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^{19}F-NMR SHIFTS AND CONFORMATIONS OF CYCLIC AND BICYCLIC TRIFLUOROACETATES

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Abstract—The trifluoroacetates of 52 stereoisomeric alcohols were prepared and their ^{19}F-NMR shifts were determined in different solvents. In dimethylsulfoxide equatorial trifluoroacetate groups are generally more deshielded than axial groups, which is reversed in most cases in carbon tetrachloride. This effect is discussed in terms of intramolecular hydrogen bonding. The differences between *endo* and *exo* trifluoroacetates of bicyclic alcohols did not follow a simple pattern. The conformational equilibria of some cyclohexane trifluoroacetates were determined with the aid of both line width and shifts of the X proton in the NMR spectra.

THE CHEMICAL shifts of ^{19}F magnetic resonance of many alcohol trifluoroacetates have been shown to be sufficiently different for identification even in mixtures.[1] Since the fluorine shielding depends much more on the molecular environment than that of protons[2] it was hoped that one could possibly use the ^{19}F-shifts of the easily accessible trifluoroacetyl (TFA) derivatives for configurational assignment and eventually for analysis of conformational distribution. The relative simplicity of ^{19}F-NMR spectra has been successfully applied to conformational analysis by Roberts *et al.*[3]. Protons in functional groups of cyclohexane are often more deshielded in the equatorial than the axial position[4] as is the case for fluorine[5] and for ring protons.[6] The calculation of conformational equilibria based on these shift differences[6] is obscured by the choice of model compound shifts,[7] but still provides a convenient means of semiquantitative evaluation.[3] A large number of steroisomeric TFA derivatives were investigated in order to look for correlations between ^{19}F shifts and the position of the TFA group.

RESULTS AND DISCUSSION

Table 1 contains TFA derivatives of alkyl cycloalkanols which are either locked in one conformation or should be present predominantly in one conformation, thus allowing the assignment of the TFA group to equatorial or axial position for each of the isomers.

The free energy difference between an axial and an equatorial TFA group in cyclohexane was reported to be $A = 0{\cdot}485$[9a] or $A = 0{\cdot}54$[9b] kcal/mole. Since the A values of all alkyl groups[10] are considerably higher ($A_{CH_3} = 1{\cdot}7$ kcal/mole), all compounds in Table 1 should predominate in the conformation which bears the alkyl group in the equatorial position, provided there is additivity of A values in these disubstituted compounds.

TABLE 1. ^{19}F CHEMICAL SHIFTS OF CYCLOALKYL TRIFLUOROACETATES IN PPM UPFIELD FROM METHYL TRIFLUOROACETATE

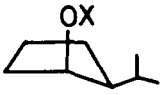
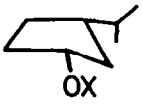
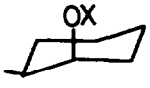
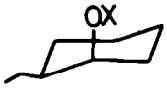
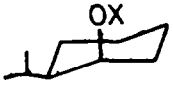
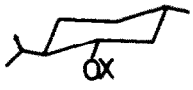
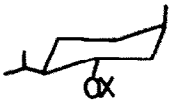
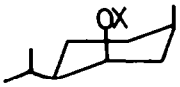
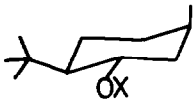
	Parent Alcohol	TFA Position		ppm (CCl_4)	ppm ($(CH_3)_2CO$)	ppm ($(CH_3)_2SO$)
	2-isopropylcyclo-pentanol	*cis*	a	0·36	0·275	0·36
		trans	e	0·505	0·425	0·45
	3-isopropylcyclo-pentanol	*cis*	e	0·385	0·345	0·34
		trans	a	0·425	0·325	0·375
	cyclohexanol			0·41		0·34
	2-methylcyclo-hexanol	*cis*	a	0·28	0·16	0·28
		trans	e	0·375	0·27	0·315
	2-ethylcyclo-hexanol	*cis*	a	0·25	0·155	0·30
		trans	e	0·33	0·265	0·315
	2-isopropyl-cyclohexanol	*cis*	a	0·345	0·21	0·365
		trans	e	0·30	0·23	0·28
	2-cyclohexyl-cyclohexanol	*cis*	a	0·355	0·22	0·41
		trans	e	0·30	0·21	0·315
	3-methylcyclo-hexanol	*cis*	e	0·45	0·35	0·355
		trans	a	0·37	0·275	0·355
	3-ethylcyclo-hexanol	*cis*	e	0·41	0·195	0·355
		trans	a	0·37	0·30	0·375

TABLE 1. cont.

