NMR STUDY OF THE KETO-ENOL EQUILIBRIUM OF ETHYL γ,γ,γ-TRIFLUOROACETOACETATE AND ITS REACTION WITH WATER AND ALCOHOLS

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Abstract– The keto-enol equilibrium of the title compound 1 has been studied by ^{19}F NMR spectroscopy at variable temperature. The results found are in agreement with those reported by previous authors using ^{1}H NMR. In addition, the reaction of 1 with water and alcohols, and the equilibrium of the starting keto-enol forms with the corresponding hydrate and hemiketals has been investigated. Some interesting features of the ^{1}H and ^{19}F NMR spectra of these compounds are also discussed.

INTRODUCTION

In connection with a research program of this laboratory devoted to the synthesis of trifluoromethyl bioanalogs of the natural juvenile hormone JH-3, we required ethyl γ,γ,γ-trifluoroacetoacetate 1 as the source of the trifluoromethyl group.[1] However, preparation of 1, according to a previously reported procedure,[2] failed to afford the expected yield. Analysis of the NMR spectra of different samples of crude ester 1 showed the presence of variable amounts of hydrated ester 2a. This result led us to develop an improved procedure to obtain pure samples

In this context, we decided to study the above equilibrium by ^{19}F NMR at different temperatures. The fact that the ^{19}F NMR spectrum of the tautomeric mixture of 1a and 1b only exhibits two well-separated sharp singlets, corresponding to each trifluoromethyl group, simplifies the spectral analysis. On the other hand, although the reaction of several α-fluorinated ketones with water and alcohols has been described,[4] the behaviour of 1 with these reagents has so far been unreported. In the present work, we study the reactions of ester 1 with water and alcohols by ^{1}H and ^{19}F NMR spectroscopy.
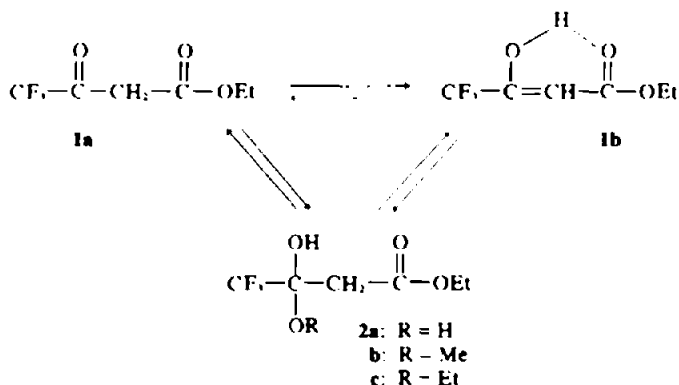
Scheme 1.

of the desired compound, as well as to study its keto-enol tautomerism and its reaction with water and alcohols.

The keto-enol tautomerism of the ester 1 had been previously established by Filler and Naqvi using the K. Meyer "indirect" method, which gave an unexpectedly low enol content (10–14%, in methanol), when compared with the values reported for fluorinated β-diketones. Subsequently, the same authors found a much higher amount of enol form (89%) by ^{1}H NMR spectroscopy of the pure liquid.[a] This value was confirmed by Burdett and Rogers (89%; $K_e = $ [enol]/[keto] at 33° = 8.1), using the same technique.[b] In addition, these authors also studied the equilibrium constants at different temperatures (−5 80°), obtaining the values of free energy, enthalpy and entropy for the tautomerization of ester 1.[b]

EXPERIMENTAL

Measurements were made with a Perkin-Elmer R-12B NMR spectrometer, operating at 60 and 56.4 MHz, with the normal probe at 33° and with the variable temperature probe. Sample tubes were not sealed. ^{1}H and ^{19}F NMR spectra were determined using TMS and trifluoroacetic acid, respectively, as external references in a sealed capillary. The measurement accuracy was estimated to be about 0.01 ppm for δ_H and 0.02 ppm for δ_F.

Standard deviations for values of log K_e lying between 0.370 and 1.010, were 5%. The enthalpy of conversion from keto to enol forms was computed by the least-squares method from the variation of the equilibrium constant in the range 0–80°, the standard Gibbs free-energy change was calculated assuming ideal behaviour: $\Delta G = -RT\ln K_e$. Based on the standard deviation of K_e, the standard error of the least-squares line (r = 0.994) and the

uncertainty of T, 95% confidence limits for ΔH and ΔS were respectively +0.34 Kcal mole⁻¹ and ±1.13 cal mole⁻¹ deg⁻¹. Since ΔH is actually temperature dependent, the value reported is only an average over the temperature range employed.

