Nuclear Magnetic Resonance Study of Hydrogen Bonding in 1,1,1-Trifluoro-2-hydroxy-4-alkanones

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Addition of fluoral at the α-carbon of 3-pentanone, cyclohexanone, 4-methyl-2-pentanone, and acetone gives 1,1,1-trifluoro-2-hydroxy-3-methyl-4-hexanone (**1***a* and *b*, diastereomers), 2-(1-hydroxy-2,2,2-trifluoroethyl)cyclohexanone (**2***a* and *b*, diastereomers), 1,1,1-trifluoro-2-hydroxy-6-methyl-4-heptanone (**3**), and 1,1,1-trifluoro-2-hydroxy-4-pentanone (**4**), respectively. Hydrogen-bonding studies, based on proton and fluorine n.m.r. measurements, show strong intramolecular >C=O···H—O bonding with relatively weak intermolecular interactions in **1***a* and **2***a*, and intermolecular F···H—O bonding in **1***b*, **2***b*, **3**, and **4**.

L'addition de fluoral sur le carbone α de la pentanone-3, cyclohexanone,méthyl-4 pentanone-2 et acétone conduit au trifluoro-1,1,1 hydroxy-2 méthyl-3 hexanone-4 (**1***a* et **1***b*, diastéréoisomères), (hydroxy-1 trifluoroéthyl-2,2,2)-2 cyclohexanone (**2***a* et **2***b*, diastéréoisomères), trifluoro-1,1,1 hydroxy-2 méthyl-4 heptanone-2 (**3**) et trifluoro-1,1,1 hydroxy-2 pentanone (**4**) respectivement. Les études sur les liaisons hydrogène, effectuées par résonance magnétique nucléaire du proton et du fluor, montrent une liaison intramoléculaire >C=O···H—O forte et des interactions intermoléculaires relativement faibles pour **1***a* et **2***a*; et une liaison intermoléculaire F···H—O pour **1***b*, **2***b*, **3** et **4**. [Traduit par le journal]

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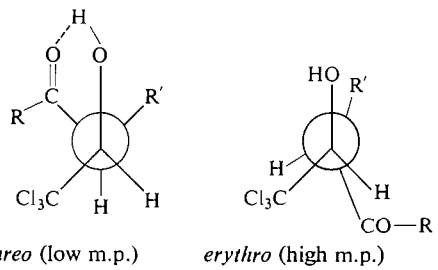
In an earlier paper (1), we have characterized several diastereomeric pairs of 1,1,1-trichloro-2-hydroxy-4-alkanones, including 1,1,1-trichloro-2-hydroxy-3-methyl-4-hexanone (Cl analogs of **1***a* and *b*) and 2-(1-hydroxy-2,2,2-trichloroethyl)-cyclohexanone (Cl analogs of **2***a* and *b*), and made configurational assignments on the basis of p.m.r. and i.r. spectral studies of hydrogen-bonding interactions and dihedral —CHOH—CHR— bond angles. The low-melting isomer of each pair was found to exhibit strong intramolecular hydrogen bonding, attributable mainly to >C=O···H—O rather than Cl···H—O interaction, and was assigned the *threo* structure while the high-melting isomer was assigned the *erythro* structure (Fig. 1).



threo (low m.p.) *erythro* (high m.p.)

FIG. 1. Structure assignments for RCO—CHR'—CHOH—CCl_3.

If, instead of chloroketols (Fig. 1), the corresponding fluoroketols are used for the spectroscopic studies, the presence of F···H—O hydrogen bonds should be discernible from their F-19 n.m.r. spectra and hence should settle the question whether halogen or the carbonyl oxygen is the preferred proton acceptor site in intramolecularly hydrogen-bonded 1,1,1-trihalo-2-hydroxy-4-alkanones. With this goal in mind, we have synthesized a series of fluoroketols and recorded their proton and fluorine n.m.r. spectra as a function of their concentrations in chloroform-*d* at room temperature.

