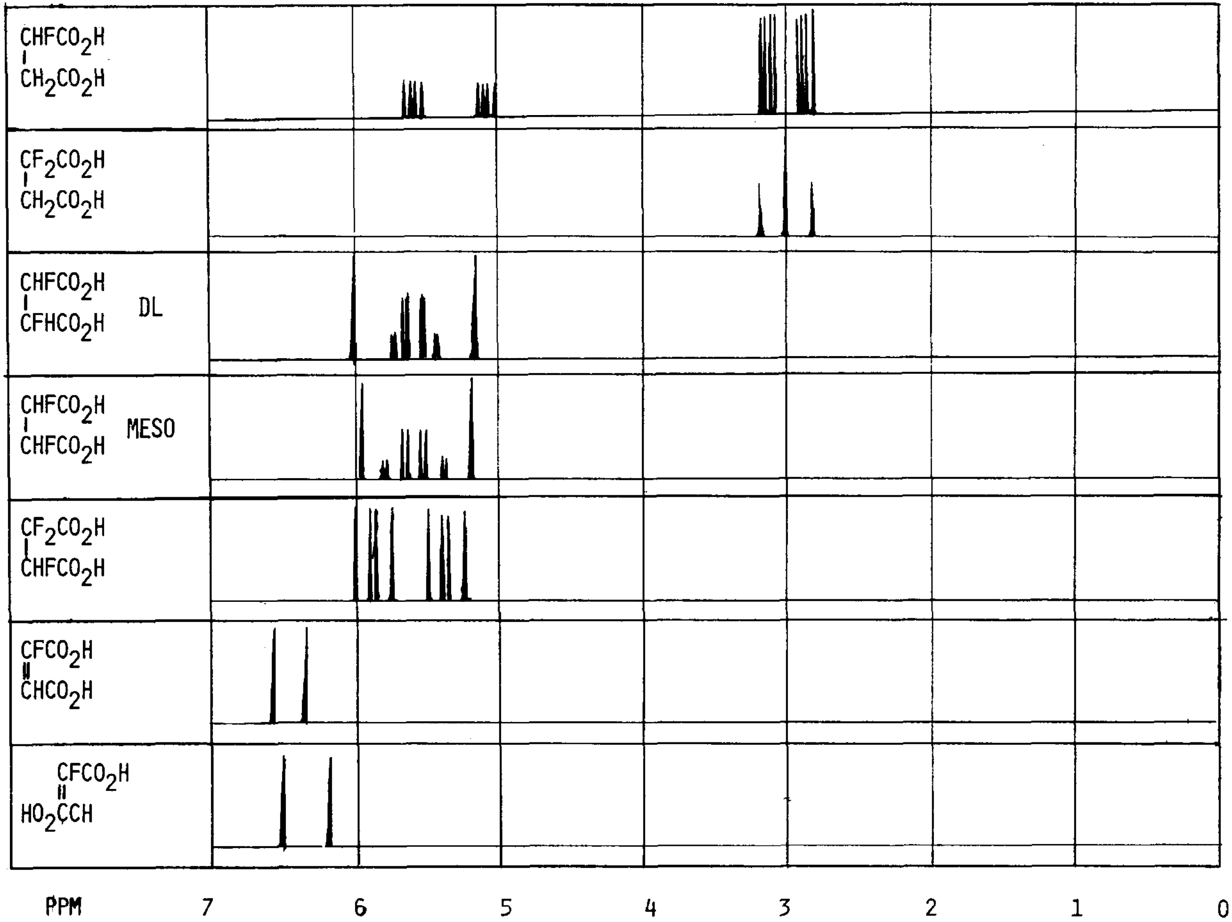

Fig. 1. ^{1}H NMR spectra of fluorinated succinic acids.

Fluorosuccinic acid was obtained by catalytic hydrogenation of fluoromaleic or difluoromaleic acid [3]. In spite of repeated recrystallizations to constant m.p. of 143° (Lit. [4] m.p. 144-145°) the acid contained up to 7.5% of succinic acid as found from the NMR spectrum. Correction of the concentrations owing to this impurity was only 0.1-0.7% of the rate constant.

