# Structure–reactivity relationships in the rate of esterification by acetylimidazole: the influence of the second hydroxy group and of the length of the *N*-ω-hydroxy-*n*-alkyl chain in 3-(*N*-methyl, *N*-ω-hydroxy-*n*-alkyl)amino-2-*tert*-butylpropan-1-ols

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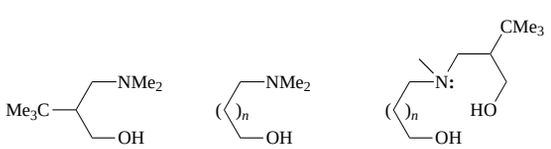
**Enforced intramolecular hydrogen bonding facilitates intramolecular general base catalysis in the acetylation of a family of α,ω-amino alcohols by acetylimidazole, and the site of acetylation when there are two hydroxy groups is determined by the relative ease of intramolecular hydrogen bonding rather than by intermolecular steric effects.**

Recently, in the context of developing a non-enzymic catalyst for the cleavage of esters and amides, we studied the influence of 2-substitution on the rate of esterification of 1,3-amino-alcohols by acetylimidazole (AcIm) in acetonitrile.[1] In accord with an intramolecular GBC mechanism, the enforced intramolecular hydrogen bonding in the 2-*tert*-butyl substituted compound **1** led to a modestly increased rate constant at room temperature compared with **3a**.[2–4] Because of the aprotic nature of the solvent acetonitrile, one may expect a further rate enhancement by inclusion of an extra hydroxy group that could serve to facilitate the formation of the oxyanion *via* intramolecular hydrogen bonding. The presence of this second hydroxy group in the reactant, however, would also reduce the basicity of the amino group, but this effect will depend on the length of the methylene chain between the hydroxy group and the amino group.[5]

In order to understand better these structure–reactivity relationships, we decided to study (*i*) the influence of the methylene chain length upon the reactivity of acetylation by acetylimidazole of a series of ω-(*N*,*N*-dimethylamine)-*n*-alkanols **2a**–**5a** and (*ii*) the relative reactivity in the same reaction of amino diols **2b** and **3b**, in which a second hydroxyalkyl group is incorporated into the 2-*tert*-butylamino alcohol **1**.




**1** **a** **2** *n* = 0, **3** *n* = 1, **4** *n* = 2, **5** *n* = 3 **b**

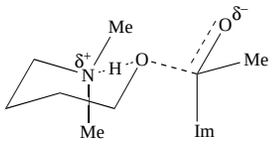
The half-lives of the *pseudo*-first-order esterification reactions of **2a**–**5a** at 23 °C were determined by $^1$H NMR spectroscopy (500 MHz) using the amino alcohols in excess (Table 1). Inspection of the results reveals that the position of **5a** in the observed order of reactivity and the difference between **4a** and **3a** on the one hand and **2a** and **5a** on the other (**4a** > **3a** ≫ **2a** and **5a**) do not correspond with expectation based solely upon the basicity of the amino groups, *i.e.* **5a** > **4a** > **3a** > **2a**.[6] Instead, the order of reactivity follows the ease of formation of an intramolecular hydrogen bond, *i.e.* **4a** > **3a** ≫ **2a** and **5a**.[4a,5c] One may expect that the changing basicity of the amino group (due to the changing number of methylene groups separating it from the hydroxy group) will have an effect upon the ease of formation of the hydrogen bond. However, there is also a conformational effect upon the ease of formation of the intramolecular hydrogen bond and hence upon the rate of acyl transfer. According to this analysis, the very low reactivity of **2a** is due to both/either (*i*) the diminished basicity of the amino group (through the inductive effect of the OH) and/or (*ii*) the inefficient geometrical arrangement for an intramolecular proton transfer (proton transfer along a linear hydrogen bond would require a four-membered ring).[7] In the case of **5a**, only the latter geometrical effect could be responsible for its low reactivity (*i.e.* an unfavourable seven-membered ring is required for a linear intramolecular proton transfer) since the inductive effect of the hydroxy group upon the base strength of the amino group will have been rendered negligible by the intervening five methylene groups. The higher reactivity of **4a** compared with **3a** is not unexpected since the former has both the more basic amino group and can accommodate the linear proton transfer within a favourable six-membered ring.[8]

