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The Methanol-Trimethoxyborane Azeotrope as a Solvent for Acid-Catalyzed Reactions. Methyl Esterification[1a]

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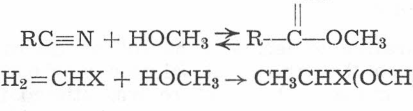
Carboxylic acids undergo a rapid and complete acid-catalyzed methyl esterification in the methanol-trimethoxyborane azeotrope. The reaction is first order in carboxylic acid and first order in strong acid catalyst. Rate constants are very similar to those in methanol alone. These observations suggest that the mechanism is the same as that in solvent, methanol-$A_{Ac}2$. The reaction can be made the basis of a convenient preparation of methyl esters. It has been used to prepare methyl benzoate, methyl lactate, and the methyl ester of phenylalanine. Acid-catalyzed acetal and ketal formation in the azeotrope is fast but incomplete. Methyl etherification of tertiary alcohols seems too limited, structurally, to be generally useful. No acid-catalyzed addition of methanol to acetonitrile or acrylonitrile could be observed.

In an accompanying paper[2] we have shown that the mobile, low boiling, 1 : 1 azeotrope formed by methanol and trimethoxyborane has no visible or uv spectrum above 220 nm, has a very simple NMR spectrum, and has a substantial window in its ir spectrum which includes the crucial carbonyl stretching region. Theory and experiment suggest that the azeotrope should be a good hydrogen bond donor and a poor hydrogen bond acceptor[2]. Since the transition states of most H^+ catalyzed reactions require fewer strong hydrogen bond acceptor sites than H^+ itself (as shown by their inverse solvent hydrogen isotope effects[3]) a solvent which is a poor hydrogen bond acceptor may accelerate such reactions. The azeotrope should also be moderately dehydrating, because of the hydrolysis of trimethoxyborane to boric acid. The present paper describes a survey of possibly useful acid-catalyzed reactions, including examples of the reactions shown in eqs. 1—5, all conducted in the presence of a strong acid catalyst.



$$\mathrm{RC{\equiv}N + HOCH_3 \rightleftarrows R{-}\overset{\overset{\displaystyle NH}{\|}}{C}{-}OCH_3} \qquad (1)$$

$$\mathrm{CH_2{=}CHX + HOCH_3 \rightarrow CH_3CHX(OCH_3)} \qquad (2)$$

$$\mathrm{R_1COR_2 + HOCH_3 + \frac{1}{3}\,B(OCH_3)_3 \rightleftarrows R_1C(OCH_3)_2R_2 + \frac{1}{3}\,B(OH)_3} \qquad (3)$$

$$\mathrm{ROH + \frac{1}{3}\,B(OCH_3)_3 \rightarrow ROCH_3 + \frac{1}{3}\,B(OH)_3} \qquad (4)$$

$$\mathrm{RCOOH} + \frac{1}{3}\,\mathrm{B(OCH_3)_3} \rightarrow \mathrm{RCOOCH_3} + \frac{1}{3}\,\mathrm{B(OH)_3} \qquad (5)$$

Of these, the first two did not proceed at useful rates; the third is very fast, but does not go to completion; and the fourth proceeds at a useful rate only when R^+ is, relatively, a *very* stable carbocation, such as the triphenylmethyl cation. The fifth reaction was the most successful. It appears to be general, goes rapidly to completion, and the product is readily separated from the solvent, catalyst, and byproduct in most cases. A kinetic study and several small-scale preparations are described.

EXPERIMENTAL

Materials

The preparation of the azeotrope and the purification of trifluoromethanesulfonic acid have been described previously[2]. Lactic acid was used as an 85% active aqueous solution, obtained from J. T. Baker Chemical Co. The other organic substances were all obtained from Aldrich Chemical Co., and were used as supplied.

Screening Experiments

Small-scale screening experiments were carried out in NMR spectrometer tubes. The NMR spectrum of an 0.5 M solution of the proposed substrate was first obtained in the azeotrope as solvent. Sufficient CF_3SO_2OH was then added to give the desired acid concentration, from 10^{-3} to 10^{-1} M. The NMR spectrum was monitored from time to time over a period up to several days. Faster reactions were allowed to proceed in the spectrometer, at 39 °C. Slower reactions were removed from the spectrometer between observations, and the reactions were allowed to proceed at room temperature, 23—26 °C. The extent of reaction was judged from the intensity of singlets due to OCH_3 groups other than that of the azeotrope.

