The formation of halogenated succinates by liquid-phase direct fluorination with elemental fluorine

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Abstract

Direct fluorination of maleic anhydride with elemental fluorine has been investigated in different solvents at low temperatures. It was discovered that the net conversion of maleic anhydride, as well as the overall yield and composition of the halogenated products, depend strongly on the experimental conditions employed. Fluorinations conducted in fluorotrichloromethane, chloroform or mixtures thereof, in the presence of sodium fluoride, resulted in good yields of halogenated succinic acid derivatives: the predominant products being 2,3-dihalogenated succinic acids. Product distributions varied widely between experiments conducted at 0 °C and −25 °C, and also between experiments conducted in neat $CHCl_3$ and in $CFCl_3/CHCl_3$ mixtures. Experimental details and some comments regarding the stereoselectivity of halogen addition are provided.

Introduction

Simple halogenated succinates and their derivatives have been known for some time. Some of the earliest examples include dibromo- and dichloro-succinates, resulting from the direct addition of either bromine or chlorine to the double bond of maleic or fumaric acids or their derivatives [1, 2]. In later years, a variety of different methods (not including the use of elemental fluorine) were employed to prepare succinate derivatives containing fluorine [3–8], and some of the mixed bromofluoro [9] and chlorofluoro [5, 6, 10–14] derivatives.

In many of the reports cited above involving the addition of one or more halogen atoms to the double bond in maleic or fumaric acid or their derivatives, the emphasis of the investigations was placed on determining the stereochemistry of halogen addition. In most cases, it was found that halogen addition proceeds in an *anti* (*trans*) fashion [1, 2, 9, 15]. Thus, maleates tend to give D,L derivatives, while fumarates yield the corresponding *meso-* or *erythro*-D,L compounds.

A great deal of work has been done with electrophilic fluorination processes in general [16–19] and specifically with the addition of F_2 to double bonds [20]. Again, much of the emphasis has focused on determining the stereoselectivity of addition. Rozen and Brand [20] concluded that the addition of F_2 and electrophilic

fluorine sources to double bonds proceeds exclusively in a *syn*(*cis*) manner. Thus, one would expect that *cis*-oriented double bonds, i.e., maleates, would tend to yield *meso* difluoro derivatives, while *trans*-oriented double bonds, i.e., fumarates, would give the D,L difluoro derivatives.

The direct addition of elemental F_2 to the double bond in diethylfumarate [21] is the only example in the literature involving such an addition to maleic or fumaric acids or their derivatives. In this example, fluorination of diethylfumarate in CF_2Cl_2 at low temperature resulted in the formation of diethyl difluorosuccinate in 10% yield. The authors gave no indication of other species formed and there was no mention of the stereochemistry of F_2 addition.

The purpose of the present work was to investigate the reaction of elemental F_2 with maleic anhydride with the aim of producing fluorinated succinates potentially useful in a wide variety of industrial polymer applications.

Experimental

General

The reagents maleic anhydride (99%), dimethyl fumarate (97%), dimethyl maleate (96%) and NaF (99%), and the solvents $CHCl_3$ (99%) and $CFCl_3$ (99%), were used as obtained from commercial sources. Fluorine

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(Air Products) was diluted (to 5% or 10% v/v) with dry nitrogen before use.

Fluorination method

The conditions used for the fluorination experiments are summarized in Table 1.

In a typical direct fluorination experiment, powdered maleic anhydride (2.63 g, 26.8 mmol), powdered sodium fluoride (2.25 g, 53.6 mmol) and 90 ml of solvent (either neat $CHCl_3$ or $CFCl_3/CHCl_3$ (2:1 v/v)) were loaded into a stirred 100 ml Parr reactor (Monel-400, model M-4565). The reactor was sealed, immersed in a low-temperature bath to achieve the desired reaction temperature (Table 2) and then flushed with dry N_2 for 15 min. Following this, a flow of F_2 diluted with N_2 (10% v/v) was delivered to the reactor until the desired amount of F_2 had been added. The reactor and contents were then flushed with dry N_2 for 30 min, followed by warming to room temperature. The 'crude' reaction mixture was heated to evaporate most of the solvent and then stirred with 100 ml of 20% H_2SO_4 until all had dissolved. The resulting aqueous mixture was extracted with diethyl ether; the ether extracts were combined and dried with $MgSO_4$, and then evaporated leaving a pale brown residue. The residue was characterized as a mixture of acids in solution by NMR spectroscopy, and as a mixture of dimethyl ester derivatives (see below) by NMR and GC–MS methods. The product distributions for each of the different fluorination conditions are summarized in Table 2.

