Intramolecular Addition of Hydroxy Groups to the Carbonyl Groups of Trihaloacetate Esters[1]

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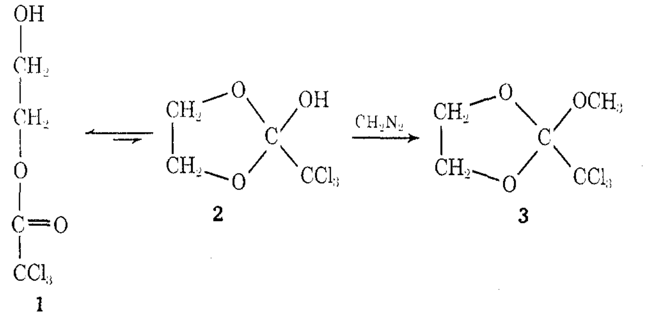
The monoesters of trifluoroacetic acid (and, in the first two cases, trichloroacetic acid) with ethylene glycol, pinacol, and isobutylene glycol have been examined by ir and pmr measurements. In the case of the pinacol esters, but not the other esters, significant amounts of both the hydroxy ester and a cyclic tautomer (a 2-trihalomethyl-1,3-dioxolan-2-ol) are detected at equilibrium. The presence of small amounts of the cyclic tautomer in all cases, however, is indicated by reaction of all the esters with diazomethane to give derivatives of 2-methoxy-2-trihalomethyl-1,3-dioxolane.

In an earlier paper correlations of rate constants and equilibrium constants for elementary reactions involving coordination of a base with an electrophilic carbon atom were discussed.[2] The reactions considered included a number of nucleophilic attacks on the carbonyl carbon atom of aldehydes and ketones. In order to extend this work to ester interchange and hydrolysis reactions, we need to know more about the stabilities of the immediate products of nucleophilic attack on esters. The immediate products are ordinarily protonated and deprotonated forms of the mono- and diesters of ortho acids, $RC(OH)_3$. Although triesters of ortho acids are well known, we are aware of no reports of direct observations on monoesters in any state of protonation and only a few reports concerning diesters. The only diester for which we have found good evidence is the product of the internal cyclization of the mono(trifluoroacetate) of *cis*-3,4-dihydroxytetrahydrofuran.[3] In the reported cyclization of *o*-benzoyloxybenzyl alcohol[4] no spectral measurements were described. The reaction of diazomethane with 2-hydroxyethyl trichloroacetate (**1**) yields the cyclic ortho ester **3**, presumably *via* the intermediate formation of **2**.[5] However, Meerwein and Sönke concluded, on the basis of density and refractive index measurements, that the equilibrium between **1** and **2** lies far on the side of **1**, as do the analogous equilibria involving the mono- and dichloroacetate esters.[6]



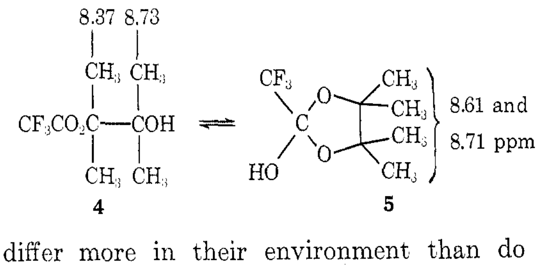
1 **2** **3**

Since a dialkyl ester of an ortho acid must be much more acidic than an ordinary alcohol, it might be easier to make direct observations on its salt than on the un-ionized ester. In fact, Swarts concluded that ethyl trifluoroacetate and sodium ethoxide give a solid isolable salt of diethyl 2,2,2-trifluoroorthoacetate.[7] Bender obtained infrared evidence for this conclusion.[8] Subsequently, tetrodotoxin has been found to be the inner salt of the diester of an ortho acid.[9,10]

We have extended some of the preceding observations in an attempt to learn whether we could make direct observations on equilibria between ordinary esters and dialkyl esters of ortho acids or their salts.

Results and Discussion

Treatment of pinacol with trifluoroacetic anhydride gave a crystalline product with the correct elemental analysis for the monoester. The proton magnetic resonance (pmr) spectrum (in carbon tetrachloride) showed a small peak at τ 6.5 ppm, attributed to the hydroxylic protons, and four larger peaks at 8.37, 8.61, 8.71, and 8.73 ppm. In benzene the difference in chemical shift between the last two peaks was 0.05 ppm and the four larger peaks were resolved enough to make it clear that the two middle peaks were of equal size and the outside peaks were each about 38% as large. It was presumed that one pair of peaks arose from the two different types of methyl groups in the monoester **4** and the other pair from the two types of methyl groups in its cyclic tautomer 4,4,5,5-tetramethyl-2-trifluoromethyl-1,3-dioxolan-2-ol (**5**). Since the two types of methyl groups in **4** seem to differ more in their environment than do those in **5**, the two inner peaks were tentatively assigned to **5** and the outer ones to **4**. Since the hydroxy group in **5** must be tremendously more acidic than that in **4**, it should hydrogen bond much more strongly to oxygen and nitrogen atoms with unshared electron pairs. Hence, the pmr spectrum was run in dioxane and acetonitrile, where the lower field outer peak (the only outer peak that was clearly visible) was only about



4 **5**

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[1] This investigation was supported in part by Grants GP-7629 and GP-14697 from the National Science Foundation.