Rates of Esterification

To measure rates, esterification was carried out with dilute solutions of the carboxylic acid (usually 0.1 M) in the azeotrope, in an ir spectrophotometer cell equipped with Irtran(R) windows. The progress of the reaction was determined from the growth of the ester carbonyl band, at frequencies between 1733 cm^{-1} and 1751 cm^{-1}. Qualitatively, the progress of the reactions could also be seen in the decay and ultimate disappearance of the acid carbonyl peaks around 1717 cm^{-1}. In each spectrum the absorptivity around 1950 cm^{-1} was used as the base line. Rate constants were obtained graphically from eq. 6.[4] Figure 1 shows a typical plot. The symbols have their usual meaning. When spectral observations were not being

$$k_1 = \frac{2.3}{t - t_0} \log \left(\frac{A_\infty - A_0}{A_\infty - A_t} \right) \qquad (6)$$

made, the reacting solution was maintained at 25.0 ± 0.1 °C in a conventional thermostat.

Preparative Experiments

In a typical preparative experiment 50 ml of azeotrope was made up with enough methanolic HCl so that the final solution was 0.09 M in HCl. To this was added 1.5 g of benzoic acid and the mixture was stirred for 10 min at room temperature (~ 25 °C). During this period the benzoic acid entirely dissolved. The azeotrope was then rapidly distilled off under vacuum at room temperature. The HCl came off with the azeotrope. This left 1.6 g of mixed solid and liquid, 83% of theoretical yield based on $C_6H_5COOCH_3$ plus 1/3 $B(OH)_3$ as the expected products. Simple distillation gave 1.0 g of methyl benzoate, identified by its ir spectrum, which was identical with that of authentic methyl benzoate.

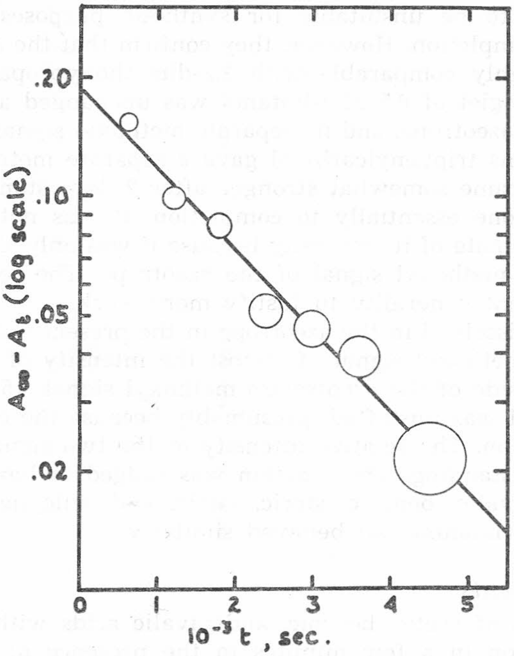


Figure 1. A typical plot for the evaluation of k_1 from eq 6. The initial (CH_3COOH) was 0.1 M. The (CF_3SO_2OH) was 0.00843 M. The slope of the plot, which was drawn subjectively, is $k_1 (t - t_0)/2.3$; k_1 is 4.47×10^{-4} sec^{-1}.

RESULTS AND DISCUSSION

Screening Experiments

The NMR spectrum of the azeotrope consists of a strong singlet (relative intensity 12) at 4.0 ppm and a weak singlet at 5.5 ppm, both measured from tetramethylsilane. Both bands are broad, but are sharpened by the addition of acid. Presumably methoxyl interchange between H and B is fast (but not infinitely fast) on the NMR time scale, in the pure azeotrope, and is catalyzed by acid.

