417. *Acylation Reactions catalysed by Strong Acids. Part II. "Acetyl Perchlorate" as a C-Acetylating Agent.*

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"Acetyl perchlorate," prepared *in situ* from silver perchlorate and acetyl chloride, is an effective acetylating agent and will convert anisole, in the absence of added solvent, into *p*-methoxyacetophenone in approximately 70% yield. The effect of adding acetic acid or acetic anhydride or both to the reaction mixture is studied in detail. The results support the view that Ac^+ and Ac_2OH^+ are both acetylating agents, the former being much the more reactive. The dehydration of the ion $AcOH_2^+$ is discussed briefly.

In Part I (J., 1950, 1203) we showed that solutions of concentrated aqueous perchloric acid in an excess of acetic anhydride contain acetylium (Ac^+) and probably acetic anhydridium (Ac_2OH^+) ions, or both, because of the occurrence of the reactions

$$H^+ + Ac_2O \rightleftharpoons Ac_2OH^+ \rightleftharpoons Ac^+ + AcOH \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

or

$$AcOH_2^+ + Ac_2O \rightleftharpoons Ac_2OH^+ + AcOH \rightleftharpoons Ac^+ + 2AcOH \quad . \quad . \quad . \quad . \quad (1b)$$

We were unable to prove conclusively whether the acetylium ion was the sole reactive species for acetylation: in fact, some qualitative evidence was advanced to support the view that both ions are active agents but that acetylium was more reactive than acetic anhydridium. In order to attempt to clarify this point we decided to investigate the use of "acetyl perchlorate" as a *C*-acetylating agent. It has been shown by Mackenzie and Winter (*Trans. Faraday Soc.*, 1948, **44**, 159, 171, 243) that "acetyl perchlorate" (acetylium perchlorate), $AcClO_4$, prepared from equimolecular amounts of silver perchlorate and acetyl chloride in acetic anhydride, is an effective catalyst for the Thiele acetylation reaction, and also for *O*-acetylation (Winter, private communication). Acetylium perchlorate was shown (*loc. cit.*) to be a "strong acid" in acetic anhydride solution, indicating the dissociation, $AcClO_4 \rightleftharpoons Ac^+ + ClO_4^-$ It was essential for our purpose to avoid, in the first place, the use of acetic anhydride since the subsequent addition of any substance capable of being acetylated would result in the formation of hydrogen ions which would clearly then undergo reaction (1*a*).

Since anhydrous silver perchlorate is freely soluble in anisole we first investigated the reaction between acetylium perchlorate and the ether alone, by adding 1 mol. of acetyl chloride to a solution of 1 mol. of the silver salt in 4 mols. of anisole. After 45 minutes (or 2 hours) at 0—5° we were able (Expt. *A*) to isolate approximately 0·7 mol. of *p*-methoxyacetophenone and to recover approximately 2·9 mols. of unchanged anisole. This result would appear at first sight to be rather surprising since anisole has a low dielectric constant, and the acetylium perchlorate prepared *in situ* would consequently not be expected to be dissociated to any appreciable extent. The production of the relatively large amount of ketone would indicate however that acetylium perchlorate is largely ionised, *i.e.*, the ion pair ($Ac^+ClO_4^-$), as distinct from being dissociated into the two ions Ac^+ and ClO_4^-. We expected therefore that if the reaction was carried out under otherwise identical conditions but in presence of a suitable amount of nitromethane,* the increased dielectric constant of the mixture would lead to an increased yield of ketone, presumably because of the increased rate of reaction; we were able to isolate at least 0·84 mol. (Expt. *B*) of *p*-methoxyacetophenone.

The effect of adding acetic acid to the original reaction mixture appeared to be the logical sequence. The yield of *p*-methoxyacetophenone remained constant (0·68 ± 0·04 mol.) in the presence of up to and including 6 mols. of acetic acid per mol. of acetylium perchlorate but showed a small decrease to 0·54 mol. when 8 mols. were added. In no case was the yield materially altered by the addition of nitromethane in such a quantity as to give a reaction mixture of approximately the same dielectric constant in comparable experiments, although generally the yields in the presence of nitromethane did tend to be very slightly higher. We do not attach undue importance to this particular observation except to emphasise that in the absence of acetic acid, the increase in yield in the presence of nitromethane was beyond the limitations of our experimental procedure. We feel justified in concluding that the results indicate the probable occurrence of the equilibrium $(Ac^+ClO_4^-) + AcOH \rightleftharpoons (Ac_2OH^+ClO_4^-)$, and that this tends to lie to the right when a relatively large amount of acetic acid is present in the reaction mixture. Furthermore, it would thus appear that acetic anhydridium perchlorate is relatively stable but is not as active as acetylium perchlorate. We are forced to this conclusion because of the experimental results when using added nitromethane, since if acetylium ions had a separate existence in acetic acid–nitromethane solution, we can see no reason why, under these conditions, the yield of ketone should not have increased in the same way as in the absence of any acid.