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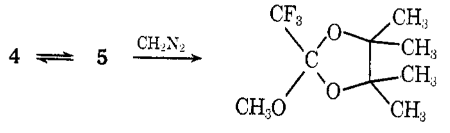
5% as large as an inner peak. This change in relative peak sizes is attributed to stabilization of **5** by hydrogen bonding to the solvent. The data in Table I show that such hydrogen bonding is probably significant even in benzene, where there is significantly more **5** present than in carbon tetrachloride. Addition of the base Dabco (1,4-diazabicyclo[2.2.2]octane) to carbon tetrachloride solutions gave pmr evidence that the equilibrium was shifted toward the cyclic tautomer **5**, which must form a salt or hydrogen-bonded complex with the base. Infrared measurements on the same solutions showed a decrease in the intensity of the absorption peak at 1780 cm^{-1}, attributed to the carbonyl group of **4**. Methylation of the mixture of **4** and **5** gave 2-methoxy-4,4,5,5-tetramethyl-2-trifluoromethyl-1,3-dioxolane (**6**), whose pmr spectra showed methyl peaks at the same chemical shifts as those of **5** and a methoxy peak split into a quartet by the trifluoromethyl group.

TABLE I
AMOUNTS OF 2-TRIHALOMETHYL-1,3-DIOXOLAN-2-OL PRESENT IN MONOTRIHALOACETATES OF PINACOL

Ester	Solvent	Dioxolan-2-ol, %
Trifluoroacetate	CCl_4	60
Trifluoroacetate	Benzene	72
Trifluoroacetate	1,4-Dioxane	95
Trifluoroacetate	MeCN	95
Trichloroacetate	CCl_4	7
Trichloroacetate	MeCN	13



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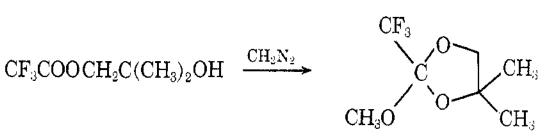
The trichloroacetate of pinacol,[11] like the trifluoroacetate, had a pmr spectrum with two pairs of singlets for the methyl protons, but there was much less cyclic tautomer present (*cf.* Table I). Larger areas could be obtained for the inner peaks by addition of Dabco. Methylation of the mixture of tautomers gave 2-methoxy-4,4,5,5-tetramethyl-2-trichloromethyl-1,3-dioxolane, whose pmr spectrum showed methyl peaks with essentially the same chemical shifts as those in **6**.

In the case of the trifluoroacetate of isobutylene glycol, which consisted largely of the isomer in which the primary alcohol group was esterified, none of the cyclic tautomer was detected. However, in this case, too, treatment with diazomethane gave the cyclic O-methylated derivative **7**, whose methyl groups had about the same chemical shifts as those of **5** and **6**.



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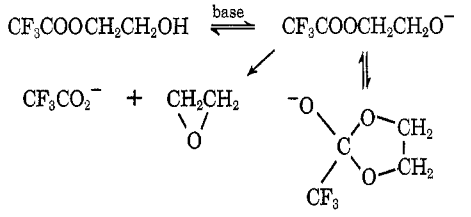
In the case of the trichloroacetate and the trifluoroacetate[12] of ethylene glycol, none of the cyclic tautomer was detected by examination of the pmr spectra. Treatment with diazomethane gave the O-methylated cyclic derivatives, each of which showed a broadened singlet for the methylene protons, which had given A_2B_2 patterns in the starting esters.

Studies of the trifluoroacetate of ethylene glycol in ethylene glycol containing the sodium salt of ethylene glycol gave some evidence for the formation of the salt of the cyclic tautomer **8**. Following the reaction in the presence of phenolphthalein by use of a stopped flow spectrophotometer showed that much of the base (in the presence of excess ester) was used up in a reaction with a half-life of less than a second. The remaining base was used up in a reaction that took place over a period of several minutes. We hypothesize that the rapid reaction is the reversible transformation of much of the reactant to **8** and that the slower reaction is at least partly a neighboring group displacement reaction to yield ethylene oxide and trifluoroacetate ions. About 70% of sodium trifluoroacetate was found (by ir measurements) to be in the product mixture, but in spite of many experiments we could never detect more than about 10% ethylene oxide.



