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Acceleration of an aminolysis reaction using a PAMAM dendrimer with 64 terminal amine groups

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Abstract—When compared to an equivalent amine concentration (*N*-acetylethylene diamine, 64 equivalents), the initial rate of a simple deacylation reaction in water was found to be greatly enhanced when using a PAMAM dendrimer with 64 terminal amine groups. This increase in initial rate is largely due to the hydrophobic binding of the substrate within the outer region of the dendrimer. As a consequence of this binding, the substrate is held in close proximity to the *reactive* amine groups on the surface of the dendrimer. It is this increase in effective molarity that results in an increase in the observed initial rate.

Enzymes act by binding their substrates in close proximity to specific functional groups capable of either reacting with the substrate or stabilising a particular transition state.[1] Synthetic, supramolecular and biomimetic chemists have adopted these principles and over many years constructed a variety of model compounds capable of mimicking the action of certain enzymes.[2] Of particular note, with respect to a macromolecular approach, are the surfactants or micellar based systems.[3]

It is well known that carrying out certain reactions in aqueous micellar media can alter the rates and pathway of many reactions, for example hydrolysis,[4] nucleophilic addition,[5] epoxidation,[6] halogenation[7] and pericyclic reactions[8] can all be affected in the presence of micelles. The mechanism of catalysis involves a combination of factors, including hydrophobic binding, transition state stabilisation and substrate concentration.[9] Despite the considerable success of micelles some major problems associated with their use still remain. Micelles are created under equilibrium conditions, so as each micelle forms it will immediately begin to fall apart. Another problematic area is that of critical micelle concentration; these can vary dramatically depending on the nature of the surfactant. Micelle formation is also temperature dependent. In order for these systems to be more efficient, a static or covalent micelle is desired. Dendrimers are spherical macromolecules that possess a large number of terminal groups.[10] When these terminal groups are either charged or polar, the resulting macromolecules possess similar structural and solubility properties to those of micelles; these macromolecules can therefore be considered as static covalent micelles. For example, a number of recent reports have described how water-soluble dendrimers can be applied as solubilisation agents, encapsulating hydrophobic guests within their hydrophobic interiors.[11,12] Although these molecules are more difficult to construct (relative to simple surfactants), they are static, exist at all concentrations and persist across a wide range of temperatures. It should therefore be possible for these molecules to catalyse or accelerate the rates of various reactions.[13]

To demonstrate the feasibility of this proposal, the initial rate of an aminolysis reaction using the PAMAM dendrimer **1** (64 terminal amine groups, purchased from Aldrich Chemicals) was measured (Fig. 1). This initial rate was compared to that obtained using 64 equivalents of the simple amine *N*-acetylethylene diamine **2** (Scheme 1).

N-Acetyl ethylenediamine was chosen as our control/test reaction because it resembles the outer domain of dendrimer **1** (shown in red) and therefore acts as an isolated and reactive unit, independent of the macroscopic dendrimer backbone. The selected process is shown in Scheme 1, this involves the reaction between an amine (dendrimer **1** or amine **2**) and *p*-nitrophenol acetate. All reactions were performed in buffered water

