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A Dendritic Active Site: Catalysis of the Henry Reaction

Amber V. Davis, Malcolm Driffield, and David K. Smith*

Department of Chemistry, University of York, Heslington, York, YO10 5DD, U.K.

dks3@york.ac.uk

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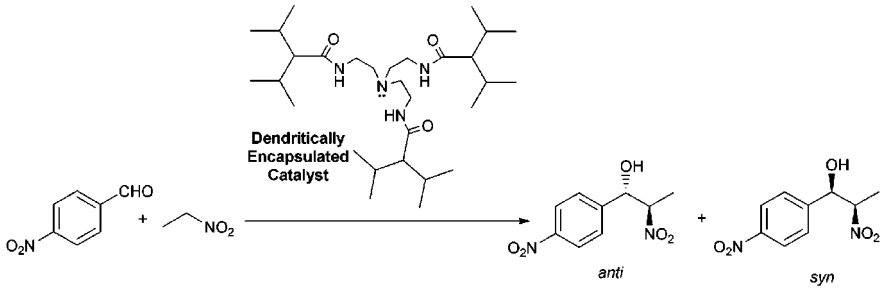
ABSTRACT



Dendrimers containing an encapsulated tertiary amine were prepared by coupling tris(2-aminoethyl)amine with dendritic branches derived from L-lysine. These dendrimers were used as catalysts in the Henry (nitroaldol) reaction between 4-nitrobenzaldehyde and nitroethane, and their catalytic performance was compared with that of triethylamine. Attachment of the dendritic shell alters the rate of reaction and influences the *syn:anti* ratio of products. It is proposed that the dendritic shell generates an encapsulated catalytically active site, mimicking the behavior of a protein superstructure.

Catalysts based on dendrimers[1] have recently generated a lot of excitement, primarily because it has been proposed that such systems will exhibit a range of unique properties. First, there is the possibility that the large size of dendritic macromolecules may lead to effective recycling of the catalyst via nanofiltration.[2] Second, there is the possibility that multiple catalytic sites distributed over a fractally branched surface will exhibit cooperative catalytic behavior.[3] Finally, there is the ability of the branched shell to generate a unique internal microenvironment[4] that may alter the regio- and stereoselectivities of reactions occurring at a catalytic site buried within the branched architecture. This last "dendritic effect" is of considerable interest given the proposal that dendrimers can act as unique functional mimics of biological systems.[5] It is, for example, well-known that the enzyme superstructure can play an important role in mediating catalysis at the active site. Dendrimers with catalytic cores exhibiting modified regioselectivities[6] or substrate selectivities[7] have been reported, although the reported magnitudes of dendritically altered stereoselectivities have been relatively modest.[8]

In 1997, Morao and Cossío reported a series of dendritically encapsulated amines[9] capable of catalyzing the Henry

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(nitroaldol) reaction.[10] These catalysts were slower than triethylamine as a consequence of the steric hindrance caused by the branching; as the dendritic generation increased, the rate of reaction decreased. The branching of the catalyst did not exhibit any effect on the diastereomeric *syn:anti* ratio of the products. However, the branching used in this study was based on relatively rigid aromatic-ether building blocks, while our studies of biomimetic dendrimers have recently shown that using flexible branching capable of forming hydrogen bonds is preferable for generating significant dendritic effects.[11]

In this paper, we therefore report tertiary amines dendritically encapsulated within a flexible peptidic shell (Figure 1). The presence of branching alters the rate of reaction and

