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STEREOCHEMISTRY OF α,α'-DIFLUOROSUCCINIC ACIDS

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SUMMARY

Treatment of both dimethyl (-)-D-tartrate (IVa) and dimethyl (+)-L-tartrate (Va) with sulfur tetrafluoride gave dimethyl meso-α,α'-difluorosuccinate (Ia). The same reagent converted dimethyl meso-tartrate (IIIa) to a racemic mixture of dimethyl D- and L-α,α'-difluorosuccinate (IIa). This outcome resulting from the replacement of hydroxyl by fluorine with inversion of configuration at one and retention of configuration at the other chiral carbon atom can be rationalized by assuming the formation of a cyclic intermediate. This is opened by a subsequent S_N2 reaction with fluoride ion followed by a four-center displacement of sulfuroxy group by fluorine. The respective configurations of the dimethyl α,α'-difluorosuccinates Ia and IIa were established by ^1H and ^{19}F NMR using an optically active chemical shift reagent and confirmed by converting the esters to the corresponding acids and these in turn to the cis- and trans-α,α'-difluorosuccinic anhydrides, respectively.

INTRODUCTION

Both diastereomers of α,α'-difluorosuccinic acid (I,II) and the corresponding dimethyl esters (Ia,IIa) have been reported in the literature. One of the diastereomeric esters was prepared by Kozlova, Sedova, Alexeeva, and Yagupolskii [1] from sulfur tetrafluoride and a dimethyl tartrate of unspecified configuration. Its hydrolysis afforded α,α'-difluorosuccinic acid, m.p. 185-186° (I). The other dimethyl

α,α'-difluorosuccinate (IIa) was prepared analogously by one of us [2] from dimethyl meso-tartrate (IIIa) and was hydrolyzed to the isomeric α,α'-difluorosuccinic acid, m.p. 208-210° (II). We report here the results of our configurational studies on these acids (I,II) and esters (Ia,IIa).

RESULTS

We treated separately dimethyl (-)-D-tartrate (IVa) and dimethyl (+)-L-tartrate (Va) with sulfur tetrafluoride. Both compounds gave a dimethyl α,α'-difluorosuccinate (Ia) which on hydrolysis afforded optically inactive α,α'-difluorosuccinic acid, apparently identical with that of Kozlova et al. [1] (m.p. 185-186°).

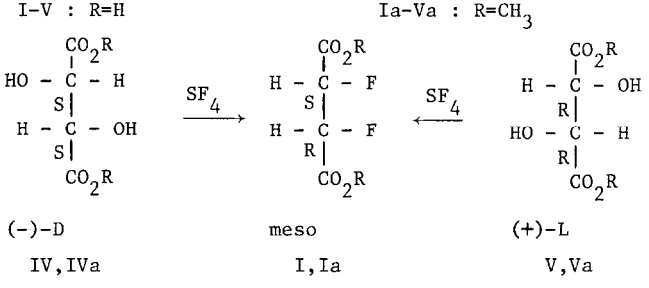
The replacement of hydroxyl groups by fluorine was not an especially clean reaction. Indeed, the conversion of all three dimethyl tartrates (IIIa, IVa and Va) to the diastereomeric dimethyl α,α'-difluorosuccinates (Ia and IIa) by sulfur tetrafluoride gave only 22-23% yields of the desired compounds. Besides large amounts of higher boiling material, compounds resulting from replacement of just one hydroxyl group by fluorine and possibly from decomposition during the distillation were present. In fact, dimethyl fluoromalate and most probably dimethyl oxidosuccinate were identified by means of NMR. These materials could not be separated even by repeated vacuum distillations. The slight negative rotation of the difluoro ester prepared from both IVa and Va may be caused by the presence of different amounts of differently rotating impurities formed during the reaction and/or the distillation. Indeed, the rotation of this dimethyl α,α'-difluorosuccinate diminished considerably after chromatographic purification.

