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IS 1-ACETYL-4-DIMETHYLAMINOPYRIDINIUM ACETATE AN INTERMEDIATE IN THE DMAP-CATALYZED ACETYLATION OF TERTIARY ALCOHOLS ?

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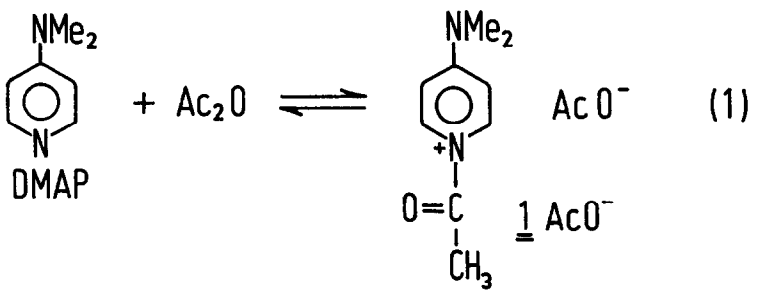
4-Dimethylaminopyridine (DMAP) is a very efficient acylation catalyst (1-3) particularly for the acetylation of tertiary alcohols (1,3,4). The reaction has been interpreted by the formation of 1-acetyl pyridinium intermediate (3,4,5) and very recently Höfle has found evidence for the presence of the 1-acetyl-4-dimethylaminopyridinium acetate ion pair in solution (3). This prompts us to report our own results on the mechanism of the reaction of acetic anhydride with tertbutanol in the presence of DMAP.

Since 1970 we have isolated a series of 1-acyl-4-dimethylaminopyridinium salts (6a-e) and we purpose to compare their reactivities with the DMAP-catalyzed reactions.

At 20°C a solution of Ac_2O (0.5 M) and DMAP (10^{-3} M) in CH_2Cl_2 shows a absorption at 312 nm analogous to that observed in 1-acetyl-4-dimethylaminopyridinium chloride (6a) and corresponding to about 5 % de $\underline{1}$ AcO^-. This peak slowly decreases and a new peak appears at 282 nm at the same wavelenght that the acetate of 4-dimethylaminopyridinium.

The position of the equilibrium 1 depends on the polarity of the solvent.



Scheme 1

Addition of p-toluenesulfonic acid leads to the formation of tosylate $\underline{1}$ TsO^- which can be precipitated by addition of ether m.p. (decomp.) : 158-165°C. Evidence for the formation $\underline{1}$ AcO^- may also be obtained by ^{13}C NMR (7) of the solution of DMAP in Ac_2O (Table 1).

	Cα	Cβ	Cγ	CH_3-N	C=O
$\underline{1}$ AcO^-	145.20	116.29	-	49.17	176.26
$\underline{1}$ BF_4^-	145.79	116.40	126.44	49.69	176.16

Table 1

Similarly a weak amount of $\underline{1}$ AcO^- (also about 5 %) may be observed by UV in mixtures of Ac_2O, tBuOH and DMAP in CH_2Cl_2.

However the presence of $\underline{1}$ AcO^- in solution does not prove that it is an intermediate : it could have been formed in a steady state in a by-pass to the main mechanistic pathway and therefore be irrelevent to the mechanism.

This question is raised because we have observed that other 1-acetyl-4-dimethyl-aminopyridinium salts (the chloride, tosylate and fluoroborate (8)) do not react with tert-butanol in $CHCl_3$, CH_3CN or AcOEt.

Apart from the nucleophilic mechanism a general base catalysis, a concerted process or the formation of an preequilibrium (vide infra) may be considered. General base catalysis has been excluded because the more basic triethylamine does not catalyse the reaction (3,4).

A concerted synchronous process with the involvement of all the reactants in the transition state (9,10) may take into account the following facts (3,4) :

a - the acylation is faster in less polar solvents which do not favor the formation of products with a considerable separation of charges (11), (however see table 2),

b - acetyl chloride is not as effective as acetic anhydride in the catalyzed acetylation reaction (however it gives a large amount of $\underline{1}$ Cl^-) (12).

In general base catalysis and pure synchronous process the cleavage of the O-H bond is rate determining and both display direct kinetic isotopic effects (10).

By H^1 NMR we have measured the second order rate constants of the reaction of tBuOH or tBuOD with Ac_2O-DMAP in $CDCl_3$ and CD_2Cl_2 at 25°C (Table 2). In both solvents the isotopic effect $\frac{ktBuOH}{ktBuOD}$ is weak and inverse. Therefore the general

basic and the concerted synchronous mechanisms are excluded.