**Table 1** Half-lives (23 °C),[a] activation enthalpies,[b] activation entropies[c] and second-order rate constants (25 °C)[d] for the alcoholysis of AcIm by **1**, **2a**–**5a**, **2b** and **3b** in acetonitrile

| | $t_{\frac{1}{2}}$/min | $\Delta H^{\ddagger}$/kJ mol$^{-1}$ | $-\Delta S^{\ddagger}$/J K$^{-1}$ mol$^{-1}$ | $k_2/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|---|---|---|
| **1**[e] | 198 | 35.3 | 180 | 14.9 |
| **2a** | *f* | — | — | — |
| **3a**[e] | 721 | 33.1 | 195 | 6.0 |
| **4a** | 151 | 23.7 | 219 | 21.2 |
| **5a** | *f* | — | — | — |
| **2b** | 80 | 32.2 | 184 | 35.3 |
| **3b** | 150 | 35.6 | 177 | 21.3 |

[a] Determined by NMR spectroscopy for the pseudo-first-order reaction (0.05 mol dm$^{-3}$ amino alcohol in ten-fold excess over AcIm). [b] Estimated probable error ±4 kJ mol$^{-1}$. [c] Estimated probable error ±14 J K$^{-1}$ mol$^{-1}$. [d] Determined by UV spectrophotometry (see text). [e] These new and preferred results for **1** and **3a** are slightly different from those reported earlier.[1] [f] Estimated at longer than 100 h.

In order to gain further insight into the mechanism of esterification of **3a** and **4a** by AcIm in acetonitrile the activation parameters were determined. For this purpose, pseudo-first-order reaction rates of the esterification were measured by monitoring the decrease in UV absorbance at 270 nm due to AcIm. The reactions were run in duplicate over at least five half-lives with the amino alcohol present in large excess (160–1300-fold). Second-order rate constants were measured in the normal




**4a–TTS**

**Fig. 1** Transition state for reaction of **4a** with acetylimidazole

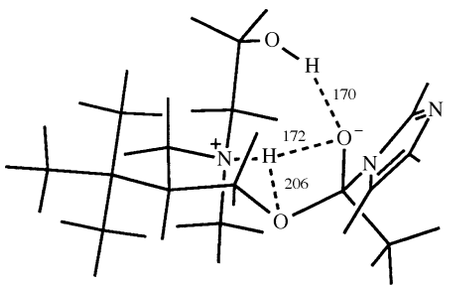



**Fig. 2** Energy-minimized geometry of the tetrahedral intermediate originating from reaction of **2b** with AcIm. Hydrogen-bond distances are given in pm.

way at five temperatures in the range of 25–65 °C and the computed activation parameters are shown in Table 1. Inspection of the results reveals that the higher reactivity of **4a** compared with **3a** is entirely due to its much lower activation enthalpy. However, note that the enthalpic stabilisation of the transition state from **4a** is offset to some extent by a less favourable entropy of activation compared with the transition state from **3a**, *i.e.* there is some degree of compensation between the activation entropy and the activation enthalpy. The former is somewhat more negative for **4a** compared with that for **3a** due to the more ordered chair-like transition state geometry (see Fig. 1, **4a**–**TTS**) which, in turn, allows the less strained arrangement for better development of new bonds in concert with the cleavage of the old ones, and hence the appreciably lower enthalpy of activation of **4a**.

The half-lives for the pseudo-first-order reactions of **2b** and **3b** were also determined as in the **a** series (Table 1). Very significantly, selective esterification of the more hindered primary hydroxy group located on the *tert*-butyl substituted fragment was observed in both cases. This is wholly in accord with our analysis above; the preferred reaction is of the hydroxy group which is involved in the enforced intramolecular hydrogen bonding. Scrutiny of the results for **1**, **2b** and **3b** (Table 1) suggests that the diminished basicity of the amino groups due to the incorporation of the second hydroxyalkyl residues in **2b** and **3b** almost cancels out the rate enhancements due to the cooperative involvement of the second hydroxy group through hydrogen bonding required by the regioselectivity. Enthalpies and entropies of activation were also determined for **2b** and **3b** (as described above) and are shown in Table 1. However, whilst they are qualitatively as expected, they provide no new insights into the mechanism. Fig. 2 shows the energy-minimized geometry of the tetrahedral intermediate originating from the reaction of **2b**, the most reactive in the series **1**, **2b** and **3b**.[9]

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8 Six-membered ring transition states are particularly favoured for linear hydrogen transfers: (*a*) E. A. Dorigo and K. N. Houk, *J. Am. Chem. Soc.*, 1987, **109**, 2195; (*b*) P. Camilleri, C. A. Marby, B. Odell, H. S. Rzepa, R. N. Shepard, J. J. P. Stervart and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1989, 1722.

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