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Reactions of cycloalkanecarboxylic acids with SF_4. IV. Fluorination of cyclohexanedicarboxylic acids with SF_4★

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Abstract

Fluorination of *trans*-cyclohexan-1,2-dicarboxylic acid with SF_4 yields a cyclization product with a *trans* configuration, 7,7,9,9-tetrafluoro-*trans*-8-oxabicyclo[4.2.0]nonane. On heating 7,7,9,9-tetrafluoro-*cis*-8-oxabicyclo[4.2.0]nonane with HF, *trans*-2-trifluoromethylcyclohexanecarbonyl fluoride and *trans*-1,2-bis-(fluoroformyl)cyclohexane are obtained as major products. Cyclization was not observed on fluorination of *cis*-cyclohexan-1,3-dicarboxylic acid with SF_4.

Keywords: Cycloalkane carboxylic acids; Sulfur tetrafluoride; Fluorination; Stereochemistry; NMR spectroscopy

1. Introduction

cis-Cyclopropan-, cyclobutan- and cyclopentan-1,2-dicarboxylic acids with SF_4 yield the corresponding cyclic $\alpha,\alpha,\alpha',\alpha'$-tetrafluoro ethers together with trifluoromethyl-substituted cycloalkanes, while *trans* isomers yield only trifluoromethyl-substituted cycloalkanes [1–3]. The cyclization of cyclohexan-*trans*-dicarboxylic acids on fluorination with SF_4 is unknown despite the fact that the corresponding cyclohexan-*trans*-dicarboxylic acid anhydride has been isolated [4].

2. Experimental details

^1H and ^{19}F NMR spectra were measured with a Bruker WP-200 (at 200.1 and 188.3 MHz respectively) NMR spectrometer using HMDS and $CFCl_3$ as internal standards, and acetone-d_6 as solvent. Low-temperature ^{19}F NMR spectra were measured with a Varian VXR-300 NMR spectrometer (at 282.1 MHz) using acetone-d_6 as solvent. ^{19}F upfield chemical shift values are negative. ^{13}C NMR spectra were measured with a Gemini 200 NMR spectrometer (at 50.3 MHz) using TMS as internal standard, and acetone-d_6 as solvent. Gas–liquid chromatography was carried out with a Chrom 5 chromatograph fitted with an FID using helium as the carrier gas, and employing a stainless-steel column (2500×3 mm) filled with 10% polyphenylmethylsiloxane on Chromatone AW (0.20–0.25 mm). Preparative GLC was carried out with a PACHV 07 chromatograph fitted with a thermal conductivity detector. A stainless-steel column (2600×12 mm) filled with 10% polyphenylmethylsiloxane on Chromatone N-AW-HMDS (0.32–0.40 mm) and with helium as the carrier gas was used. All boiling and melting points are reported uncorrected.

2.1. Treatment of carboxylic acids with SF_4. General procedure

Method A

The acid (0.05 mol) and SF_4 (0.3 mol) were reacted in a stainless-steel cylinder under autogenous pressure, with the reaction time and temperature as indicated in Table 1. The gaseous products were released and the liquid residue subjected to ^{19}F NMR spectral monitoring. The crude products were washed with 5% aqueous ammonia. Liquid products **2**, **3**, **7**, **8** and **20** were isolated by steam-distillation, separated, dried over $MgSO_4$ and purified by distillation or by preparative GLC. Solid products **15** and **16**, obtained by filtration of the residue, were dried and crystallized from benzene.

Method B

Sulfur tetrafluoride (1 g, 10 mmol) was bubbled through a solution of the acid (0.2 g, 1.2 mmol) in anhydrous hydrogen fluoride (1 g, 50 mmol). HF was removed and the residue subjected to ^{19}F NMR spectral

★Dedicated to Professor L.M. Yagupolskii on the occasion of his 70th birthday.

