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HYDROGENOLYSIS OF CARBON-FLUORINE BONDS IN CATALYTIC HYDROGENATION

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SUMMARY

In contrast to the strong stability of saturated fluorine compounds in catalytic hydrogenation, allylic and vinylic fluorine atoms are displaced by hydrogen relatively readily. Hydrogenolysis of carbon-fluorine bonds accompanies addition of hydrogen across double bonds in methyl 4-fluoro-3-methyl-2-pentenoate, in fluoromaleic, fluorofumaric, difluoromaleic and difluorofumaric acids. The extent of hydrogenolysis is affected by the catalyst and by the solvent. A concerted mechanism is offered to explain the readiness of the hydrogenolysis in allylic and vinylic fluorides.

INTRODUCTION

Replacement of fluorine by hydrogen in catalytic hydrogenations is generally much more difficult than that of the other halogens [1,2]. However, several tens of hydrogenolyses of carbon-fluorine bonds have been recorded and reviewed in the literature [3,4]. Of these, only very few involve sp^3 carbon-fluorine bonds. This type of bond is hydrogenolyzed only at very energetic conditions at a minimum temperature of 100°C [5,6,7].

On the other hand, allylic, benzylic, vinylic and aromatic fluorine atoms are replaced by hydrogen fairly easily, very often at room temperature [3,4]. This is also true of fluorine atoms in α-position to nitro groups [8].

RESULTS

In our laboratory several cases of easy and unexpected hydrogenolysis of allylic and vinylic fluorine atoms were encountered. Catalytic hydrogenation of methyl 4-fluoro-3-methyl-2-pentenoate (I) gave, depending on the reaction conditions, varying ratios of methyl 4-fluoro-3-methylpentanoate (II) (product of addition of hydrogen) and methyl 3-methylpentanoate (III) (product of addition of hydrogen and hydrogenolysis) [9].

$$CH_3CHFC(CH_3)=CHCO_2CH_3 \text{ (I)} \xrightarrow[\text{Pd, Rh or Pt; R.T.}]{H_2} CH_3CHFCH(CH_3)CH_2CO_2CH_3 \text{ (II)} + CH_3CH_2CH(CH_3)CH_2CO_2CH_3 \text{ (III)}$$

On the other hand, no hydrogenolysis of the carbon-fluorine bond took place in a brominated derivative of I, methyl 2-bromo-4-fluoro-3-methyl-2-pentenoate (IV) which was recovered unscathed after catalytic hydrogenations under extremely vigorous conditions (Table I).

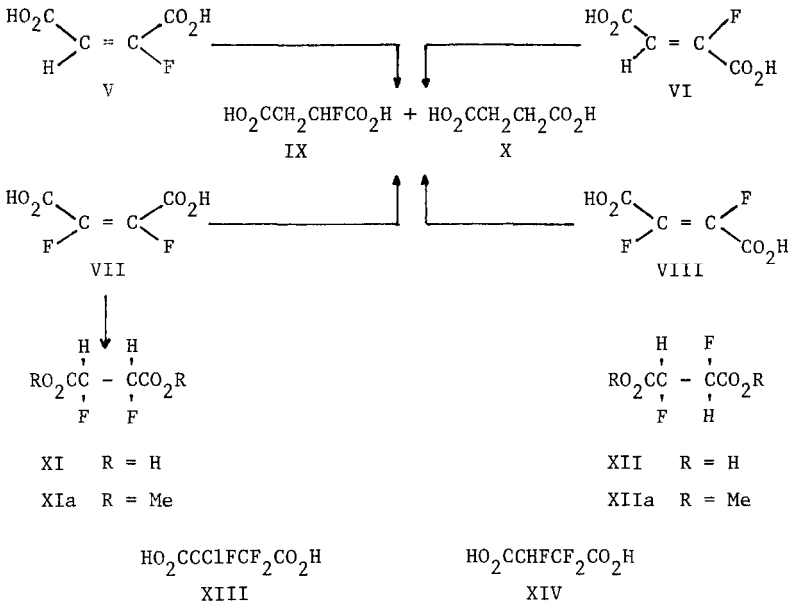
$$CH_3CHFC(CH_3)=CBrCO_2CH_3 \xrightarrow[\text{catalyst}]{H_2} \text{N.R.}$$

Table I

Hydrogenation Conditions Applied to Methyl 2-Bromo-4-fluoro-3-methyl-2-pentenoate IV

Catalyst	PtO_2			Pt	Pt(30%) Asbestos		Pd(10%) Charcoal				
Amount %	20	20	20	20	50	50	10	10	10	10	45
Solvent	AcOH						Et_2O				
Temperature, °C	25	65	80	80	70	25	25	25	55	75	25
Pressure, atm.	70	75	80	80	70	70	1	70	70	70	70
Time, hrs.	18	24	16	3	5	2	24	6	3	10	22

Hydrogenolysis of vinylic fluorines was found to take place very readily during catalytic hydrogenations of fluoromaleic acid (V), fluorofumaric acid (VI), difluoromaleic acid (VII) and difluorofumaric acid (VIII).



