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The effect of size on the rate of an aminolysis reaction using a series of amine terminated PAMAM dendrimers

John L. Burnett, Amy S. H. King, Ian K. Martin and Lance J. Twyman*

Chemistry Department, Dainton Building, University of Sheffield, Sheffield S3 7HF, UK

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Abstract—When compared to an equivalent amine concentration of ethylenediamine, the initial rate of a simple aminolysis reaction in water (at pH 8.5) was found to be greatly enhanced by the use of amine terminated PAMAM dendrimers of generations 1–5 (with 4, 8, 16, 32 and 64 terminal amines, respectively). The fourth generation dendrimer gives the maximum rate enhancement, even when compared to the larger 64 amine terminated dendrimer. The observed increase in aminolysis rates is due to hydrophobic binding of the substrate within the outer region of the larger dendrimers, which results in the substrate being held in close proximity to the reactive amine groups on the surface. Another contributory factor is transition state stabilisation by the internal amide groups within the dendrimers. The trend in reactivities of dendrimers is discussed and provides strong evidence that both these effects are responsible for the enhanced rates of aminolysis. © 2002 Published by Elsevier Science Ltd.

Dendrimers are monodisperse, highly symmetrical macromolecules with a tree-like complexity and a high density of terminal groups.[1] The surface functionality can be tailored, for example, adapting the terminal groups to make them more or less hydrophilic can change their solubility properties. When these terminal groups are either charged or polar the resulting dendrimers have similar structural and solubility properties to micelles. There are numerous reports in the literature that micelles can be used to catalyse certain reactions including hydrolysis,[2] nucleophilic addition,[3] epoxidation,[4] halogenation,[5] and pericyclic reactions.[6] However, there are some problems associated with their use, for example, micelles form under equilibrium conditions (so they are constantly collapsing and reforming) and they can only form above the critical micelle concentration (CMC). Dendrimers, however, have the advantage of being present at all concentrations and over a wide range of temperature, i.e. they can be considered as static covalent micelles and this has important implications for catalysis. Ford[7] has demonstrated the use of 'micelle-like' dendrimers with charged surface groups for the catalysis of decarboxylation and hydrolysis reactions, and the enhanced rate here is due solely to the highly charged nature of the dendrimer surface, which results in concentration of the hydrophobic substrate molecules at the surface. Recent reports have also described the use of water soluble dendrimers with polar surface groups as solubilising agents, which encapsulate hydrophobic guests in their interiors.[8,9] Therefore, it is feasible that these two features can be combined and dendrimers with polar surface groups and an accessible hydrophobic interior can be used to catalyse or accelerate various reactions.[10]

Previously, the feasibility of this proposal was demonstrated within our group,[11] when it was shown that the initial rate of an aminolysis reaction can be greatly enhanced by using a PAMAM dendrimer with 64 terminal amine groups. This initial rate was compared to that obtained using 64 equivalents of the simple, mononuclear amine, *N*-acetyl ethylenediamine (NAEDA), which resembles the outer domain of the dendrimer and therefore acts as an isolated, reactive unit independent of a dendrimer backbone. A 22-fold increase in rate was observed with the dendrimer **5** compared to *N*-acetyl ethylenediamine. It was postulated that there were two factors responsible for this rate enhancement. Firstly, the dendrimer is acting as a static covalent micelle, and is solubilising the hydrophobic *p*-nitrophenyl acetate within the outer hydrophobic region of the dendrimer. Once bound, the *p*-nitrophenyl acetate group is held in close proximity to the dendrimers outer reactive amine groups and this increase in the effective molarity of the reactive species contributes significantly to the observed rate enhancement. A second factor involves the dendrimers internal amide groups. It was felt that these may be able to stabilise the transition state as it forms during the aminolysis

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* Corresponding author. Fax: +44-(0)114-273-8673; e-mail: l.j.twyman@sheffield.ac.uk