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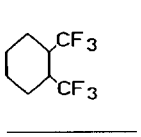
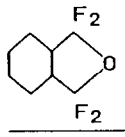
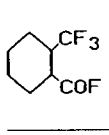
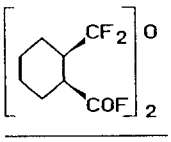
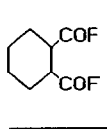
Table 1
Reactions of cyclohexanecarboxylic acids with SF_4

Acid	Method	Temperature (°C)	Time (h)	Composition of reaction mixture (%)								
												
				cis (2)	*trans* (7)	*cis* (3)	*trans* (8)	*cis* (11)	*trans* (9)	*cis* (12)	*cis* (13)	*trans* (10)
1	B	20	–	0	0	0	0	0	0	0	100	0
1	A	20	8	0	0	18	0	4	0	7	71	0
1	A	60	3	2	0	60	0	11	0	4	23	0
1	A	100	3	8	2	67	0	4	2	5	12	0
1	A	140	3	4	8	64	7	0	10	2	5	0
6	B	20	–	0	0	0	0	0	0	0	100	0
6	A	20	8	0	0	0	17	0	3	0	0	80
6	A	60	3	0	0	0	20	0	11	0	0	69
6	A	140	3	0	4	3	69	0	23	0	0.5	0.5
17	B	20	–	0	0	0	0	100	0	0	0	0
17	A	140	6	30	50	0	0	0	20	0	0	0
17[a]	A	140	6	45	30	0	0	0	25	0	0	0
18	B	20	–	0	0	0	0	0	100	0	0	0
18	A	140	6	0	5	0	0	0	95	0	0	0
18[a]	A	140	6	0	60	0	0	0	40	0	0	0
19	A	−6	18	90 of **20**							10 of **21**	
19	A	20	18	100 of **20**								

[a]With added HF (0.05 mol).

monitoring. The physical properties and analyses of the products are given in Table 2, and NMR data in Table 3.

2.2. Hydrolysis of carboxylic acid amides. General procedure

Sodium nitrite (0.05 mol) was added to a solution of amides **15** or **16** (0.01 mol) in 15 ml of 70% sulfuric acid and the reaction mixture heated at 70 °C for 0.5 h. The reaction mixture was then diluted with cold water, extracted with ether and dried over $MgSO_4$. After removal of the solvent, the product **17** was purified by distillation, and product **18** was purified by sublimation.

2.3. Hydrogenation of 1,2-bis(trifluoromethyl)benzene (4), 1H,3H-1,1,3,3-tetrafluorophthalane (5) and 2-trifluoromethylbenzamide (14). General procedure

A solution consisting of compound **4**, **5** or **14** (0.05 mol) in 20 ml of trifluoroacetic acid and $PtO_2 \cdot H_2O$ [5] was shaken under hydrogen (0.11 MPa). The catalyst was filtered off and the filtrate washed with water and with 10% aqueous sodium bicarbonate. The product (**2** or **3**) was dried over $MgSO_4$ and distilled. The product **15** was filtered and purified by sublimation.

2.4. Isomerization of cis-2-trifluoromethylcyclohexane-1-carbamide (15)

A solution of compound **15** (1 g, 5 mmol) in 2 ml of 50% aq. acetic acid was passed through a column (20–25 °C, 20×1 cm) packed with Al_2O_3. The filtrate was neutralized with 30% aq. sodium hydrocarbonate and the precipitated product filtered and purified by sublimation to yield 0.7 g (70%) of compound **16**.

2.5. Treatment of 7,7,9,9-tetrafluoro-cis-8-oxabicyclo-[4.2.0]nonane with HF

A solution of 7,7,9,9-tetrafluoro-*cis*-8-oxabicyclo-[4.2.0]nonane (**3**) (0.5 g, 2.5 mmol) in anhydrous HF (1 g, 50 mmol) was heated in a stainless-steel cylinder at a temperature of 140 °C for 1 h. ^{19}F NMR spectral monitoring of the reaction mixture showed the presence of compounds **9** (42%), **10** (42%), **12** (2%) and **13** (14%).