Results and Discussion

Reaction of Fluoral with Ketones

The fluoroketols were prepared by crossed aldol condensation of fluoral with the respective aliphatic ketones in glacial acetic acid – sodium acetate medium using a modification of the procedure described previously (2) for chloral–ketone condensations (eq. 1). Cyclohexanone and 3-pentanone gave two diastereomeric products, respectively, while only one ketol was obtained from the reaction of acetone with fluoral. In the case of 4-methyl-2-pentanone, only the ketol (**3**) resulting from fluoral addition

[1] $RCOCH_2R' + CF_3CHO \rightarrow RCOCHR'—CHOHCF_3$

1*a* and *b* R = Et, R' = CH_3 **3** R = *i*-Bu, R' = H
2*a* and *b* R—R' = —$(CH_2)_4$— **4** R = CH_3, R' = H

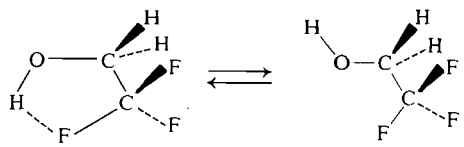
at the α-methyl carbon could be isolated from the product mixture although the F-19 n.m.r. spectrum of the crude product showed the presence of traces of the isomeric methylene condensation product, 1,1,1-trifluoro-2-hydroxy-3-isopropyl-4-pentanone. In contrast, no 1,1,1-trichloro-2-hydroxy-3-isopropyl-4-pentanone was detected in the reaction mixture formed from chloral and 4-methyl-2-pentanone (2). Thus, addition at the methylene carbon is sterically inhibited by the bulky isopropyl substituent but, with the relatively small fluoral molecule as electrophile, this steric hindrance is less pronounced than with chloral.

Anhydrous fluoral (b.p. −19°) was obtained by treatment of commercial fluoral hydrate with concentrated sulfuric acid and phosphorus pentoxide (3) and trapping at −78°. The gas was then bubbled into a mixture of ketone, acetic acid, and sodium acetate at the desired reaction temperature (70–100°) using a slow stream of nitrogen to prevent oxidation. Although anhydrous fluoral appears to interact strongly with the solvent (acetic acid) and react fairly rapidly with the ketone, evaporation losses during its preparation and low fluoral hydrate reagent purity are believed to be the main reasons for the low product yields. Diastereomeric fluoroketols were separated and purified by adsorption chromatography on silicic acid and elution with chloroform.

Hydrogen Bonding Studies by Nuclear Magnetic Resonance

Proton magnetic resonance measurements on alcohols and amines have shown that hydrogen bond formation is accompanied by a displacement of the chemical shift of the protons involved toward lower magnetic field strength (4, 5). When the OH group of a molecule forms a hydrogen bond to a donor atom X, the electronic structure and hence the magnetic susceptibility of that OH bond are altered leading to a change in the magnetic shielding. Thus it is the generation of a strong electric field in the vicinity of the OH bond which causes the observed downfield shift (6).

Trifluoromethylcarbinols which are structurally closely related to the fluoroketols under discussion have been studied spectroscopically to establish conformational preferences as a function of hydrogen bonding interactions. Cannon and Stace (7) have reported a "free" OH stretching band for trifluoroethanol in carbon tetrachloride solution (3617 cm^{-1}) which persisted even in the pure liquid state (3628 cm^{-1}). They have interpreted this observation as evidence for the absence of intramolecular F···HO bonding. Oki and Iwamura (8) found an OH band for trifluoroethanol in 0.003 *M* carbon tetrachloride solution which was asymmetric on the high-frequency side and explained it in terms of an unresolved doublet due to *trans* ⇆ *gauche* isomerism and restricted rotation about the carbon–oxygen single bond (eq. 2). They

[2] 

gauche *trans*

concluded from a mathematical resolution of the doublet that trifluoroethanol exists predominantly in the intramolecularly hydrogen-bonded *gauche* form. A temperature-dependent *trans* ⇆ *gauche* equilibrium (eq. 2), with a relatively small population in the *trans* form, was also observed by Krueger and Mettee (9).