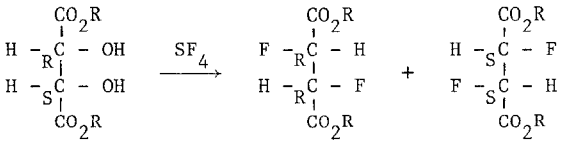
In order to avoid the above-mentioned difficulties of purifying the ester Ia prepared from IVa and Va, an attempt was made to prepare α,α'-difluorosuccinic acid I by reaction of sulfur tetrafluoride directly with (-)-D-tartaric acid IV and (+)-L-tartaric acid (V), respectively. However, this was unsuccessful; the only product isolated was racemic tartaric acid. To assign the correct configuration to these diastereomers, we measured the NMR spectra of dimethyl esters Ia and IIa in the presence of the chiral shift reagent tris-[3-(trifluoromethylhydroxymethylene)-d-camphorato]-europium [3]. In ordinary achiral NMR solvents both esters give AA'XX' patterns for the -CHF-CHF- portion of the molecule [2]. The coupling constants are easily measured, but they do not seem to be particularly

useful in making configurational assignments. However, the spectra change dramatically in the presence of the chiral shift reagent. The fluoro-ester Ia from D(or L)-tartrate gave a spectrum which was clearly ABXY, whereas the ester IIa from meso-tartrate gave two overlapping AA'XX' patterns.

The ABXY pattern for Ia indicates the meso-configuration. The protons (and fluorines) in the meso-form are enantiotopic by internal comparison. They become diastereotopic in the presence of the chiral shift reagent and, hence, become slightly nonequivalent in the NMR. The spectrum, therefore, changes from AA'XX' in $CDCl_3$ to ABXY in the presence of chiral shift reagent. The two overlapping AA'XX' patterns for IIa of equal intensity are consistent with a racemic mixture of the D and L forms of the ester. By internal comparison the protons (and fluorines) in both the D and L forms are homotopic and thus are not unequally affected by the chiral shift reagent. However, the protons (and fluorines) in the D ester are enantiotopically related to those in the L ester. These become diastereotopic in the presence of the chiral shift reagent. Thus, the D-ester gives an AA'XX' spectrum, and the L-ester gives a (slightly shifted) second AA'XX' spectrum.

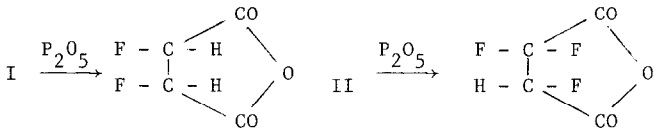
These configurational assignments were further confirmed by NMR analysis of the corresponding anhydrides VI and VII which were prepared by distillation of I and II, respectively, with phosphorus pentoxide. The AA'XX' pattern for the -CHF-CHF-portion of the molecule yielded a value of 9.3 Hz for the vicinal H-F coupling in VI and 17.3 Hz for the corresponding vicinal HF coupling in VII. The smaller coupling, as seen in VI, is consistent with an anticlinal arrangement of H and F (the "cis" anhydride), and the larger HF coupling (in VII) is consistent with a synperiplanar relationship between H and F (the 'trans' anhydride) [4]. Not only is this conclusion consistent with the Karplus-type relationship theoretically predicted vicinal HF coupling [4], but it is also substantiated by examination of published NMR data for somewhat related structures [5].



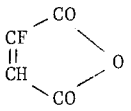


meso D L

III,IIIa II,IIa



VI VII



VIII

DISCUSSION

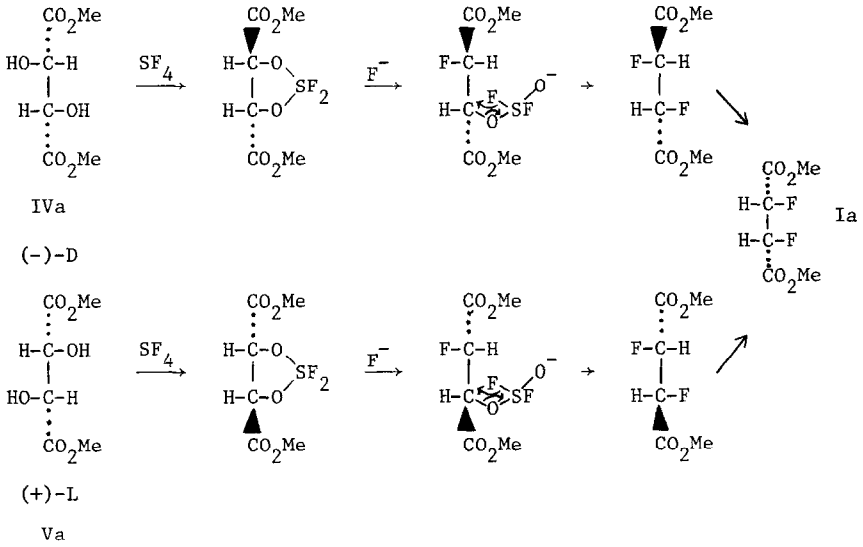
The stereochemistry of the replacement of a hydroxy group by fluorine is complex. Both retention and inversion of configuration have been observed when chiral hydroxy compounds were treated with hydrogen fluoride [6,7,8], 2-chloro-1,1,2-trifluorotriethylamine [9,10,11], tetrafluorophosphorane [12], sulfur tetrafluoride [13], or dialkylamino-sulfur trifluoride [14,15,16]. The difference in the stereochemical outcome evidently stems from differences in the mechanisms involved.