$HO_2CCClFCF_2CO_2H$
XIII

$HO_2CCHFCF_2CO_2H$
XIV

The fluoro acids V and VI yielded mixtures of fluorosuccinic acid (IX) and succinic acid (X) in ratios depending on reaction conditions, especially on the catalyst and the solvent.

Catalytic hydrogenation of difluoromaleic acid (VII) produced only little, if any, meso-1,2-difluorosuccinic acid (XI). Major products were again fluorosuccinic (IX) and succinic acids (X). Difluorofumaric acid (VIII) gave only IX and X. The product of addition of hydrogen — DL-1,2-difluorosuccinic acid (XII) was not formed. The proof of configurations of XI and XII will be reported shortly. The results of catalytic hydrogenation of compounds V, VI, VII and VIII are listed in Table II.

From the results in Table II it can be seen that the outcome of a hydrogenation of a fluorinated butenedioic acid depends strongly on experimental conditions. Hydrogenations over palladium in ether give predominately, if not exclusively, products of addition of hydrogen across the double bonds. Hydrogenations over rhodium and Raney nickel give more hydrogenolysis, especially in aqueous and, in particular, alkaline solutions This finding is somewhat surprising since rhodium (on alumina) is recommended as a very selective catalyst for preventing hydrogenolysis of halogens [10].

An interesting observation was made during the reduction of chlorotrifluorosuccinic acid (XIII). Since its reduction to trifluorosuccinic

Table II

Hydrogenation of Fluorinated Butenedioic Acids (25°, 1 atm.) [a]

Compound	Catalyst	Amount %	Solvent	Recovered Starting Material	XI	IX	X	XIV	Comments
V	10% Pd/C	10	Et_2O			94.0	6.0		Different solvents
	10% Pd/C	37	H_2O			75.0	25.0		
VI	10% Pd/C	10	Et_2O			96.7	3.3		
	10% Pd/C	7.5	Et_2O			98.5-	1.5-		Different solvents
	10% Pd/C	10	H_2O	17.2		64.0	18.8		
	10% Pd/C	10	H_2O KOH	9.0		50.0	41.0		2 equiv. [b]
	5% Rh/C	10	H_2O	34.6		19.7	45.7		0.5 hrs — Different reaction times
	5% Rh/C	10	H_2O	4.5		62.2	33.3		20 hrs
VII	10% Pd/C	11.5	Et_2O	18.8	37.5	41.2	2.5		-70° — Different temperature
	10% Pd/C	9.2	Et_2O		19.0	70.0	11.0		25°
	10% Pd/C	10	H_2O			67.0	33.0		Different amounts of catalysts
	10% Pd/C	33	H_2O			32.6	67.4		
	5% Rh/C	33	H_2O			11.0	89.0		Different catalysts
	Raney Ni	150	H_2O			20.0	80.0		Aqueous suspension
VIII	10% Pd/C	50	H_2O			59.0	41.0		
XIII	10% Pd/C	18	H_2O KOH	19.5		24.1	25.8	30.6	2 equiv. [b]
	10% Pd $CaCO_3$	50	H_2O NaOH	15.8		5.3	13.2	65.7	2 equiv. [b]
XIV	10% Pd/C	40	H_2O					100	No reaction Different pH
	10% Pd/C	50	H_2O NaOH			3.7	32.3	64.0	2.5 equiv. [b]

a) The results are calculated from the ^1H and ^{19}F NMR spectra of the residues obtained after filtering off the catalyst and evaporating the residue in vacuo.
b) The hydrogenated acids were obtained, after filtration and acidification, by ether extraction of the filtrate.

acid (XIV) in dioxane according to the literature [11] did not go to completion, reduction with zinc in methanol was used to replace the chlorine by hydrogen. The resulting trifluorosuccinic acid XIV was accompanied by varying amounts of fluorosuccinic acid IX and succinic acid X.