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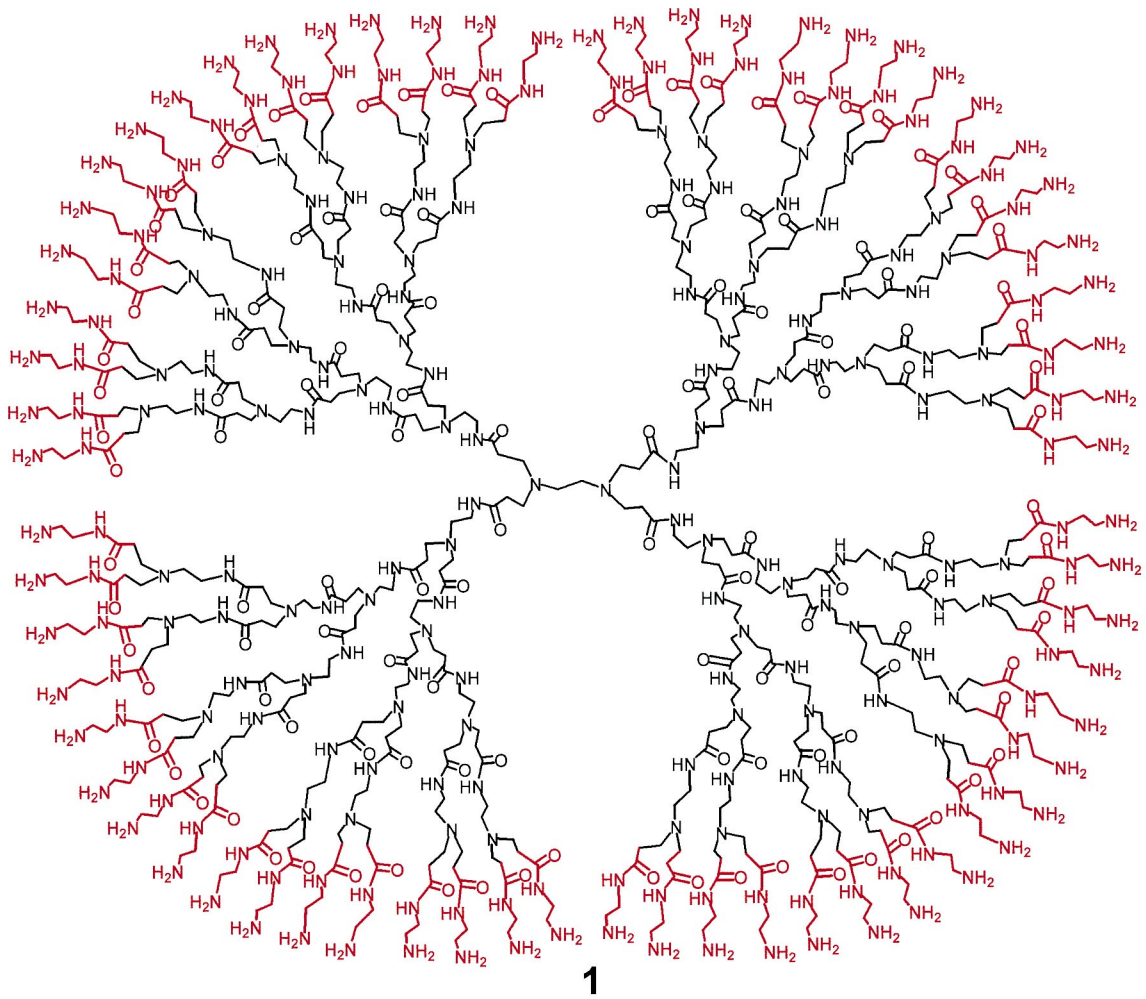
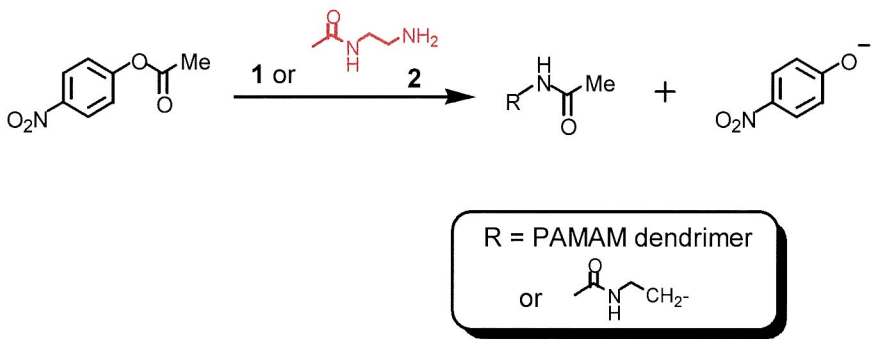


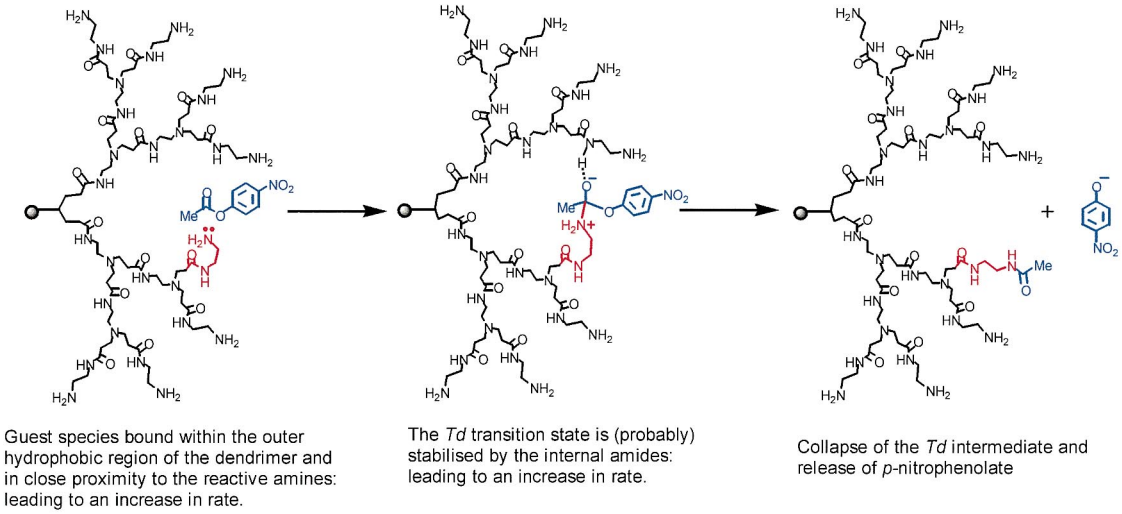
Figure 1. PAMAM dendrimer **1** with 64 terminal amine units. The *N*-acetylethylene diamine terminal units are shown in red.