When the reaction between acetylium perchlorate (1 mol.) and anisole (4 mols.) was carried out in the presence of acetic anhydride (3 mols.) under otherwise identical conditions (Expt. 1), we obtained, as expected, an entirely different result. The yield of *p*-methoxyacetophenone was increased from approximately 0·7 mol. to approximately 1·6 mols. and thus exceeded that stoicheiometrically possible on the acetylium perchlorate used. This result proves conclusively that the reaction, $PhOMe + Ac^+ \longrightarrow OMe\cdot C_6H_4\cdot COMe + H^+$, is followed by reaction (1*a*) (above). The yield of ketone was unaltered by addition of 2 mols. of acetic acid (Expt. 2), but in this series of experiments we found that addition of nitromethane caused, in this particular case (Expt. 4), a marked increase in the yield of ketone to approximately 1·9 mols., thus indicating quite clearly that if the reaction, $Ac^+ + AcOH \longrightarrow Ac_2OH^+$, does occur to any appreciable extent then the acetic anhydridium ion is also capable of converting anisole into *p*-methoxyacetophenone. The reaction $Ac_2OH^+ + PhOMe \longrightarrow OMe\cdot C_6H_4\cdot COMe + AcOH_2^+$, would thus be followed by reaction (1*b*) (above).

Increasing the amount of acetic acid to 12 mols. (Expts. 5—7, 9, 10) resulted in the steady diminution in the yield of ketone to approximately 0·8 mol., thus affording a clear indication that acetylium ions do react with acetic acid to give the much less reactive, but nevertheless still active, acetic anhydridium ions. We should point out, however, that in these experiments the dielectric constant of the reaction mixture was steadily reduced by the increasing amount of acetic acid, and we fully expected that since acetic anhydride was present in this series of experiments as distinct from our first series, the yield of ketone would be influenced by added nitromethane. Comparison of Expts. 7 and 8 (as well as 2 and 4) shows quite clearly that such is the case : the yield of ketone being increased by at least 25%.

An alternative explanation is that the equilibria in reactions (1*a*) and (1*b*) lie well to the right and that the effect of added acetic acid is to *inactivate* some of the acetylium ions as acetic

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* We have also used methyl cyanide as a diluent with very similar results : nitromethane is however a much more satisfactory solvent.

anhydridium ions. The result of adding nitromethane would thus be to favour the dissociation, $Ac_2OH^+ \longrightarrow Ac^+ + AcOH$. We suggest however that the results in acetic acid alone do not support this alternative explanation.

Except where stated otherwise 0·05 g.-mol. of silver perchlorate was dissolved in anisole (0·2 g.-mol.), and acetic anhydride (0·15 g.-mol.), acetic acid (amount in g.-mol. given in column 2), and acetyl chloride (0·05 g.-mol.) added dropwise with shaking. All the experiments were carried out at 0—5°, and the mixture was kept for 45 minutes. In the experiments (*B*, 4, 8) carried out with nitromethane as solvent the amount used was always twice the combined weights of anisole, acetic anhydride, and acetic acid. Expts. *A* and *B*, included for comparison, are those in which *neither* acetic acid *nor* acetic anhydride was present.

Expt.	AcOH present, g.-mol.	$MeO{\cdot}C_6H_4{\cdot}COMe$ isolated, g.-mol.	PhOMe recovered, g.-mol.	Residue from distillation,* g.	Remarks.
A.	0	0·034	0·144	0·3	
B.	0	0·042	—	0·2	$MeNO_2$ added.
1.	0	0·079	0·09	1·0	
2.	0·1	0·08	0·1	0·2	
3.	0·1	0·073	0·1	0·1	PhOMe added last.
4.	0·1	0·093	—	0·4	$MeNO_2$ added.
5.	0·2	0·069	0·1	0·4	
6.	0·3	0·059	0·12	0·3	
7.	0·4	0·051	0·12	0·1	
8.	0·4	0·063	—	0·4	$MeNO_2$ added.
9.	0·5	0·048	0·13	0·2	
10.	0·6	0·039	0·133	0·3	

* The residue consists largely of *p*-methoxyacetophenone which was identified as the 2 : 4-dinitrophenylhydrazone.