Ethyl γ,γ,γ-trifluoroacetoacetate was prepared according to the method of Burdon and McLoughlin,[2] with minor modifications to ensure reproducible yields and product purity. The violence of the reaction was reduced by simultaneous dropwise addition of ethyl acetate and ethyl trifluoroacetate (2:1 ratio) over a suspension of sodium wire in ethyl ether, and the final drying over $MgSO_4$ was followed by treatment with molecular sieves. The highest yield of ester 1 obtained was 55%, containing less than 3% of hydrate. Redistillation of this material afforded samples with no detectable amount of hydrate by NMR analysis, which were used in the present study.

The reactions with water, methanol and ethanol were carried out in the NMR sample tube by adding respectively an equimolecular amount of each reagent, previously purified by standard procedures, to the fluorinated ester 1, resulting in all cases to a homogeneous mixture. The NMR spectra were registered after 2 h at room temp. and the results did not change significantly over a period of 24 h.

RESULTS AND DISCUSSION

Figure 1 shows the plot of log K_e vs the reciprocal of the absolute temperature for the keto-enol tautomerism of ester 1. The thermodynamic data obtained are given in Table 1. Our data are in agreement with those reported by Burdett and Rogers[3c] using ¹H NMR spectroscopic analysis, shown also in Table 1 for comparison.

Table 2 shows the ¹⁹F chemical shifts for trifluoromethyl groups of keto and enol tautomers. We have
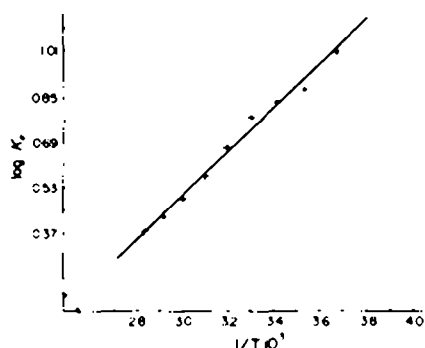

Fig. 1. The temperature dependence of log K_e for the tautomerization of ethyl γ,γ,γ-trifluoroacetoacetate.

observed that ¹⁹F chemical shifts of both forms are unaffected, within experimental error, by temperature changes in the range studied, as has been found for proton chemical shifts.[3c]

The reaction of 1 with water and alcohols was carried out under conditions similar to those reported by Kodama, Sato and Arakawa[4b] for trifluoroacetylacetone 3:
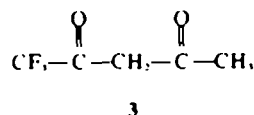
$$CF_3-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$$

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Table 1. Thermodynamic data for enolization of ethyl γ,γ,γ-trifluoroacetoacetate[a]

	log K_e	ΔG (33°) (Kcal/mole)	ΔH (Kcal/mole)	ΔS (33°) (cal/mole deg)
¹⁹F NMR	0.71[b]	-0.99	-3.56	-8.40
¹H NMR	0.78[c]	-1.09[c]	-3.91[c]	-9.21[c]

[a] Pure liquid. [b] Value taken from graph log K_e vs 1/T (range 0–80°). [c] Value taken from Ref. 3c.

Table 2. ¹⁹F NMR chemical shifts of CF_3 groups in equilibrium mixtures of ethyl γ,γ,γ-trifluoroacetoacetate reactions with water and alcohols at 33°[a]

	keto	enol	hydrate	hemiketal
ester (pure liq.)	-2.20	2.36		
ester-H₂O[b]			-10.59	
ester-H₂O[c]	1.81	2.59	9.97	
ester-H₂O[d]	-1.42	2.95	9.45	
ester-MeOH[d]	1.79	2.60		-4.96[e]
ester-EtOH[d]	-1.60	2.79		-5.15[f]

[a] Trifluoroacetic acid was used as external reference in a sealed capillary. Negative values indicate higher fields. [b] Sample containing 2% of hydrate. [c] Sample containing 40% of hydrate. [d] Sample containing an equimolecular amount of both reagents (see Table 3). [e] Quartet, J = 1.3 Hz. [f] Unresolved multiplet.

Since ketone 3 is almost 100% enolized, these authors considered that attack of water or alcohol takes place exclusively on the enol form. However, in our case, when the ¹⁹F NMR spectrum was run immediately after the addition of water to ester 1, an increase of the [E]/[K] ratio was observed, whereas a decrease of this ratio should be expected from the polarity change in the system. This result suggest that addition of water occurs preferentially on the keto form and that this reaction should be faster than the keto-enol tautomerism.[†] On the other hand, the equilibrium constants for the reaction of trifluoroacetylacetone with water, methanol and ethanol

Table 3. Percentages of components present in the reaction mixtures under equilibrium conditions at 33°

	2	1a	1b
ester-H₂O (1:1)	84 2a	5	11
ester-MeOH (1:1)	92 2b	2	6
ester-EtOH (1:1)	88 2c	2	10

[†] In acetopyruvic acid, water attacks the keto form and it was proved that this reaction is five times slower than the keto-enol tautomerism.[?] In this case, due to the influence of the CF_3 group, the rate of ketone hydration should be greatly enhanced.

