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STEREOCHEMISTRY OF FREE RADICAL ADDITIONS OF METHANOL AND ACETALDEHYDE TO PERFLUORINATED CYCLOALKENES

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SUMMARY

γ-Ray and peroxide-initiated additions of methanol and acetaldehyde to perfluorocyclo-butene (3), -pentene (4), and -hexene (5) gave mixtures of stereo-isomers in most cases. Stereospecific cis-addition of acetaldehyde to (5) occurs under γ-initiation. A simple ^{19}F n.m.r. method is advanced to distinguish the geometric isomers.

INTRODUCTION

The carbon-hydrogen bond is not easily used as a functional group, although reactions which involve homolytic fission of C-H, followed by e.g. addition to an alkene, are of course well known [1]. Processes of this type but involving additions to fluorinated alkenes, provide a convenient synthetic route to some functional fluorine-containing compounds [1-5]. Furthermore, the use of γ-rays presents a particularly easy way of initiating these reactions and this technique has been used extensively by many workers [6]. Methanol and acetaldehyde react in

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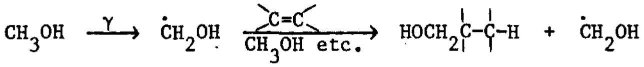
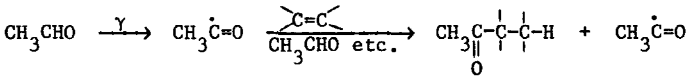
this way to give the corresponding alcohol (1) and ketone (2) respectively [1].



$$CH_3OH \xrightarrow{\gamma} \dot{C}H_2OH \xrightarrow[CH_3OH\ etc.]{>C=C<} HOCH_2\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-H + \dot{C}H_2OH$$

(1)



$$CH_3CHO \xrightarrow{\gamma} CH_3\dot{C}=O \xrightarrow[CH_3CHO\ etc.]{>C=C<} CH_3\underset{\underset{O}{\|}}{C}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-H + CH_3\dot{C}=O$$

(2)

RESULTS AND DISCUSSION

In the present study, we have been investigating the stereochemistry of addition of methanol and acetaldehyde to perfluorocyclobutene (3), -pentene (4), and -hexene (5) by γ-ray addition and, for comparison, by peroxide initiation. Other workers [4, 7-11] have described some free-radical additions to these fluorinated cycloalkenes and stereochemistry has been assigned in the addition of ethanol and acetaldehyde to perfluorocyclobutene by relating structures to vinyl derivatives which, themselves, were assigned by dipole-moment measurement [7]. More recently [11], adducts of perfluorocyclohexene have been assigned by analysis of ^{19}F n.m.r. spectra. Here, we try to integrate the full series and demonstrate that there is a simple and clear basis for assignment of stereochemistry from the n.m.r. spectra and that these assignments are also quite consistent with those of previous workers.

Reactions with methanol or acetaldehyde, under γ-ray initiation at room temperature, were carried out by sealing the perfluorocycloalkene with excess of the reagent in a Carius tube, after careful degassing of the mixtures. For comparison, analogous reactions initiated by benzoyl peroxide were carried out at ca. 85°C.

Yields of adducts are shown in Table 1 and no telomers were produced under these conditions. In most cases, mixtures of geometric isomers were obtained and the observed ratios are indicated. Isomers of the various methanol adducts were very difficult to separate; only the perfluorocyclobutene systems could be separated cleanly by preparative-scale g.l.c. and indeed, the perfluorocyclohexene systems could only be partly resolved by analytical-scale g.l.c. In contrast, isomers of the acetaldehyde adducts were readily separated by fractional distillation.