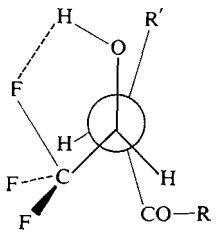
Because of their structural similarity to the fluoroketols (**1***a* and *b*, **2***a* and *b*, **3**, and **4**) under investigation, we have included 1,1,1-trifluoro-2-propanol (**5**) and 2,2,2-trifluoroethanol (**6**) as part of our hydrogen-bonding studies. The chemical shift data are summarized in Table 1. The upfield shift of the hydroxyl proton on dilution observed for all eight compounds is typical for the behavior of intermolecularly hydrogen-bonded aggregates of solute molecules being broken up into monomeric species. The dilution shifts measured for the fluoroketols **1***b*, **2***b*, **3**, and **4** are similar to those for the trifluoromethylcarbinols **5** and **6**, with relatively steep slopes at lower concentrations, suggesting similar hydrogen-bonding interactions for all six compounds. Since the monomeric species of **5** have already been shown to exist predominantly in the intramolecularly hydrogen-bonded *gauche* form (7–9), it is reasonable to assume that the hydroxyl protons of the monomeric species of **1***b*, **2***b*, **3**, and **4** are also hydrogen-bonded to fluorine (Fig. 2).

The i.r. spectra of **1***b*, **2***b*, **3**, and **4**, taken in carbon tetrachloride solution at as low a concentration as 0.005 *M*, show a broad peak at 3520 cm^{-1} with a small shoulder at 3600 cm^{-1}

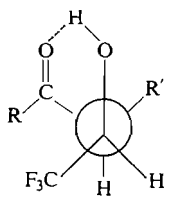
TABLE 1. Fluorine and hydroxyl proton chemical shifts for $RCOCHR'CHOHCF_3$ and CF_3CHROH

Compound	Mol fraction	Chemical shift OH*	Chemical shift CF_3†	Compound	Mol fraction	Chemical shift OH*	Chemical shift CF_3†
1*a*	0.29	261	−4332	**3**	0.23	255	−4494
	0.14	260	−4332		0.11	243	−4484
	0.07	256	−4333		0.05	232	−4483
	0.03	255	−4334		0.02	223	−4477
1*b*	0.29	245	−4346	**4**	0.28	261	−4503
	0.14	230	−4336		0.14	249	−4495
	0.07	215	−4329		0.07	237	−4488
	0.03	204	−4323		0.03	224	−4485
2*a*	0.23	273	−4254	**5**	0.41	257	−4614
	0.11	268	−4254		0.20	230	−4601
	0.05	262	−4254		0.10	191	−4593
	0.02	259	−4254		0.05	161	−4587
2*b*	0.23	235	−4296	**6**	0.38	239	−4398
	0.11	221	−4282		0.19	218	−4381
	0.05	210	−4277		0.09	198	−4368
	0.02	196	−4270		0.04	176	−4360

*In Hz downfield from TMS in $CDCl_3$ at 60 MHz (accuracy ± 1 Hz).
†In Hz downfield from $CFCl_3$ in $CDCl_3$ at 56.4 MHz (accuracy ± 1 Hz).



erythro



threo

1*b* R′ = CH_3, R = Et
2*b* R—R′ = —$(CH_2)_4$—
3 R = *i*-Bu, R′ = H
4 R = CH_3, R′ = H

1*a* R′ = CH_3, R = Et
2*a* R—R′ = —$(CH_2)_4$—

FIG. 2. Conformational assignments for $RCOCHR'CHOHCF_3$.[1]

pointing to a preponderance of hydrogen-bonded OH groups in the monomeric species. Finally, the downfield dilution shift observed in the fluorine n.m.r. spectra (Table 1) shows clearly that the halogen atoms are involved in intermolecular hydrogen-bond formation to the hydroxyl groups of these compounds. The larger proton dilution shifts reported earlier for the chlorine analogs of **1***b* and **2***b* may be taken as evidence for the larger chlorine atom being a somewhat better hydrogen bond acceptor site than fluorine.