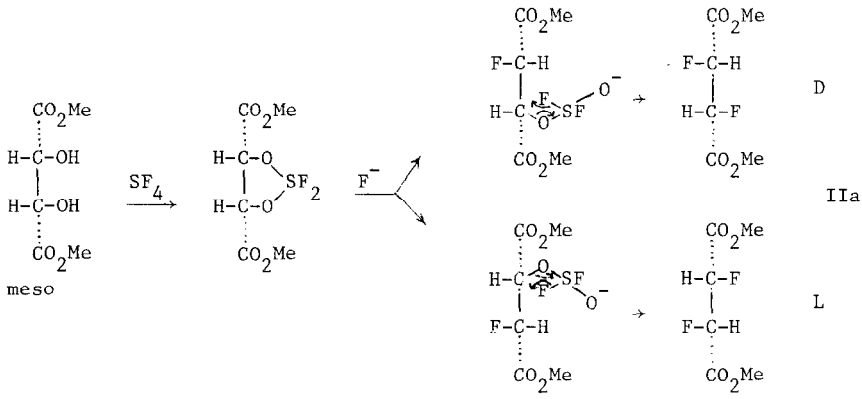
Although the above mentioned reagents used for the replacement of a hydroxy group by fluorine may not react by the same mechanism, for each of them essentially three pathways may be considered: 1. S_N1 type reaction with the formation of carbonium ions, 2. S_N2 type reaction of nucleophilic displacement by fluoride ion of groups such as $-OCF(CHClF)NEt_2$, OPF_3Ph, $O-SF_3$ or $-O-SF_2NR_2$; and 3. concerted four-center mechanism through a four- or six-membered transition state. Mechanism 1 would give, with compounds containing only one chiral center and hydroxyl on the chiral carbon atom, mainly racemization. Mechanism 2 would give inversion, and mechanism 3 complete retention. Most of the examples reported in the literature do not seem to involve racemization. Some involve retention [12,15], some

inversion [14], and many both [6,7,9,10,16]. However, the situation is complicated by the fact that most of the published cases involve compounds with more than one center of chirality, and some of the assignments of the configuration of the products may not be well proven [11].

From the results of our experiments, we can conclude that in the case of the replacement of hydroxyls by fluorine in dimethyl tartrates the reaction takes place with inversion of configuration at one, and retention of configuration at the other chiral carbon. Such an assumption explains why methyl D- and L-tartrate give the same dimethyl meso-α,α'-difluoro-succinate, and dimethyl mesotartrate gives dimethyl DL-α,α'-difluoro-succinate.

Inversion of configuration at one and retention of configuration at the other chiral center can be satisfactorily explained by a two-step mechanism involving the formation of a cyclic intermediate (retention of configuration), followed first by a back-side opening of the ring by fluoride ion (inversion of configuration), and finally concerted intra-molecular displacement of the sulfuroxy group by fluorine (retention of configuration) [17].





EXPERIMENTAL

Melting points were taken in Thomas-Hoover Unimelt apparatus and are not corrected. Gas-liquid chromatography was carried out on Varian 920 Chromatograph with thermal conductivity detector and helium as a carrier gas at a flow rate of 100 ml/min. Optical rotation was measured in a 10 cm cell using Model 70 polarimeter (O. C. Rudolph and Sons, Inc.) and sodium lamp as a source of light.