TABLE 1

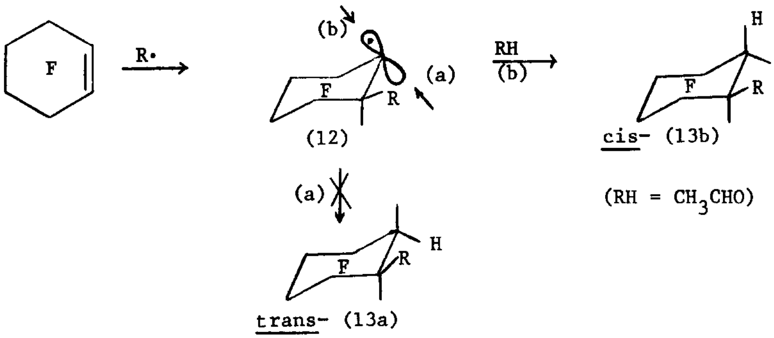
Additions of methanol and acetaldehyde to perfluorocycloalkenes

Cycloalkene[a]		Methanol		Acetaldehyde	
		% Conversion	Trans/Cis Ratio	% Conversion	Trans/Cis Ratio
 (3)	(γ)[b]	85	8.7 (6)	67	3.4 (9)
	(P)	57	5.0	88	2.6
 (4)	(γ)	68	1.0 (7)	81	0.84 (10)
	(P)[c]	64	1.4	49	0.63
 (5)	(γ)	79	0.7 (8)	87	entirely cis (11)
	(P)	67	0.4	89	0.05

[a] F in the centre of the ring indicates that all unmarked bonds are to fluorine.
[b] Induced by γ-rays at room temperature.
[c] Induced by benzoyl peroxide at ca. 85°C.

Structural assignment of the geometric isomers is described later and we have been careful, where possible, to establish in separate experiments that the isomers are not equilibrated under the conditions of preparation i.e. the product mixtures arise from kinetic control. In Table 1, there is a pronounced trend, from perfluorocyclobutene to perfluorocyclohexene, for the proportion of the cis-isomer to increase and, in addition, this trend is greater with acetaldehyde in comparison with corresponding additions of methanol. Indeed, it is quite remarkable that, in the γ-ray induced addition of acetaldehyde to perfluorocyclohexene (5) only the cis-isomer (11) is detectable and it is, obviously, of interest to consider a possible basis for this observation.

The e.s.r. spectra of cyclohexyl radicals are consistent with rapidly interconverting chair conformers with a planar radical centre (12). Therefore, it might be anticipated that radical addition to a



(12)

cis- (13b)

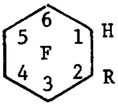
(RH = CH_3CHO)

trans- (13a)

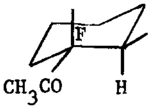
cyclohexene system would, in the first instance, produce an intermediate planar radical (12). Approach of RH to the intermediate radical from the direction (a) or (b) could then be affected by steric effects. In the absence of any consideration of the steric effects of RH a product with a hydrogen atom in the axial position (13b) is, no doubt, preferable to the isomer (13a) with a fluorine atom in the axial position. However, there is probably a subtle competition between this effect of axial fluorine and the preference of RH to approach (12) via (a), than (b) which would vary with the steric requirements of RH. Nevertheless, at the present time, we are unable to advance a clear cut explanation for the observed high stereoselectivity in the addition of acetaldehyde to perfluorocyclohexene.

Assignment of stereochemistry to the adducts

Analysis of the ^{19}F n.m.r. data on polyfluorinated cyclic systems is complex but fluorinated cyclohexanes are probably the most extensively studied of the series [13-15]. Even so, adducts of the general formula (14) cannot yet be completely analysed because of the complexity that arises from the presence of large long-range spin coupling.



(14)



(11)

However, in the case of (14, R = CH_3CO), which is a single geometric isomer i.e. compound (11), it is possible to effect sufficient analysis of the data to be confident that the structure is the cis-isomer, with $COCH_3$ equatorial and H axial. For simplicity, compound (11) is represented as an undistorted cyclohexane although, as will be argued later, this is very unlikely to be the case. In the ^{19}F n.m.r. spectrum of (11) there are twelve resolved complex bands in the low field region, a broad unresolved band from CFR, and a complex band from CFH at highest field. The bands associated with the CF_2 groups are shown in Table 2 (signals numbered with increasing field) and Indor experiments assigned

TABLE 2

^{19}F n.m.r. data for the adduct (11)

Peaks[a]	δ_A[b] (ppm)	δ_B (ppm)	J_{AB} (Hz)
1,2a,7,8	120	134	280 ± 5
3,5,9,10	124	140	285 ± 5
2b,4,11,12	123	145	290 ± 5
6	128	128	not measurable

[a] $CFCOCH_3$ δ 193 ppm CFH δ 231 ppm.