DL-2,3-Difluorosuccinic acid was prepared according to the literature [5] from meso-tartaric acid. M.p. 207-208° (Lit. m.p. 208-210°).

meso-2,3-Difluorosuccinic acid was obtained analogously from D- or L-tartaric acid [5,6]. M.p. 182-184° (Lit. m.p. [5] 182-184°, [6] 185-186°).

Trifluorosuccinic acid was prepared according to the literature [7]. M.p. 107-111° (Lit. m.p. 111-112°).

MEASUREMENTS

The fluorinated acid (0.0015 mol) was dissolved in a 3 ml volumetric flask in deuterium oxide, 0.90 ml of 1.00 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 difference in the temperature of filling and that of the calibration of the flask). The flask was kept in the ice bath until all the measurements were completed. An aliquot - 0.5 ml - was transferred into a 5 mm NMR tube, this was inserted into the probe of the instrument, and the ^{1}H NMR spectra were recorded at preset intervals at a given temperature. Separate aliquots were used for measurements at different temperatures (60°, 75° and 90°).

With the above concentrations of chemicals, the starting concentration of the acid (in form of its disodium salt) $[A]_0$ was 0.05 M. The starting concentration of the base $[B]_0$ was 0.20 M (two of the six equivalents of the base being consumed for the neutralization of the fluorinated acid).

In several experiments using the same concentration of the fluorinated acid but different concentrations of the base a special volumetric flask with marks at 1.5 ml and 3.0 ml volumes was used. After preparing the solution for the measurement at the above concentrations, $[A]_0 = 0.05$, $[B]_0 = 0.20$, exactly one half of the solution in the special volumetric flask was pipetted off and used for the measurement. Then 0.000075 mol of the same fluorinated acid was added into the flask, followed by 1.05 ml of 1.00 N sodium deuteroxide, and the flask was filled to the 3.0 ml mark with deuterium oxide. In this way the concentrations of the acid $[A]_0$ and of the base $[B]_0$ were made 0.05 M and 0.40 M, respectively. Other concentrations were fixed analogously.

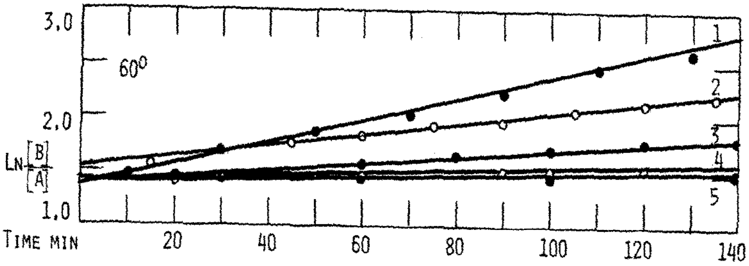

Fig. 2. Plot of ln [B]/[A] versus time; 1, $HO_2CCF_2CH_2CO_2H$; 2, $HO_2CCHFCH_2CO_2H$; 3, meso-$HO_2CCHFCHFCO_2H$; 4, DL-$HO_2CCHFCHFCO_2H$; 5, $HO_2CCF_2CHFCO_2H$.
[B] Concentration of sodium deuteroxide.
[A] Concentration of the acids.

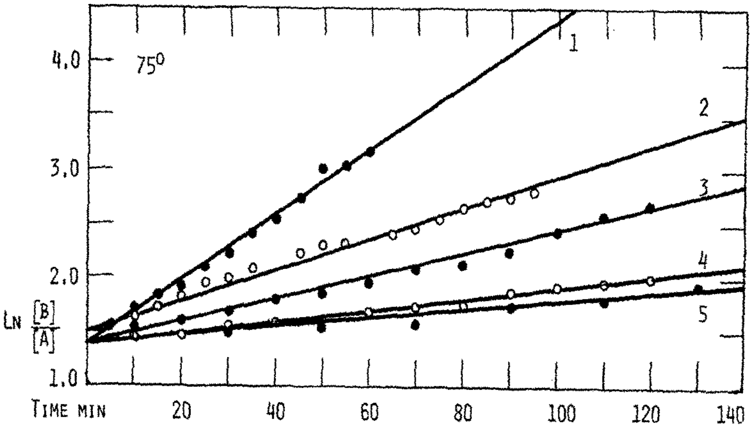

Fig. 3. Plot of ln [B]/[A] versus time; 1, $HO_2CCF_2CH_2CO_2H$; 2, $HO_2CCHFCH_2CO_2H$; 3, meso-$HO_2CCHFCHFCO_2H$; 4, DL-$HO_2CCHFCHFCO_2H$; 5, $HO_2CCF_2CHFCO_2H$.
[B] Concentration of sodium deuteroxide.
[A] Concentration of the acids.