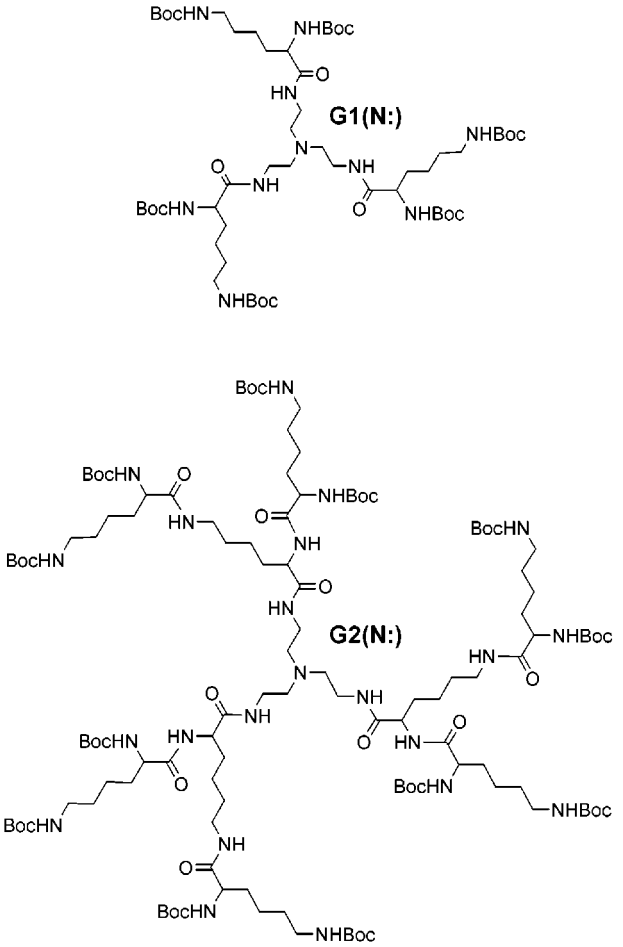

Figure 1. Dendrimers **G1(N:)** and **G2(N:)** with encapsulated tertiary amines for catalysis of the nitroaldol reaction.

also influences the diastereoselectivity of the reaction, presumably as a consequence of the ability of the branched shell to generate a defined microenvironment at the catalytically active amine, mimicking the effect of an enzyme superstructure and creating a dendritic "active site".

The synthesis of these novel dendrimers was achieved using a convergent strategy to give products with high purity. Synthesis was achieved using DCC/HOBt mediated peptide coupling reactions between tris(2-aminoethyl)amine and preformed dendritic branches[12] composed of lysine groups with a carboxylic acid at the focal point. First generation dendrimer **G1(N:)** formed smoothly in THF solution in reasonable yield (62%) and was purified by silica column chromatography. The formation of second generation dendrimer **G2(N:)** was markedly slower and progressed over a 14-day period, with heating of the reaction mixture to 60 °C being required. Hindrance of the coupling reaction was fully expected given the steric demands of the relatively small core and the convergent strategy employed in the synthesis.[13] The low reactivity also provides an indication that the amine at the core of this dendrimer should be deeply encapsulated within the branches. After gel permeation chromatography, **G2(N:)** was isolated in 22% yield and fully characterized by all available methods.[14]