Esterification method

A typical esterification involved heating 0.3 g of the fluorinated acid mixture from above with 2–3 ml each of 50% H_2SO_4, CH_3OH and 1,2-dichloroethane, to 70–80 °C for 5–10 min. After the specified time, the dichloroethane component was separated, washed with H_2O until neutral and then dried with $MgSO_4$.

Gas chromatography–mass spectrometry (GC–MS)

Mixtures of dimethyl ester halosuccinate derivatives were characterized in part with the use of GC–MS methods, and the conditions used are summarized in Table 3. Typical chromatograms of non-polar and chiral column analyses are given in Fig. 1 and the data is summarized in Table 4.

NMR spectroscopy

Proton and ^{19}F NMR spectra were obtained at 300.13 and 282.41 MHz, respectively, on a Bruker ACP-300 NMR spectrometer and were referenced with respect to neat $CFCl_3$ (^{19}F) and TMS (^1H). A positive chemical shift denotes a resonance occurring to high frequency of the reference substance. NMR data for the products identified in the course of this work are summarized in Table 4.

Results and discussion

A variety of experimental conditions were employed in the direct fluorination of maleic anhydride. Analyses of the resultant mixtures (after acid hydrolysis) using NMR and GC–MS methods [22–24] have shown them to contain varying amounts of fluorinated, chlorinated or mixed chlorofluoro succinate derivatives (structures are given in Fig. 2). The different experimental conditions employed and the distribution of products arising from each set of experimental conditions are summarized in Tables 1 and 2, respectively. Data for

TABLE 1. Reaction conditions employed in the direct fluorination of maleic anhydride experiments I–VI

Expt. No.	MA^a (mmol)	NaF (mmol)	F_2^b (mmol)	Solvent	Temp.^{c} (°C)	MA^d conversion (%)
I	21.8	49.3	189	$CFCl_3$	−25	22
II	21.3	52.9	248	$CHCl_3$	−25	41
IIIe	64.3	131.2	593	$CFCl_3/CHCl_3$ 2:1 v/v	−25	40
IV	26.8	53.6	631	$CHCl_3$	−5	100
V	23.3	43.8	516	$CFCl_3/CHCl_3$ 2:1 v/v	0	100
VI	23.4	44.1	517	$CFCl_3/CHCl_3$ 2:1 v/v	0	98

^{a}MA = maleic anhydride.
^{b}Fluorine (5% or 10% v/v diluted with nitrogen) addition was regulated via the use of Teledyne Hastings–Raydist flow controllers (CST-M, F_2; CST, N_2).
^{c}Temperatures are approximate (±2 °C).
^{d}Conversion was determined by analysis of the crude product for maleic acid (after hydrolysis).
^{e}In experiment III a larger volume reactor was used, so the amounts of reagents used were increased proportionally.

TABLE 2. Product distribution[a] from fluorination experiments I–VI

Expt. No.	Difluorosuccinate[b] (mol%)	Trifluorosuccinate (mol%)	Fluoromaleates/ fumarates[c] (mol%)	Chlorofluorosuccinate[d] (mol%)	Dichlorosuccinate[e] (mol%)
(I)[f]	96	3	0	0	0
II	72	5	9	13	1
III	86	2	3	9	0
IV	14	2	3	36	45
V	71	3	5	17	4
VI	67	1	5	20	7

[a]Product distribution represents the mol% of each major species in the product fraction with conversion extrapolated to 100%.
[b]Structures given in Fig. 2 as A and A'.
[c]Included are both mono and difluoro isomers.
[d]Structures given in Fig. 2 as B and B'.
[e]Structures given in Fig. 2 as C and C'.
[f]Approximately 1% monofluorosuccinate was also identified in expt. I.