3. Results and discussion

As reported previously [6], fluorination of *cis*-cyclohexan-1,2-dicarboxylic acid with SF_4 at 60 °C and 100 °C yields 7,7,9,9-tetrafluoro-8-oxabicyclo-[4.2.0]nonane (70% and 59%) and 1,2-bis(tri-

Table 2
Physical properties and yields of compounds prepared

Compound No.	B.p. [m.p.] (°C)	n_D^{21}	d_4^{21} (g cm^{-3})	Elemental analyses				Yield (%)
					Found (%)	Molecular formula	Calc. (%)	
2	145	1.3592	1.3422	C	43.8	$C_8H_{10}F_6$	43.7	5[a]
				H	4.6		4.6	
3[b]	170	1.3870	1.2960	C	43.5	$C_8H_{10}F_4O$	43.6	60
				H	4.4		4.6	
7	141	1.3540	1.3452	C	43.7	$C_8H_{10}F_6$	43.7	5[a]
				H	4.6		4.6	
8	162–163	1.3803	1.3358	F	51.5	$C_8H_{10}F_4O$	51.8	55
15	[107–108]	–	–	C	49.1	$C_8H_{12}F_3NO$	49.2	5[a]
				H	6.1		6.2	
				N	7.2		7.2	
16	[181–183]	–	–	C	48.9	$C_8H_{12}F_3NO$	49.2	15
				H	6.1		6.2	
				N	7.1		7.2	
17	100/2 mmHg	1.4180	1.2857	C	50.5	$C_8H_5F_3O_2$	50.5	85
				H	2.5		2.6	
18	[60–62]	–	–	C	50.4	$C_8H_5F_3O_2$	50.5	90
				H	2.6		2.6	
20	137	1.3520	1.3051	C	43.6	$C_8H_{10}F_6$	43.7	72
				H	4.6		4.6	

[a]After purification by preparative GLC.
[b]Lit. value [6]: b.p. 169 °C; n_D^{20} 1.3820; d_4^{20} 1.2944.

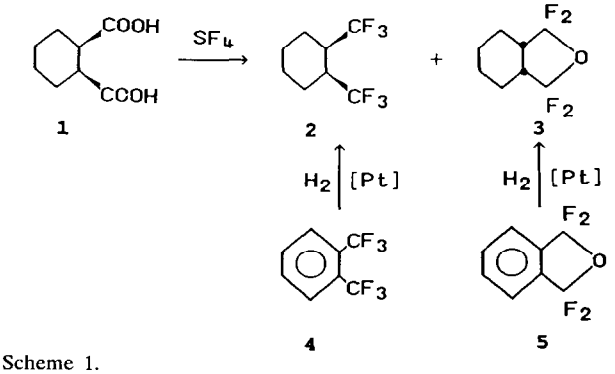
fluoromethyl)cyclohexane (3% and 7%), respectively. It was noted that acids with the carboxylic groups in the *cis* positions were particularly favourable towards cyclization, affording cyclic ethers in the highest yields.

We have found that the *trans*-carboxylic groups of cyclohexan-1,2-dicarboxylic acid (**6**) also give the cyclization product, 7,7,9,9-tetrafluoro-*trans*-8-oxabicyclo-[4.2.0]nonane (**8**) in high yield. To determine the structure of one we undertook, as in a previous study [6], the fluorination of *cis*-cyclohexan-1,2-dicarboxylic acid (**1**) with SF_4.

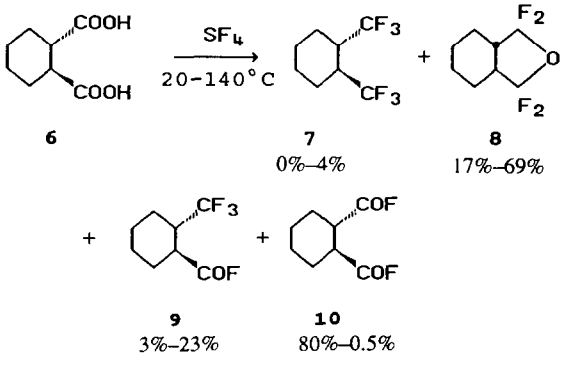
From its spectroscopic and physical properties, 7,7,9,9-tetrafluoro-*trans*-8-oxabicyclo[4.2.0]nonane (**8**) prepared by the fluorination of *trans*-cyclohexan-1,2-dicarboxylic acid (**6**) could be distinguished from the compound prepared by fluorination of *cis*-cyclohexan-1,2-dicarboxylic acid (**1**) with SF_4. However, 7,7,9,9-tetrafluoro-*cis*-8-oxabicyclo[4.2.0]nonane (**3**) prepared from 1,1,3,3-tetrafluorophthalane (**5**) [7] by hydrogenation [8] was identical to the compound prepared by fluorination of *cis*-cyclohexan-1,2-dicarboxylic acid (**1**) with SF_4. A similar picture was observed in the case of 1,2-bis(trifluoromethyl)cyclohexane (**2**) (Scheme 1).