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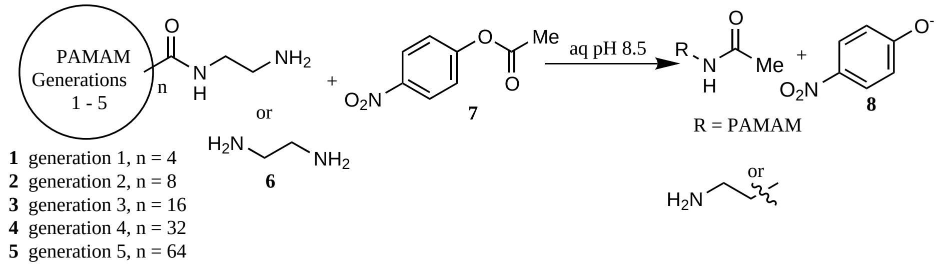
reaction. Such stabilisation effects have been reported for aminolysis reactions involving other branched multi amines.[12] In order to gain more information about the importance of these two factors, we decided to investigate a series of dendrimers from generations 0–5 and determine at what stage significant rate enhancement occurs.

The selected aminolysis process studied is shown in Scheme 1, and involves the reaction between an amine (dendrimer or ethylenediamine) and *p*-nitrophenyl acetate. This is a particularly suitable reaction for investigation as the product **8** is a good leaving group, which is yellow in colour and can be monitored by measurement of its UV absorbance ($\lambda_{\max}$ at 410 nm). Once again, *N*-acetyl ethylenediamine was chosen as the control/test reaction. All reactions were performed in buffered water at pH 8.5 (Tris buffer 0.1 M) and the acylated amine is produced as well as the *p*-nitrophenolate **8**. A control experiment was performed to measure the background rate of hydrolysis of *p*-nitrophenyl 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 to take account of this. A series of experiments was carried out[13] with EDA (generation 0) and dendrimer generations 1–5 (the starting concentration of amine groups was the same for each experiment). A solution of known concentration of *p*-nitrophenyl acetate in acetonitrile was added to the dendrimer/EDA in aqueous buffer and detection of the product **8** began immediately. Formation of the product **8** was followed by measurement of the UV absorbance at 410 nm at regular time intervals over the course of the reaction (until saturation was reached). In addition to UV absorbance measurements, the reaction of the dendrimer with 64 terminal amine groups (**5**) was monitored by GC mass spectrometry, which revealed a very small, insignificant peak for the *hydrolysis* product, acetic acid (as expected due to the low rate of background hydrolysis measured). This confirms that the reaction occurring is *aminolysis* (Scheme 1), rather than a simple *hydrolysis* catalysed by the presence of the amine dendrimers.

The rate profiles for the reactions clearly demonstrated that the order of reactivity is EDA = NAEDA<G1<G2<G3<G5<G4. Using the linear regions of the graphs obtained during the first 3 min of each reaction (Fig. 1), initial reaction rates were ascertained and the trend of dendrimer reactivities as a function of generation number is shown in Table 1.[14] This demonstrates that there is a rapid increase in the initial aminolysis rate from G0 (EDA) up to generation 4 (which has a 28-fold rate enhancement relative to the control), then a decrease in rate is observed for generation 5 with 64 terminal amine groups (although it is still 21 times more reactive than the control).