TABLE 3. Gas chromatography–mass spectrometry

	Non-polar column analysis	Chiral column analysis
Instrument	Finnigan 1020 quadrupole	Finnigan ion trap detector (ITD 800)
Mass range scanned	29–350	45–250
Cycle time	1.5 s	0.5 s
MS manifold temperature	100 °C	190 °C
Ionization mode	electron	electron
Electron energy	70 eV	70 eV
GC column	25 m×0.20 mm i.d., 0.33 μm film thickness, Hewlett Packard HP-5	30 m×0.256 mm i.d., 0.25 μm film thickness, J&W Cyclodex B
Carrier gas	helium	helium
Flow rate	1.17 ml min^{-1} (at 50 °C)	0.75 ml min^{-1} (at 50 °C)
Head pressure	16 psig. Column directly interfaced to MS vacuum manifold	15 psig. Column interfaced to MS vacuum manifold via an open-split interface
Sample size	0.5 μl	0.2 μl
Split ratio	10:1	30:1
Temperatures (°C)	injector, 290 interface, 300	injector, 180 interface, 200
Column temperature program	1 min at 30 °C, ramped at 8 °C min^{-1} to 300 °C	isothermal at 110 °C

experiment VI are included to demonstrate the re-producibility of results which was found for each set of experimental conditions.

A number of comments must be made concerning the experimental conditions summarized in Table 1. In each experiment, an excess of NaF was used to 'quench' any HF formed and thereby prevent unwanted secondary reactions. Similarly, a large excess of F_2 was used in each case to compensate for anticipated inefficiencies in F_2 utilization in this reactor configuration. The solvents $CFCl_3$ and $CHCl_3$ were investigated separately but also found to be useful in combination (Rozen and Gal [25] had shown the effectiveness of the $CFCl_3$/ $CHCl_3$ solvent system for direct fluorination experiments and also explained the important role of $CHCl_3$ in this

system). Finally, the temperature was varied between 0 °C and −25 °C to enhance the differences in product distribution obtained.

In all experiments the identities and relative ratios of stereoisomers of the halogenated products were determined using a combination of NMR spectroscopy and GC–MS (see Table 4). The ^{1}H and ^{19}F NMR parameters of many of the products observed here are in excellent agreement with those published previously [8]. The use of non-polar capillary GC–MS was particularly useful for the resolution and identification of the 2,3-dihalogenated diastereomeric pairs. In Fig. 1(a), the resolution of diastereomeric pairs, i.e., A and A' representing meso- and D,L-2,3-difluorosuccinate, respectively, is depicted. Further chromatographic res-

TABLE 4. NMR and non-polar GC–MS data on the products of fluorination

Species[a]	NMR data[b,c]	GC–MS data [m/z(%)]
2-Fluorosuccinate H_2⏤H_1 F_4⏤H_3	$^1H\delta_1 = 2.99$; $^1H\delta_2 = 3.05$; $^1H\delta_3 = 5.15$. $^{19}F\delta_4 = -190.10$. $^2J_{3,4} = 48.0$, $^3J_{1,4} = 28.0$, $^3J_{2,4} = 25.2$	133(13); 59(100)
2,3-Difluorosuccinate F⏤H F⏤H	$^1H\delta = 5.75$. $^{19}F\delta = -202.30$. $^2J_{HF} = 47.0$, $^3J_{HF} = 25.0$, $^3J_{FF} = 13.5$, $^3J_{HH} = 2.1$	2 peaks 151(13); 93(30); 73(25); 64(24); 59(100); 45(12)
2,3-Difluorosuccinate F⏤H H⏤F	$^1H\delta = 5.80$. $^{19}F\delta = -206.60$. $^2J_{HF} = 45.4$, $^3J_{HF} = 29.8$, $^3J_{FF} = 9.0$, $^3J_{HH} = 2.0$	2 peaks 151(13); 93(30); 73(25); 64(24); 59(100); 45(12)
2,2,3-Trifluorosuccinate F_2⏤F_1 H_4⏤F_3	$^1H\delta_4 = 5.58$. $^{19}F\delta_1 = 115.81$; $\delta_2 = -118.80$; $\delta_3 = -208.86$. $^2J_{1,2} = 268.6$, $^2J_{3,4} = 45.4$, $^3J_{1,3} = 12.2$, $^3J_{1,4} = 14.2$, $^3J_{2,3} = 12.0$, $^3J_{2,4} = 9.8$,	141(9); 111(45); 91(15); 82(11); 74(8); 63(9); 59(100)
2-Chloro-3-fluorosuccinate Cl⏤H_1 H_2⏤F_3	$^1H\delta_1 = 4.43$; $^1H\delta_2 = 5.72$. $^{19}F\delta_3 = -196.17$. $^2J_{2,3} = 48.1$, $^3J_{1,3} = 24.4$, $^3J_{1,2} = 1.8$	2 peaks 167(13); 147(10); 119(50); 73(45); 59(100); 45(18)
2-Chloro-3-fluorosuccinate Cl⏤H_1 F_3⏤H_2	$^1H\delta_1 = 4.26$; $^1H\delta_2 = 5.65$. $^{19}F\delta_3 = -194.23$. $^2J_{2,3} = 48.0$, $^3J_{1,3} = 11.8$, $^3J_{1,2} = 8.1$	2 peaks 167(13); 147(10); 119(50); 73(45); 59(100); 45(18)
2,3-Dichlorosuccinate	*meso*:$^1H\delta = 4.09$. $^3J = 2.0$ D,L: $^1H\delta = 4.15$. $^3J = 5.3$	2 peaks 185(12); 183(20); 179(16); 147(20); 137(18); 135(52); 113(17); 91(15); 89(47); 85(30); 61(19); 59(100)
2,3-Difluorobut-2-enoate	$^{19}F\delta = -142.05$	121(68); 92(40); 89(20); 77(37); 62(40); 61(35); 60(35); 59(100)
Fluorofumarate	$^1H\delta = 6.31$. $^{19}F\delta = -106.86$. $^3J = 30.5$	not identified
Fluoromaleate	$^1H\delta = 6.50$. $^{19}F\delta = -101.20$. $^3J = 20.1$	not identified