[b] Shifts relative to $CFCl_3$ calculated from values obtained from C_6F_6 as internal standard, according to the relationship $\delta_{CFCl_3} = \delta_{C_6F_6} + 163$. The spectrum was recorded on a 10% v/v solution in CCl_4.

the bands as arising from overlapping AB quartets, with a geminal coupling, $^2J_{FF}$, in the region of 280 Hz. Saturating the solution with the lanthanide shift reagent, $Yb(fod)_3$ showed that the AB quartet comprising peaks 1, 2a, 7, 8 arise from the CF_2 group at the 3-position (i.e. closest to CH_3CO), since these peaks are the most affected.

The spectrum of (11) did not change appreciably over a temperature range -100 to +100°C, indicating that the compound is essentially in a fixed conformation, in contrast to polyfluorocyclohexanes [13-15]. We can, therefore, assume that the CH_3CO group is in an equatorial position. Consequently, in order to determine the structure of (11) we must establish whether the fluorine atom at the 1-position is in an axial or equatorial position. On the basis of a relationship between ^{19}F shielding and internal electric fields, Emsley [16] has suggested that the axial fluorine of a CF_2 group in perfluorocyclohexane derivatives resonates at the lower field value and this point is amply illustrated in the work of Thomas and co-workers [13,14] who examined the ^{19}F n.m.r. spectra of various polyfluorocyclohexanes, whose geometric arrangements of groups had been established by careful chemical studies by Tatlow and co-workers [17]. It may be assumed, therefore, that when δ_{AB} is significant then the lower field component arises from axial fluorine. In order to distinguish the position of the 1-F, we have attempted to calculate the chemical shifts for this fluorine atom both in the axial and equatorial position. It is probable that a substituent group R (where R = CH_2OH, CH_3CO) will effect the neighbouring CF_2 groups in a way similar to that of CF_3 and, therefore, we have derived substituent shift parameters from 4-H-perfluoromethylcyclohexane [14], shown in Table 3, for use in calculating values for systems like (14).

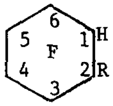
TABLE 3

Substituent chemical shifts in (14)

Substituent		Shift of F (ppm)					
		1a	1e	2a	2e	3a	3e
1 R ($\equiv CF_3$)	equatorial	+24		-4	-11	-2	-2
1 H	axial		+72	+4	-14	-3	+1
	equatorial	+48		-3	-11	-3	-3

TABLE 4

Calculated and observed ^{19}F chemical shifts for (14)

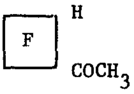
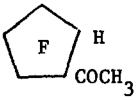
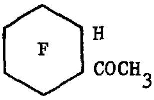
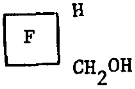
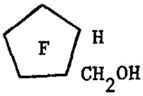
		Calculated		Observed
		H-equatorial	H-axial	
	3a	117	117	120
	3e	128	132	134
	4a	119	122	124
	4e	137	140	139
	5a	121	121	123
	5e	139	143	145
	6a	119	126	128
	6e	129	126	128
	1a	207	224	231
	2a	184	191	193

The signals for CF_2 at positions 4-, 5-, and 6- are assigned, in Table 4, to give the best fit with the observed signals but the signals due to 3a- and 3e-F, assigned by the lanthanide shift experiment, are also very close to the calculated values. More important, there is a very clear distinction between the two possibilities for 1-F and 2-F, the experimental and calculated values for 1-H in the axial position, being in very good agreement. Julien and co-workers [11] have recently reported and examined the ^{19}F n.m.r. spectrum of (11) and our conclusions are in accord.