These data together with certain additional evidence, as given below, allow the interpretation of the results of fluorination as follows.

Fluorination of *trans*-cyclohexan-1,2-dicarboxylic acid (**6**) with SF_4 yields mainly the *trans* products **7–10** (Scheme 2).



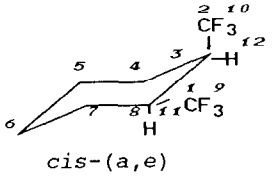
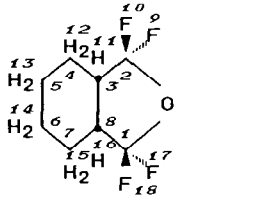
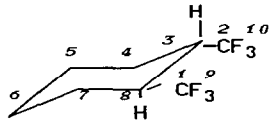
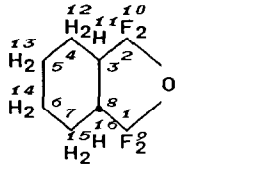
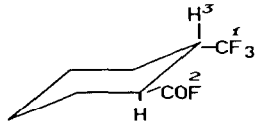
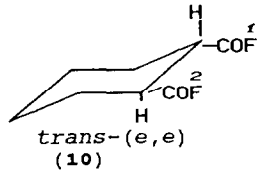
Scheme 1.



Scheme 2.

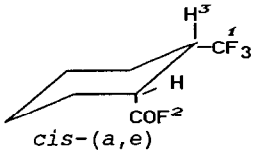
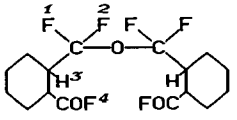
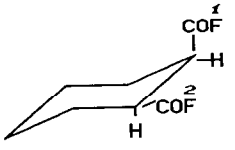
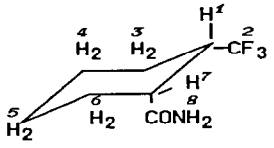
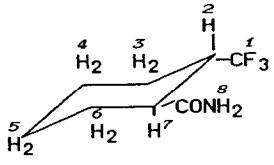
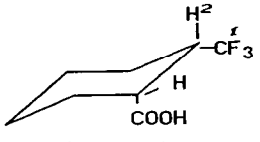
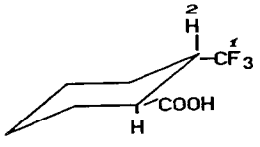
Fluorination of *cis*-cyclohexan-1,2-dicarboxylic acid (**1**) with SF_4 yields the *cis* products **2**, **3** and **11–13** together with smaller amounts of the *trans*

