BASE CATALYZED ENOLIZATION AND HYDROGEN EXCHANGE OF TRIFLUOROACETONE. A COMPARISON TO ACETONE

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SUMMARY

The kinetics of the pyridine catalyzed hydrogen exchange of 1,1,1-trifluoroacetone in 50% D_2O-dioxane have been measured using ^{1}H-NMR. Rates of hydrogen exchange of acetone were also measured under comparable conditions and the rate of deuterium uptake by trifluoroacetone was found to exceed that of acetone by a factor of 1700 at 25°C. However trifluoroacetone is known to be extensively hydrated under these conditions. The hydrogen exchange of trifluoroacetone is interpreted as most probably proceeding through proton abstraction by pyridine from the free ketone to form the enolate followed by deuteration on carbon, with the rate of proton abstraction from trifluoroacetone exceeding that of acetone by a factor of 10^5 to 10^6. Other possibilities are also considered.

INTRODUCTION

The influence of fluoro substituents on the acidity of carbon-hydrogen bonds has long been a topic of chemical research [1], and there has been continued study of the reactivity of partially fluorinated hydrocarbons [2]. Studies of gas phase reactivity of fluorinated hydrocarbons have now

appeared [3], and the concept of negative hyperconjugation (eg. 1) [4a] continues to attract experimental [4b] and theoretical attention [5].
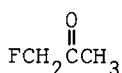
$$\text{Ph-}CF_3 \quad \longleftrightarrow \quad \overset{+}{\text{Ph}}=CF_2\ F^-\qquad (1)$$
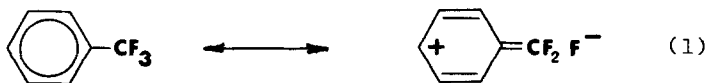
Studies of other types of fluorinated carbon acids have included measurements of the equilibrium acidities in DMSO solution of $CF_3SO_2CH_3$, $CF_3SO_2CH_2CH_3$, $CF_3SO_2CH(CH_3)_2$, and $CF_3SO_2\underline{c}$-Pr [6]. It was found that $CF_3SO_2CH_3$ with a pK_a of 18.8 was 12 pK_a units more acidic than $CH_3SO_2CH_3$. Fluoronitro-methanes $FCHXNO_2$ have also been studied [7], but contrary to what might have been expected, fluorine was found to be acid weakening in this series relative to the other halogens and even hydrogen. One example of this behavior is shown in Table 1, and other examples were also reported. A variety of possible causes of this sizeable effect were cited, but no firm conclusion was reached.

TABLE 1

pK_a HCXClNO$_2$ in H_2O, 25°C

X	Cl	H	F
pK_a	5.99	7.20	10.14

Kinetic studies of fluorinated ketones include studies of fluoroacetone (1) [8], 1,3-difluoroacetone (2) [8], 1,1,1-trifluoro-2,4-pentanedione(3) [9], and some other 1,1,1-trifluoro-2,4-diketones [9]. Gas phase acidities have also been reported for 1 and 2 [10].

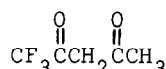$$FCH_2\overset{\overset{\textstyle O}{\|}}{C}CH_3 \qquad FCH_2\overset{\overset{\textstyle O}{\|}}{C}CH_2F \qquad CF_3\overset{\overset{\textstyle O}{\|}}{C}CH_2\overset{\overset{\textstyle O}{\|}}{C}CH_3$$
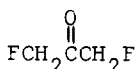
1   2   3

Relative rate constants, statistically corrected, for deuterium exchange catalyzed by NaOAc in 3/1 AcOD/D$_2$O for the fluoroacetones and some reference compounds are shown (Table 2) [8]. Relative gas phase acidities [10], defined as $\Delta\Delta H^\circ_{298}$ using acetone as the standard, are also included in Table 2 for comparison. Striking features of these include the greater reactivity of chloroacetone as opposed to fluoro-acetone, and the absence of a correspondence between the effects of one and two fluorines in solution and in the gas phase. However it was pointed out [8] that hydration of the carbonyl group may occur and influence the solution phase reactivities, but the extent of this effect was not assessed [8].

