## Aromatic Acylation of Hydroxy Groups via the Rare S<sub>N</sub>1 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  $S_N$ 1 type mechanism.

The mechanism of acylation of hydroxyls in solution has been a popular field of study.<sup>1</sup> Recent discussion<sup>2,3</sup> on the solvolysis of benzoyl halides in polar, protic, media has focussed on a continuous  $S_N 1-S_N 2$  spectrum including mixed  $S_N 2$  synchronous and  $S_N 2$  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.<sup>4</sup>

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<sup>5</sup> for 4-substituted 2,6-dimethylbenzoyl chlorides (2), whose hydrolyses under neutral and acidic conditions were proposed to proceed *via* an  $S_N$ 1 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<sup>6</sup> in  $S_N 2$ 



Figure 1. Steric hindrance to  $S_N 2$  attack on (1).



Scheme 1. Acylium ion trapping by nucleophilic catalysts.

<sup>+</sup> Correspondence address: Fisons plc, Pharmaceuticals Division, Research and Development Laboratories, Bakewell Road, Loughborough LE11 0RH, U.K. 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 <sup>1</sup>H and <sup>13</sup>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<sup>7</sup> for the acetyl chloride analogue, (3c).

Spectroscopic data (UV, IR, <sup>1</sup>H and <sup>13</sup>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

Table 1. Acylation rate constants in aprotic solvents.<sup>a</sup>

			$10^4 \times k_2$
Acid chloride	Alcohol	Solvent	$(mol^{-1}s^{-1}dm^3)$
(1)	Methanol	$CH_2Cl_2$	300900ь
	Butan-1-ol	$CH_2Cl_2$	200
	Testosterone	$CH_2Cl_2$	85
	17α-methyl testosterone	CH <sub>2</sub> Cl <sub>2</sub>	27
	Diethylene glycol	MeCN	100300 <sup>b</sup>
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	0.41c
3,5-Dinitrobenzoyl	Butan-1-ol	Toluene	0.026 <sup>d</sup>

<sup>a</sup> 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. <sup>b</sup> Reaction was too fast to follow accurately under these conditions of analysis. <sup>c</sup> From ref. 8. <sup>d</sup> From ref. 9.



 $S_N$ 2-type nucleophilic attack in a similar way to the adjacent methyl groups in (2). The  $S_N$ 1 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  $S_N$ 1 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  $S_N$ 1 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.‡

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