Table 3
NMR data for compounds prepared

Formula	Nucleus	number	Signal struct.	Chemical shift δ (ppm)	J (Hz)
 cis-(a,e) (2)	C	1, 2	q	128.1	$^1J_{1-9}=^1J_{2-10}=285$
	C	3, 8	q	40.8	$^2J_{3-10}=^2J_{8-9}=28$
	C	4, 7	s	24.0	
	C	5, 6	s	23.2	
	F	9, 10	m	−65.2	
	F	9	d	−68.6[a]	$^3J_{9-11}=10$
	F	10	d	−59.5[a]	$^3J_{10-12}=10$
	H	11, 12	m	2.8	
 cis-(a,e) (3)	C	1, 2	dd	130.8	$^1J_{1-17}=^1J_{1-18}=270$ $^1J_{2-9}=^1J_{2-10}=270$
	C	3, 8	dd	41.6	$^2J_{3-10}=^2J_{3-9}=25$ $^2J_{8-17}=^2J_{8-18}=25$
	C	4, 7	s	22.1	
	C	5, 6	s	21.7	
	F	9, 17	dd *AB*	−69.0	$^2J_{9-10}=^2J_{17-18}=143.0$ $^3J_{9-11}=^3J_{17-16}=10.3$
	F	10, 18	dd *AB*	−77.7	$^2J_{10-9}=^2J_{18-17}=143.0$ $^3J_{10-11}=^3J_{18-16}=10.3$
 trans-(e,e) (7)	H	11, 16	m	2.9	
	H	12–15	m	1.6	
	C	1, 2	q	127.9	$^1J_{1-9}=^1J_{2-10}=285$
	C	3, 8	q	41.5	$^2J_{3-10}=^2J_{8-9}=28$
	C	4–7	s	25.0	
	F	9, 10	m	−68.2	
 trans-(e,e) (8)	C	1, 2	t	129.4	$^1J_{1-9}=^1J_{2-10}=270$
	C	3, 8	m	47.0	
	C	4, 7	s	24.7	
	C	5, 6	s	23.9	
	F	9, 10	AA'BB'	−80.5	
	H	11, 16	m	2.0	
	H	12, 15	AB	1.6	$J_{AB}=10.0$
	H	13, 14	m	1.1	
 trans-(e,e) (9)	F	1	d	−71.3	$^3J_{1-3}=8.0$
	F	2	s	36.4	
 trans-(e,e) (10)	F	1, 2	s	35.3	

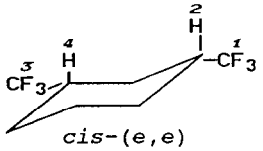
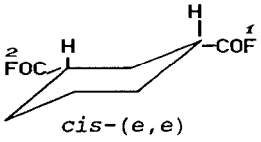
(continued)

Table 3 (*continued*)

Formula	Nucleus	number	Signal struct.	Chemical shift δ (ppm)	J (Hz)
 *cis*-(a,e) **(11)**	F	1	d	−68.4	$^3J_{1-3}=8.5$
	F	2	s	35.9	
 **(12)**	F	1	dd *A*B	−89.3	$^2J_{1-2}=138.0$, $^3J_{1-3}=13.0$
	F	2	dd A*B*	−72.4	$^2J_{2-1}=138.0$, $^3J_{2-3}=13.0$
	F	4	s	47.1	
 *cis*-(a,e) **(13)**	F	1, 2	s	35.9	
 *cis*-(a,e) **(15)**	H	1	q	2.3	$^3J_{1-2}=8.8$
	F	2	d	−68.6	$^3J_{2-1}=8.8$
	H	3–6	m	1.0–2.0	
	H	7	m	2.8	
	H	8	bs	6.1(6.8)	
 *trans*-(e,e) **(16)**	F	1	d	−70.5	$^3J_{1-2}=8.3$
	H	2	qd	2.4	$^3J_{2-1}=8.3$, $^3J_{2-7}=3.6$
	H	3–6	m	1.0–2.0	
	H	7	m	2.6	
	H	8	bs	6.2(6.9)	
 *cis*-(a,e) **(17)**	F	1	d	−68.0	$^3J_{1-2}=8.5$
 *trans*-(e,e) **(18)**	F	1	d	−70.8	$^3J_{1-2}=7.4$

(*continued*)

Table 3 (*continued*)

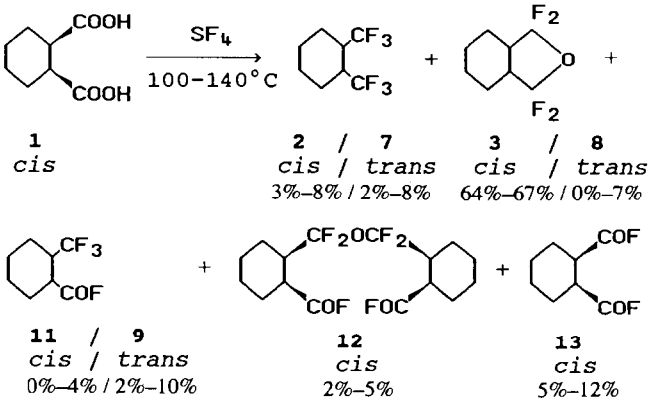
Formula	Nucleus number		Signal struct.	Chemical shift δ (ppm)	J (Hz)
 *cis*-(e,e) (20)	F	1, 3	d	−73.7	$^3J_{1-2}=^3J_{3-4}=7.8$
 *cis*-(e,e) (21)	F	1, 2	s	39.7	

[a]Measured at −67 °C.