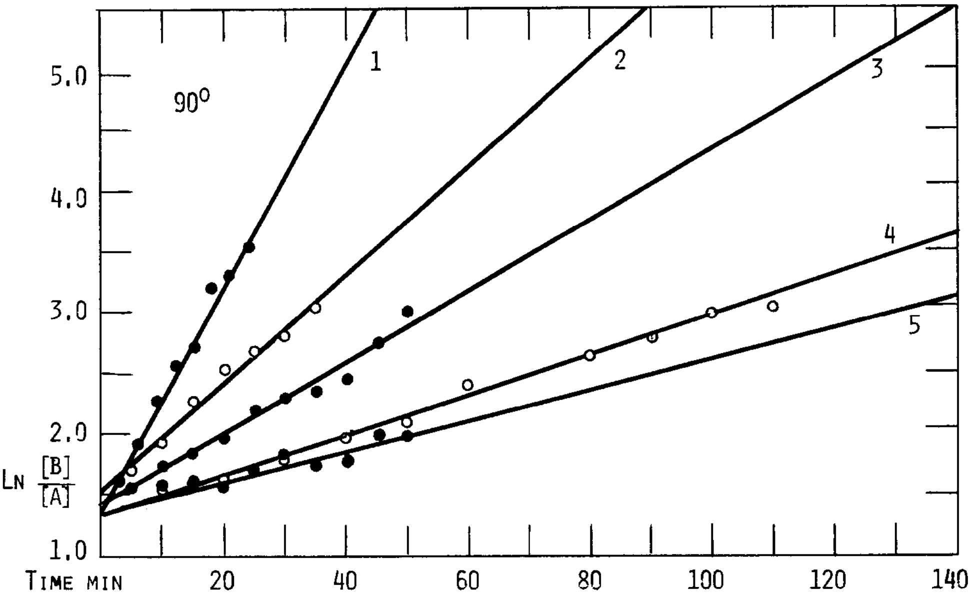

Fig. 4 Plot of ln [B]/[A] versus time; 1, $HO_2CCF_2CH_2CO_2H$; 2, $HO_2CCHFCH_2CO_2H$; 3, meso-$HO_2CCHFCHFCO_2H$; 4, DL-$HO_2CCHFCHFCO_2H$; 5, $HO_2CCF_2CHFCO_2H$.
[B] Concentration of sodium deuteroxide.
[A] Concentration of the acids.

After the spectra have been recorded and the individual NMR signals integrated concentrations of the acid and the base were determined from the ratios of the signals of the starting saturated acid and the resulting unsaturated acid (taking into consideration the number of hydrogens involved in each signal).

In the case of trifluorosuccinic acid which is converted to a proton-free product - difluoromaleic acid - a standard, sodium 3-trimethylsilyl propanesulfonate, was added and the decrease of the starting material was calculated with respect to the standard. In contrast to the literature [7] we did not find any difluorofumaric acid as a product of the dehydrofluorination of trifluorosuccinic acid.