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The strongly electron-withdrawing trihalomethyl group attached to the carbonyl group of our esters must greatly increase the equilibrium constants for addition of hydroxy groups to the carbonyl groups. Addition is further favored by the possibility of forming a five-membered ring. Even so, the fraction of cyclic tautomer present at equilibrium in the case of 2-hydroxyethyl trifluoroacetate was too small to detect directly. Only when there were several methyl groups present to favor ring formation still more (or when the hydroxy and trifluoroacetoxy groups are held next to each other, as in the case of the trifluoroacetate of *cis*-3,4-dihydroxytetrahydrofuran) is the stability of the cyclic dialkyl ortho ester comparable to that of the open-chain hydroxy ester. Examination of the steric and polar substituent constants of trichloromethyl and trifluoromethyl groups suggests that the smaller tendency of the trichloroacetate of pinacol to cyclize is probably largely the result of steric hindrance.

Experimental Section

Trifluoroacetylation of Pinacol.—Various methods of treating pinacol with trifluoroacetic acid gave only pinacolone. Reaction of 10.5 g (50 mmol) of trifluoroacetic anhydride and 5 g (49 mmol) of pinacol in 10 g of benzene at about 25° for 2.5 hr was found by glpc on diethylene glycol succinate (DEGS) to give a major amount of a new product, almost as much pinacolone, and about 15% as much pinacol. The combined products of two such reactions were rid of pinacol by fractional distillation at 35–78° (9.5 mm). Refractionation of the latter fractions from this distillation gave material that showed only one peak on glpc on DEGS: bp 40° (2.5 mm); mp 45–52°; ir[13] (CCl_4) 1200, 1780, 1360, 2990, 3010, 1380, 3600, and 1450 cm^{-1}.

Anal. Calcd for $C_8H_{13}O_3F_3$: C, 44.86; H, 6.11; F, 26.60. Found: C, 45.01; H, 6.12; F, 26.54.

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[13] In order of decreasing intensity.

2-Methoxy-4,4,5,5-tetramethyl-2-trifluoromethyl-1,3-dioxolane.—The product of the trifluoroacetylation of pinacol (a mixture of **4** and **5**) was added to a solution of diazomethane in ether and the resultant mixture was separated by glpc on DEGS. The product that had given the only major new glpc peak had a pmr spectrum (CCl_4) consisting of a quartet ($J_{FH} \cong 1.3$ Hz) at τ 6.65 and two singlets, each with an area twice that of the quartet, at 8.63 and 8.70 ppm. The ir showed no absorption band in the carbonyl region.

Trichloroacetate of Pinacol.—The product [bp 75–78° (0.05 mm); ir (CCl_4) 1760 ($C{=}O$) and 3590–3000 cm^{-1} (OH)] of the reaction of trichloroacetic acid with tetramethylethylene oxide[11] had a pmr spectrum (CCl_4) consisting of a slightly broadened hydroxy peak at τ 7.50, two methyl peaks, each almost six times as large, at 8.37 and 8.71, and two more methyl peaks, each about 8% as large as the larger methyl peaks, at 8.55 and 8.66 ppm. The pmr spectrum in acetonitrile was quite similar except that the peaks at 8.55 and 8.66 were about 15% as large as those at 8.37 and 8.71 ppm.

2-Methoxy-4,4,5,5-tetramethyl-2-trichloromethyl-1,3-dioxolane.—The trichloroacetate of pinacol was added to a solution of diazomethane in ether and the resultant mixture was separated by glpc on DEGS. The material from the only new glpc peak had no carbonyl band in its ir spectrum and a pmr spectrum consisting of three singlets with a ratio of 1:2:2.

Trifluoroacetates of Isobutylene Glycol.—Reaction of 9.5 g of trifluoroacetic acid and 8 g of isobutylene glycol in 10 g of benzene was allowed to proceed for 20 hr at 25°. Distillation gave 6 g of colorless liquid, bp 65° (20 mm), ir 1780 cm^{-1} ($C{=}O$). The pmr spectrum showed singlets at τ 8.68 and 5.80 ppm (areas, 3:2) attributed to the methyl and methylene groups of the primary ester 2-hydroxy-2-methylpropyl trifluoroacetate and two more singlets (τ 8.45 and 6.24 ppm) 3% as large attributed to the methyl and methylene groups of the tertiary ester 1,1-dimethyl-2-hydroxyethyl trifluoroacetate. This mixture reacted with diazomethane in ether to give, after separation by preparative glpc, 2-methoxy-4,4-dimethyl-2-trifluoromethyl-1,3-dioxolane: ir[13] (CCl_4) 2990, 1360, 1240, 1370, 1450, and 2950 cm^{-1}; pmr (CCl_4) τ 6.09 (s, 2, CH_2), 6.62 (s, 3, OCH_3), 8.53 (s, 3, CCH_3), and 8.61 ppm (s, 3, CCH_3).