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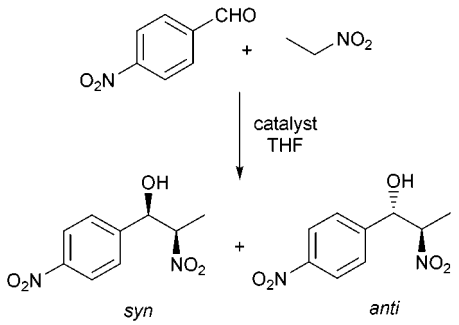
(14) Characterization data for new dendritic compounds. **G1(N:)**: mp 85−95 °C; $[\alpha]^{293}_{D}$ −5.15 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 4.28 (3H, br s, COC*H*(R)NH), 3.43 (3H, m NCH_2CH_2NH), 3.29 (3H, m, NCH_2CH_2NH), 3.15 (6H, br t, CH_2CH_2NH), 2.67 (6H, m, NCH_2CH_2NH), 1.75−1.95, (72H, m, CH_2, CH_3); ^{13}C NMR (500 MHz, CD_3COCD_3) δ 173.4 (CONH), 156.5 (NHCOBoc), 79.2 ($OC(CH_3)_3$), 78.2 ($OC(CH_3)_3$), 55.3 (COCH(R)NH), 40.6 (CH_2CH_2NH), 38.6 (NCH_2CH_2NH) 33.0 (NCH_2CH_2-NH), 30.5−29.2 (CH_2 groups buried under solvent), 28.6 (CH_3), 23.4 (CH_2); ν_{max} (KBr disc) 3504*m*, 3350*m*, 2977*m*, 2933*m*, 1692*s*, 1657*s*, 1530*w*, 1416*s*, 1366*s*, 1253*m*, 1170*s*, 1045*w*; *m/z* (electrospray) 1153.6 ($[M + Na]^+$, 100), 1154.6 (57), 1131.6 ($[M]^+$, 35); HRFAB-MS $C_{54}H_{102}N_{10}O_{15}Na$ *m/z* calcd 1153.7424, found 1153.7427. **G2(N:)** mp 100−110 °C.; $[\alpha]^{293}_{D}$ −13.6 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 5.28 (12H, br s, N*H*Boc), 4.41 (4H, br, COC*H*(R)NH), 4.05 (5H, br d, COC*H*(R)NH), 3.21 (14H, s, CH_2NH and NCH_2CH_2NH), 3.03 (12H, s, CH_2NH and NCH_2CH_2NH), 2.60 (6H, m, NCH_2CH_2NH), 1.90−1.24, (162H, m, CH_2, CH_3); ^{13}C NMR (500 MHz, MeOD) δ [some peaks are overlapping] 175.1 (CONH), 173.8 (CONH), 158.4 (CONHBoc), 157.9 (CONHBoc), 157.7 (CONHBoc), 80.6 ($OC(CH_3)_3$), 80.5 ($OC(CH_3)_3$), 79.8 ($OC(CH_3)_3$), 56.1 (COCH(R)NH), 54.8 (COCH(R)NH), 54.5 (COCH(R)NH), 41.0 (CH_2CH_2NH), 40.1 (CH_2CH_2-NH), 39.0 (NCH_2CH_2NH), 33.3 (NCH_2CH_2NH), 30.6 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 26.1 (CH_3), 24.2 (CH_3), 24.2 (CH_3); ν_{max} (KBr disc) 3744*w*, 3328*m*, 2977*m*, 2935*m*, 1690*s*, 1653*w*, 1521*s*, 1436*s*, 1366*m*, 1250*m*, 1172*s*, 1046*w*; *m/z* (electrospray) $C_{120}H_{222}N_{22}O_{33}$ requires 2501.2; found 1250.7 ($[M]^{2+}$, 65), 1261.8 ($[M + Na]^{2+}$, 48), 1269.9 ($[M + K]^{2+}$, 35), 1201.2 ($[M - Boc]^{2+}$, 100) [appropriate isotope peaks for these main peaks were also observed at half mass unit intervals].

These dendrimers were then investigated for their ability to catalyze the nitroaldol reaction between 4-nitrobenzaldehyde and nitroethane in THF (Scheme 1). This reaction was

Scheme 1. Nitroaldol Reaction between 4-Nitrobenzaldehyde and Nitroethane.



performed using 4-nitrobenzaldehyde (89 mg, 0.59 mmol) and nitroethane (0.5 mL, 9.2 mmol, excess) in THF (0.5 mL) (the use of THF as a cosolvent was necessary to ensure solubility of the dendritic catalysts) with tertiary amine as catalyst (15 mol %). The reaction was followed by TLC and when complete was worked up by rotary evaporation. The crude mixture was then subjected to ^{1}H NMR spectrometry in $CDCl_3$. Integration of the NMR spectrum allowed the extent of reaction to be determined and, in addition, allowed the *syn:anti* ratio of products to be calculated.[9,15,16] All reactions were performed multiple times; the yields and *syn:anti* ratios showed good reproducibility.

Four different catalysts were employed in the study: triethylamine (NEt_3) and DIPEA (*N*,*N*-diisopropyl ethylamine) as model systems and branched catalysts **G1(N:)** and **G2(N:)**. The results are tabulated in Table 1.

Table 1. Average % Conversions and *syn:anti* Ratios of Nitroaldol Reaction between *p*-Nitrobenzaldehyde and Nitroethane Using Various Different Catalysts (All 15 mol %), Assessed Using ^{1}H NMR on the Evaporated Crude Reaction Mixture

catalyst	time (h)	% conv	*syn:anti*	de[a]
none	48	none		
NEt_3	1	85	57:43	+14
DIPEA	1	95	56:44	+12
NEt_3 + acetamide[b]	0.5	91	55:45	+10
G1(N:)	48	92	42:58	−16
G2(N:)	24	94	54:46	+8

[a] Diastereomeric excess of the *syn* product. [b] Acetamide used as a 10 mol % additive.

