Aromatic Acylation of Hydroxy Groups *via* the Rare S_N1 Reaction Pathway

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The unusual reactivity of anthracene-9-carbonyl chloride indicates its acylation of low concentrations of hydroxy groups in aprotic organic solvents to proceed *via* an S_N1 type mechanism.

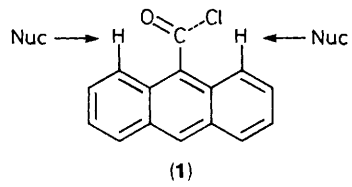
The mechanism of acylation of hydroxyls in solution has been a popular field of study.[1] Recent discussion[2,3] on the solvolysis of benzoyl halides in polar, protic, media has focussed on a continuous S_N1–S_N2 spectrum including mixed S_N2 synchronous and S_N2 addition–elimination (A–E) pathways. We report here the unusual kinetic properties exhibited by an aromatic acid chloride, anthracene-9-carbonyl chloride (**1**), during its evaluation as a fluorogenic reagent in the trace analysis of hydroxy compounds.[4]

The alcoholysis rate constants for (**1**) are three orders of magnitude greater than typical values reported for aromatic acid chlorides (Table 1). Amongst aroyl chlorides similar reactivities have only been reported by Bender and Chen[5] for 4-substituted 2,6-dimethylbenzoyl chlorides (**2**), whose hydrolyses under neutral and acidic conditions were proposed to proceed *via* an S_N1 mechanism with a highly labile, planar, acylium ion as intermediate.

Another unexpected phenomenon was the effect of tertiary organoamine bases on the reactivity of (**1**); preparation of esters in dichloromethane and chloroform was retarded by their use. Specifically, the derivatisation rate of diethylene glycol with (**1**) in acetonitrile was slowed more by the use of pyridine than triethylamine, and no reaction of (**1**) with butan-1-ol in dichloromethane was observed in the presence of the hypernucleophilic catalyst, 4-dimethylaminopyridine.

The organoamine bases act as nucleophilic catalysts[6] in S_N2 A–E reactions through the formation of a highly labile acyl–amine adduct (**3**); quantitative formation of the intermediates (**3a**) and (**3b**) in solution was observed by IR and ^1H and ^{13}C NMR spectroscopies. Similar adducts of (**1**) with triethylamine and pyridine were observed in solution by IR spectroscopy. Indeed (**3b**) was isolated and found to be remarkably stable in water with a half life of >10 h compared to 3.9 min reported[7] for the acetyl chloride analogue, (**3c**).

Spectroscopic data (UV, IR, ^1H and ^{13}C NMR) indicates the carbonyl group in (**1**) to be perpendicular to the anthracene ring and thus not conjugated with it (Figure 1). The adjacent peri-hydrogens are sterically responsible for this geometry, simple molecular models indicate these to block



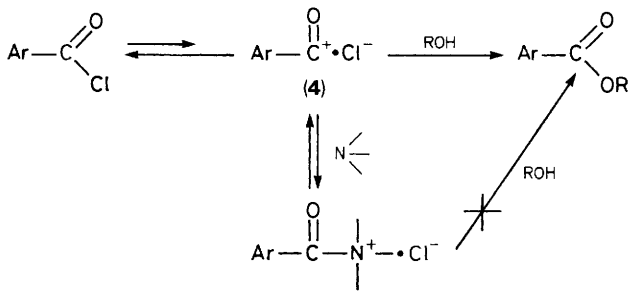
(**1**)

Figure 1. Steric hindrance to S_N2 attack on (**1**).

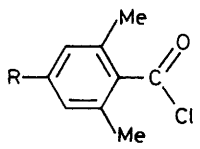
Table 1. Acylation rate constants in aprotic solvents.[a]

Acid chloride	Alcohol	Solvent	$10^4 \times k_2$ ($mol^{-1}\,s^{-1}\,dm^3$)
(**1**)	Methanol	CH_2Cl_2	300—900[b]
	Butan-1-ol	CH_2Cl_2	200
	Testosterone	CH_2Cl_2	85
	17α-methyl testosterone	CH_2Cl_2	27
	Diethylene glycol	MeCN	100—300[b]
Benzoyl	Butan-1-ol	CH_2Cl_2	0.069
	Butan-2-ol	CH_2Cl_2	0.023
4-Nitrobenzoyl	Testosterone	CH_2Cl_2	0.055
	Methanol	MeCN	0.41[c]
3,5-Dinitrobenzoyl	Butan-1-ol	Toluene	0.026[d]

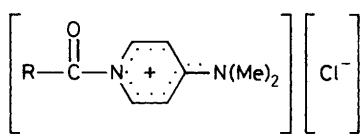
[a] Experimentally obtained at room temperature with analysis by HPLC (all except benzoyl chloride) or at 25 °C by GLC (benzoyl chloride) for, typically, submillimolar quantities of alcohols. [b] Reaction was too fast to follow accurately under these conditions of analysis. [c] From ref. 8. [d] From ref. 9.



Scheme 1. Acylium ion trapping by nucleophilic catalysts.



(**2**)**a**; R = H
b; R = Me
c; R = OMe



(**3**)**a**; R = 9-anthryl
b; R = 4-nitrophenyl
c; R = Me

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S_N2-type nucleophilic attack in a similar way to the adjacent methyl groups in (**2**). The S_N1 route is also favoured electronically as the planar acylium intermediate (**4**) is stabilised by conjugation not available to the parent acid chloride.

The behaviour of the supposed catalysts is consistent with an S_N1 mechanism for (**1**) because the reactive intermediate, (**4**), is captured in the formation of the acyl–ammonium adduct (Scheme 1). The greater the latter's stability the more acylium ion is trapped hence 4-dimethylaminopyridine is the most effective observed inhibitor of acylation by (**1**).

The major conclusion from the experimental evidence is that (**1**) reacts *via* an S_N1 pathway. The limited data on relative reactivities towards hydroxyls suggests (**1**) to be an even more extreme case than (**2**) of steric hindrance, changing both the mechanism and speed of acylation.‡

‡ The hydrolysis of (**2a**) is *ca.* 300 times faster than that of benzoyl chloride in 99:1 acetonitrile: water[5] while (**1**) acylates n-butanol *ca.* 3000 times faster than benzoyl chloride in dichloromethane.

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