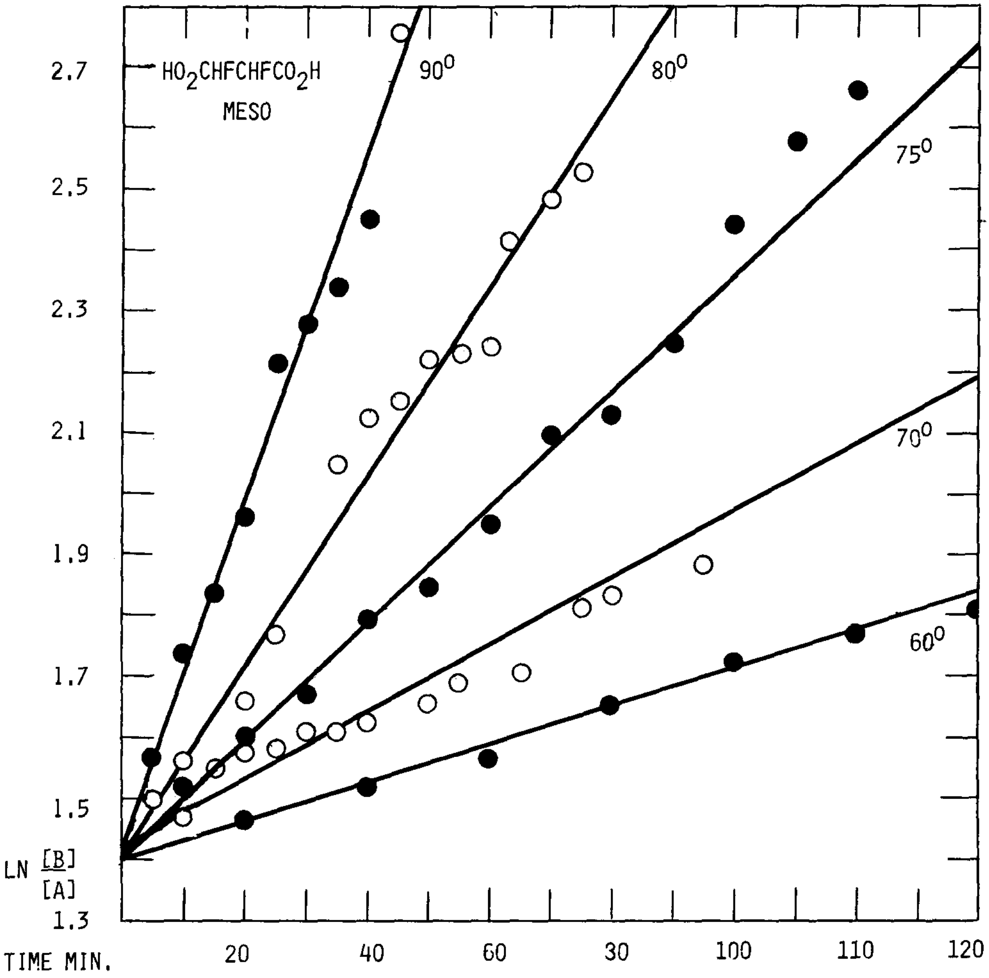

Fig. 5. Plot of ln [B]/[A] versus time for meso-$HO_2CCHFCHFCO_2H$ at temperature 60°, 70°, 75°, 80° and 90°C. [B] Concentration of sodium deuteroxide, [A] Concentration of meso-2,3-difluorosuccinic acid.

TABLE 1

Rate constants ($k_2 \times 10^3$ mol ℓ^{-1} sec^{-1}) and half-life times (min) of dehydrofluorination of fluorinated succinic acids at concentrations:

Acid	Temperature °C		
	60°	75°	90°
$HO_2CCHFCH_2CO_2H$	0.432 (±2.7%)	1.50 (±2.9%)	4.92 (±6.6%)
	(81 min)	(26 min)	(11 min)
$HO_2CCF_2CH_2CO_2H$	1.15 (±3.1%*)	3.65 (±3.8%**)	10.3 (±5.0%)
	(56 min)	(21 min)	(6.5 min)
$HO_2CCHFCHFCO_2H$	0.308 (±4.2%)	1.17 (±4.0%)	3.30 (±6.3%)
meso	(200 min)	(60 min)	(19 min)
$HO_2CCHFCHFCO_2H$	0.16 (±4.8%)	0.562 (±2.6%)	1.75 (±3.1%)
DL	(778 min)***	(106 min)	(38 min)
$HO_2CCF_2CHFCO_2H$	0.127 (±6.9%)	0.41 (±4.8%)	1.28 (±18.6%)
	(419 min)***	(152 min)	(42 min)

*k_2 found by titration [2]: 1.68 (43.5 min).

**k_2 found by titration [2]: 4.0-4.6 (23.5 min).

(The discrepancies may be due to the different species measured: fluoride ion in the titrimetric method, and unsaturated fluoro acid in the NMR method.