at pH 8.5 (TRIS buffer, 0.1 M).[14] In all cases an acylated amine is produced along with *p*-nitrophenolate (which could be monitored by UV at 390 nm), as shown in Scheme 1.

Control experiments were performed to measure the background rate of hydrolysis for the *p*-nitrophenol acetate in the aqueous buffer. The initial rate for the background hydrolysis was found to be extremely slow; nevertheless, all subsequent aminolysis rates were adjusted taking this into account. The rate profile for both reactions (corrected for the background hydrolysis) is shown in Fig. 2. These graphs clearly demonstrate that the rate of aminolysis is greater for the dendrimer than it is for an equivalent amount of *N*-acetyl-ethylenediamine. Using the linear region of the graphs, obtained during the first 5% of reaction, initial rates of 1×10^{-8} Ms^{-1} and 4×10^{-10} Ms^{-1} were obtained for dendrimer **1** and *N*-acetyl-ethylenediamine **2**, respectively: this equates to a 25-fold rate acceleration.



Scheme 1. Aminolysis of *p*-nitrophenol acetate.



Scheme 2. The three proposed steps involved in the dendrimer assisted aminolysis reaction.

This 25-fold enhancement in rate can be attributed to two factors. Firstly, the dendrimer is acting as a static covalent micelle, and is solubilising the hydrophobic *p*-nitrophenol acetate within the outer hydrophobic region of the dendrimer. Once bound the *p*-nitrophenol acetate group is held in close proximity to the dendrimers outer reactive amine groups. This leads to an increase in the effective molarity of the two reactive species (the amine and the *p*-nitrophenol acetate). The increase in concentration (i.e. the higher effective molarity), therefore contributes significantly to the observed rate enhancement. A second factor involves the dendrimers internal amide groups. These may be able to stabilise the transition state as it forms during the aminolysis reaction, see Scheme 2. Such stabilisation effects have been reported for aminolysis reactions involving other branched multi amine compounds.[15]

In conclusion, we have demonstrated that water-soluble dendrimers can be applied as static, covalent micelles. In particular, we have demonstrated that the water-soluble PAMAM dendrimer with 64 terminal amine groups can accelerate an aminolysis reaction 25-fold (when compared to an equivalent amine concentration of *N*-acetyl ethylenediamine).

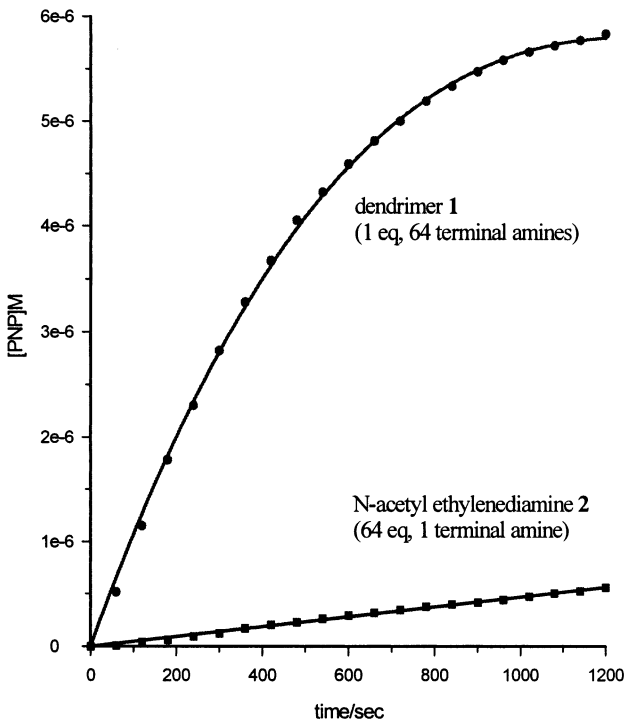


Figure 2. Rate profile for aminolysis reaction using dendrimer **1** and *N*-acetyl ethylenediamine **2**.

Acknowledgements

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