Tetrahedron Letters No. 11, pp 949 - 952, 1978. Pergamon Press. Printed in Great Britain.

A COMPARISON OF LEAVING-GROUP ABILITIES IN REACTIONS OF POWERFUL METHYLATING AGENTS

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(Received in USA 2 December 1977; received in UK for publication 23 January 1978)

Methyl esters of very strong acids ("superacids") are commercially available for use as methylating agents. Also, more exotic esters of these acids are easily prepared and have found uses in solvolytic studies of otherwise unreactive substrates[1]. Several kinetic studies have been performed on methyl[2,3] and ethyl[4,5] trifluoromethanesulfonates and methyl[5] and ethyl[5,6] fluorosulfonates but these studies have been mainly concerned with establishing S_N2 character and with comparison of the leaving-group abilities with those for "conventional" alkylating agents There does not appear to have been any systematic investigation of their relative leaving-group abilities.

Since trifluoromethanesulfonic acid and fluorosulfonic acid have approximately equal acidities[7], one would expect a close similarity between the leaving-group abilities of their anions in reactions of esters. Also, in acetic acid, both acids are rather stronger than perchloric acid[7,8], suggesting (but not requiring) that the leaving-group abilities of their conjugate bases will be greater than for perchlorate. On the other hand, methyl perchlorate has been claimed[9,10] to be the most reactive of the methyl esters and, because of this conflict between prediction and claimed behavior, it has been included in this study. Methyl perchlorate is not commercially available and, indeed, it is a highly explosive and dangerous material which we have prepared[11] only as a solution in benzene, hexane, or dioxane.

Lewis and Vanderpool[3], under conditions where they were just able to measure approximately the fast S_N2 reaction rates with p-nitrophenoxide in sulfolane for methyl trifluoromethanesulfonate, found the Meerwein salt trimethyloxonium tetrafluoroborate to be too reactive for measurement by their spectroscopic technique. We have included the trimethyloxonium ion within our study in an attempt to obtain the first quantitative kinetic data for the relatively rapid nucleophilic substitution reactions of this substrate.

The four substrates, trimethyloxonium ion, methyl trifluoromethanesulfonate, methyl fluorosulfonate, and methyl perchlorate, have each been studied under four different reaction conditions: solvolysis in the protic solvents water and methanol, solvolysis in the aprotic solvent acetonitrile, to give the nitrilium ion[6,12] $(CH_3CNCH_3)^+$, and reaction with 0.015 to 0.15$\underline{M}$ tetra-n-butylammonium benzenesulfonate in acetonitrile to give methyl benzenesulfonate[2,13]. The solvolysis reactions were followed by quenching portions in acetone at -78°, or in acetone saturated with lithium chloride, and titrating against sodium methoxide in methanol to a Lacmoid (resorcinol blue) endpoint. Even at the lower end of the liquid temperature range for water, the hydrolysis of the trimethyloxonium ion was too fast for our titration technique. Data for the other eleven possible combinations of substrate and solvent are presented in Table I. The values reported in both Table I and Table II for the trimethyloxonium ion are experimental values without any statistical correction for three equivalent reaction sites within the substrate.

TABLE I

First-order Rate Coefficients for Solvolyses of Methyl Derivatives in Various Solvents.

Temp, °C	Substrate	Solvent	$10^5 k_1$, sec.$^{-1}$[a]
0.3	$MeOSO_2CF_3$	H_2O[b]	438[c]
0.3	$MeOSO_2F$	H_2O[b]	145
0.0	$MeOClO_3$	H_2O[b]	5.04[d]
0.3	$MeOSO_2CF_3$	MeOH[e]	311
0.3	$MeOSO_2F$	MeOH[f]	103
0.0	$MeOClO_3$	MeOH[g]	5.12[h]
-23.4	$Me_3O^+PF_6^-$	MeOH[i]	302
-23.4	$MeOSO_2CF_3$	MeOH[i]	24.8
-23.4	$MeOSO_2F$	MeOH[i]	8.06
-23.4	$MeOClO_3$	MeOH[j]	0.43[k]
0.3°	$Me_3O^+PF_6^-$	CH_3CN	7.26
0.3°	$Me_3O^+SbCl_6^-$	CH_3CN	7.23
-0.1°	$MeOSO_2CF_3$	CH_3CN	1.52[l]
0.0°	$MeOSO_2F$	CH_3CN	0.575
0.3°	$MeOClO_3$	CH_3CN[e]	0.0667[m]