NMR spectra were taken on Varian EM 390 NMR Spectrometer at 90 MHz for ^{1}H and 84.6 MHz for ^{19}F using TMS and HFB as internal standards and carbon tetrachloride, deuteriochloroform and d_6-acetone as solvents.

Chemicals

Solvents and chemicals were of commercial grade; meso-Tartaric acid, m.p. 146-8° (monohydrate); 160-165° (anhydrous). Lit. m.p. 165-166° [18]. (-)-D-Tartaric acid, m.p. 172-4°, had $[\alpha]_D^{20}$ -13.7°(c=10,H_2O), Lit. m.p. 173.2° [19]. (+)-L-Tartaric acid, m.p. 169-72°, had $[\alpha]_D^{20}$ + 13.2° (c=10,H_2O). Lit. m.p. 172.1° [20]; $[\alpha]_D^{15}$ +13.7° [21].

Dimethyl Tartrates (IIIa, IVa, Va)

Dimethyl tartrates were prepared by saturating mixtures of equal parts of the tartaric acid and methanol with hydrogen chloride in an ice bath. Dimethyl meso-tartrate (IIIa) crystallized; yield 67.5%, m.p. 113-114° (acetone). Lit. m.p. 111° [22].

(-)-D-Dimethyltartrate (IVa) was isolated by evaporation and vacuum distillation at 100-116°/0.08 mm (yield 57%), m.p. 50-52.5°. $[\alpha]_D^{20}$-4.4° (c=10,acetone). Lit. m.p. 48°, 50° [23].
(+)-L-Dimethyl tartrate (Va), isolated by evaporation and vacuum distillation at 100-115°/0.08 mm (yield 60%), had m.p. 52-53° and 61-62° (two modifications); $[\alpha]_D^{20}$ + 5.0°(c=10,acetone). Lit. m.p. 48°, 50°, 61° [23]; α_D^{20} = 5.17° (acetone) [24].

Dimethyl meso-α,α'-Difluorosuccinate (Ia)

Following the procedure described in the literature [1,2], both dimethyl (-)-D- and (+)-L-tartrates were separately treated with an excess of about 3-4 equivalents of sulfur tetrafluoride at 110° for 5.5-6 hours in stainless steel cylinders. The products were purified by distillation at 50-56°/0.06 mm to give 22-23% yields of Ia. Even the doubly distilled products showed slight optical rotation $[\alpha]_D^{16}$-1.1°, when prepared from (-)-D-tartrate; $[\alpha]_D^{17}$-0.45°, when prepared from (+)-L-tartrate. After purification by column chromatography over silica gel (elution with benzene), the two samples showed the respective optical rotations $[\alpha]_D^{19}$-0.75° and $[\alpha]_D^{22}$-0.30°. NMR values have been reported [2].

Dimethyl DL-α,α'-Difluorosuccinate (IIa)

Racemic IIa was prepared according to the literature [2], b.p. 60-67°/0.07 mm. NMR values have been reported [2].

Determination of Configuration of Ia and IIa by NMR

For the NMR analysis, approximately 25 mg of ester was mixed with varying amounts of the shift reagent, tris-3-(trifluoromethylhydroxymethylene)-d-camphorato europium, in 0.5 ml of $CDCl_3$, such that substrate/lanthanide mole ratios of 0.1 to 0.5 were realized. The racemic ester (IIa), gave an AA'XX' spectrum which broadened and separated into two overlapping AA'XX' patterns as the substrate/lanthanide ratio approached 0.5. Under these conditions, the separation found between the two patterns was slightly more than 5 Hz. (0.055 ppm). The meso ester (Ia) gave an AA'XX' spectrum which gradually changed to ABXY as the shift reagent was added. With large amounts of shift reagent, the chemical

shift difference realized between the (now diastereotopic) protons is estimated to be about 2 Hz. (0.022 ppm), based on a comparison between the experimental spectrum and a family of computer-drawn spectra with different values for $\Delta\nu_{AB}$ and $\Delta\nu_{XY}$. The difference in chemical shifts for the fluorine nuclei in Ia is estimated to be about 1 Hz (0.011 ppm).

