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A REVISED MECHANISM FOR THIRD ORDER ALCOHOLYSES OF ACID CHLORIDES IN APROTIC SOLVENTS

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It has recently been shown[1] that reactions of alkyl chloroformates with silver nitrate in acetonitrile proceed with either a rate limiting nucleophilic attack (the rate also being influenced by the partitioning of the intermediate to reactants or products) or a rate determining electrophilic assistance but not both simultaneously. This is in contrast to the reactions of alkyl halides under identical conditions, where there is strong evidence for simultaneous nucleophilic and electrophilic action.[2,3]

Since, under good conditions for simultaneous nucleophilic and electrophilic action, at least one reaction at an acyl carbon is not subject to both influences, we were led to question whether the kinetic term of second order in alcohol observed in several third order alcoholyses of acid chlorides in aprotic solvents is really due to simultaneous nucleophilic and electrophilic attack, as has been generally believed.[4,5]

We chose as our initial system the methanolysis of p-nitrobenzoyl chloride in acetonitrile. Acetonitrile was chosen as solvent since good purification techniques are available,[6] and for good reproducibility at low (>0.01M) methanol concentrations, high purity of both reactants and solvent was found to be an essential prerequisite.

The extent of reaction could be conveniently determined by sampling from bulk and titration (in cold acetone) of the acid developed against standard triethylamine in toluene using resorcinol blue as indicator:

$$\underline{p}\text{-}NO_2C_6H_4COCl + MeOH \longrightarrow \underline{p}\text{-}NO_2C_6H_4COOMe + HCl$$

For concentrations of methanol below 1 M the rate of reaction (in M sec^{-1}) followed the rate law: $10^4 \frac{d[HCl]}{dt} = 0.41[PNBC][MeOH] + 3.31[PNBC][MeOH]^2$, where $[PNBC] = [p\text{-}NO_2C_6H_4COCl]$. Above 1 M in methanol the observed rates are slightly higher than those predicted from the above equation. This may be due to a minor incursion of terms of higher order than two in methanol but it probably merely reflects that, at the higher methanol concentrations, the reaction can be considered as a solvolysis in a mixed solvent of varying composition rather than as a simple methanolysis with acetonitrile as solvent.

TABLE I

Initial second order rate coefficients, $k_2(\underline{M}^{-1}\ sec^{-1})$, for methanolysis of p-nitrobenzoyl chloride in acetonitrile at 25.0°.

[MeOH]:	0.01	0.02	0.04	0.08	0.16	0.32	0.64	0.96	1.28	1.60
10^4k_2:	0.51	0.49	0.55	0.63	0.93	1.48	2.55	3.91	5.19	6.17

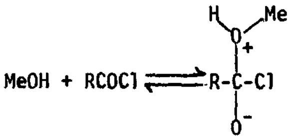
One approach to investigating the role of the second methanol molecule in the kinetic term of second order in methanol is to add phenol to the reaction. Although suggested by Gould several years ago[4], this approach has apparently not been attempted. Since phenol is considerably more acidic in character than methanol, it will be extremely efficient in an electrophilic capacity but poor in a nucleophilic capacity; for example, phenols have been shown to be much more efficient than alcohols for electrophilic promotion of reactions of *tert.*-butyl bromide in nitromethane.[7] Indeed, phenol alone was found to react very slowly with p-nitrobenzoyl chloride in acetonitrile; $k_2 \sim 20 \times 10^{-8}\ \underline{M}^{-1}\ sec^{-1}$ at 25.0°, for [PhOH] in the range 0.6 to 1.2 M. Mixtures of phenol and methanol were found to react with p-nitrobenzoyl chloride at essentially the same rate as the corresponding methanolysis in the absence of phenol.

TABLE II

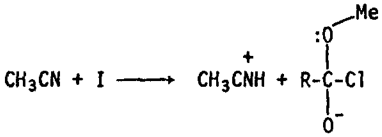
Initial second order rate coefficients, $k_2(\underline{M}^{-1}\ sec^{-1})$, for methanolysis of p-nitrobenzoyl chloride in acetonitrile at 25.0° in the presence of phenol.