Catalytic hydrogenation of XIII over palladium on charcoal and especially over palladium on calcium carbonate in the presence of a base (the classical method for replacement of halogens by hydrogen) [12] gave, in addition to XIV, also considerable amounts of IX and X. Since trifluorosuccinic acid XIV is perfectly stable to hydrogenation over palladium in aqueous solutions, it has to be assumed that IX and X resulted from the hydrogenation of difluoromaleic acid VII and difluorofumaric acid VIII formed by dehydrofluorination of trifluorosuccinic acid in an alkaline medium during the hydrogenation.

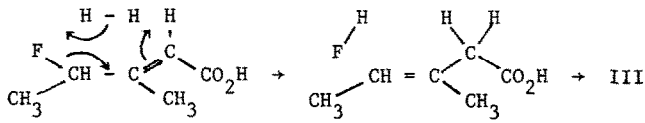
As reference compounds, meso-1,2-difluorosuccinic acid (XI) and DL-1,2-difluorosuccinic acid (XII) were synthesized by acid hydrolysis of the respective methyl esters (XIa) and (XIIa) prepared from the appropriate tartrates by means of sulfur tetrafluoride. Compounds XI and XIa were described in the literature [13], XII and XIIa are new.

Since the yields of the dimethyl difluorosuccinates left much to be desired, an attempt was made to prepare 1,2-difluorosuccinic acids by hydrolysis of diethyl 1,2-difluorosuccinate which in turn was synthesized by zinc coupling of ethyl fluoroiodoacetate. However, this method did not give satisfactory results either.

DISCUSSION OF THE RESULTS

Hydrogenolysis of Allylic Fluorine

The sharp contrast between the stability of fluorine in esters I and IV suggests some involvement of the adjacent double bond in the hydrogenation process. A concerted mechanism with a six-membered transition state may well account for the surprisingly easy hydrogenolysis of fluorine:



In the bromoester IV the bulky bromine atom prevents the molecule of hydrogen from attacking the double bond, and neither addition of hydrogen nor hydrogenolysis of fluorine take place.

Hydrogenolysis of Vinylic Fluorine

Displacement of fluorine by hydrogen in the hydrogenations of fluoromaleic acid V and fluorofumaric acid VI to form succinic acid could be viewed from two angles:

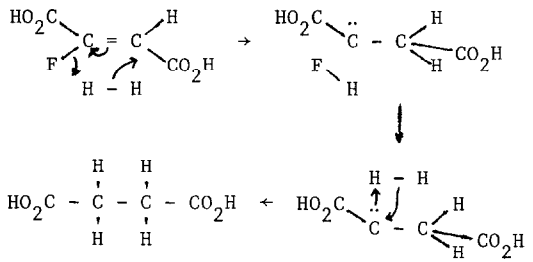
a) Direct displacement of vinylic fluorine by hydrogen could give an unsaturated acid which could be hydrogenated to succinic acid.

This sequence is unlikely since the fluorine-free unsaturated acid, maleic or fumaric, was never found in the products even in trace amounts.

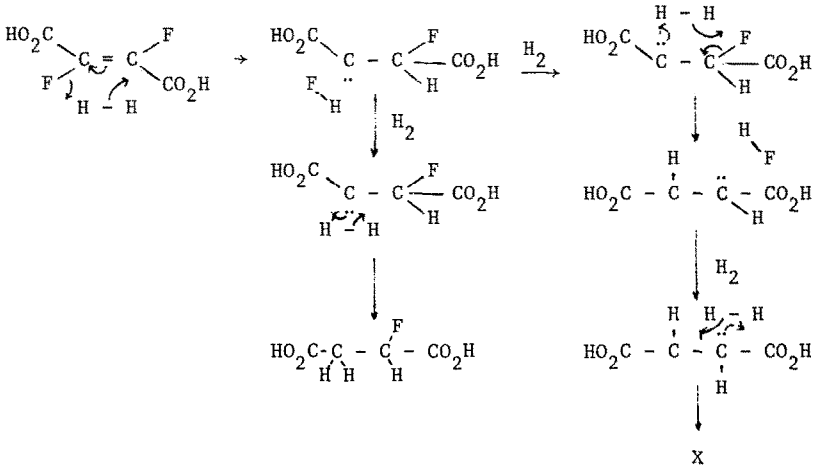
b) Primary addition of hydrogen could yield fluorosuccinic acid which could eliminate hydrogen fluoride and the resulting unsaturated acid could be further hydrogenated to succinic acid.

This sequence does not occur either since fluorosuccinic acid is perfectly stable under the hydrogenation conditions and does not eliminate hydrogen fluoride when treated with palladium or rhodium on charcoal in aqueous solutions at room temperature for 88 hours.