^{19}F chemical shifts are contained in Table 5 for the CFH and CFR positions for various derivatives. For the cyclohexane adducts, there is a very good correlation between these observed and the calculated values contained in Table 4, which adds further weight to the process. However, what is surprising is that there is a remarkable similarity between corresponding chemical shifts for the whole series of adducts and we advance this method as a simple way of assigning these geometric isomers. We can have confidence in the cyclohexene series because of the partial analysis of ^{19}F n.m.r. data, already described, and the structures of the adducts (9) of acetaldehyde to perfluorocyclobutene (3), have been assigned [7] on the basis of dipole moment measurements. Since two

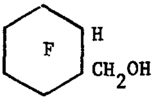
TABLE 5

^{19}F n.m.r. data for CFR and CFH positions in methanol and acetaldehyde adducts.

Adduct	Trans				Cis			
	B.p. (°C)	G.l.c.^{a}	^{19}F δ^{b}		B.p. (°C)	G.l.c.^{a}	^{19}F δ^{b}	
			CFR	CFH			CFR	CFH
 (9)	116	2	173	214	100	1	196	223
 (10)	128	2	174	215	112	1	191	228
 (11)	143	2	176	214	128	1	193	231
 (6)	128	1	182	219	141	2	198	225
 (7)	139	1	181	214	c	2	195	225

continued

TABLE 5 continued

Adduct	Trans				Cis			
	B.p.	G.l.c.[a]	^{19}F δ[b]		B.p.	G.l.c.[a]	^{19}F δ[b]	
			CFR	CFH			CFR	CFH
 (8)	c	1	189	209	c	2	195	232

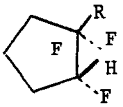
[a] Order of emergence from a column packed with 2-cyanoethylmethylsilicone.

[b] p.p.m., measured from $CFCl_3$ as external reference, positive shifts to high field.

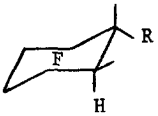
[c] Pure sample of the isomer could not be obtained.

extremes of the series can be accepted with confidence, it seems reasonable to accept the method also, for the cyclopentane derivatives.

It is quite surprising that the chemical shifts for CFH and CFR, contained in Table 5 are so close for the three types of system. The stereochemical relationship of groups in e.g. a cis-derivative (15) of cyclopentane would normally be quite different from the relationship of these groups in a corresponding cyclohexane (16). Nevertheless, it is



(15)



(16)

quite likely that, in the highly fluorinated derivatives corresponding to (15) and (16), considerable distortion takes place to minimise the eclipsing of C-F bonds in derivatives of (15) and to minimise 1,3-interactions in (16). The resultant of these distortions is likely to be a much closer angular relationship of groups in the cyclohexane derivatives in comparison with corresponding cyclopentane or cyclobutane derivatives, than is normally the case.

Boiling points and order of g.l.c. retention time (Table 5) for the methanol adducts are in the expected order with cis-isomers having higher b.pts. and longer retention times. The acetaldehyde adducts also give a consistent series but, in this case, the trans-isomers give the higher b.p. and longer retention times. Clearly, these physical properties are a useful guide in relating stereochemistry of compounds within a series but are not useful between different series.

EXPERIMENTAL

Irradiations by gamma-rays were achieved by exposure at room temperature to a ^{60}Co source, housed in a purpose-built chamber. All addition reactions were carried out using glass Carius tubes of ca. 100 cm.^{3} volume and the reactants were degassed before sealing the tubes under vacuum. Fractional distillations were carried out using a Buchi Fischer Spaltrohr Column HMS 500 apparatus. ^{19}F N.m.r. spectra were recorded with a Varian A56/60D spectrometer; chemical shifts are quoted with reference to external $CFCl_3$ (upfield positive). Isomer ratios were obtained both from g.l.c. peak area measurements using a gas density balance detector and from ^{19}F n.m.r. integrations of high field signals.