TABLE 2

Relative rates of NaOAc catalyzed hydrogen exchange and relative gas phase acidities (35 and 42°C)

|	$CH_3\overset{O}{\overset{\|}{C}}CH_3$		$FCH_2\overset{O}{\overset{\|}{C}}CH_3$		$FCH_2\overset{O}{\overset{\|}{C}}CH_2F$		$CH_2Cl\overset{O}{\overset{\|}{C}}CH_3$	
k(rel)	1.0	1.0	6.5	35	30	30	1400	100
$\Delta\Delta H^\circ_{298}$	54.9		43.5	49	36.0			
(kcal/mol)			(±0.5)	(±2)	(±0.5)			

The reported effects of fluorine on the acidities of 2,4-pentanedione are also remarkable [9]. Thus although 3 is reported to have an equilibrium acidity 2 pK$_a$ units greater than $CH_3COCH_2COCH_3$ its kinetic acidity measured by tritium exchange in water is actually less by a factor of 2 [9].

This result was explained by an assumed high degree of hydration of the fluoro compounds, although again the degree of hydration was not discussed. The gas phase acid dissociation of 1,1,1-trifluoro-2,4-pentanedione (3) was 15.2 kcal/mol more favorable than 2,4-pentanedione, so the trifluoro substituent was almost as effective in stabilizing the anion in this case as for acetone [10].

The gas phase acidity of 1,1,1-trifluoroacetone (4) has recently been measured [10] and proton loss from this compound is 19.7 kcal/mol more exothermic than from acetone. This result indicates a sizeable stabilization of the enolate 5 by the CF_3 group.
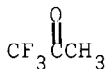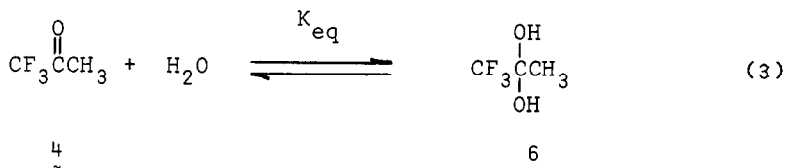

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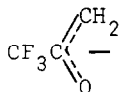
5

Progress has also been made in the comparison of gas phase acidities and equilibrium acidities in DMSO [11], but these studies have not yet encompassed fluorinated derivatives.

Studies of solution phase acidities of 4 or other trifluoromethyl ketones in solution are conspicuous by their absence, despite the great amount of study of hydrogen exchange on other simple ketones [6, 12]. Remarkably even the simple deuterated material CF_3COCD_3 (4-d$_3$) has not been reported. This compound could be useful in other mechanistic studies of fluorinated systems [13].

Two possible difficulties may be envisaged that could interfere with efforts to measure the base-catalyzed enolization of compounds such as trifluoroacetone (4) in solution. One is the known aldol condensation of 4 in basic solution (eq. 2) [14]; another is the known tendency of 4 to hydrate in aqueous solution [15].

$$CF_3\overset{\overset{O}{\|}}{C}CH_2^- \ + \ CF_3\overset{\overset{O}{\|}}{C}CH_3 \ \longrightarrow \ CF_3\overset{\overset{O}{\|}}{C}CH_2\underset{\underset{CF_3}{|}}{\overset{\overset{O^-}{|}}{C}}CH_3 \qquad (2.)$$

5   4

$$CF_3\overset{\overset{O}{\|}}{C}CH_3 \ + \ H_2O \ \overset{K_{eq}}{\rightleftharpoons} \ CF_3\underset{\underset{OH}{|}}{\overset{\overset{OH}{|}}{C}}CH_3 \qquad (3)$$

4   6
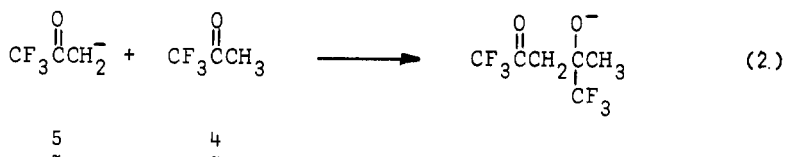
RESULTS

Hydrogen isotope exchange of 1,1,1-trifluoroacetone (4) and acetone was observed by ^{1}H-NMR in 50% D_2O-dioxane with added pyridine catalyst. The spectra showed a signal due to the hydrate 6 from trifluoroacetone at $\delta = 1.54$, and at very high concentrations of trifluoroacetone in this medium a signal at $\delta = 2.34$ was also observed, which is apparently due to the free ketone 4. The signals due to the ketone and the hydrate were well separated from those due to the dioxane. Rate constants were derived from the decrease of the integral of the signal due to the hydrate 6 relative to the dioxane peak at different temperatures and pyridine concentrations. Rate constants for acetone were obtained in a similar fashion using the signal due to the ketone. The rate data are listed in Table 3.