***Based on extrapolation

TABLE 2

Rate constants (k_2 x 10^3 mol ℓ^{-1} sec^{-1}) and half-life times (min) of dehydrofluorination of fluorinated succinic acids at different concentrations of base at 90°

Acid	Concn. of Acid	Concn. of Base	K_2x10^3 mol/L/sec	Half-life Time, min
$HO_2CCHFCHFCO_2H$ meso	0.05 M	0.20 M	3.17 ± 5.1%	21 min
	0.05 M	0.443 M	2.63 ± 6.1%	10 min
$HO_2CCHFCFHCO_2H$ DL	0.05 M	0.20 M	0.953 ± 6.7%	60 min
	0.05 M	0.40 M	1.41 ± 6.3%	26 min
$HO_2CCF_2CHFCO_2H$	0.05 M	0.15 M	1.17 ± 3.8%	75 min
	0.05 M	0.40 M	1.51 ± 19%	17 min

TABLE 3

Activation Energies (kcal/mol) of Dehydrofluorination of Fluorinated Succinic Acids

Acid	$CHFCO_2H$ | CH_2CO_2H	CF_2CO_2H | CH_2CO_2H	$CHFCO_2H$ | $CHFCO_2H$ meso	$CHFCO_2H$ | $CFHCO_2H$ DL	CF_2CO_2H | $CHFCO_2H$
E_{act} (kcal/mol)	19.3	17.3	18.8	17.9	18.3

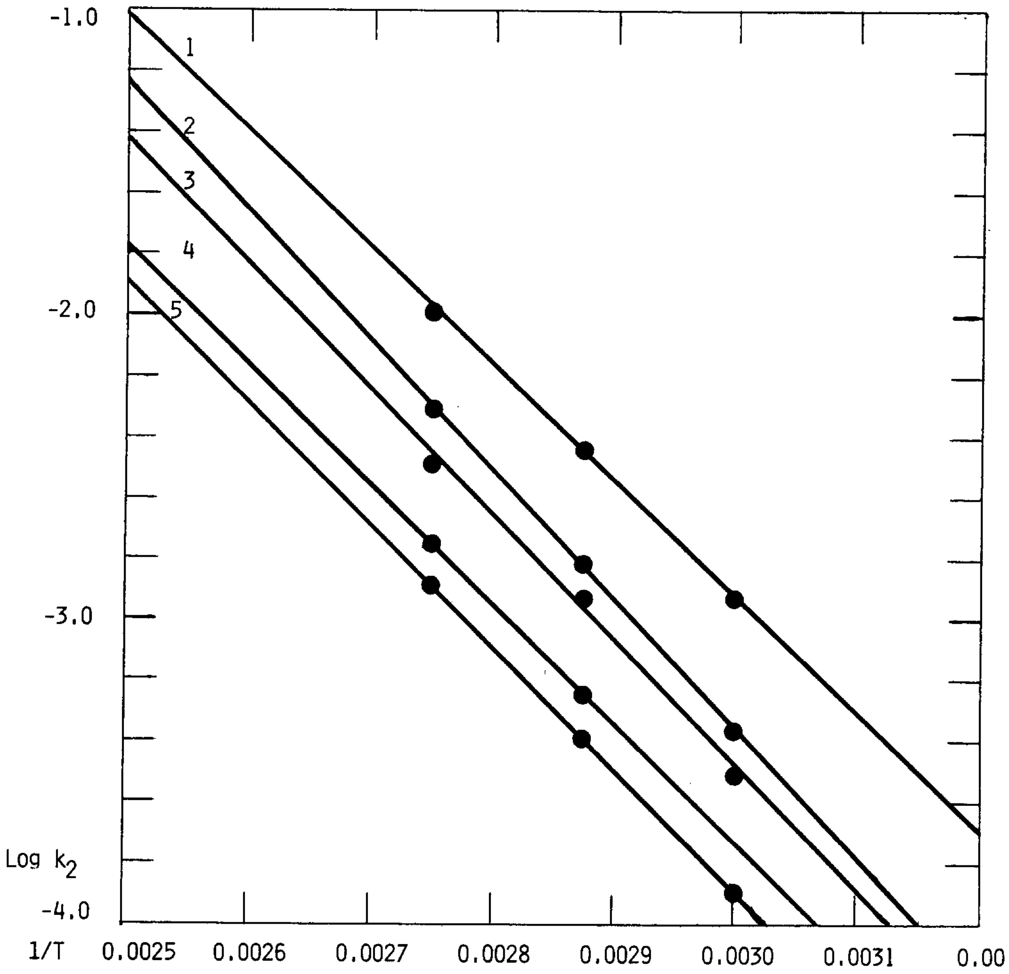

Fig. 6. Arrhenius plot k_2 versus 1/T.