[MeOH]:	0.02	0.02	0.02	0.02	0.02	0.02	0.32	0.32	0.32
[PhOH]:	0.00	0.014	0.028	0.056	0.16	0.64	0.00	0.32	0.64
10^4k_2 :	0.49	0.59	0.61	0.63	0.59	0.62	1.48	1.33	1.59

The lack of catalysis by added phenol argues strongly against any representation of the mechanism which involves electrophilic assistance to chloride ion removal by hydroxylic addenda. An attractive alternate formulation involves nucleophilic attack by a methanol molecule to give an intermediate I followed by proton removal from I to give a new intermediate II with either a solvent molecule (overall second order kinetics) or a second methanol molecule (overall third order kinetics) acting as the base.

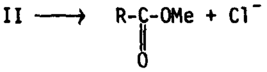
(1)  (I)

$$\mathrm{MeOH} + \mathrm{RCOCl} \rightleftharpoons \mathrm{R{-}C(Cl)(O^-)(\overset{+}{O}(H)Me)} \quad \text{(I)}$$

(2a)  (II)

$$\mathrm{CH_3CN} + \mathrm{I} \longrightarrow \mathrm{CH_3C\overset{+}{N}H} + \mathrm{R{-}C(Cl)(O^-)(:OMe)} \quad \text{(II)}$$

(2b) $\mathrm{MeOH} + \mathrm{I} \longrightarrow \mathrm{Me\overset{+}{O}H_2} + \mathrm{II}$

(3) 

$$\mathrm{II} \longrightarrow \mathrm{R{-}C({=}O){-}OMe} + \mathrm{Cl^-}$$

Regeneration of the carbonyl group from I will lead preferentially to loss of methanol rather than chloride and a collapse to reactants rather than products. After proton abstraction, the group lost on regeneration of the carbonyl group is chloride rather than methoxide and collapse will now lead to products rather than reactants. Proton loss from I, to give II, constitutes an essential step in the mechanism leading to ester formation.

If our theory is correct, other bases should also be capable of accelerating the reaction and to an extent determined by their ability to abstract a proton from I. Unfortunately, addenda of this type will also, in competition with the methanol, interact at the acyl carbon. There is however one base which can be used; the chloride ion, although it will react rapidly at the acyl carbon, will merely regenerate the original p-nitrobenzoyl chloride by a symmetrical exchange. Chloride ion was added as tetraethylammonium chloride and a tremendous acceleration of the reaction was observed, presumably due to the introduction of a new path for proton removal from I.

(2c) $\mathrm{Cl^-} + \mathrm{I} \longrightarrow \mathrm{HCl} + \mathrm{II}$

As reaction progressed the catalysis was inhibited due to complexing of the chloride ion by the developing hydrogen chloride to give the hydrogen dichloride anion:

$$\mathrm{HCl} + \mathrm{Cl^-} \rightleftharpoons \mathrm{HCl_2^-}$$

TABLE III

Initial second order, k_2($\underline{M}^{-1}$ sec^{-1}), and third order, k_3($\underline{M}^{-2}$ sec^{-1}), rate coefficients for the reaction of 0.02 $\underline{M}$ methanol with 0.04 $\underline{M}$ $\underline{p}$-nitrobenzoyl chloride in acetonitrile at 0.0° in the presence of tetraethylammonium chloride.

$[NEt_4Cl]$:	0.000	0.0135	0.019	0.027	0.039	0.052	0.065	0.135	0.162
10^3k_2 :	0.009	14	18	25	36	53	67	118	146
k_3^a :		1.04	0.95	0.93	0.92	1.02	1.03	0.87	0.90

a $\frac{d[HCl]}{dt} = k_3[PNBC][MeOH][NEt_4Cl]$.

The rate of acid production from 0.04 $\underline{M}$ $\underline{p}$-nitrobenzoyl chloride in its reaction with 0.02 $\underline{M}$ methanol at 0.0° is increased by 15,000 fold upon the addition of 0.16 $\underline{M}$ tetraethylammonium chloride. The constant values for the third order rate coefficients (table III) indicate, even for such large accelerations, the absence of any approach towards a limiting rate; this requires that formation of I be a facile process, with the overall rate severely restricted by I almost always reverting to reactants and, especially in the absence of tetraethylammonium chloride, only very occasionally does I undergo conversion to II and hence to products.

That the acceleration does indeed involve a specific role for the chloride ion and not just a very powerful salt effect was shown by adding tetraethylammonium perchlorate, a salt containing an extremely weakly basic anion, as a substitute for the corresponding chloride salt. The methanolysis rates were essentially unaffected by concentrations of tetraethylammonium perchlorate of up to 0.16 $\underline{M}$.

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