[a]All species are dimethyl esters.
[b]The methyl (^1H) resonances have been omitted. Chemical shifts are given in ppm and coupling constants are given in Hz.
[c]Chemical shift and coupling constant information for second-order spectra were determined with the use of either PANIC (Bruker) or NMR1 (NMR Inc.) iterative software programs.

olution of the diastereomers into individual enantiomers was possible with the use of a chiral stationary phase (J&W Cyclodex B) where, in all cases, the later eluting peak of each diastereomer pair in Fig. 1(a) was shown to be the optically active *threo-* or D,L-racemic pair. All racemates, including the *erythro* and *threo* diastereomers of 2-chloro-3-fluorosuccinate were at least partially resolved (see Fig. 1(b)).

In all experiments the measured ratio of *meso* and D,L diastereomers of 2,3-difluorosuccinate was approximately equal, while, for the 2,3-chlorofluoro and 2,3-dichlorosuccinate diastereomers, the *threo*-D,L and D,L isomers, respectively, were clearly more abundant than their *erythro*-D,L and *meso* counterparts, respectively. In all cases, the observed product distribution is thought

to represent the thermodynamically favored situation, i.e., little energy difference is expected between diastereomers of difluorosuccinate, while the energy difference between diastereomers of dichlorosuccinate is presumably large because of significant repulsive forces between eclipsing chlorine atoms in the *meso* compound.