In sharp contrast to the behavior of **1***b*, **2***b*, **3**, and **4**, dilution results in a very small upfield shift in the absorption position for the hydroxylic protons of the *threo*-fluoroketols **1***a* and **2***a*. Huggins, Pimentel, and Shoolery (10) have interpreted this flattening of the dilution shift curve as being due to the intrusion of intramolecularly hydrogen-bonded species even at relatively high concentrations. Since the position of the hydroxylic proton relative to the fluorine atoms has not been changed in going from one diastereomer (**1***b* or **2***b*) to the other (**1***a* or **2***a*) and the shape of the dilution shift curves now is drastically different from that observed for the carbonyl-free trifluoromethylcarbinols **5** and **6**, we must conclude that in **1***a* and **2***a* intramolecular hydrogen bonding occurs to the carbonyl group rather than to the halogen atom. This conclusion is further supported by the following experimental observations: (*a*) the F-19 n.m.r. spectra of **1***a* and **2***a* show negligible dilution shifts (Table 1) pointing to the non-involvement of fluorine in hydrogen-bond formation, and (*b*) the i.r. spectra of **1***a* and **2***a* at high dilution exhibit a broad absorption peak at 3520 cm^{-1} with a weak shoulder at 3600 cm^{-1} indicating the presence of hydrogen-bonded hydroxyl groups.

[1]The H—C—C—H dihedral angles for the *erythro* (140°) and *threo* (60°) forms of the fluoroketols have been assumed to be similar to the values reported for the corresponding chlorine analogs.

A comparison of hydroxyl proton chemical shifts ($\delta_{OH}°$) at infinite dilution, obtained by extrapolation of the data listed in Table 1, is informative and shows that **1***a* and **2***a* absorb at approximately the same magnetic field strength (250 Hz downfield from TMS); the same relationship applies to the pairs **1***b* and **2***b* (185 Hz), and **3** and **4** (210 Hz), respectively. Thus, the structure of the alkyl groups R and R′ has a negligible effect on $\delta_{OH}°$ while the nature of specific intramolecular hydrogen-bonding interactions causes considerable chemical shift differences. The higher $\delta_{OH}°$ values for **1***a* and **2***a* relative to **1***b* and **2***b*, respectively, indicate that the hydroxyl proton is deshielded more by hydrogen bonding to carbonyl oxygen than by hydrogen bonding to fluorine. It is also noteworthy that the F-19 absorption of **1***b*, **2***b*, **3**, **4**, **5**, and **6** is shifted *downfield* on dilution while the H-1 absorption is shifted *upfield*. These opposite trends are to be expected since hydrogen-bonding interactions cause a decrease in the symmetry of the fluorine p-orbital which overlaps with the hydroxyl proton 1s-orbital, and the resulting increase in the fluorine paramagnetic screening term shifts the CF_3 resonance peak to lower magnetic field (11, 12). The $\delta_{OH}°$ values for the chlorine analogs of **1***b*, **2***b*, and **3** are approximately 190, 190, and 200 Hz, respectively (extrapolation of data reported in ref. 1), *i.e.*, substitution of fluorine by chlorine has only a small effect on the OH proton chemical shift. This is in agreement with $\delta_{OH}°$ values reported in the literature (3) for trichloro- and trifluoroethanol and has been attributed to similar bond polarities for trichloro- and trifluoromethyl groups.

In conclusion, a strongly concentration-dependent equilibrium between monomeric and intermolecularly hydrogen-bonded species prevails in fluoroketols **1***b*, **2***b*, **3**, and **4** while **1***a* and **2***a* form strong intramolecular hydrogen bonds even at low concentrations.

Experimental

Melting points are uncorrected. I.r. spectra were run in CCl_4 solution on a Perkin–Elmer 457 or Beckman IR-12 spectrometer, u.v. spectra in 95% ethanol on a Unicam SP-200 instrument. N.m.r. spectra were recorded in $CDCl_3$ on a Varian A56/60 spectrometer, using TMS as internal standard for proton spectra (60 MHz) and $CFCl_3$ as external standard for F-19 spectra (56.4 MHz). Analytical-scale separations of diastereomeric 1,1,1-trifluoro-2-hydroxy-4-alkanones and other v.p.c. analyses were performed on a Varian Aerograph Model 1200-1 HY-FI III gas chromatograph using a 5 ft × 1/8 in. column packed with 5% SE-52 or 1% OV-17 on Aeropak 30 (column temperature 50–85°) and nitrogen as carrier gas (30 ml/min). Trifluoroethanol (Aldrich) and 1,1,1-trifluoro-2-propanol (Aldrich) were purified by fractional distillation.