In Part I (*loc. cit.*) we did not study the effect of added nitromethane on the activity of the acetic anhydride–aqueous perchloric acid mixtures. We now show that, in accordance with expectation, the yield of *p*-methoxyacetophenone obtained from anisole is increased to much the same extent as in the experiments using acetylium perchlorate. We have also compared mixtures of the same composition prepared with either 72% perchloric acid or acetyl chloride–silver perchlorate, the only difference being that the latter mixture contains suspended silver chloride, and we find as expected, that the amount of acetylation is the same irrespective of the method of preparation. In these experiments, we had necessarily—for reasons discussed fully in Part I—to add the anisole to the solution containing acetylium. We first investigated (Expt. 3) the effect of this mode of addition : the yield of ketone was not quite as good as in Expts. 1 and 2 but showed clearly the increase over the stoicheiometric amount.

We wish to emphasise that the yields of *p*-methoxyacetophenone quoted throughout this paper and Part I (*loc. cit.*) were those actually isolated. When we isolated the ketone from artificial mixtures with anisole by using the same experimental technique, we could recover 90% of the ketone. We do not think it worth while to apply a correction of approximately 10% to our quoted yields, but it is clear that the actual yields are in excess of those given.

We also showed in Part I that a reagent containing only acetic and perchloric acids is not an acetylating agent. We decided to study the possibility of dehydrating the acetic acidium ion to the acetylium ion. For this purpose we treated the reagent in the cold with phosphoric oxide, and then with anisole at room temperature. In spite of the fact that the reaction mixture was heterogeneous, we had no difficulty in isolating 15% of *p*-methoxyacetophenone. We suggest that the reaction involved is :

$$AcOH_2^+ + P_2O_5 \longrightarrow Ac^+ + 2HPO_3$$

rather than the sequence

$$2AcOH + P_2O_5 \longrightarrow Ac_2O + 2HPO_3;\quad Ac_2O + HClO_4 \longrightarrow Ac^+ + ClO_4^- + AcOH.$$

We have also discovered that when a little 72% perchloric acid is added to an excess of acetic anhydride, and the mixture kept at room temperature, the resulting acetylium ions acetylate the mixture of acetic anhydride and acid (produced in the original reaction) since a positive iodoform reaction can be obtained after 1 hour. We have not yet been able to identify the crystalline reaction product which separates from such mixtures in small amount, but it must clearly contain the group $CH_3{\cdot}CO{\cdot}C{\lessdot}$. The same reaction occurs more slowly at 0°. We have also shown that acetylium perchlorate will react rapidly (within 10 minutes) with acetic anhydride to give presumably the same compound but that reaction with acetic acid does not occur within 18 hours at room temperature : addition of acetic anhydride to the mixture results in the rapid production of the iodoform-producing substance.

EXPERIMENTAL.

Materials.—Acetyl chloride and acetic anhydride were AnalaR reagents. Acetic acid was purified by Orton and Bradfield's method (*J.*, 1924, 960). Anisole, nitromethane, and methyl cyanide were all dried and redistilled. Silver perchlorate was dried over phosphoric oxide in a vacuum desiccator containing also a dish of solid potassium hydroxide : it was not used in any experiment until a perfectly clear solution in benzene was obtained. To ensure that no absorption of water occurred during the weighing of the salt, the required amount was left in the reaction flask in the desiccator for at least 24 hours and then re-weighed before use.

Experiments in Absence and Presence of Acetic Acid.—Acetyl chloride (0·025 g.-mol.) alone or a solution in the appropriate amount of glacial acetic acid was added over a period of 15—17 minutes to a cooled solution of silver perchlorate (0·025 g.-mol.) in anisole (0·1 g.-mol.) so that the temperature remained between 0° and 5°. In those cases where nitromethane (or methyl cyanide) was used (see Table and Introduction) this was mixed with the silver perchlorate solution. The reaction mixture was kept at 0—5° for 45 minutes after the addition of all the acetyl chloride and was then poured on ice.

In all the above and subsequent experiments the customary precautions for the exclusion of moisture were taken.

Experiments in Presence of Acetic Anhydride.—Silver perchlorate (0·05 g.-mol.) was dissolved in a mixture of acetic anhydride (0·15 g.-mol.) and anisole (0·2 g.-mol.), and the appropriate amount of glacial acetic acid was then added. In experiments where nitromethane (or methyl cyanide) was used, the above solution was diluted further with the appropriate amount (see Table). After the solution had cooled to 0°, acetyl chloride (0·05 g.-mol.) was added dropwise with shaking, over a period of 15—20 minutes so that the temperature remained between 0° and 5°. Frequently on complete addition of the acetyl chloride the temperature rose uncontrollably to *ca.* 8°, especially in the more concentrated mixtures, where efficient mixing of the stiff paste was difficult. After being kept for a further 45 minutes at 0—5° the reaction mixture was poured on crushed ice (150—200 g.), this stage being marked by a transient violet coloration of varying intensity.