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

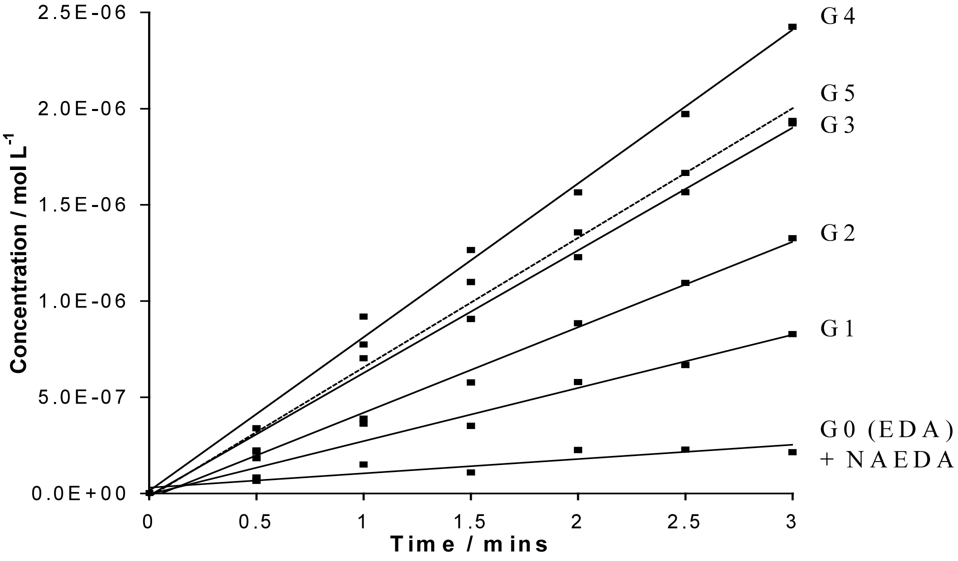


Figure 1. Linear regions of the curves of concentration versus time for EDA and **1**–**5** during the aminolysis reaction.

Table 1. Initial rates of aminolysis for EDA and **1**–**5** and initial rates relative to EDA

Generation	Amines per molecule	Concentration (mM)[a]	Initial rate (M s^{-1})	Relative rate to EDA
0	2	3.2	4.03×10^{-10}	1
1	4	1.6	2.40×10^{-9}	5.95
2	8	0.8	5.20×10^{-9}	12.89
3	16	0.4	9.02×10^{-9}	22.35
4	32	0.2	1.12×10^{-8}	27.56
5	64	0.1	8.63×10^{-9}	21.4

[a] Relative amine concentration is 6.4 mM in each case (and *p*-nitrophenyl acetate concentration is 0.014 mM).

As expected, the results confirm that there is a hydrophobic effect operating here, i.e. the larger dendrimers (>generation 2) are acting as static covalent micelles and solubilising the *p*-nitrophenyl acetate within the inner hydrophobic regions of the dendrimers. This increase in effective molarity of the reagents therefore contributes significantly to the observed rate enhancements in the larger dendrimers. As postulated previously, the rate enhancements can also be attributed to a second factor involving the dendrimers internal amide groups, which are able to stabilise the tetrahedral transition state formed between the amine and the *p*-nitrophenyl acetate. The presence of this transition state stabilisation effect accounts for the fact that the small dendrimers (generations 1 and 2) have faster aminolysis rates than the simple amine, EDA (G0). For example, the first generation dendrimer (four amines) is six times more reactive than EDA, despite the fact that it is still effectively a small molecule that does not provide a hydrophobic environment for substrate molecules. Thus, it is clear that there is no hydrophobic effect operating and the substantial increase in rate is due solely to the ability of the first generation dendrimer to form a tetrahedral intramolecular transition state, which lowers the energy of activation (ΔG) for the aminolysis reaction and results in a faster rate. As the dendrimers increase in size, the increase in initial rates continues (up to generation 4). Therefore, we conclude that this increase in rate is due to transition state stabilisation and hydrophobic binding.

This observed trend in reactivity was not surprising, considering the properties of the PAMAM dendrimers. It has been reported in the literature that there is a transition from an extended to a globular closed shell conformation for related amine terminated dendrimers.[15] Similarly, we have observed that there is a change in behaviour, i.e. a break in the pattern regarding rate enhancement between generation 4 (32 amines) and 5 (64 amines). The fourth generation dendrimer still has a relatively open and flexible structure, which allows substrate molecules to enter and reside in the large hydrophobic interior (and facilitates the formation of the T_d transition state), so a maximum in the rate enhancement for this dendrimer is observed, i.e. the conditions are optimum for aminolysis rate enhancement. The initial rate with the 64 amine dendrimer is lower than for generation 4 (and similar to that observed for generation 3), which is presumably due to the fact that the surface of the dendrimer is highly crowded preventing access of the substrate molecules to the hydrophobic environment within the dendrimer.

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13. An acetonitrile solution of *p*-nitrophenyl acetate (0.14 M, 0.1 ml) was added to a solution of amine (6.4 mM w.r.t. amine groups) in buffered water at pH 8.5 (0.1 M TRIS buffer, 1.9 ml) in a quartz UV cuvette (with stirring, at room temperature) and the UV absorbance at 410 nm was measured every 30 s over a period of 20 min.
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