It may be assumed that a concerted mechanism similar to that proposed for the hydrogenolysis of allylic fluorine may be operating for a vinylic fluorine as well:



A similar mechanism could be assumed for the conversion of difluoromaleic acid VII and difluorofumaric acid VIII to fluorosuccinic IX and succinic acid X.



Here, too, the direct displacement of vinylic fluorine is unlikely since the intermediates - fluoromaleic or fluorofumaric acid - were never found among the products. Displacement of fluorine in saturated 1,2-difluorosuccinic acids does not take place under the hydrogenation conditions as proved by complete stability of acids XI and XII to hydrogen in the presence of palladium in aqueous solutions at room temperatures.

To test the stability of carbon-fluorine bond in saturated fluoro compounds 1,1-difluorosuccinic acid and trifluorosuccinic acid were also subjected to catalytic hydrogenation in aqueous solutions. Both proved to be completely stable. However, trifluorosuccinic acid was partly converted to fluorosuccinic acid IX and succinic acid X when the hydrogenation was carried out in the presence of alkali. Evidently, dehydrofluorination to difluorofumaric acid preceded the proper hydrogenation.

EXPERIMENTAL

Melting points were taken in Thomas-Hoover Unimelt apparatus and are not corrected. Gas-liquid chromatography was carried out on Varian 920 with thermal conductivity detector and helium as a carrier gas at a flow rate of 100 ml/min. Infrared spectra were taken on Unicam SP 1025 Infrared Spectrophotometer. NMR spectra were taken on JEOL PS 100 Spectrometer and Varian EM 390 NMR Spectrometer using TMS, HFB and TFA as internal standards. Chemical shifts and coupling constants are listed in Table III.

Table III

^{1}H and ^{19}F NMR Data on Fluorinated Butenedioic Acids and Esters

Compound	^{1}H NMR (TMS); ^{19}F NMR (HFB); J in Hz
V	=CH-, 6.50(d); J_{HF}=18; =CF-, 63.8(d); J_{HF}=18
VI	=CH-, 6.33(d); J_{HF}=30; =CF-, 57.3(d), J_{HF}=30
IX[a)]	∂_1 2.97, ∂_2 3.06, ∂_3 5.33(ddd); J_{12}=-17.0, J_{13}=7.7, J_{14}=22.5, J_{23}=3.7, J_{24}=27.7, J_{34}=47.4; ϕ -CHF- -26.5
XI meso[a)]	-CHFCHF, 5.60; -CHFCHF-, -37.1; $J_{HF\ gem}$=47.0, $J_{HF\ vic}$=23.2, $J_{HH\ vic}$=1.8, $J_{FF\ vic}$=13.9
XIa meso[a)]	OCH_3, 3.82; -CHFCHF-, 5.62; -CHFCHF-, -38.4; J's identical with those of XI
XII DL[a)]	-CHFCHF-, 5.60; -CHFCHF-, -42.6; $J_{HF\ gem}$=45.5; $J_{HF\ vic}$=30.8; $J_{HH\ vic}$=1.7; $J_{FF\ vic}$=9.1
XIIa DL[a)]	OCH_3, 3.88; -CHFCHF-, 5.63, -CHFCHF-, -43.4; J's identical with those of XII
XIII[a)]	-CClF-, 36.6(dd), $-CF_2-$, 47.2(dd), 54.3(dd); $J_{FF\ gem}$=274.9, $J_{FF\ vic}$=5.8, 12.5
XIV[a)]	∂_4 5.62(ddd), ϕ_1 48.4(ddd), ϕ_2 45.4(dt), ϕ_3 -44.2(dt); J_{12}=269.7, J_{13}=13.0, J_{14}=14.6, J_{23}=12.1, J_{24}=10.0, J_{34}=45.9±0.5
	$-CH_2-$, 3.32(t); J_{HF}=15; $-CF_2-$, 59.6(t); J_{HF}=15

a) The complex AA'BB' spectra of compounds XI and XII, the ABX spectrum of compound XIII, and ABXR spectra of compounds IX and XIV have been interpreted by Dr. H. M. Bell using computer-assisted iterative least-squares line-matching procedure.

Chemicals

All common chemicals used were of commercial grade. Catalysts were from Engelhard Industries (10% palladium on charcoal or on calcium carbonate or 5% rhodium on charcoal) and from W. R. Grace & Co. (Raney nickel) (a gift).