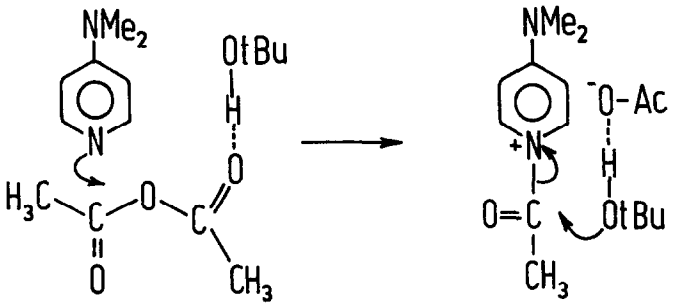
	δ $(\underline{CH_3})_3COH(D)$	δ $(\underline{CH_3})_3COAc$	ktBuOH [a]	ktBuOD [a]	$\frac{ktBuOH}{ktBuOD}$
$CDCl_3$	1.22	1.43	57.10^{-4}	70.10^{-4}	0.81 ± 0.2
CD_2Cl_2	1.23	1.43	29.10^{-3}	34.10^{-3}	0.84 ± 0.2

a : 1 $mole^{-1}$ min^{-1}

Table 2

We propose the following scheme :

$$tBuOH + Ac_2O \rightleftharpoons tBuOH \cdots Ac_2O \qquad (3)$$



Scheme 2

Rate determining nucleophilic attack of DMAP on a Ac_2O-tBuOH complex formed in a preequilibrium (13) gives an ion pair solvated by tBuOH. Then this alcohol which stays in the close vicinity reacts rapidly with the carbonyl of the acetylpyridinium ion to give the tert-butyl acetate (16).

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1 - L.M. LITVINENKO and A.I. KIRICHENKO. Dokl. Akad. Nauk SSSR, 1967, 176, 97.
2 - W. STEGLICH and G. HOFLE. Angew. Inter., 1969, 8, 981.
3 - G. HOFLE, W. STEGLICH and H. VORBRUGGEN. Angew. Inter., 1978, 17, 569.
4 - A. HASSNER, L.R. KREPSKI and V. ALEXANIAN. Tetrahedron, 1978, 34, 2069.

5 - K.A. CONNORS and K.S. ALBERT. J. Pharm. Sciences, 1973, 62, 845.

6a- M. WAKSELMAN and E. GUIBE-JAMPEL. Tetrahedron Letters, 1970, 1521 and 4715.

b- E. GUIBE-JAMPEL and M. WAKSELMAN. Bull. Soc. Chim. Fr., 1971, 2555.

c- M. WAKSELMAN and E. GUIBE-JAMPEL in : A. LOFFET "Peptides 1976", Editions de l'Université de Bruxelles, 1976, p. 131.

d- E. GUIBE-JAMPEL and M. WAKSELMAN. Synthesis, 1977, 772.

e- G. GUILLOT-EDELHEIT, M. LALOI-DIARD, E. GUIBE-JAMPEL and M. WAKSELMAN. J. Chem. Soc. Perkin II, in press.

7 - R. MATUSCH. Arch. Pharm., 1975, 308, 644.

8 - tBuOH do not react with 1-Boc-4-dimethylaminopyridinium fluoroborate (6d). $\underline{1} \equiv BF_4^-$ is prepared in situ from Ac_2O and DMAP, HBF_4.

9 - ex : C_6H_5COCl + MeOH + Et_3N in tetrachloroethylene (10a).

10a- S.V. BOGATKOV, Z.P. GOLOVINA and E.M. CHERKASOVA. Dokl. Akad. Nauk SSSR, 1976, 229, 98.

b- E.M. CHERKASOVA, S.V. BOGATKOV and Z.P. GOLOVINA. Russian Chem. Rev., 1977, 46, 246.

11 - T.G. BONNER and K. HILLIER. J. Chem. Soc. Perkin II, 1973, 1828.

12 - The solvent effect (a) has been explained by the collapse of the charged tetrahedral intermediate to non-charged products (4). The second result (b) has been interpreted by the difference of reactivity between tightly- (the chloride) and loosely-bound (the acetate) ion pair (3).

13 - Inverse isotopic effects are generally due to the formation of an equilibrium before the rate determining step (14). For long H-bonds deuterium substitution leads to a strenghening of the bond (15). Consequently the preequilibrium 3 way be slightly shifted to the right and the reaction go faster for tBuOD.

14 - P. LASLO and Z. WELVART. Bull. Soc. Chim. Fr., 1966, 2412.

15 - S.N. VINOGRADOV and R.H. LINNELL "Hydrogen bonding" Van Nostrand New York, 1971, p. 124.

16 - Primary and secondary alcohols are able to react with 1-acetyl-4dimethylaminopyridinium ions but the rates are slowler than in the DMAP-catalyzed reactions ; in these cases the acylation may occur by two competitive pathways. Anhydride may be generated in situ from the parent acid and DCC (17-19).

17 - S.S. WANG, C.C. YANG, I.D. KULESHA, M. SONENBERG and R.B. MERRIFIELD, Int. J. Pept. Protein Res. 1974, 6, 103.

18 - B. NEISES and W. STEGLICH, Angew Inter 1978, 17, 522.

19 - A. HASSNER and V. ALEXANIAN, Tetr. Lett. 1978, 4475.

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