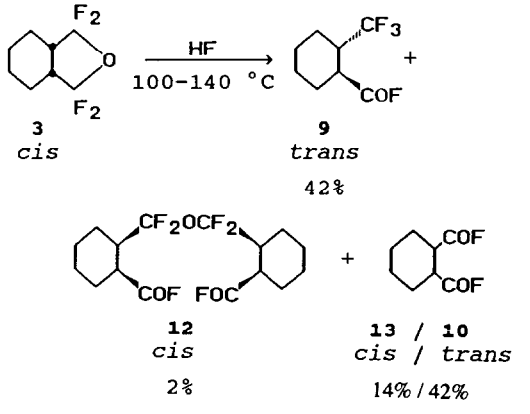
products **7–9** at temperatures of 100 °C and over (Scheme 3).

Cleavage of 7,7,9,9-tetrafluoro-*cis*-8-oxabicyclo-[4.2.0]nonane (**3**) in the presence of HF with formation of 2-trifluoromethylcyclohexanecarbonyl fluoride has been described previously [6], but whether the structure of the compound was *cis* or *trans* was not determined. We found that 7,7,9,9-tetrafluoro-*cis*-8-oxa-bicyclo[4.2.0]nonane (**3**) in the presence of HF at 100 °C and higher temperatures undergoes cleavage mainly into the *trans* products **9** and **10** (Scheme 4).

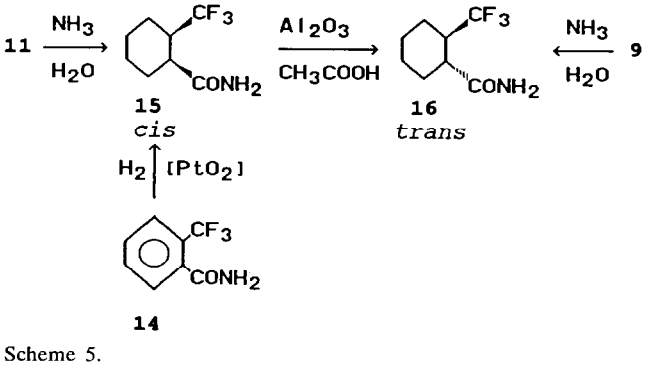
The structures of the fluoroanhydrides **9** and **11** were proved by ammonolysis into amides **16** and **15**, followed by acid hydrolysis into acids **17** and **18**. Amide **15** was also prepared by the hydrogenation of 2-trifluoromethylbenzamide (**14**) [7] in accordance with a previous method [8]. It is interesting to note that isomerization of *cis*-2-trifluoromethylcyclohexanecarboxylic acid amide (**15**) into the *trans* isomer **16** takes place on passing a solution through an Al_2O_3/HAc column at room temperature (Scheme 5).



Scheme 3.



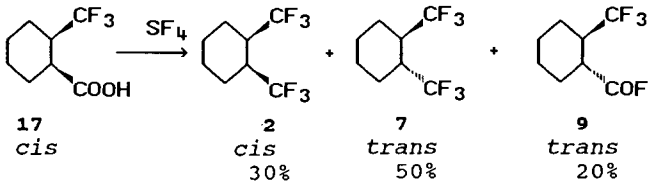
Scheme 4.



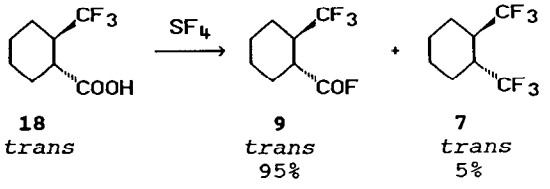
Scheme 5.

Fluorination of *cis*-2-trifluoromethylcyclohexane-1-carboxylic acid (**17**) with SF_4 at 140 °C proceeds with isomerization to yield the *cis*- and *trans*-1,2-bis(trifluoromethyl)cyclohexanes **2** and **7** and *trans*-2-trifluoromethylcyclohexanecarbonyl fluoride (**9**) (Scheme 6).

