The Second Ionization Constant of Hexafluoroacetone Hydrate and the Stability of Species of the Type $R_2C(O^-)_2$[1]

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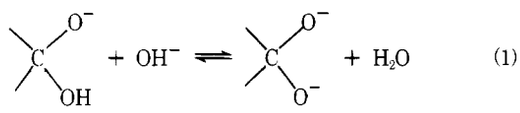
The thermodynamic pK_1 and pK_2 values for hexafluoroacetone hydrate (1,1,1,3,3,3-hexafluoro-2,2-propanediol) in water at 25 °C have been found to be 6.76 and 13.53, respectively. It is estimated that 5.63 of this 6.77 change in pK values arises from the substituent effect of the negative charge two carbons away from the acidic hydroxyl group in the monoanion [$HOC(CF_3)_2O^-$], 0.54 from internal hydrogen bonding in the monoanion, and 0.60 from a statistical effect.

There are many reactions, including the Cannizzaro reaction,[2] the basic hydrolysis of amides,[3] the rearrangements of glyoxal[4] and phenylglyoxal[5] in base to give salts of α-hydroxy acids, and the alkaline cleavage of chloral hydrate,[6,7] β-diketones,[8] ketonylpyridinium ions,[9] β-keto sulfones,[10] 2,6-dihalobenzaldehydes,[11] and phenylpropargyl aldehyde,[12] among others, that have been found to proceed via intermediates having a carbon atom to which two $-O^-$ groups are attached. In order to interpret more fully the kinetic data obtained in such reactions it would be desirable to have a value for the equilibrium constant for the formation of such a species from the monoanion, which is also an intermediate in all the reactions referred to. The equilibrium constant for such a reaction (eq 1) is a function of the second ionization of a *gem*-diol. A



(1)

number of first ionization constants of *gem*-diols have been determined and a Taft equation correlation has been made for a set of eight values.[12] If the substituent effect of an α-O^- substituent could be determined in any specific case it could be used in estimating the second ionization constants. Inasmuch as the second ionization constant is expected to be much smaller than the first, it should be most easily determined in the case of the most acidic *gem*-diol. The most acidic *gem*-diol we are aware of is hexafluoroacetone hydrate (1,1,1,3,3,3-hexafluoro-2,2-propanediol), whose pK_1 has been found to be 6.58 in water at 25 °C.[13] We have therefore determined pK_2 for this compound.

Results

The second ionization constant of hexafluoroacetone hydrate was determined by potentiometric titration in a manner similar to that used previously for the first ionization constant of phenylglyoxal hydrate,[5] except for modifications because of differences in the charge types of the species involved. The titrations were carried out in pairs. One solution contained hexafluoroacetone hydrate; the second was a "matching" solution used, in essence, to calibrate the readings on the pH meter. The first solution was titrated with standard sodium hydroxide to the first end point and then an equivalent amount of additional sodium hydroxide was added, with the pH being read when 0.1, 0.2, 0.3, etc., of it had been added. During the titration the ionic strength is continuously increasing. It was not practical to have the ionic strength of the matching solution increase during the titration in exactly the same way that the ionic strength of the ketone hydrate solution did, but the matching solution was made up so that its ionic strength was essentially equal to that of the ketone hydrate solution at one of the points at which the pH was measured. It was considered that the titration started when the first equivalence point had been reached, that is, that a solution of the monosodium salt of hexafluoroacetone hydrate was being titrated. The matching solution had essentially the same volume and contained a model salt or salts. The same volumes of the same sodium hydroxide solution as was used to titrate the ketone hydrate were added and the pHs read. In one set of titrations the model salt was sodium acetate, whose anion, like the anions derived from the ketone hydrate, has two oxygen atoms attached to the same carbon atom. In another set the model salt was sodium fluoride, whose anion has the full negative charge localized essentially on one atom, like the monoanion of hexafluoroacetone hydrate. In the third set of titrations the matching solutions contained mixtures of sodium fluoride and sodium sulfate so that they contained mixtures of monoanions and dianions, just as the ketone hydrate solutions do during the addition of the second equivalent of base.