1. $HO_2CCF_2CH_2CO_2H$.
2. $HO_2CCHFCH_2CO_2H$
3. meso - $HO_2CCHFCHFCO_2H$
4. DL-$HO_2CCHFCHFCO_2H$
5. $HO_2CCF_2CHFCO_2H$

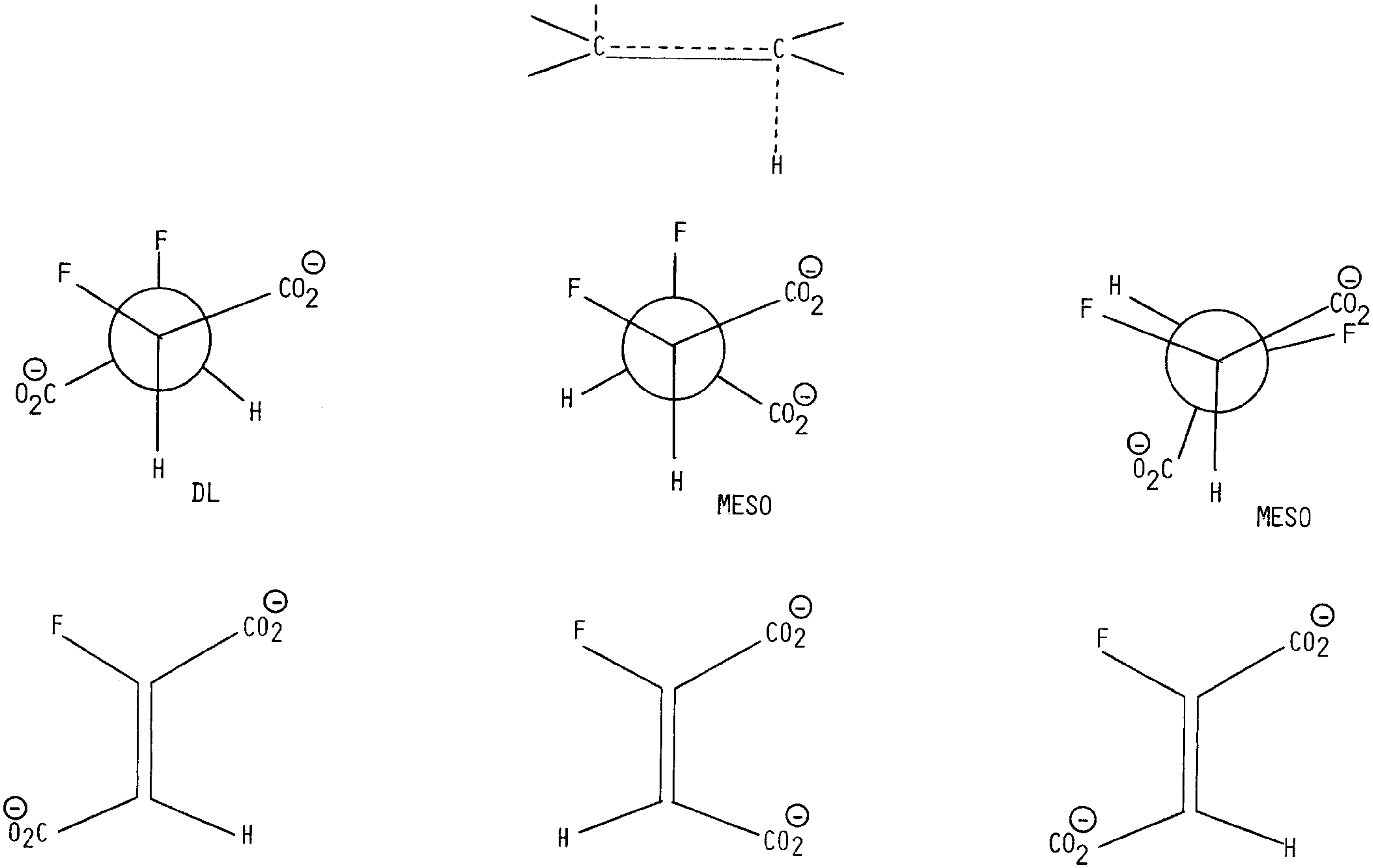

Fig. 7. Transition states of dehydrofluorination.