Neither acetonitrile nor acrylonitrile, when added to the azeotrope, causes the development of a new signal in the methoxyl region after several days. Both show unchanging spectra essentially the same as those they show in other solvents. It was, therefore, concluded that neither substance reacts with the azeotrope. Acetone, phenylacetaldehyde, acetophenone, and isobutyraldehyde all caused the immediate development of a methyl signal downfield from that of the azeotrope in the presence of 10^{-3} M CF_3SO_2OH. Both solutions also developed new singlets in the aliphatic region. However, neither reaction went to completion, as indicated by the persistence of the signals of the unchanged starting materials. Acetone appeared to be about 50% converted to its dimethyl ketal. No hemiacetal or hemiketal was observed. At 0.1 M CF_3SO_2OH the methyl peaks of acetone and those of its ketal were beginning to broaden and merge, and the methoxyl peak was beginning to merge with that of the azeotrope. This suggests a half-life for conversion of about 0.1 sec. These reactions appear to be unsuitable for synthetic purposes because of their failure to go to completion. However, they confirm that the azeotrope is mildly dehydrating; roughly comparable with 2,2-dimethoxypropane.

The strong singlet of 0.5 M *t*-butanol was unchanged after 4 hr in 0.1 M CF_3SO_2OH in the azeotrope, and no separate methoxyl signal developed. Under the same conditions triphenylcarbinol gave a separate methoxyl singnal after 15 min, which became somewhat stronger after 2 days standing. The reaction may well have gone essentially to completion. It was not possible to make a quantitative estimate of its intensity because it was only slightly to the high--field side of the methoxyl signal of the azeotrope. The reaction was judged to be of insufficient generality to justify more work.

Acetic acid, dissolved in the azeotrope in the presence of 0.1 M CF_3SO_2OH, gave a separate methoxyl signal of almost the intensity of the methyl signal, to the high-field side of the azeotrope's methoxyl signal, 15 min after mixing. The methyl signal was unshifted, presumably because the ester gives a signal at the same position. The relative intensity of the two signals was unchanged even after 24 hr standing. The reaction was judged to have gone essentially to completion. Pivalic, benzoic, steric, lactic, and salicylic acids, as well as leucine and phenylalanine, all behaved similarly.

Kinetic Experiments

The reactions of acetic, benzoic, and pivalic acids with the azeotrope all went to completion in a few minutes in the presence of 0.1 M CF_3SO_2OH, as judged by changes in their ir spectra. In solutions containing 0.1 M acetic acid, k_1 for its conversion to ester was directly proportional to (CF_3SO_2OH) for values for the latter between 1.6×10^{-3} and 2×10^{-2}, as shown in Figure 2.

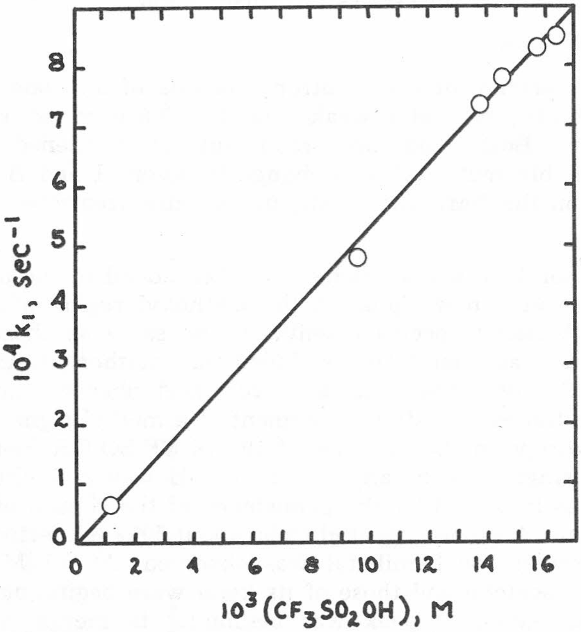


Figure 2. The rate of CF_3SO_2OH catalyzed esterification of 0.1 M acetic acid as a function of the strong acid concentration. The slope of this plot is k_2, 5.3×10^{-2} M^{-1} sec^{-1}.