The results of fluorinations performed at $-5\ °C$ and $0\ °C$ indicate that quantitative conversion of maleic anhydride to halogenated succinate derivatives occurred at these higher temperatures. In $CFCl_3/CHCl_3$ solvent, the primary products found were 2,3-difluoro- and 2,3-chlorofluorosuccinate. However, in $CHCl_3$ solvent, the 2,3-dichloro- and 2,3-chlorofluorosuccinate derivatives dominated.
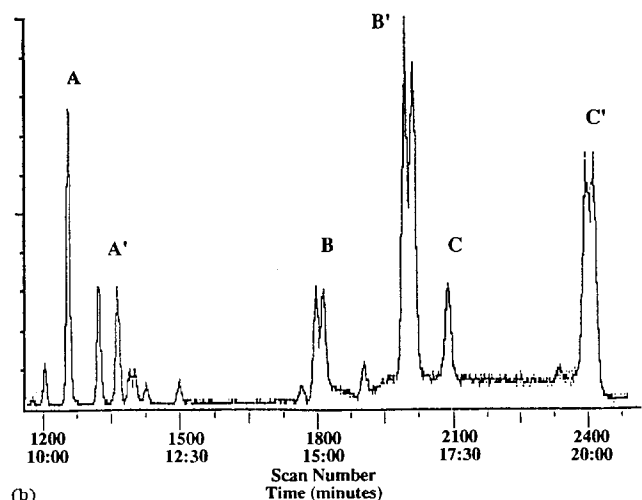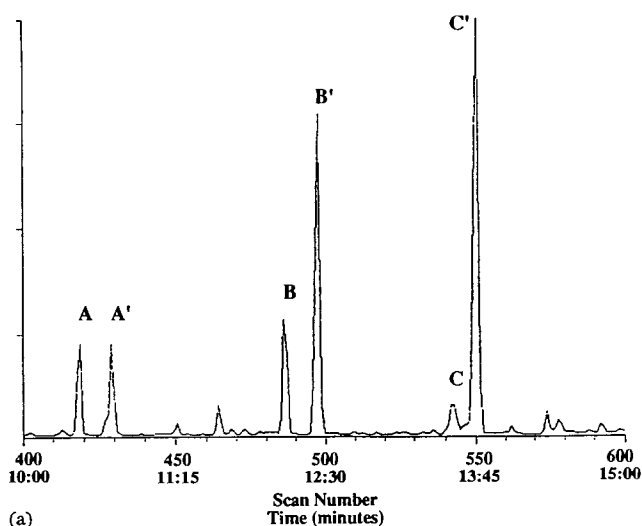
Fig. 1. Segments of the total ion current GC–MS chromatograms. (a) Separation on the non-polar column. (b) Separation on the Cyclodex B column. Structures assigned to A, A', B, B', C and C' are shown in Fig. 2.
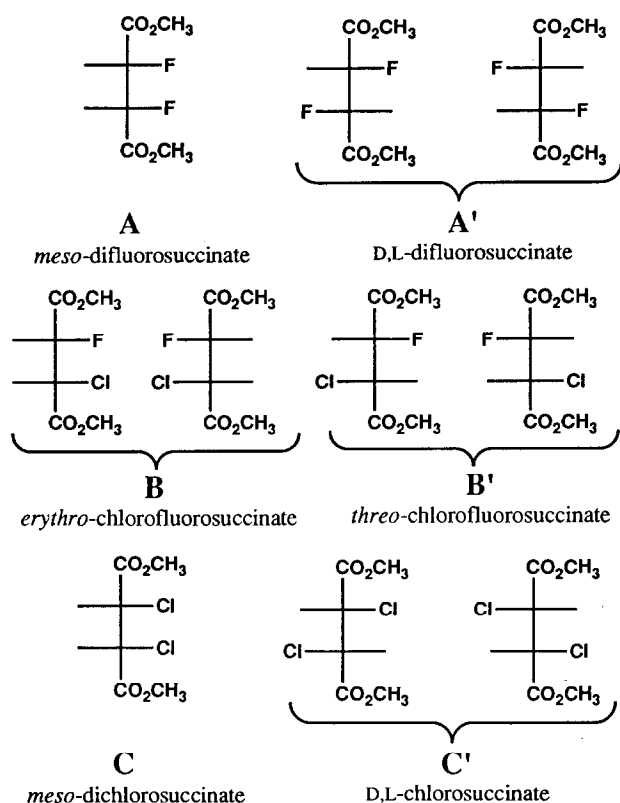

Fig. 2. Structures of the halogenated succinate isomers identified in Fig. 1 as A, A', B, B', C and C'.

The results of fluorinations performed at −25 °C are significantly different from those obtained at higher temperatures. The dominant products at this lower temperature were either 2,3-difluorosuccinate or the starting material, with very little chlorine-containing contribution. The conversion of maleic anhydride was apparently significantly affected by the nature of the solvent employed (twice as much conversion was observed when polar $CHCl_3$ was employed), but in all cases was less than that observed at higher temperatures.

There appears to be less radical activity at −25 °C than at 0 °C, as expected. Thus, at the lower temperature almost no chlorinated products were formed (which presumably would result from F· attack on the chlorinated solvent and subsequent reactivity of the chlorine

species). At the higher temperature, chlorine-containing radicals become more involved, and in fact, in $CHCl_3$, they seem to be the dominant reactive species.

From our results, we cannot specify with certainty the reaction mode of the halogenation of maleic anhydride under the conditions employed. However, since we expect F_2 to add strictly syn, but observed both meso and D,L diastereomers, even for 2,3-difluoro derivatives, we know that the reactions are not strictly molecular electrophilic additions but rather have a significant radical component. In fact, radical processes are thought to be predominant. Thus, in the case of difluorination where one would expect meso-2,3-difluorosuccinate to be the major product [20], the product distribution observed reveals no evidence of stereospecific control. In contrast, the net addition of 'ClF' across the double bond giving the 2,3-chlorofluoro derivatives clearly favors the formation of the threo-D,L enantiomers. This, possibly by coincidence, indicates anti addition and is consistent with a previous report [26] which showed that the addition of the interhalogens, BrF and IF, to double bonds, proceeds in a stereospecific anti mode. Finally, the formation of the dichlorosuccinate derivatives is thought to occur by a radical mechanism because it is hard to envision the formation

of Cl_2 and a subsequent *anti* addition of this to the double bond under these conditions.

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