RESULTS AND DISCUSSION

The results of the measurements made at 60°, 75°, and 90° are shown in Fig. 2-5.

Fig. 2-4 are plots of ln[B]/[A] versus time at 60°, 75° and 90° for all the five fluorinated succinic acids. It can be seen that the rate of elimination of hydrogen fluoride decreases in the order: 2,2-difluoro-, fluoro- > meso-2,3-difluoro-> DL-2,3-difluoro > and trifluorosuccinic acid. The quantitative data, rate constants and half-life times, are listed in Table 1.

Fig. 5 shows a plot of ln[B]/[A] versus time of meso-2,3-difluorosuccinic acid at 60°, 70°, 75°, 80° and 90°. The results of the measurements of the rate of dehydrofluorination of meso- and DL-2,3-difluorosuccinic acids and of trifluorosuccinic at different concentrations of the base are presented in Table 2, which lists the rate constants and half-life times. The results confirm the second order kinetics of the reaction.

Fig. 6 shows the Arrhenius plot of log of k_2 versus reciprocal absolute temperatures for all the five fluorinated succinic acids. The activation energies calculated from the lines in Fig. 6 are listed in Table 3.

CONCLUSIONS

Based on the kinetic measurements of the elimination of hydrogen fluoride from fluorinated succinic acids the following conclusions can be drawn:

Dehydrofluorination of fluorinated succinic acids follows second order kinetics as proven by linear relationship of the logarithm of the concentration of base over the concentration of the saturated fluorinated acid versus time (Fig. 2-5), and by half-life times at different concentrations of the base (Tables 1 and 2).

Comparative preliminary experiments with 2-bromo-3-fluorosuccinic acid (compare also ref. 1) showed that only hydrogen fluoride, and not hydrogen bromide, is eliminated under basic conditions. This means that the rate-determining step in the dehydrohalogenation is not the carbon-halogen bond breaking but rather carbon-hydrogen bond breaking.

Anionic mechanism (Elcb) can be ruled out since no hydrogen-deuterium exchange was ever observed under the conditions used. Our results can be best accomodated by Bunnett's theory of variable transition state [8] (Fig. 7). With poor leaving groups such as fluoride ion the transition state approaches that of carbanion with carbon-hydrogen bond weakened. Such 'acidification' of hydrogen at carbon β- to fluorine has been recorded and is well documented

[9]. In view of that it is not surprising that 2,2-difluorosuccinic acid eliminates hydrogen fluoride faster than 2-fluorosuccinic acid. On the other hand it is hard to rationalize the decreasing rates of dehydrofluorination in the rest of the series (Table 1).

It came as a surprise that meso-2,3-difluorosuccinic acid eliminated hydrogen fluoride about twice as fast as its DL-diastereomer. In the case of the corresponding dibromosuccinic acids dehydrohalogenation took place much faster from the DL than from the meso form.

While dehydrofluorination of trifluorosuccinic acid gave difluoromaleic acid, all the rest of the fluorinated succinic acids gave only trans acids, i.e. fumaric or fluorofumaric acid, respectively. This finding is in agreement with the expected transition state for trans elimination, with the exception of meso-2,3-difluorosuccinic acid which should give fluoromaleic acid. Since it gave exclusively fluorofumaric acid (without a trace of fluoromaleic acid) we have to assume that, in this particular case, cis elimination took place. From Fig. 7 it follows that in the transition state for dehydrofluorination of the meso-2,3-difluorosuccinic acid in a trans mode the two negatively charged and bulky carboxylate groups would be close together. Transition state for cis dehydrofluorination accomodates the two carboxylates better. The eclipsing of hydrogen and fluorine may not mean too great a steric hindrance because of the relatively small volume of fluorine atom. In fact the eclipsed conformation may even be assisted by intramolecular hydrogen bonding which could also help the elimination of hydrogen fluoride by changing the leaving group (fluoride to hydrogen fluoride).

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