At 67.3°C rates for trifluoroacetone were measured at 6 concentrations of pyridine spanning a ten-fold variation in concentration. Second-order rate constants derived from K_{obs}/[pyridine] were reasonably constant (average deviation 8%) with no apparent dependence of the deviations upon pyridine concentration. Similar but less comprehensive results were obtained for acetone and at the other temperatures as well.

TABLE 3

Rates of hydrogen exchange of ketones in 50/50

D_2O-dioxane catalyzed by pyridine.

$T(^{\circ}C)$	pyridine (M)	$k_{obs}(s^{-1}x10^4)^a$	$k_2(M^{-1}s^{-1}x10^4)^b$
		trifluoroacetone	
67.3	1.56	8.30($\pm$1.9%)	5.32(-2%)
	0.718	3.54($\pm$1.8%)	4.93(-9%)
	0.477	2.78($\pm$2.2%)	5.83($+7$%)
	0.344	1.66($\pm$3.6%)	4.83(-11%)
	0.239	1.43($\pm$2.8%)	5.98($+10$%)
	0.159	0.910($\pm$7.0%)	5.72($+5$%)
		ave	5.44($\pm$7%)
83.5	0.279	6.06($\pm$4.5%)	21.7($+8$%)
	0.235	4.51($\pm$0.0%)	19.2(-4%)
	0.193	3.94($\pm$3.2%)	20.4($+2$%)
	0.0745	1.39($\pm$2.1%)	18.6(-7%)
		ave	20.0($\pm$5%)
99.8	0.0973	7.95($\pm$3.0%)	81.7($\pm$5%)
	0.0796	6.23($\pm$2.7%)	78.3(-2%)
		ave	80.0($\pm$2%)
		acetone	
67.3	1.55	0.0119($\pm$2.1%)	0.00768
83.5	1.61	0.0325($\pm$4.0%)	0.0202(-1%)
	0.896	0.0166($\pm$0.6%)	0.0185(-9%)
	0.536	0.0121($\pm$4.9%)	0.0225($+10$%)
		ave	0.0204($\pm$7%)

TABLE 3. (cont'd)

T(°C)	pyridine (M)	$k_{obs}(s^{-1}x10^4)^a$	$k_2(M^{-1}s^{-1}x10^4)^b$
99.8	0.253	0.0169(+4.0%)	0.0669(-5%)
	0.106	0.00781(+1.7%)	0.0737(+5%)
		ave	0.0703(+5%)

[a] average of at least two runs in each case, average deviation in parentheses. [b] Deviations from the mean in parentheses.

TABLE 4

Comparison of the reactivity of trifluoroacetone and acetone

T(°C)	$k_2(M^{-1} s^{-1}) \times 10^4$		$\frac{k(trifluoroacetone)}{k(acetone)}$
	trifluoroacetone[a]	acetone[b,c]	
67.3	5.44	0.00384	1400
83.5	20.0	0.0102	1960
99.8	80.0	0.0351	2280
25.0	$6.5x10^{-2}$ [d]	$3.9x10^{-5}$ [e]	1700[f]

[a] $\Delta H* = 20.2$ kcal/mol, $\Delta S* = -14$ e.u.
[b] Rates statistically corrected
[c] $\Delta H* = 16.6$ kcal/mol, $\Delta S* = -40$ e.u.
(calculated from rates at all 3 temperatures).
$\Delta H* = 19.4$ kcal/mol, $\Delta S* = -32$ e.u. (calculated from rates at 99.8 and 83.5°C)
[d] Calculated from rates at other temperatures
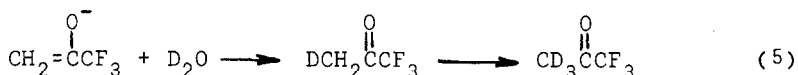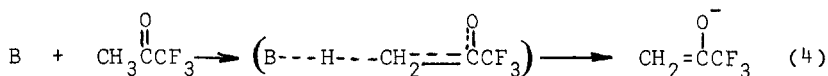[e] Calculated by extrapolating the rates at 83.5 and 99.8°C to 25°C
[f] The rate of acetone at 25.0°C extrapolated using all the measured rates is 9.68×10^{-9} M^{-1} s^{-1}, leading to a rate ratio k(trifluoroacetone)/k(acetone) of 680 at this temperature.