Additions to perfluorocyclohexene (5)

(a) By gamma-ray initiation

(i) Methanol. A mixture containing perfluorocyclohexene (5) (29.1 g, 111 mmol) and methanol (47.7 g, 1490 mmol) was irradiated to a total dose of 3.0 x 10^7 rad. The mixture was then washed with water, separated, dried ($MgSO_4$) and filtered. Distillation gave 2,H-decafluorocyclohexylmethanol (8) (25.9 g, 79%) but failed to separate the geometric isomers. Analysis: Found: C, 29.0; H, 1.4; F, 64.3%. Calc. for $C_7H_4F_{10}O$: C, 28.59; H, 1.37; F, 64.59%.

(ii) Acetaldehyde. A mixture containing perfluorocyclohexene (5) (21.8 g, 83.2 mmol) and acetaldehyde (37.04 g, 84.2 mmol) was irradiated to a total dose of 3.0 x 10^7 rad. Distillation gave cis-2,H-decafluorocyclohexylmethylketone (11) (nc) (22.10 g, 87%) b.p. 128°C. Analysis: Found: C, 31.4; H, 1.1; F, 61.8. $C_8H_4F_{10}O$ requires C, 31.37; H, 1.31; F, 62.09.

(b) By benzoyl peroxide initiation

(i) Methanol. A mixture containing perfluorocyclohexene (5) (41.2 g, 157 mmol), methanol (23.5 g, 734 mmol) and benzoyl peroxide (0.75 g) was heated at 95°C for 24½ hours. The mixture was then washed with water, separated, dried ($MgSO_4$) and filtered. Distillation gave (8) (30.94 g, 67%).

(ii) Acetaldehyde. A mixture containing perfluorocyclohexene (5) (32.4 g, 124 mmol), acetaldehyde (14.32 g, 325 mmol) and benzoylperoxide (0.64 g) was heated at 90°C for 23½ hours. Distillation gave (11-*cis*) (30.64 g, 81%) and from the pot residue a further amount of this isomer (1.40 g, 3.7%) was separated by preparative g.l.c. (di-isodecyl phthalate) as well as *trans*-2,H-decafluorocyclohexylmethylketone (11-*trans*) (nc) (1.37 g, 3.6%) b.p. 143°C. Analysis: Found: C, 31.6; H, 1.1. $C_8H_4F_{10}O$ requires C, 31.37; H, 1.31.

Additions to perfluorocyclopentene (4)

(a) By gamma-ray initiation

(i) Methanol. A mixture containing perfluorocyclopentene (4) (34.73 g, 164 mmol) and methanol (17.29 g, 540 mmol) was irradiated to a total dose of 1.59×10^7 rad. The mixture was then washed with water, separated, dried ($MgSO_4$) and filtered. Distillation gave 2,H-octafluorocyclopentylmethanol (7) (24.7 g, 68%) but failed to separate the geometric isomers. A pure sample of *trans*-2,H-octafluorocyclopentylmethanol (7-*trans*) (nc), b.p. 139°C was isolated by preparative g.l.c. (2-cyanoethylmethylsilicone). Analysis: Found: C, 29.5; H, 1.7; F, 61.9. $C_6H_4F_8O$ requires C, 29.51; H, 1.64; F, 62.30.

(ii) Acetaldehyde. A mixture containing perfluorocyclopentene (4) (19.08 g, 90 mmol) and acetaldehyde (19.25 g, 440 mmol) was irradiated to a total dose of 1.59×10^7 rad. Fractional distillation gave *cis*-2,H-octafluorocyclopentylmethylketone (10-*cis*) (nc) (10.2 g, 44.3%) b.p. 112°C (Analysis: Found: C, 33.0; H, 1.2; F, 59.6. $C_7H_4F_8O$ requires C, 32.81; H, 1.56; F, 59.38) and *trans*-2,H-octafluorocyclopentylmethylketone (10-*trans*) (nc) (8.47 g, 36.8%) b.p. 128°C. Analysis: Found: C, 32.8; H, 1.8; F, 59.6. $C_7H_4F_8O$ requires C, 32.81; H, 1.56; F, 59.38.