To further test the validity of our conclusions we performed additional computer simulations of spectra. We first attempted to simulate the doubled AA'XX' pattern, seen with the racemic ester (IIa) in the presence of shift reagent, under the assumption that it might possibly be the meso form. However, computer-simulated ABXY spectra, using a wide variety of chemical shifts and coupling constants, bore no resemblance to the experimental spectrum. Likewise, we tried to simulate the ABXY spectrum of the shifted meso ester (Ia), assuming it was a pair of overlapping AA'XX' patterns. This, too, was unsuccessful. We, therefore, feel that our assignment of configuration is unequivocal.

meso-α,α'-Difluorosuccinic Acid (I)

Hydrolysis of the products prepared from both tartrates (IVa and Va) by refluxing with 5% hydrochloric acid as described previously [2] gave the same α,α-difluorosuccinic acid I (mixed melting point test), melting after repeated crystallization from benzene-acetone or benzene-ether mixtures at 182-184°.

This melting point matches that reported in the literature [1] (185-186°). This finding proves that the tartaric acid esters used by the Russian authors [1] without any indication as to their structures were most probably (+)-L (or (-)D or racemic) tartaric acid esters but not meso-tartaric acid esters.

NMR values have been reported [2].

DL-α,α'-Difluorosuccinic Acid (II)

Racemic II was prepared according to the literature [2], m.p. 209-210° (benzene-ether). NMR values have been reported [2].

cis-α,α'-Difluorosuccinic Anhydride (VI) (nc)

Distillation of 0.49 (0.0032 mol) of I with 0.6 g (0.0042 mol, 4.0 equiv.) of phosphorus pentoxide from a microflask gave 0.1 g (23%) of VI, b. 150-155°. NMR: δH=5.63(TMS), δF=-50.0(HFB), J_{HF}(gem)=49.2, J_{HF}(vic)=9.3, J_{HH}=5.6(or 2.8), J_{FF}=2.8(or 5.6).

Both anhydrides VI and VII were accompanied by fluoromaleic anhydride (VIII), since a rapid dehydrofluorination took place during the dehydration. All the anhydrides are very rapidly hydrolyzed to the respective acids.

trans-α,α'-Difluorosuccinic Anhydride (VII) (nc)

Distillation of 0.4 g (0.0026 mol) of II with 0.6 g (0.0042 mol, 4.85 equiv.) of phosphorus pentoxide from a microflask gave 0.1 g (28%) of VII, b. 145-150°. NMR: δH=5.95(TMS), δF=-41.5(HFB), J_{HF}(gem)=50.0, J_{HF}(vic)=17.3, J_{HH}=7.0(or 4.5), J_{FF}=4.5(or 7.0).

Reaction of (-)-D-Tartaric and (+)-L-Tartaric Acid with Sulfur Tetrafluoride and Hydrogen Fluoride

The acid (3.0 g, 0.02 mol) was dissolved in 50 ml of anhydrous hydrogen fluoride in a 100 ml polyethylene bottle, and 5.0 ml (9.5 g, 0.09 mol) of sulfur tetrafluoride was condensed in the solution cooled in a Dry Ice-acetone bath. After one hour at -78°, the reaction mixture was evaporated at the same temperature in a stream of argon. A beige solid residue was stirred with 20 ml of water, filtered from 0.2-0.3 g of an insoluble material, and the filtrate was evaporated to dryness at reduced pressure. The crystalline residue was recrystallized from 2 ml of water giving 0.45 g (15%) (from (-)-D-tartaric acid) or 0.43 g (14.3%) (from (+)-L-tartaric acid) of racemic tartaric acid, m.p. 209-210°, Lit. m.p. 205° [25].

Fluoromaleic Acid and Dimethyl Fluoromalate

Although pure fluoromalic acid and its dimethyl ester were not isolated, their presence in crude α,α'-difluorosuccinic acids and esters was proved by NMR: δH (-CHF-) = 5.30, J_{HF}(gem)=48, J_{HH}=2; δH (-CH(OH)) = 4.70; J_{HF}(vic)=24, J_{HH}=2; δF = -37.1(HFB); J_{HF}(gem)=48, J_{HF}(vic)=24.

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