Preparation of Anhydrous Fluoral

Using a modification of the procedure described in the literature (3), 53 g (0.45 mol) of fluoral hydrate (practical, Columbia Organic Chemicals) was added dropwise (2 h) to a stirred, preheated (90–95°) mixture of 83 ml concentrated sulfuric acid and 22 g of phosphorus pentoxide, and the fluoral (b.p. −19°) was swept with nitrogen into a cold trap (−78°). After completion of the addition, heating and stirring was continued for another hour. The anhydrous product (27 g = 61% yield) was used for the aldol condensations (see below) without further purification. The formation of small amounts of an unidentified, white polymeric material in the glass tubing leading to the trap was noticed in all experiments.

Reaction of Fluoral with 3-Pentanone

A mixture of 56.5 g (0.66 mol) of freshly distilled 3-pentanone, 39.6 g (0.66 mol) of glacial acetic acid, and 1.55 g (0.019 mol) of anhydrous sodium acetate was placed in a 500-ml three-necked flask fitted with condenser, thermometer, and gas inlet tube. Using a slow stream of nitrogen, anhydrous fluoral gas, prepared from 0.45 mol of commercial fluoral hydrate (see before), was evaporated slowly from a condensing trap by removing the cooling bath and bubbled into the magnetically stirred reaction mixture over a 1-h period. The temperature rose to 34° and some unreacted fluoral was collected in a second trap (−78°) connected to the condenser. The mixture was then heated in an oil bath at 84° for 17½ h, allowed to cool, filtered (NaOAc), and distilled (aspirator) to leave a yellow liquid residue which, on fractional high-vacuum distillation, gave 8.3 g (10% yield) of a mixture of *erythro-* and *threo*-1,1,1-trifluoro-2-hydroxy-3-methyl-4-hexanone (**1***a* and *b*). The diastereomers were separated by column chromatography on silicic acid (Mallinckrodt, Analytical Reagent, 100 mesh).

1*a*: b.p. 55–58°/1.0 mm; n.m.r. ($CDCl_3$) τ 8.95 (t, 3H, CH_3CH_2), 8.75 (d, 3H, CH_3CH), 7.43 (q, 2H, CH_3CH_2), 7.00 (m, 1H, CH_3CH), and 5.97 (broad peak, 1H, CHOH); i.r. (0.1 *M* CCl_4) 3450 cm^{-1} (OH; shoulders at 3530 and 3600) and 1710 (CO; shoulder at 1720).

1*b*: b.p. 60–63°/1.0 mm; n.m.r. ($CDCl_3$) τ 8.95 (t, 3H, CH_3CH_2), 8.73 (d, 3H, CH_3CH), 7.42 (q, 2H, CH_3CH_2), 7.02 (m, 1H, CH_3CH), and 5.58 (broad m, 1H, CHOH); i.r. (0.05 *M* in CCl_4) 3520 cm^{-1} (OH; shoulder at 3600) and 1715 (CO; shoulder at 1720); u.v. (EtOH) λ_{max} 216 nm (ε 80) and 273 nm (ε 35).

Reaction of Fluoral with Cyclohexanone

Anhydrous fluoral prepared from 0.45 mol of fluoral hydrate was bubbled into a mixture of 84.3 g (0.86 mol) of cyclohexanone, 51.6 g (0.86 mol) of acetic acid, and 2.03 g (0.025 mol) of sodium acetate as described before and the reagents were heated at 95° for 17 h. The normal work-up procedure yielded 63.7 g of crude product from which 30.3 g (35% yield) of a mixture (ratio 3:7 by v.p.c.) of the two fluoroketols **2***a* and *b* was obtained by frac-

tional distillation under high vacuum (68–76°/0.05 mm). The diastereomers were separated by adsorption chromatography (see before).