(b) By benzoyl peroxide initiation [9]

(i) Methanol. A mixture containing perfluorocyclopentene (4) (41.5 g, 196 mmol), methanol (25.3 g, 790 mmol) and benzoyl peroxide (0.60 g) was heated at 95°C for 24½ hours. The mixture was then washed with water, separated, dried ($MgSO_4$) and filtered. Distillation gave (7) (30.60 g, 64.0%).

(ii) Acetaldehyde. A mixture containing perfluorocyclopentene (4) (59.26 g, 279 mmol), acetaldehyde (49.05 g, 1.11 mol) and benzoyl peroxide (0.74 g) was heated at 80°C for 115 hours. Fractional distillation gave (10-*cis*) (21.94 g, 30.6%) b.p. 112°C and (10-*trans*) (13.85 g, 19.4%) b.p. 128°C.

Additions to perfluorocyclobutene (3) [7]

(a) By gamma-ray initiation

(i) Methanol. A mixture containing perfluorocyclobutene (3) (18.5 g, 114 mmol) and methanol (11.58 g, 362 mmol) was irradiated to a total dose of 5.63 x 10^6 rad. The mixture was then washed with water, separated, dried ($MgSO_4$) and filtered. Distillation at reduced pressure gave 2,H-hexafluorocyclobutylmethanol (6) (18.83 g, 85%) but failed to separate the geometric isomers. Preparative g.l.c. (di-isodecylphthalate) gave *trans*-2,H-hexafluorocyclobutylmethanol (6-*trans*) b.p. 128°C (Analysis: Found: C, 30.7; H, 2.1; F, 58.3. Calc. for $C_5H_4F_6O$: C, 30.93; H, 2.06; F, 58.76) and *cis*-2,H-hexafluorocyclobutylmethanol (6-*cis*) b.p. 141°C. Analysis: Found: C, 31.0; H, 2.5; F, 58.2. Calc. for $C_5H_4F_6O$: C, 30.93; H, 2.06; F, 58.76.

(ii) Acetaldehyde. A mixture containing perfluorocyclobutene (3) (20.51 g, 127 mmol) and acetaldehyde (23.28 g, 530 mmol) was irradiated to a total dose of 1.46 x 10^7 rad. Fractional distillation gave *cis*-2,H-hexafluorocyclobutylmethylketone (9-*cis*) (4.0 g, 15%) b.p. 100°C (Analysis: Found: C, 35.1; H, 2.2; F, 54.9. Calc. for $C_6H_4F_6O$: C, 34.95; H, 1.94; F, 55.34) and *trans*-2,H-hexafluorocyclobutylmethylketone (9-*trans*) (13.7 g, 52.5%) b.p. 116°C. Analysis: Found: C, 34.7; H, 1.9; F, 55.9. Calc. for $C_6H_4F_6O$: C, 34.95; H, 1.94; F, 55.34.

(b) By benzoyl peroxide initiation

(i) Methanol. A mixture containing perfluorocyclobutene (3) (11.1 g, 68 mmol), methanol (9.48 g, 296 mmol) and benzoyl peroxide (0.17 g) was heated at 80°C for 19½ hours. Work up and distillation as above gave (6) (7.52 g, 56.6%).

(ii) Acetaldehyde. A mixture containing perfluorocyclobutene (3) (9.4 g, 58 mmol), acetaldehyde (10.11 g, 230 mmol) and benzoyl peroxide (0.2 g) was heated at 80°C for 19½ hours. Fractional distillation gave (9-*cis*) (3.13 g, 24.3%) b.p. 100°C and (9-*trans*) (8.24 g, 64.1%) b.p. 116°C.

Irradiation of stereoisomers

Small samples of a range of stereoisomers were placed in Pyrex n.m.r. tubes with an excess of methanol (for an alcohol adduct) or acetaldehyde (for a methylketone adduct) and degassed before sealing under vacuum. The ^{19}F n.m.r. spectra of the samples were recorded and they were then irradiated by gamma-rays before the spectra were recorded again. In no case was a signal due to the alternative isomer detected.

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