	Parent Alcohol	TFA Position	ppm (CCl_4)	ppm $(CH_3)_2CO$	ppm $((CH_3)_2SO)$
	3-isopropyl-cyclohexanol	*cis* e	0·40	0·325	0·315
		trans a	0·38	0·295	0·405
	3-t-butylcyclo-hexanol	*cis* e	0·37	0·315	0·285
		trans a	0·42	0·33	0·445
	4-methylcyclo-hexanol	*cis* a	0·395	0·285	0·355
		trans e	0·415	0·345	0·33
	4-isopropyl-cyclohexanol	*cis* a	0·39	0·31	0·39
		trans e	0·40	0·35	0·32
	4-t-butylcyclo-hexanol	*cis* a	0·43	0·345	0·44
		trans e	0·40	0·335	0·315
	3-methylcyclo-heptanol	*cis* e	0·44	0·39	0·39
		trans a	0·445	0·355	0·41
	menthol	e	0·31		0·31
	neomenthol	a	0·295		0·375
	isomenthol	e	0·355		0·355

	neoisomenthol	a?	0·53	0·61
	2-t-butyl-5-methylcyclo-hexanols: *trans, cis*	e	0·64	0·675
	*cis, trans*	a	0·445	0·54
	*trans, trans*	e	0·61	0·62
	*cis, cis*	a	0·645	0·77

In order to test the conformational assignments which could be doubtful because of unknown substituent effects (see below), the conformational equilibria of some trifluoroacetates were estimated using both the chemical shifts[6a] and line widths[6b] of the X proton (see Table 2). The *A* value calculated from the line widths of TFA cyclohexane agrees very closely with the low temperature integration values.[9] The other numbers show consistently that the pertinent equilibria have less than 20% of the conformation with axial alkyl; the deviations in the calculated A_{TFA}-values of the disubstituted compounds seem to be large enough to indicate some deviation from additivity. For the conformational assignments one can refer to the extensively studied alkyl cycloalkanols,[11] since the TFA group exerts an influence similar to the OH group (A_{OH} = 0·52 kcal/mole in aprotic solvents[10]).

Shift measurements in CCl_4 (Table I) show that only a few compounds have the equatorial TFA group more deshielded than the axial. If dimethylsulfoxide (DMSO) is used as solvent, the situation becomes reversed, showing the isomer with predominantly equatorial TFA at lower field. These observations may be rationalized by considering intramolecular hydrogen bonding in addition to molecular anisotropy. Intermolecular hydrogen bonding of fluorine with alkane protons[12] has been documented as well as intramolecular bridging in fluoroalcohols.[13] It is known that in hydrogen bonds the distance between the bridging atoms is considerably smaller than the sum of the van der Waals radii.[14] Consequently bridging of fluorine with

weakly acidic protons may require the fluorine atoms to approach the protons very closely. This condition could be better fulfilled by a TFA group in the axial position considering interaction with 1,3-diaxial protons. Any bridging will heavily affect ^{19}F shielding, hence, in CCl_4 axial TFA may absorb at lower magnetic field. The exception in the case of the t-butyl compounds indicates that here the anisotropy effect predominates due to the completely fixed system. Correspondingly, the rather widely fixed isopropyl derivatives show only a very small difference in CCl_4.

Intramolecular hydrogen bonding of the TFA carbonyl group will explain the results as well; the resulting inductive effects on the very polarizable C–F bonds could lead to greater shielding differences than are observed in the $-OOCCH_3$ shifts[4] of cyclic acetates. DMSO is known to be extremely effective in hydrogen bonding[15] and is therefore expected to interrupt intramolecular hydrogen bridging in the trifluoroacetates. Thus, in DMSO one can observe the dominating effect of molecular anisotropy, which leads to lower field absorption of isomers with equatorial TFA (see Table I), the differences being magnified in the case of the t-butyl and isopropyl compounds and reversed in the other derivatives.

The 2-alkyl cycloalkyl compounds behave differently, as they generally do in the methods using the X proton for conformational analysis.[6b] This deviation could be explained by hydrogen bonding in the 1,2-diequatorial conformation, where the equatorial TFA may approach closely the 2-alkyl group. This might explain too why even in DMSO the equatorial TFA (in the 2-alkyl compounds) appears less deshielded, whereas in the more fixed 2-isopropyl compound the anisotropy effect takes preference.