[a] Each run was performed, at least, in duplicate; standard deviations were in the range of 1 to 4% for the slower runs and ranged up to 8% for some of the faster runs. [b] Containing 2% dioxane. [c] With 2% CH_3CN replacing the 2% dioxane, a value of 374 x 10^{-5}sec.$^{-1}$ was obtained. [d] From ref. 14. [e] Containing 2% hexane. [f] Containing either 2% benzene or 2% p-dioxane (same value for k_1 obtained). [g] Containing 2% cyclohexane. [h] From ref. 15. [i] Containing 2% CH_3CN. [j] Containing 2% benzene. [k] By extrapolation of data from ref. 11. [l] From ref. 13. [m] With 4% and 6% hexane, values for k_1 are 0.0619 x 10^{-5} and 0.0610 x 10^{-5}sec.$^{-1}$, respectively.

The nucleophilic substitution reaction with benzenesulfonate anion was analyzed several minutes after addition of portions to methanol at room temperature; unchanged substrate produced acid and the product (at least 10^3 times less reactive) was essentially unchanged. The results are presented in Table II.

For all four nucleophilic substitution reactions, the ordering of the reactivities is identical: $Me_3O^+ > MeOSO_2CF_3 > MeOSO_2F > MeOClO_3$. The reactivities, relative to methyl perchlorate, are as follows:

(i) in water at 0°, (too fast for measurement): 87:29:1.0.

(ii) in methanol at -23.4°, 700:58:19:1.0.

(iii) in acetonitrile at 0°, 109:23:8.6:1.0.

(iv) in acetonitrile containing benzenesulfonate at 0°, fast: 17:6.9:1.0 and, for 0.0170 M tetra-n-butylammonium benzenesulfonate at -23.4; Me_3O^+ reacts 11.3 times as rapidly as $MeOSO_2CF_3$.

TABLE II

Second - order Rate Coefficients for the Reactions of Tetra-n-butylammonium Benzenesulfonate with Methyl Derivatives in Acetonitrile.

Temp, °C	Substrate	10^3k_2, $M^{-1}sec^{-1}$ [a]
-0.1°	$MeOSO_2CF_3$	85.7[b]
0.3°	$MeOSO_2F$	35.0
0.3°	$MeOClO_3$	5.08[c]
-23.4°	$Me_3O^+PF_6^-$	77.1[d]
-23.6°	$MeOSO_2CF_3$	6.81[b]

[a] All runs performed at least in duplicate and standard deviations within the range of 1-4% of value. [b] From ref. 13. [c] Solvent contains 2% hexane; with 4% and 6% hexane, values are 5.15×10^{-3} and $5.35 \times 10^{-3} M^{-1} sec^{-1}$, respectively. [d] The value varies with the initial tetra-n-butylammonium benzenesulfonate concentration and is reported for a 0.0170 M initial concentration.

As observed qualitatively by Lewis and Vanderpool[3], the Meerwein salt is more reactive than the trifluoromethanesulfonate ester but our quantitative data show that the rate difference is not very large. Indeed, for all four reactions studied, throughout our series of powerful methylating agents the overall difference in relative reactivities is less than 10^3 and for the three commercially available reagents the rate variation is less than by a factor of 40. Contrary to the statements of Koskikallio[9] and Robertson, Annesa, and Scott[10] and consistent with predictions based upon the relative acidities of the parent acids[7,8], the perchlorate ester has been found to be less reactive than either the trifluoromethanesulfonate ester or the fluorosulfonate ester.

When a nucleophilic substitution reaction of a neutral substrate is transferred from a protic to an aprotic solvent, there is usually a magnification of leaving-group effects[16,17]. In the present case, the opposite effect is observed. A magnification is normally observed because the better leaving groups are usually also those better able to internally disperse the developing negative charge and these, in turn, will be less influenced by any reduction in the charge dispersal through external solvation. Although perchlorate is the poorer leaving group it is, with the four equivalent oxygens in the fully developed anion, probably the best of the three anionic leaving groups in terms of dispersing the developing charge and solvolysis of its esters will be handicapped less than those of trifluoromethanesulfonate or fluorosulfonate on transfer from water or methanol to acetonitrile.

The results have implications for synthetic scale methylations. Clearly, nothing would be gained by use of the non-commercially available and explosive methyl perchlorate and, on the other hand, even without statistical correction for three equivalent methyl groups, the trimethyloxonium ion was found to be only 5 to 12 times more reactive than methyl trifluoromethanesulfonate. Since low solubility is often a problem when Meerwein salts are used, the trifluormethanesulfonate or the somewhat less reactive, but also less expensive, fluorosulfonate ("Magic Methyl") may well be the reagent of choice for a relatively difficult methylation.

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