2*a*: b.p. 68–70°/0.05 mm; n.m.r. ($CDCl_3$) τ 7.0–8.5 (broad multiplet, 9H), and 5.90 (broad multiplet, 1H, C*H*OH); i.r. 3462 cm^{-1} (OH; shoulders at 3550 and 3620; 0.005 *M* in CCl_4) and 1705 (CO; 0.1 *M* in CCl_4); u.v. (EtOH) λ_{max} 223 nm (ε 88) and 280 nm (ε 38).

2*b*: m.p. 35–37°, b.p. 74–76°/0.05 nm; n.m.r. ($CDCl_3$) τ 7.0–8.5 (broad multiplet, 9H) and 5.28 (sharp quartet of doublets, 1H, C*H*OH); i.r. 3628 cm^{-1} (OH; 0.005 *M* in CCl_4) and 1710 (CO; 0.1 *M* in CCl_4); u.v. (EtOH) λ_{max} 204 nm (ε 35) and 281 nm (ε 31).

*Preparation of 1,1,1-Trifluoro-2-hydroxy-6-methyl-4-heptanone (**3**)*

Anhydrous fluoral prepared from 0.425 mol of fluoral hydrate was bubbled into a mixture of 70.0 g (0.70 mol) of 4-methyl-2-pentanone, 32.0 g (0.53 mol) of acetic acid, and 6.0 g (0.073 mol) of sodium acetate as described before and the reagents were heated at 110° for 3 h. Work-up and fractional distillation gave 12.0 g (14% yield) of **3**, m.p. 13–15°, b.p. 77–80°/1.25 mm, which was further purified by column chromatography. The fluorine n.m.r. spectrum revealed the presence of small amounts of the two diastereomeric 1,1,1-trifluoro-2-hydroxy-3-isopropyl-4-pentanones (doublets at 4368 and 4386 Hz upfield from $CFCl_3$). Characterization of **3**: n.m.r. ($CDCl_3$) τ 9.07 (d, 6H, $(CH_3)_2C$), 7.65 (m, 3H, $CHCH_2CO$), 7.22 (m, 2 diastereotopic protons, CH_2CHOH) and 5.48 (m, 1H, C*H*OH); i.r. (0.1 *M* in CCl_4) 3520 cm^{-1} (OH; broad, with shoulder at 3620) and 1715 (CO); u.v. (EtOH) λ_{max} 212 nm (ε 400) and 269 nm (ε 180).

*Preparation of 1,1,1-Trifluoro-2-hydroxy-4-pentanone (**4**)*

Fluoral was generated from 0.43 mol of fluoral hydrate (see before) and admitted into a mixture of 49.9 g (0.86 mol) of acetone, 51.6 g (0.86 mol) of acetic acid, and 2.03 g (0.025 mol) of sodium acetate over a 45 min period. The reagents were heated at 70° (oil bath temperature) for 72 h. after which time most of the solvent and unreacted ketone were removed at aspirator vacuum (oil bath below 60°). The remaining yellow-green liquid was taken up in methylene dichloride, washed with aqueous $NaHCO_3$ solution and water, dried ($MgSO_4$), and distilled (after CH_2Cl_2 evaporation) to give 18 g (27% yield) of 1,1,1-trifluoro-2-hydroxy-4-pentanone (**4**), b.p. 45–50°/0.7 nm. Removal of the last traces of acetic acid by extraction and distillation proved to be difficult in this case due to the high volatility (sublimation) of this compound. A pure product sample was obtained by adsorption chromatography (see before). Characterization of **4**: n.m.r. ($CDCl_3$) τ 7.75 (s, 3H, CH_3CO), 7.17 (m, 2 diastereotopic protons, CH_2) and 5.48 (m, 1H, C*H*OH); i.r. (0.1 *M* in CCl_4) 3520 cm^{-1} (OH; broad, with shoulder at 3620) and 1725 (CO).

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