    Comparative rates are listed in Table 4. The reaction
of acetone at 67.3°C was so slow that it was felt that this
rate constant was less reliable than those at higher temper-
atures so only the latter were used in calculating a rate at
25°C. The plot of ln k/T vs. 1/T for acetone for all three
temperatures also did not give a straight line, and this is
attributed to inaccuracy of the 67.3°C rate. Therefore the
activation parameters (Table 4) calculated using only the
two higher temperatures are considered to be more reliable.

    When trifluoroacetone was kept at 100°C for 2 days in
a 50/50 mixture of dioxane and a pH 10 buffer (Na_2HPO_4-Na_3PO_4)
or 0.1 N NaOH no change in the NMR spectrum of the trifluoro-
acetone was observed and no signals attributable to possible
aldol product as in eq. 2 were observed. Thus the rate of
this reaction must be at least 10^4 slower than the rate of
enolization.

DISCUSSION

    The generally accepted mechanism for base catalyzed
hydrogen exchange of ketones is a process involving rate
limiting proton abstraction from the ketone by the base lead-
ing to an enolate intermediate which is then deuterated by
solvent [12]. This process for trifluoroacetone is shown
in eq. 4 and 5. The first order dependence of the rate on

$$B \; + \; CH_3\overset{O}{\overset{\|}{C}}CF_3 \longrightarrow \left(B\text{---}H\text{---}CH_2\overset{O}{\underset{\|}{=\!=}}\overset{\|}{C}CF_3\right) \longrightarrow CH_2=\overset{O^-}{\underset{|}{C}}CF_3 \quad (4)$$

$$CH_2=\overset{O^-}{\underset{|}{C}}CF_3 \; + \; D_2O \longrightarrow DCH_2\overset{O}{\overset{\|}{C}}CF_3 \longrightarrow CD_3\overset{O}{\overset{\|}{C}}CF_3 \quad (5)$$

pyridine concentration is as expected for this mechanism, and
the large negative entropies of activation are consistent with
other ketone deuterations [16].

If the mechanism of eq. 4 and 5 holds for trifluoro-
acetone then for a proper comparison of the rate of proton
abstraction for trifluoroacetone relative to that of acetone
the observed rate of deuterium exchange for trifluoroacetone
would have to be corrected for the degree of hydration (eq. 3).
It has been reported [15] that the equilibrium ratio
[hydrate]/[ketone] is 35 for trifluoroacetone in H_2O at 25°C.
We are conducting a thorough study of the kinetics and
equilibrium of trifluoroacetone hydration, and the prelimin-
ary indication is that in D_2O-dioxane this ratio may be some-
what higher. This suggests that the rate ratio for proton
abstraction from trifluoroacetone relative to acetone (not
statistically corrected) is 10^5 to 10^6.

This rate difference corresponds to a difference in
ΔH^* of the two reactions of about 7 kcal/mol, as compared
to the gas phase difference in $\Delta H°$ of 19.2 kcal/mol.

Evidently much of the greater equilibrium acidity of
trifluoroacetone relative to acetone is not manifested in the
transition state for ionization.

Alternative mechanisms to the scheme of eq. 4 and 5
may also be considered. It is possible that step 4 is so
fast that dehydration of the ketone hydrate would be rate
limiting. Direct conversion of the hydrate to enol or
enolate is also conceivable. Tests for these other pathways
are beyond the scope of the current investigation but it is
to be hoped that ongoing investigations into the hydration/
dehydration of trifluoroacetone will illuminate this question.

In summary hydrogen isotope exchange of trifluoroacetone
has been demonstrated for the first time, and the mechanism
of steps 4 and 5 provides a satisfactory explanation for the
available data, but more rigorous tests to exclude conceiv-
able alternatives are desirable.

EXPERIMENTAL

The medium for each rate run was prepared by mixing 0.50 mL D_2O and a weighed amount of pyridine and diluting to 1.0 mL with dioxane. Ketone was then added (0.075 mL 4 or 0.062 mL acetone) and the solution was divided into two NMR tubes which were sealed. For rate measurements a tube was heated in the bath, withdrawn at intervals, cooled, the methyl signal in the ^1H NMR integrated relative to the dioxane signal, and the tube replaced in the bath. Typically heating periods between measurements were at least 5 min, and 4 to 6 kinetic points, plus zero and infinite time measurements, were recorded.

ACKNOWLEDGEMENT

REFERENCES

1 (a) D. Holtz, Prog. Phys. Org. Chem., 8 (1971) 1. (b) R.D. Chambers, Fluorine in Organic Chemistry, Wiley, New York, (1973). (c) W.A. Sheppard and C.M. Sharts, Organic Fluorine Chemistry, Benjamin, New York, (1969). (d) L.M. Stock and M.R. Wasielewski, Prog. Phys. Org. Chem., 13 (1981) 253.