If hexafluoroacetone hydrate is abbreviated as H_2Fa the equilibrium constant we are seeking, K_h, is defined in

$$K_h = a_{Fa}/(a_{HFa}a_{OH}) \tag{2}$$

Using the Davies equation,[14] which has the form of

$$\log \gamma = -0.509\left(\frac{\sqrt{\mu}}{1+\sqrt{\mu}} - 0.2\mu\right) \tag{3}$$

for a unicharged ion at 25 °C, and making the usual assumption that the logarithm of an ionic activity coefficient is proportional to the square of the charge on the ion, permits us to express K_h in terms of concentrations and activity coefficients as shown in

$$K_h = \frac{[Fa^{2-}]\gamma^2}{[HFa^-][OH^-]} \tag{4}$$

in which γ is the activity coefficient of a unicharged ion. From the fact that the autoprotolysis constant of water must be the same in both solutions and the assumption that the observed pH is equal to $-\log a_{H^+}$, we obtain

$$[OH^-] = (\gamma_m/\gamma)[OH^-]_m 10^{pH-pH_m} \tag{5}$$

in which the subscript m's refer to the properties of the matching solution at the same point in the titration. The properties of the matching solution are known, as is the pH of the ketone hydrate solution. The concentration of the dianion is that shown in eq 6, and that of the monoanion in eq 7

$$[Fa^{2-}] = [OH^-]_m - [OH^-] \tag{6}$$

$$[HFa^-] = [H_2Fa]_t - [Fa^{2-}] \tag{7}$$

in which $[H_2Fa]_t$ is the total concentration of H_2Fa in all forms. Substitution of eq 5, 6, and 7 into eq 4 leaves K_h as the only unknown. The result may be rearranged to give eq 8, a quadratic in a, the activity of hydrogen ions in the H_2Fa so-

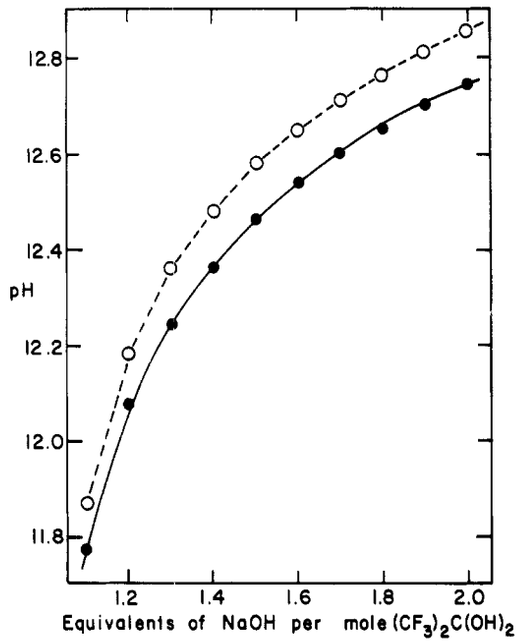


Figure 1. Titration of hexafluoroacetone hydrate with sodium hydroxide: ●, pH of the hexafluoroacetone hydrate solution; ○, pH of the matching solution.

lution. Solution for a permits a nonlinear least-squares treatment[15] of the data on all ten points in a given titration to obtain the best value of K_h.

$$\gamma^4 a^2/(a_m\gamma_m) + \gamma[K_h([OH^-]_m - [H_2Fa]_t) - \gamma^2]a - K\gamma_m a_m[OH^-]_m = 0 \quad (8)$$

Inasmuch as the uncertainties in pH were thought to be more nearly constant than the uncertainties in a, it was the sum of the squares of the fractional deviations in a, that is, $\Sigma(1 - a_{calcd}/a_{obsd})^2$, that was minimized.

The data for the case in which 0.07 M sodium acetate was used are plotted in Figure 1. The pH values obtained in the hexafluoroacetone hydrate solutions are shown as solid circles and those for the matching solution as open circles. The dashed line simply connects the open circles, but the solid line connects the pH's that may be calculated from the open circles and the least-squares best value of K_h, which is listed in the first line of Table I. From the results summarized in Table I we conclude that pK_2 for hexafluoroacetone hydrate is 13.53 ± 0.03.

We considered the possibility that during our titrations with base the hexafluoroacetone hydrate was undergoing a cleavage reaction of the type known to occur with chloral hydrate. This cleavage would replace the monoanions formed from the ketone hydrate by the much less basic trifluoroacetate ions. We therefore titrated 0.07 M ketone hydrate with 2 M sodium hydroxide until more than 2 equiv of base had been added. After the solution had stood at 25 °C for 20 min we back-titrated with 2 M hydrochloric acid and obtained essentially the reverse of the curve that we had obtained in the forward titration. This (and the fact that no gas was evolved) shows that no significant amount of decomposition of the ketone hydrate takes place during the titration.