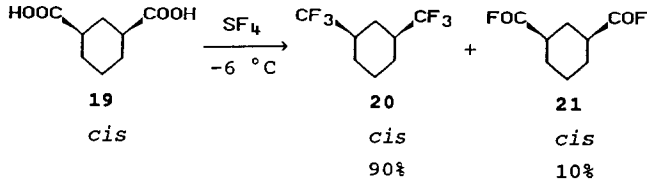
On fluorination of *trans*-2-trifluoromethylcyclohexane-1-carboxylic acid (**18**) with SF_4 at 140 °C, formation of the *cis* products was not observed and the main



Scheme 6.



Scheme 7.



Scheme 8.

product was *trans*-2-trifluoromethylcyclohexanecarbonyl fluoride (**9**) (Scheme 7).

Fluorination of *trans,cis,trans*-1,2,3,4-cyclopentanetetracarboxylic acid with SF_4 yields products corresponding to 1,3-cyclization of the carboxylic groups [3]. The possibility of some 1,3-cyclization could not be excluded. However, fluorination of *cis*-1,3-cyclohexanedicarboxylic acid (**19**) with SF_4 yields *cis*-1,3-bis(trifluoromethyl)cyclohexane (**20**) as a major product, and the formation of the products of 1,3-cyclization was not observed (Scheme 8).

It is well known [9] that in a *cis*-1,2-disubstituted cyclohexane one substituent must be axial and the other equatorial. In *trans*-1,2-disubstituted compounds, both may be equatorial or both axial, but for 1,3-compounds the reverse applies; the *trans* isomer must have the *ae* conformation and the *cis* isomer may be *aa* or *ee*. Since both *cis*- and *trans*-1,2-bis(trifluoromethyl)cyclohexanes **2** and **7** and *cis*-1,3-bis(trifluoromethyl)cyclohexane (**19**) were available, assignment of the NMR chemical shifts of trifluoromethyl groups as *e* or *a* was readily determined.

As shown in Ref. [10], the ^{19}F NMR chemical shift of axial CF_3 groups is less than that of equatorial CF_3 groups in 4-substituted cyclohexanes (−67 and −74 ppm). Controlled cooling of *cis*-1,2-bis(trifluoromethyl)-cyclohexane (**2**) led to an extreme broadening of the ^{19}F signal (−24.5 °C) at −65.2 ppm and separation (−67 °C) into two peaks at −59.5 (*a*) and −68.6 ppm (*e*). (Measurement of the areas under the resolved peaks gave the *ea* equilibrium constant K as 5.73×10^{-3} and hence, the *ea* free energy difference ΔG_{CF_3} as 10.2 kcal mol^{-1}.) The broad ^{19}F signal at −68.2 ppm for *trans*-1,2-bis(trifluoromethyl)cyclohexane (**7**) on this basis may be attributed to the *ee* conformer. Vicinal HF coupling constants were poorly resolved and estimation by peak half-width gave a value of approximately 8–10 Hz.

As shown in Ref. [11], ^{19}F NMR chemical shift values for axial and equatorial CF_3 groups are −65.4 and −73.3 ppm in *trans*-1,3-bis(trifluoromethyl)cyclohexane. The ^{19}F doublet at −73.7 ppm for *cis*-1,3-bis(trifluoromethyl)cyclohexane (**19**) may be attributed to the *ee* conformer. Apparently, the carboxyl groups of starting acid **19** are also in the *ee* conformation. This is in accord with its ability to readily yield trifluoromethyl derivatives with SF_4. In contrast to equatorial carboxyl groups, the axial groups in cyclohexane-1,1-dicarboxylic acid yield only the fluoroanhydride with SF_4 even under forced conditions [12]. Recently this has also been noted in the fluorination of cyclohexane-1,1,4,4-tetracarboxylic acid with SF_4 [13].

In agreement with the present experimental data, we assume that isomerization must occur at the carbonyl fluoride stage, where the α-hydrogen atom has sufficient mobility for enolization.

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