1,1-Difluorosuccinic acid was a product of PCR, fluorofumaric acid was a gift of E.I. duPont and Company, Wilmington, Delaware. Difluoromaleic anhydride, difluoromaleic, difluorofumaric, fluoromaleic, fluorofumaric, chlorotrifluorosuccinic, and trifluorosuccinic acids were prepared according to the literature [11]. meso-Difluorosuccinic acid and its methyl ester were also prepared according to the literature [13]. Preparations of methyl 4-fluoro-3-methyl-2-pentenoates and of methyl 2-bromo-4-fluoro-3-methyl pentenoate are described in D. Butina's thesis [9].

Dimethyl DL-1,2-Difluorosuccinate XIIa (nc)

The title compound was prepared by slightly modifying the procedure for the preparation of its diastereomer [13].

A 75 ml stainless steel cylinder fitted with a shut-off valve for 110 atm pressure and a magnetic stirring bar was charged with 6.53 g (0.0366 mol) of dimethyl mesotartrate prepared according to the literature [14]. The cylinder was cooled with a Dry Ice-acetone bath, and 13.6 g (0.125 mol) of sulfur tetrafluoride was condensed in the cylinder. The cylinder was heated in an oil bath at 110° for 7 hrs. After cooling the cylinder was bled-off at a temperature up to 40°, opened, the contents were diluted with 30 ml of ether, the solution was washed with two 6 ml portions of water, stirred for two hours with sodium fluoride to remove hydrogen fluoride, filtered and evaporated at 40° and 12 mm. The residue was distilled to give 19.5% yield of XIIa, b.p. 60-85°/0.07 mm, 95-107°/11 mm, m.p. 50-53°.

DL-1,2-Difluorosuccinic Acid (XII) (nc)

Hydrolysis of 1.18 g (0.0065 mol) of XIIa by refluxing with 23 ml of 3% hydrochloric acid for 4 3/4 hours followed by evaporation of the solution at 40° and 15 mm gave 0.99 g (99%) of XII. Three recrystallizations from carbon tetrachloride-acetone or benzene-ether mixtures gave a

compound, m.p. 208-210° (after drying at 80-90° at 0.05 mm). Mixed melting point with the meso-diastereomer was 120-145°.

Analysis: Found: C, 30.38, 31.46: H, 2.42, 2.64. Calculated for $C_4H_4F_2O_4$(154.1): C, 31.18, H, 2.62.

Alkaline Hydrolysis of Dimethyl-DL-1,2-difluorosuccinate (XII)

According to the literature [13], 0.63 g (0.00346 mol) of XIIa was stirred and refluxed with 23 ml of 3% solution of sodium bicarbonate for 2 hrs. The product contained DL-1,2-difluorosuccinic acid XII and fluorofumaric acid VI in a ratio of 45:55. Refluxing of this mixture (0.34 g) with 0.5 g of sodium carbonate in 8.5 ml of water for 1.25 hr. raised the ratio to 33:67%, and refluxing the resulting mixture with 10% sodium hydroxide for three hours gave a mixture of XII and VI in a ratio of 25:75%.

This experiment together with the acidic hydrolysis proves the unlikeliness of the formation of acetylenedicarboxylic acid by mere contact with water as claimed in the literature [15].

Ethyl Fluoroiodoacetate

Ethyl chlorofluoroacetate (28 g, 0.2 mol) was added to a solution of 36 g (0.24 mol) of sodium iodide in 150 ml of boiling acetone, and the mixture was stirred and refluxed for 6 hours. After cooling to solid salts were removed by suction filtration, the dark brown filtrate was evaporated at 40-45°/10 mm, the oily residue containing salts was washed with 30 ml of water, the organic layer was decolorized by shaking with 18 ml of a 20% solution of sodium bisulfite, washed with 10 ml of water, dried with anhydrous magnesium sulfate and distilled to give 34.43 g (74%) of ethyl fluoroiodoacetate, b.p. 60-73°/12-13 mm. Lit. b.p. 180°C [16].

Diethyl 1,2-Difluorosuccinate (a Mixture of Diastereomers XI and XII, R = C_2H_5) (nc)

A solution of 11.6 g (0.05 mol) of ethyl fluoroiodoacetate in 70 ml of ether was stirred magnetically with 8.1 g (0.125 mol) (2.5 equiv.) of zinc dust under a reflux condenser. After fifteen minutes a spontaneous refluxing started. The mixture was stirred at room temperature for 46 hours. Thereafter, the mixture was filtered, the sediment was washed with 70 ml of ether, the combined ether solutions were shaken up with dilute

hydrochloric acid until clear, then washed with 10 ml of a solution of sodium bisulfite, 10 ml of water, evaporated in vacuo, and distilled over a range of 95-111° at 12 mm to give 1.44 g (27.4%) of XI and XII ($R=C_2H_5$), b.p. 98-100°/12 mm.

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