The proportionality constant, k_2, was 5.3×10^{-2} M^{-1} sec^{-1}. The average deviation of points from the linear relation is 5% which is about the expected uncertainty in k_1. In solutions, all containing 1.7×10^{-3} M CF_3SO_2OH, the values of k_1 were 1.30×10^{-4}, 0.99×10^{-4}, and 0.72×10^{-4} sec^{-1} for (CH_3COOH) 0.05, 0.10, and 0.40, respectively. These changes appear to be outside the uncertainties of the measurements, but they are too small to suggest serious mechanistic complications. They may well be due to increased dimerization of the acetic acid at the higher concentrations. The addition of 2% excess trimethoxyborane to the reaction mixture increases k_1 by $\sim 20\%$ while the addition of 1% excess methanol reduces it by $\sim 8\%$. These effects, particularly the former, seem to be outside the scatter. Values of k_2 were also obtained for benzoic and pivalic acid. All are shown in Table I, along with the analogous quantities obtained in methanol as a solvent[5].

The close similarity between k_2 values in the azeotrope and those in methanol, shown in Table I, suggests that the $A_{Ac}2$ mechanism operates in the former medium, as it does in the latter[6]. In the azeotrope CF_3SO_2OH appears to be entirely ionized but incompletely dissociated in the concentration range used to esterify acetic acid ($\sim 30\%$ dissociated at the lower end of the range, $\sim 10\%$ at the upper end)[2]. It has been shown, however, that ion pair formation constants in the azeotrope are relatively insensitive to structure. If this insensitivity extends to the esterification transition state, ion pairs, $CF_3SO_2O^-H^+$, and dissociated ions, H^+, would have about the same catalytic coefficients. This would help account for the similarity between k_2 values in methanol (in which the strong acid is almost completely dissociated) and in the azeotrope. It would also account for the observation of constant k_2 values in a range of strong acid concentrations over which the degree of dissociation is changing significantly.

TABLE I

Rates of Acid-Catalyzed Methyl Esterification

Substance	k_2[a]	k_2[b]
CH_3COOH	5.3×10^{-2}	5.9×10^{-2}
C_6H_5COOH	2.5×10^{-4}	1.9×10^{-4}
$(CH_3)_3CCOOH$	1.1×10^{-3}	1.9×10^{-3}

[a] At 25 °C in the methanol-trimethoxyborane azeotrope. [b] At 25 °C in solvent, methanol[5].

Preparative Experiments

The methyl esters of benzoic acid, lactic acid and phenylalanine were prepared by the method described in the experimental section. In the case of lactic acid an 85% aqueous solution was used without removing the water. In all cases spectrophotometric methods indicated that the reactions went to completion, and yields of ester plus boric acid after distilling away the solvent and the HCl were near quantitative. The yield of distilled methyl benzoate was

59%, and that of methyl lactate was 24%. Methyl lactate was distilled under vacuum, but polymerization in the pot nevertheless seems to have reduced the isolated yield. The product from phenylalanine was discolored and was lost in attempted further purification without being weighed. Each preparation was carried out only once and it is clear that the isolated yields are not optimal. We believe that the present method of methyl esterification can be made to compare favorably in cost, convenience, yield, and generality, with other available methods[7,8]. It appears to be particularly useful for hydroxy acids, like lactic.

REFERENCES AND NOTES

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SAŽETAK

Azeotropna smjesa metanol-trimetoksiboran kao otapalo za kiselo katalizirane reakcije. Priprava metil estera.

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Brza i potpuna kiselo katalizirana priprava metilnih estera karboksilnih kiselina može se provesti u azeotropnoj smjesi metanol-trimetoksiboran. Reakcija je prvog reda s obzirom na karboksilnu kiselinu, i prvog reda obzirom na jaku kiselinu koja služi kao katalizator. Konstante brzine reakcije vrlo su slične konstantama u čistom metanolu. Ta opažanja pokazuju da je mehanizam isti kao u metanolu — $A_{Ac}2$. Opisana reakcija može služiti kao osnova za prikladnu pripremu metilnih estera. Upotrijebljena je za pripravu metil-benzoata, metil-laktata i metil-estera fenilalanina. Kiselo katalizirano nastajanje acetala i ketala u ovoj azeotropnoj smjesi je brzo, no ne teče do kraja. Priprava metilnih etera tercijarnih alkohola previše je ograničena strukturom spoja da bi bila od općenite koristi. Kiselo katalizirana adicija metanola na acetonitril ili akrilonitril nije opažena.

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