Trifluoroacetate of Ethylene Glycol.—A mixture of the mono- and diesters, prepared by the literature procedure,[12] was separated by preparative glpc on DEGS to give 2-hydroxyethyl trifluoroacetate, whose pmr spectrum (CCl_4) showed two approximate triplets of equal size at τ 5.34 and 6.02 ppm plus the hydroxyl peak. Methylation by diazomethane gave 2-methoxy-2-trifluoromethyl-1,3-dioxolane: ir[13] (CCl_4) 2910, 2990, 2950, 1430, 1450, 1310, 1360, 1270, 1340, and 2850 cm^{-1}; pmr (CCl_4) τ 5.77 (s, 4, CH_2), 6.60 ppm (s, 3, OCH_3).

Reaction of 2-Hydroxyethyl Trifluoroacetate with Sodium 2-Hydroxyethoxide.—The same results were obtained in this reaction when the diester 1,2-bis(trifluoroacetoxy)ethane was used as when the monoester 2-hydroxyethyl trifluoroacetate was used. Presumably the diester is very rapidly transformed to the monoester under the reaction conditions. Since the diester is more easily obtained in a pure form it was more commonly used. In a typical experiment, 0.2 g of sodium was dissolved in 2.5 ml of anhydrous ethylene glycol under nitrogen. The mixture was cooled to 0° and excess diester was added. After 30 min the pmr of the reaction mixture showed the presence of monoester and ethylene oxide. In other experiments the reaction mixture was evacuated through a trap cooled in liquid nitrogen, which was subsequently found to contain ethylene oxide. The identity of the epoxide was established by glpc on DEGS and SE-30 as well as by pmr. However, in some experiments it was not found, and in no case was its yield greater than about 10%.

Known amounts of the diester were added to standard solutions of sodium 2-hydroxyethoxide in ethylene glycol and absorbance measurements made at the 1680 cm^{-1} absorption maximum for the trifluoroacetate ion. Comparison of standard solutions of sodium trifluoroacetate in ethylene glycol containing the same concentration of sodium 2-hydroxyethoxide as that found by titration to remain in the reaction solution showed that about 1.4 mol of sodium trifluoroacetate had been formed per mole of diester used.

Registry No.—**4**, 13388-92-6; **4** trichloro analog, 36978-04-8; **5**, 36978-05-9; **5** trichloro analog, 36978-06-0; **6**, 36978-07-1; **7**, 36978-08-2; 2-methoxy-4,4,5,5-tetramethyl-2-trichloromethyl-1,3-dioxolane, 36978-09-3; 2-hydroxy-2-methylpropyl trifluoroacetate, 36978-10-6; 1,1-dimethyl-2-hydroxyethyl trifluoroacetate, 36978-11-7; 2-hydroxyethyl trifluoroacetate, 667-32-3; 2-methoxy-2-trifluoromethyl-1,3-dioxolane 36978-13-9.

Stereochemistry of Medium-Sized-Ring Cyclopropylcarbinyl Radical Rearrangement[1]

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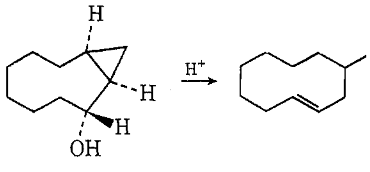
tert-Butyl *anti*-bicyclo[7.1.0]decane-2-percarboxylate (**1**) was prepared and assigned stereochemistry by conversion to *anti*-bicyclo[7.1.0]decan-2-ol. Photolytic or thermal decompositions gave complex product mixtures. The formation of both cis and trans cyclodecenes indicates that the cyclopropylcarbinyl radical does not give a stereospecific ring expansion.

Previous work[2] has shown that *anti*-bicyclo[7.1.0]decan-2-ol undergoes an acid-catalyzed, stereospecific ring expansion to *trans*-cyclodec-3-en-1-ol (eq 1) and



(1)

that the syn isomer stereospecifically gives the cis ring expanded product. These results suggest the intermediacy of nonclassical carbonium ions capable of maintaining stereochemistry. However, an argument could be made for classical ions that maintain stereochemistry because of some property of the medium-sized ring system. For example, the stereospecific ring expansions could result from the least motion rearrangements of two classical ions that do not readily undergo conformational interconversion.[3]

The behavior of the corresponding radical is interesting in this regard because radicals do not generally show nonclassical behavior.[4] If the radicals were to

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(1) We thank the Research Corporation for support of this work.

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