2 (a) K.J. Klabunde and D.J. Burton, J.Am. Chem. Soc., 94 (1972) 820. (b) A. Streitwieser, Jr., P.J. Scannon, and H.M. Niemeyer, ibid., 94 (1972) 7936. (c) A. Streitwieser, Jr., D. Holtz, G.R. Ziegler, J.O. Stoffer, M.L. Brokaw, and F. Guibé, ibid., 98 (1976) 5229.

3 S.A. Sullivan and J.L. Beauchamp, J. Am. Chem. Soc., 98 (1976) 1160. For a review of gas phase acidities see M.J. Pellerite and J.I. Brauman, Stud. Org. Chem., Compr. Carbanion Chem., Part A, 5 (1980) 55.

4 (a) J.D. Roberts, R.L. Webb, and E.A. McElhill, J. Am. Chem. Soc., 72 (1950) 408. (b)J.H. Sleigh, R. Stephens, and J.C. Tatlow, J. Chem. Soc. Chem. Commun. (1969) 921; J. Fluorine Chem., 15 (1980) 411.

5   (a) J.G. Stamper and R. Taylor, J. Chem. Res. Synop. (1980)
    128. (b) R.C. Bingham, J. Am. Chem. Soc., 97 (1975) 6743.
    (c) A. Pross, D.J. DeFrees, B.A. Levi, S.K. Pollack, L.
    Radom, and W.J. Hehre, J. Org. Chem., 46 (1981) 1693.
    (d) Y. Apeloig, J. Chem. Soc. Chem. Commun., (1981) 396.

6   (a) F.G. Bordwell, Pure and Applied Chem., 49 (1977) 963.
    (b) F.G. Bordwell, J.C. Branca, C.R. Johnson, and N.R.
    Vanier, J. Org. Chem., 45 (1980) 3884. (c) F.G. Bordwell,
    J.E. Bartmess, and J.A. Hautala, ibid., 43 (1978) 3095.
    (d) F.G. Bordwell, N.R. Vanier, W.S. Matthews, J.B.
    Hendrickson, and P.L. Skipper, J. Am. Chem. Soc., 97 (1975)
    7160.

7   H.C. Adolph and M.J. Kamlet, J. Am. Chem. Soc., 88 (1966)
    4761.

8   J. Jullien and Ngyuen-Thoi-Lai, Bull Soc. Chim. Fr., (1970)
    3948; (1968) 4669.

9   (a) J.R. Jones and S.P. Patel, J. Am. Chem. Soc., 96 (1974)
    574. (b) R.G. Pearson and R.L. Dillon, ibid., 75 (1953)
    2439. (c) J.C. Reid and M. Calvin, ibid., 72 (1950) 2948.

10 (a) F. Faird and T.B. McMahon, Can. J. Chem., 58 (1980)
    2307. (b) J.B. Cumming and P. Kebarle, ibid., 56 (1978) 1.

11 F.G. Bordwell, J.E. Bartmess , G.E. Drucker, Z. Margolin
    and W.S. Matthews , J. Am. Chem. Soc., 97 (1975) 3226.

12 (a) G. Lamaty in 'Isotopes in Organic Chemistry', Vcl. 2;
    E. Buncel and C.C. Lee, Eds. Elsevier, New York, 1976.
    (b) 'Comprehensive Carbanion Chemistry', Part A, E. Buncel,
    T. Durst, Eds., Elsevier, New York, 1980. (c) O.A. Reutov,
    I.P. Beletskaya and K.P. Butin, "CH-Acids", Pergamon,
    New York, 1978. (d) F. Hibbert, Compr. Chem. Kinet., 8
    (1977) 97.

13 M.P. Jansen, K.M. Koshy, N.N. Mangru, and T.T. Tidwell,
    J. Am. Chem. Soc., 103 (1981) 3863.

14 E.T. McBee, D.H. Campbell, R.J. Kennedy, and C.W. Roberts,
    J. Am. Chem. Soc., 78 (1956) 4597.

15 J.P. Guthrie, Can. J. Chem., 53 (1975) 898.

16 (a) G.A. Abad, S.P. Jindal, and T.T. Tidwell, J. Am. Chem.
    Soc., 95 (1973) 6326. (b) R.A. Cox and J. Warkentin,
    Can. J. Chem., 50 (1972) 3242.