From the pH (6.68) at the half-equivalence point and the Davies equation we calculate a thermodynamic pK_1 of 6.76 for the ketone hydrate. This is slightly higher than the previously reported value of 6.58,[13] but it is not clear at what ionic strength the literature value was determined or whether it is a thermodynamic ionization constant or not.

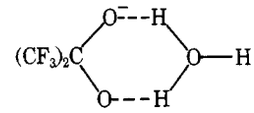
Table I. Acidity of Hexafluoroacetone Hydrate in Water at 25 °C[a]

NaX	[NaX],[b] M	$[Na_2SO_4]$,[b] M	K_h[c]	pK_2
NaOAc	0.0700	0	2.74 (0.05)	13.56
NaOAc	0.0800	0	3.13 (0.03)	13.50
NaF	0.0764	0	2.95 (0.04)	13.53
NaF	0.0764	0	2.85 (0.04)	13.55
NaF	0.0600	0.0100	2.90 (0.06)	13.54
NaF	0.0600	0.0200	2.99 (0.05)	13.52

[a] In all cases the initial total concentration of ketone hydrate was 0.076 ± 0.004 M and that of the sodium hydroxide titrating solution was 2.03 ± 0.05 M. [b] Initial concentration. [c] The parenthesized figures are estimated standard deviations.[15]

Discussion

There is a difference of 6.77 between the pK_1 and pK_2 values we have obtained for hexafluoroacetone hydrate. Of this, 0.60 is a statistical effect, leaving 6.17 as the difference in substituent effects between the α-OH and α-O^- substituents. This is rather larger than the value 4.4 estimated for the ΔpK produced by a charge two atoms away from the acidic hydroxy group using the method of Branch and Calvin.[16] However, the method of Branch and Calvin gives a pK_a of 10.8 for $HOCH_2NMe_3^+$, whose pK_a is actually 9.33.[17] If Branch and Calvin's charge effect had been 5.87 instead of 4.4 their method of estimation of pK_a values would have given the right answer for $HOCH_2NMe_3^+$. A Taft-equation correlation used previously to estimate the acidities of certain α-amino alcohols[18] gives a pK of 14.89 for the hydroxylic proton in $HOCH_2NMe_2$; this leaves 5.56 as the effect of the positive charge in $HOCH_2NMe_3^+$ (neglecting the effect of the extra methyl group). Some of these estimates of the effect of a charge two atoms away from the acidic hydroxy group are almost as large as the ΔpK effect of 6.17 we observe for hexafluoroacetone hydrate, but the differences are all in the direction that would be expected if the monoanion $HOC(CF_3)_2O^-$ were stabilized by internal hydrogen bonding, as Middleton and Lindsey have suggested.[13] Such stabilization of the monoanion can have no effect on the product K_1K_2, which is the equilibrium constant for dissociation of the ketone hydrate to give two protons and the dianion. Hence if the α-hydroxy substituent stabilizes the $-O^-$ by hydrogen bonding, either directly or via intervening water molecules (as in 1), this will increase K_1 and decrease K_2. Therefore $pK_2 - pK_1$



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measures not only the destabilization of the new $-O^-$ group that is formed by the one already present but also the destabilization resulting from loss of the internal hydrogen bond. Middleton and Lindsey's principal argument for the internal hydrogen bond is the fact that the statistically corrected ΔpK_1 produced on replacing the α-hydrogen atom of 1,1,1,3,3,3-hexafluoro-2-propanol by a hydroxy group to get hexafluoroacetone hydrate is 2.42 (2.14, using our pK_1 value), whereas the statistically corrected pK_1 observed for replacing the α-hydrogen atom of phenyltrifluoromethylcarbinols by a hydroxy group is about 1.6. Decreases of about 1.6 in the statistically corrected pK are also noted in the replacement of α hydrogen by hydroxy in methanol,[19,20] 2,2,2-trichloroethanol,[19,20] and 2,2,2-trifluoroethanol.[19,21] The extent of stabilization resulting from internal hydrogen bonding would be expected to increase with increasing acidity of the hydroxylic

proton. The fact that no more such stabilization seems to be occurring in $Cl_3CCH(OH)O^-$ or $F_3CCH(OH)O^-$ than in $HOCH_2O^-$ suggests that in none of the three cases does the internal hydroxy group compete significantly with hydrogen bonding by the more acidic protons of water. The more acidic proton in $HOC(CF_3)_2O^-$ can compete, however, and the result is a ~0.54 larger increase in pK produced on replacing α hydrogen by α-hydroxy. If this interpretation is correct, the negative charge in $HOC(CF_3)_2O^-$ is increasing the pK by 6.17 − 0.54 or 5.63 units. Thus, we would estimate that phenylglyoxal hydrate, for example, whose pK_1 is 11.19,[18] has a pK_2 of 17.42.