Isolation of p-*Methoxyacetophenone.*—In both the above procedures the silver chloride in the reaction mixtures was dissolved by the cautious addition of the minimum amount of aqueous ammonia (*d* 0·88), and the residual oil extracted with ether. The ethereal extract was washed with dilute (2N.) ammonia solution and then twice with water. The dried (Na_2SO_4) extract was then evaporated and the residue fractionated at about 4 mm., whereby a good separation of the ketone, b. p. 110—115°/3·8 mm., from unchanged anisole was obtained. The ketone solidified on cooling and was frequently identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 223°.

Synthetic mixtures of *p*-methoxyacetophenone and anisole were submitted to the same treatment. The recovery of ketone was never less than 90% and occasionally was as high as 93%.

Comparison of Acetylium Perchlorate and Perchloric Acid–Acetic Anhydride Mixtures.—(*a*) A mixture of acetic anhydride (0·155 g.- mol.) and nitromethane (53·0 g.) was cooled to below 0° and 72% perchloric acid (3·5 g. ≡ 0·025 g.-mol. of $HClO_4$) added over a period of 18 minutes so that the temperature remained between 0° and 5°. Anisole (0·1 g.- mol.) was then added during 3 minutes and the mixture kept at 0—5° for a further 45 minutes. The deep orange-red reaction mixture was poured on crushed ice (*ca.* 150 g.), and the resulting oil extracted with ether. The ethereal solution was washed twice with dilute ammonia solution (2N.) and twice with water, and was then dried (Na_2SO_4). Distillation (as above) gave *p*-methoxyacetophenone (5·2 g. ≡ 0·035 g.-mol.), identified as the 2 : 4-dinitrophenylhydrazone.

(*b*) Silver perchlorate (0·025 g.-mol.) was dissolved in a mixture of acetic anhydride (0·075 g.-mol.) and nitromethane (53·0 g.), and the solution cooled to below 0°. Glacial acetic acid (0·135 g.-mol.) mixed with acetyl chloride (0·025 g.-mol.) was added during 17—18 minutes, the temperature being kept between 0° and 5°. Anisole (0·1 g.-mol.) was then added (3—4 minutes) and the mixture kept for 45 minutes at 0—5° before being poured on crushed ice. *p*-Methoxyacetophenone (5·3 g. ≡ 0·035 g.-mol.) was isolated as described above.

Dehydration of Acetic Acidium with Phosphorus Pentoxide.—72% Perchloric acid (7·0 g. ≡ 0·05 g.-mol. of $HClO_4$) was cautiously added to acetic anhydride (0·11 g.-mol.) so that the temperature did not exceed 35°. The solution was cooled to 0° and phosphoric oxide (0·05 g.-mol.) was added gradually with constant shaking followed by anisole (0·1 g.-mol.), so that the temperature remained between −2° and 1°. The colourless mixture was kept at 0° for 45 minutes and then allowed to warm to room temperature whereupon it developed a pink colour. After 22—23 hours the mixture consisted of two layers, a deep orange-red liquid (*A*) and a brownish, glassy lower layer (*B*). The liquid (*A*) was poured on crushed ice and the material (*B*) was shaken with crushed ice until decomposed whereby an oil separated. The combined oily products were extracted with ether, a small amount of tarry material separating at this stage. After the ethereal solution had been washed with sodium carbonate, sodium hydroxide, and with water, it was dried (Na_2SO_4) and evaporated. Fractionation of the residue gave anisole (0·058 g.-mol.) and *p*-methoxyacetophenone (2·3 g. ≡ 0·015 g.-mol.), m. p. 34—37°, together with non-distillable material (1·1 g.).

Acetylation of Acetic Anhydride by Acetylium.—(*a*) 72% Perchloric acid (1 c.c.) was added to acetic anhydride (100 c.c.) and the mixture left at room temperature. The mixture soon became brown and after four days stout needles began to separate.

Such solutions gave a positive iodoform reaction when sodium hydroxide was used in the cold after 30 minutes. The development of colour was retarded by addition of acetic acid.

(*b*) Acetyl chloride (1·0 g.) was added to silver perchlorate (2·6 g.) dissolved in acetic anhydride (25 c.c.). The mixture rapidly became coloured and a positive iodoform reaction was obtained within 10 minutes. Crystalline material separated slowly from the solution. The same phenomenon has been observed by Winter (private communication).

(*c*) Acetyl chloride (1·0 g.) was added to silver perchlorate (2·6 g.) dissolved in glacial acetic acid (25 c.c.). The mixture remained colourless during the subsequent 21—22 hours and did not give an iodoform reaction. Addition of acetic anhydride (10 c.c.) to the mixture caused a faint positive iodoform reaction to be obtained after 30 minutes.

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