Conformational investigations of trisubstituted cyclohexanols of the menthol type by the established ^{1}H-NMR procedures suffers through poorly understood interactions between the closely arranged substituents.[16] Nevertheless the TFA derivatives of menthols were included in the present study, and also the corresponding t-butyl compounds with a fixed geometry.[17] The four menthol TFA fit into the picture showing the equatorial TFA group to be more deshielded except in the menthol/neomenthol case in CCl_4, where two 1,3-diaxial hydrogen bonds are possible. The t-butyl menthol however, which unquestionably contains the TFA group in the equatorial position (this was secured by ^{1}H-NMR, see Table 2) show the ^{19}F signal at higher field, although in DMSO the difference is remarkably smaller. Whereas it seems to be a rather general rule that the difference between ^{19}F shifts in equatorial and axial TFA groups in DMSO is negative, any attempt to use quantitatively the ^{19}F shifts for the calculation of conformational equilibria failed. The determination of $K = (\tau_a - \tau)(\tau - \tau_e)$[6] (using 4-t-butyl cyclohexane values for τ_a and τ_e) gave for the unsubstituted cyclohexane $A = +0{\cdot}8$ kcal/mole, but for the TFA derivative of *cis*-3-methyl cyclohexane, for example, an equilibrium with 43% diaxial conformer (using 3-t-butyl cyclohexane TFA/F shifts for τ_a and τ_e).

The calculations using H_x-NMR (Table 2) show clearly that F . . . . H bonding in the measured compounds does not substantially change the conformational equilibria. The only indication for a slight stabilization of axial flourine groups can be seen in the fact, that the *A* value of TFA is smaller than that of the OAc group (0·5 versus 0·7[7] kcal/mole), although van der Waals interaction would predict it to be equal or larger.

Table 3 contains trifluoroacetates with a fixed geometry, allowing an unambiguous assignment of the equatorial/axial or *exo/endo* positions.

TABLE 2. ^{1}H NMR DATA OF X PROTONS IN TRIFLUOROACETATES AND THEIR CONFORMATIONAL EQUILIBRIA

Cyclohexanol	τ(ppm)[a]	$W_{\frac{1}{2}}$(Hz)[b]	Eq_τ(%)[c]	Eq_w(%)[d]	A_{TFA}[e](kcal/mole)
cis-4-t-butyl	4·76	10·55			
trans-4-t-butyl	5·17	30·25			
cis-3-t-butyl	5·11	31·4			
trans-3-t-butyl	4·64	10·5			
Cyclohexanol	5·02	24·3	36	30	0·50
cis-4-methyl	4·81	13·35	88	86	0·62
trans-4-methyl	5·14	32·2	0	0	
cis-4-i propyl-	4·82	12·45	85	90	0·78
cis-3-methyl-	5·09	31·6	0	0	
trans-3-methyl-	4·70	12·2	88	92	0·25
trans-3-ethyl	4·72	13·2	75	78	0·52
trans-2-t-butyl					
cis-5-methyl	5·05[f]	29[g]	0	0	
cis-2-t-butyl-*trans*-5-methyl	4·5[f]	10[g]	100	100	

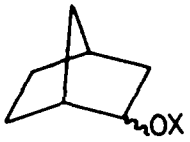
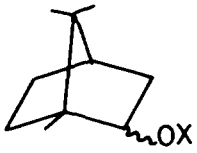
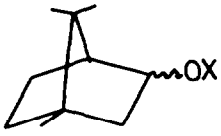
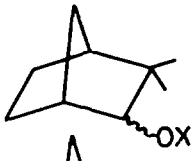
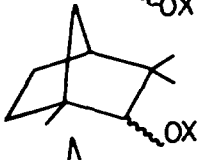
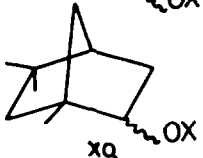
[a] ± 0·02 ppm
[b] ± 0·3 Hz
[c] Percent of axial TFA in equilibrium, calculated from τ
[d] Percent of axial TFA in equilibrium, calculated from $W_{\frac{1}{2}}$
[e] Free conformational energy of TFA from Eq_w using A values of 1·70, 1·75, 2·10 (kcal)mole) for CH_3, C_2H_5, CH $(CH_3)_2$, respectively and assuming additivity in the disubstituted compounds
[f] ± 0·05 ppm
[g] ± 1·0 Hz

Inspection of bicycloheptane models reveals, that here hydrogen bonding of *endo* and *exo* TFA groups could be equally possible. In addition, the approach of DMSO molecules may be somewhat hindered in comparison to the monocyclic compounds.