Experimental Section

Hexafluoroacetone hydrate (PCR) was used without further purification. The strengths of its aqueous solutions were determined by titration with standard base. Potentiometric titrations were carried out using a Radiometer automatic titrator (ABU 1, PHM 26, and SBR 2c with a type B electrode) with a 2.5-mL buret in the manual mode. The total elapsed time for a titration was less than 15 min and the temperature of the solution was 25.0 ± 0.2 °C.

Registry No.—Hexafluoroacetone hydrate, 677-71-4.

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Chemistry of Trifluoroacetic Anhydride–Haloacetic Acid Reactions with Medroxyprogesterone

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Reaction of medroxyprogesterone with bromoacetic acid–trifluoroacetic anhydride at 25 °C for 1 h gives, after workup, complete recovery of starting material. The same reaction conducted at 65 °C for 1 h produces an inseparable mixture of products. Treatment of the mixture with dilute ethanolic HCl permits isolation of medroxyprogesterone 17-trifluoroacetate and the transhalogenated product medroxyprogesterone 17-chloroacetate, in approximately equal amounts. Substituting ethanolic HBr during the second reaction step provides medroxyprogesterone 17-bromoacetate in 25–30% overall yield. Similar results were obtained with 17α-hydroxy-4-pregnene-3,20-dione. When phenylacetic acid is substituted for bromoacetic acid in the reaction sequence analogous results are obtained. Reaction of medroxyprogesterone at 65 °C in trifluoroacetic anhydride alone gives two products shown to be medroxyprogesterone 17-trifluoroacetate and 3,17α-dihydroxy-6α-methyl-3,5-pregnadien-20-one bis(trifluoroacetate). Electron-withdrawing substitutents on acetic acid appear to direct the mixed anhydride reaction, and this effect is discussed. Both medroxyprogesterone 17-bromoacetate and 17α-bromoacetoxyprogesterone inactivate the enzyme 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53) from *Streptomyces hydrogenans* in a time-dependent and irreversible manner while the corresponding chloroacetoxy and trifluoroacetoxy esters do not.

A series of bromoacetoxyprogesterone isomers was previously synthesized in this laboratory to serve as active site directed irreversible inhibitors to study the active site topography of 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53) from *Streptomyces hydrogenans*.[1] Among these alkylating agents, 16α-bromoacetoxy-4-pregnene-3,20-dione, 11α-bromoacetoxy-4-pregnene-3,20-dione, and 17β-bromoacetoxy-4-estren-3-one terminate pregnancy in rats.[2,3] Continuation of these enzymological and reproductive biological investigations required the synthesis of 17α-bromoacetoxyprogesterone (17α-bromoacetoxy-4-pregnene-3,20-dione) and medroxyprogesterone bromoacetate (17α-bromoacetoxy-6α-methyl-4-pregnene-3,20-dione). The latter compound is a steroid alkylating agent structurally analogous to medroxyprogesterone acetate, a powerful progestin.[4] The present report describes the result obtained when the tertiary hydroxyl steroid precursors were treated with haloacetic acid–trifluoroacetic anhydride mixtures under a variety of conditions.

Treatment of medroxyprogesterone (**1a**, Scheme I) with a bromoacetic acid–trifluoroacetic anhydride mixture at 25 °C for 1 h gave, after workup, recovery of starting material. Under similar reaction conditions a variety of aliphatic carboxylic acids are reported to give good yields of the corresponding medroxyprogesterone 17-esters.[4] Therefore, the earlier described reaction conditions had to be modified in order to obtain the desired 17-halo acetates.

When we conducted the mixed anhydride reaction at 65 °C, TLC analysis of the crude product revealed that at least four new compounds had been formed, and 30–40% of the starting material remained unreacted. This mixture could not be separated by either TLC or column chromatography. Since it was likely that some of the products contained a 3-enol ester function[7] we attempted to simplify the mixture by selectively