The Influence of Anchoring Substitution in 1,3-Amino Alcohols on the Rate and Mechanism of Esterification by Acetylimidazole and by *p*-Nitrophenyl Acetate

Ivan Steels,[a] Pierre J. De Clercq*[a] and Howard Maskill*[b]

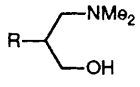
[a] *Department of Organic Chemistry, University of Gent, Krijgslaan, 281 (S.4), B-9000 Gent, Belgium*
[b] *University of Newcastle upon Tyne, Department of Chemistry, Newcastle upon Tyne NE1 7RU, UK*

Enforced intramolecular hydrogen bonding in 2-*tert*-butyl-3-(*N*,*N*-dimethylamino)propan-1-ol is shown by the competitive alcoholysis of *p*-nitrophenyl acetate and 1-acetylimidazole in acetonitrile, and by the corresponding second-order rate constants and activation parameters, to influence both the rate and the mechanism of catalysed acyl transfer.

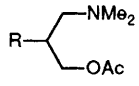
Recently, we have started to investigate the possibility of enforcing the proximity of the terminal functional groups in 1,3-disubstituted propane fragments by the incorporation in the 2-position of anchoring substituents, *e.g.* quaternary substituents such as a *tert*-butyl group.[1] Here, we focus on 1,3-disubstituted amino alcohols such as **1** in which intramolecular hydrogen bonding between the terminal groups may be enforced by the anchoring 2-substituent.

Concentration-dependent IR spectroscopic measurements in chloroform show the presence of an intramolecular hydrogen bond both in **1a** and in **1b**.† On the other hand, comparison of the ^{1}H NMR spectral data of **1a** and **1b** immediately reveals the rigid nature of the preferred geometry of the anchored derivative **1b**. Whereas the resonances of the geminal protons at C-1 and C-3 in **1a** show the expected triplets, the corresponding protons in **1b** are clearly different and behave as axial and equatorial protons in a six-membered chair conformation (Table 1). Of special diagnostic value is the occurrence of a long range W-type coupling between the 'equatorial' protons at C-1 and C-3.‡

In order to assess further the anchoring potential in **1b**, the reactivities of **1a** and **1b** in esterification by *p*-nitrophenyl acetate (PNPA) and 1-acetylimidazole (AcIm) are compared. Many studies have shown that the hydrolysis of PNPA, a reactive ester with a good leaving group, is catalysed by amino alcohols;[2] in several cases, reaction has been shown to occur by initial nucleophilic attack of the amine (Nuc) followed by fast acyl transfer to the alcohol moiety.[3,4] On the other hand, the amino alcohol catalysed hydrolysis of AcIm, a reactive amide possessing a much poorer leaving group, is always subject to general base catalysis (GBC).[3] However, one may expect the GBC pathway of an amino alcohol with an enforced intramolecular hydrogen bond to be facilitated and the Nuc pathway to be impeded.[5] These expectations are nicely corroborated by competition experiments in which equivalent

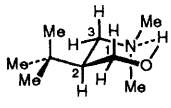


1a; R = H
b; R = CMe_3



2a; R = H
b; R = CMe_3

Table 1 ^{1}H NMR spectral data of **1b** in CD_3OD (500 MHz)

		H-1[a]			H-3[a]	
		(a)	(e)	H-2	(a)	(e)
	δ	3.64	3.84	1.61	2.56	2.47
	^2J/Hz	10.3	10.3	—	12.2	12.2
	^3J/Hz	9.2	3.8	—	12.2	2.8
	^4J/Hz	—	2.3	—	—	2.3

[a] Assignments as axial (a) and equatorial (e) on the basis of the intramolecular H-bonded chair geometry shown.

† Upon dilution to 0.02 mol dm^{-3}, disappearance of the peak at 3460 cm^{-1} (intermolecular H-bonded OH) is observed while the peaks at 3684 cm^{-1} (free OH) and at 3620 cm^{-1} (intramolecular H-bonded OH) remain.

‡ The same pattern is observed in [$^2H_6$]benzene, $CDCl_3$, $(CD_3)_2SO$ and CD_3OD.

Table 2 Activation enthalpies (kJ mol^{-1}) and entropies (J K^{-1} mol^{-1}) for the alcoholysis of PNPA and AcIm by **1a** and **1b** in acetonitrile[a]

	AcIm		PNPA	
	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
1a	28.7	−210	55.3	−138
1b	39.0	−170	44.7	−170

[a] Reactions performed with a large excess of **1** (towards PNPA and AcIm) in 0.05–0.30 mol dm^{-3} concentration range.

amounts of **1a** and **1b** react with AcIm and PNPA in acetonitrile at 24 °C.§ We found that for the alcoholysis of AcIm the ratio k**1b**/k**1a** = 4.0, whereas with PNPA the ratio k**1b**/k**1a** = 0.66.

Second-order rate constants were also measured for the esterification of **1a** and **1b** by PNPA and AcIm in acetonitrile at four different temperatures over a range of 30 °C, and the corresponding activation parameters were determined.[6] The results are shown in Table 2.