For some bicyclo[2.2.1.]heptanes it was demonstrated that the *exo* protons are deshielded compared to the *endo* protons.[4] For protons in groups attached to bicycloheptanes the differences between *exo* and *endo* shifts are often very small and sometimes irregular.[19] This turned out to be the case for the ^{19}F shifts of bicycloheptane TFA too. In three pairs of isomers the *exo* group is less deshielded, which would be in accord with a change of molecular anisotropy going from the cyclohexane chair to the boat form. The results with the fenchol TFA, however, show clearly that substituent effects may alter the pattern completely. The values for the investigated decalin derivatives however are compatible with the findings in the cyclohexane series, as to be expected with the absence of substituent effects in these compounds.

It should be noted finally, that the cyclohexane results (Table 1) in DMSO alone could be rationalized too if one assumes the DMSO to complex with and therefore to deshield preferentially the equatorial TFA group. Apart from being unlikely in view of the reversion by solvent change (Table 1) this hypothesis can be ruled out by the results with the bicycloheptane compounds. Here the *exo* group is less hindered than the *endo* group (with the possible exception of the borneol) and should therefore be more deshielded, which is actually not the case (see Table 3).

TABLE 3. ^{19}F CHEMICAL SHIFTS OF BICYCLIC TRIFLUOROACETATES IN ppm UPFIELD FROM METHYLTRIFLUOROACETATE

	Parent alcohol	TFA position	CCl_4	$(CH_3)_2SO$
	*endo*-2-norborneol	*endo*	0·235	0·20
	exo-2-norborneo	*exo*	0·45	0·37
	borneol	*endo*	0·25	0·205
	isoborneol	*exo*	0·535	0·525
	epiborneol	*endo*	0·265	0·205
	epiisoborneol	*exo*	0·63	0·575
	*endo*-camphenilol	*endo*	0·09	
	exo-camphenilol	*exo*	0·155	
	α-fenchol	*endo*	0·06	0·085
	β-fenchol	*exo*	0·06	0·085
	*endo*-isofenchol	*endo*	0·33	0·36
	exo-isofenchol	*exo*	0·33	0·30
	*cis-cis*-1-decalol	e	0·29	
	*trans-cis*-1-decalol	a	0·235	
	*cis-cis*-2-decalol	e	0·415	
	*trans-cis*-2-decalol	e	0·425	

EXPERIMENTAL

NMR spectra. ^{19}F shift measurements were carried out on a Varian HA-60 spectrometer (56·4 MHz) at 30–35° with side band calibration using at least 5 scans. Spectra were taken down to a concentration of usually 0·1 M, where the shifts did not change within instrument accuracy. 2% Methyl trifluoroacetate was added as internal standard. ^1H measurements were performed on a Varian A 60 spectrometer at 37° in 1–2 M CCl_4 solns. H_χ shifts and line widths were measured by averaging 6–8 scans at 250 Hz sweep width. Before and after each run the sweep width was calibrated using TMS, methyl trifluoroacetate and tetrabromoethane in CCl_4 and their reported τ-values.[2]

Materials. 4-t-Butyl-, 4-methyl-, 3-methyl- and 2-methyl cyclohexanol were purchased and separated by GLC. All other alcohols were gifts from Professor W. Hückel; the configurational assignments of some mixtures were checked by ^1H-NMR.

Trifluoroacetates. The esters were prepared as described previously [1a] by mixing 100 mg alcohol and 1 ml trifluoroacetic anhydride; too vigorous reactions were avoided by dilution with CCl_4. Trifluoroacetic anhydride and trifluoroacetic acid were removed by repeated evaporation, each time adding fresh CCl_4. Esters forming potentially stable carbonium ions may undergo isomerization [1a], i.e. camphene hydrate gave only isobornyl TFA. Hence all possibly isomerizing esters were checked by their ^1H-NMR spectra, which could be compared with the corresponding acetates or other derivatives.[10]

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