Table 4. ^{1}H NMR chemical shifts in equilibrium mixtures of ethyl γ,γ,γ-trifluoroacetoacetate reactions with water and alcohols[a]

	CH (enol)	-OCH$_2$ (ketalic) 2c	CH$_2$ (keto)	-OCH$_3$ 2b	-CH$_3$ 1, 2a-2c
ester (pure liq.)	5.63		3.77		
ester-H$_2$O[b]	5.91				3.08
ester-MeOH[b]	5.83			3.58(q)[c]	2.94[d]
ester-EtOH[b]	5.83	3.90 (m)			2.92[d]

[a] TMS was used as external reference in a sealed capillary. [b] Equimolecular mixtures at equilibrium position at 33°. [c] J = 1.3 Hz. [d] Broad absorption band, resolved in benzene solution in two bands.

at 19° were respectively 1.53, 0.72 and 0.26 mole^{-1}.[4b] However, as shown in Table 3, in the corresponding reactions of 1 the relative amount of hydrate 2a is lower than that of kemiketals 2b and 2c.

The α-methylene protons in hemiketals 2b and 2c, being magnetically non equivalent should give rise to an AB system, as in the case of trifluoroacetylacetone 3.[4b] Accordingly, the unresolved absorption observed for ketals 2b and 2c, when recorded in benzene solution was split into two bands, which can be rationalized as the central peaks of the expected AB system. On the other hand, as shown in Table 4, the methoxy protons of hemiketal 2b and the corresponding methylene protons of 2c are split, the former appearing, as a quartet (J = 1.3 Hz), and the latter as a quartet of broad bands indicating some coupling other than that of the adjacent methyl group. These splittings can be rationalized by a long-range fluorine-hydrogen coupling through five bonds. In fact, although we could not achieve optimal resolution, it was clearly visible in the ^{19}F NMR spectra that absorption bands corresponding to trifluoromethyl groups of both hemiketals were abnormally wide in comparison with those of keto and enol forms. In addition, at expanded scale, the absorption of fluorine atoms of 2b appeared as a quartet with a coupling constant of the same order of that measured for the methoxy protons. Conversely, the corresponding broad fluorine absorption of 2c was not resolved as a triplet, as expected; its multiplicity, though, was evident.

The long-range coupling of hydrogen and fluorine nuclei separated by five or more chemical bonds has received considerable attention,[6] although the exact nature of its mechanism is still unknown. Myhre and co-workers, from their studies on alkylfluorobenzenes and the results previously published by other authors on fluorinated steroids, proposed a relationship between ($^5J_{HF}$) and the corresponding internuclear distance.[6a] Moreover, Adcock and Rizvi, from their studies on substituted fluoronaphtalenes, postulated that long-range coupling was a spatial phenomenon and that significant coupling only occurs when the fluorine-hydrogen closest approach is within the sum of their van der Waals radii

(ca. 2.55 A).[6b] Recently, Wasylishen and Barfield, from theoretical INDO-FPT calculations, concluded that the phenomenon usually described as "through space" coupling is actually a very complicated combination of proximity and bond orientation effects.[6c]

In the present case, the examination of molecular models of compounds 2b and 2c revealed that the proximity requirement between hydrogen and fluorine atoms could be fulfilled. As depicted in Fig. 2, this proximity requirement could be facilitated by two particular factors: (a) hydrogen-bonding between the hydroxyl and carbonyl groups that can force the molecule to adopt a rigid conformation with the trifluoromethyl group in a "pseudo equatorial" position; and (b) an electrostatic repulsion between non bonded electron pairs of oxygen and fluorine atoms, that favours the shown conformation of the alkoxy group.[†] On the other hand, the low value observed for $^3J_{HF}$ is probably the result of an average situation, promoted by molecular motion that can affect the relative orientation of the bonds implicated.[6c]
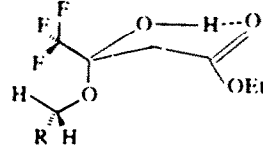

Fig. 2.

Finally, the fact that ^{19}F NMR absorption of trifluoromethyl group of hydrate 2a appears at a significantly higher field than those of hemiketals 2b and 2c, could be rationalized by a modification of the conformation depicted in Fig. 2, promoted by hydrogen-bonding of the hydroxyl groups—of 2a to carbonyl groups—either intra or intermolecularly; this interaction would enhance the electron density of the oxygen of the hydroxyl groups and bring its non-bonded electrons closer to the fluorine atoms, increasing their shielding.

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[†] Although the existence of intramolecular hydrogen-bonding (H . . F) has only been unambiguously demonstrated for acidic hydrogen atoms, as in o-trifluoromethylphenol,[7] in the present case, some kind of electrostatic interaction could contribute to a further stabilization of the conformation depicted above, as it has been postulated for o-fluoroacetophenone.[4b]

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