We take as our starting point the GBC mechanism for the reaction of **1a** with AcIm and consider the effect of the anchoring substituent. In this mechanism, the hydroxy proton, which is to some extent intramolecularly hydrogen bonded to the amino group, transfers fully as the oxygen bonds to the carbon of the carbonyl group. This bimolecular process, in which the formation of the nitrogen–hydrogen and oxygen–carbon bonds is coupled to the breaking of the oxygen–hydrogen bond and to a reduction in bond order of the carbonyl group, involves the development of an increasingly polar and hence more solvated state. As seen in Table 2, the low $\Delta H^{\ddagger}$ and substantially negative $\Delta S^{\ddagger}$ are fully in accord with this mechanism.

Compound **1b** has a more rigid structure with a stronger hydrogen bond enforced by the anchoring substituent. The proton, therefore, is already further along its trajectory for transfer in the GBC mechanism than in the corresponding reaction of **1a**; consequently, the gain in energy as the N–H bond develops further in the formation of the activated complex is smaller than from **1a**. Furthermore, the increase in polarity associated with the formation of the activated complex from the more strongly intramolecularly hydrogen bonded initial state and the attendant increase in solvation will be smaller from **1b** than from **1a**. Both changes would be expected to contribute to the larger $\Delta H^{\ddagger}$ and the latter effect accounts for the significantly less negative $\Delta S^{\ddagger}$ for **1b**. These appreciable differences between the activation parameters for the reactions of **1a** and **1b** with AcIm by a common mechanism have opposite and, interestingly, almost cancelling effect upon reactivity at normal temperatures.

The activation parameters for the reaction of substrate **1b** with the other acetylating agent, PNPA, in the same solvent are strikingly similar to those for its reaction with AcIm and suggest that this reaction also proceeds by GBC. However, comparison of the activation parameters for reaction with PNPA of **1a** with those of **1b** shows a trend opposite to the one in their reactions with AcIm. As seen in Table 2, compound **1a** now has a significantly less negative $\Delta S^{\ddagger}$ but larger $\Delta H^{\ddagger}$ than **1b**, and comparison with the values for reaction of **1a** with AcIm rules out a common mechanism. It appears, therefore, that the absence of the anchoring substituent in **1a**, and hence the weaker intramolecular hydrogen bond, allows **1a** to react with PNPA by nucleophile catalysis rather than GBC.

I. S. thanks the National Fund for Scientific Research (NFWO, Belgium) for a position as Research Assistant and the ERASMUS programme for a grant. The National Fund for Scientific Research (Belgium) is thanked for financial assistance to the laboratory and for a research grant (FKFO No. 2.0006.87). Financial help of the Belgian Ministry for Scientific Affairs is also gratefully acknowledged.

Received, 18th November 1992; Com. 2/06152J

§ The relative reactivities are taken as the ratio of the acylated derivatives as determined by ^{1}H NMR integration of CH_2OAc. Reactions (0.05 mol dm^{-3} concentration) were run to completion with **1a** : **1b** : acylating reagent 1 : 1 : 0.3 for AcIm and 1 : 1 : 0.1 for PNPA. The same ratios are observed after shorter reaction times (*ca.* 35% conversion) indicating true kinetic control.

References

1 F. A. J. De Corte and P. J. De Clercq, *Bull. Soc. Chim. Belg.*, 1988, **97**, 493; P. Missiaen and P. J. De Clercq, *Bull. Soc. Chim. Belg.*, 1988, **97**, 993; S. Cauwberghs, P. J. De Clercq, B. Tinant and J. P. Declercq, *Tetrahedron Lett.*, 1988, **29**, 2493.

2 K. I. Skorey, V. Somayaji and R. S. Brown, *J. Am. Chem. Soc.*, 1989, **111**, 1445; and references cited therein.

3 (*a*) L. Anoardi and U. Tonellato, *J. Chem. Soc., Chem. Commun.*, 1977, 401; (*b*) V. Somayaji, K. I. Skorey, R. S. Brown and R. G. Ball, *J. Org. Chem.*, 1986, **51**, 4866; (*c*) M. N. Khan, *J. Org. Chem.*, 1985, **50**, 4851.

4 Direct attack of nucleophilic oxygen *via* *N*,*O*-cooperativity has also been reported, see, *e.g.* (*a*) J. Hine and M. N. Khan, *J. Am. Chem. Soc.*, 1977, **99**, 3847; (*b*) M. M. Werber and Y. Shalitin, *Bioorg. Chem.*, 1973, **2**, 202.

5 For examples of intramolecular hydrogen bonded tertiary amino alcohols in aqueous solution, see references 3(*c*) and 4(*a*).

6 Reaction rates were measured by monitoring the decrease in UV absorbance at 260 nm for AcIm and by monitoring the increase in UV absorbance at 420 nm for PNPA. See further, I. M. Gordon and H. Maskill, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1951.