Using NEt_3 as catalyst, the reaction proceeded very rapidly as observed by TLC. After just 1 h, the reaction was complete by TLC and provided a crude yield of 85%. Using DIPEA as catalyst gave rise to a very similar rate of reaction. The reaction using **G1(N:)** as catalyst, however, was much more sluggish; 48 h were required for completion to be indicated by TLC. Interestingly, however, when using catalyst **G2-(N:)** the reaction was markedly quicker than with **G1(N:)**, giving excellent yields of >90% after only 24 h. This was a surprising result given the encapsulated, hindered nature of this amine.

It might be expected that the dendritic branching would provide increasing hindrance to the access of relatively bulky organic substrates to the deeply encapsulated tertiary amine group, as previously observed by Morao and Cossío. As a general rule, such steric factors are dominant in catalysis at dendritic cores. In one notable literature example, however, electronic effects have been shown to enhance the rate of reactions within dendrimers.[17] It can be hypothesised that the Henry reaction is more rapid using **G2(N:)** than **G1(N:)**, because that the flexible peptidic dendritic shell creates a polar, hydrogen-bonding microenvironment well-suited to the stabilization of the charged intermediates involved in the catalytic process.

To illustrate the fact that enhanced polarity does indeed increase the reaction rate of this base-catalyzed nitroaldol reaction, 10 mol % of acetamide ($MeCONH_2$) was added to the NEt_3-catalyzed reaction. This polar, hydrogen bonding additive caused a significant increase in rate (as assessed by TLC), with the reaction being complete after only 30 min. This result is therefore consistent with the polarity of the second generation dendrimer going some way toward off-setting its steric hindrance.

Also of considerable interest was the effect of dendritic functionalization on the *syn:anti* ratio of nitro alcohol products. Using NEt_3 as catalyst gave rise to a slight excess of the *syn* product (*syn:anti*, 57:43). A very similar result was observed with DIPEA as catalyst (*syn:anti*, 56:44). Using dendritic catalyst **G1(N:)**, however, consistently reversed this selectivity, favoring the *anti* product (*syn:anti*, 42:58), a change in de of 30%. When the reaction was catalyzed by **G2(N:)**, however, the reaction was less selective for either *syn* or *anti* product (*syn:anti*, 54:46), a result mirrored to some extent by the use of acetamide as an additive with NEt_3 as catalyst.

These are intriguing results, with the preferred diastereomer being changed by the presence of dendritic branching, and they contrast with the results of Morao and Cossío, whose dendritic catalysts had no reported effect on the *syn:anti* ratio.

It was suggested that the longer reaction times required when using catalyst **G1(N:)** may give rise to product

(15) The crude mixture obtained from the reaction was consistent with being a mixture of *syn/anti* products and a little unreacted aldehyde. For full characterization data of the nitro alcohol products, see: Ballini, R.; Bosica, G. *J. Org. Chem.* **1997**, *62*, 425−427.

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epimerization, favoring the *anti* product and causing the observed change in selectivity. Therefore, a control reaction was performed in which NEt_3 was used as catalyst and the reaction was left for 48 h. This reaction generated products with a *syn:anti* ratio of 57:43, identical to the reaction left for just 1 h. This result indicates that epimerization over time is not an important consideration in this case.

The possible reasons for the diastereoselectivity being influenced by dendritic functionalization are therefore:

(a) *Steric hindrance* from the flexible dendritic branches. This could control the attack of the deprotonated nitroethane on the aldehyde, favoring the observed product.

(b) *Hydrogen bonding interactions* between the amide groups in the dendritic shell (which can act as hydrogen bond donors) and the developing O^- in the transition state (which can accept a hydrogen bond). Such interactions could, if well organized, favor the formation of a given product via transition state stabilization.

The presence of hydrogen bond interactions could also explain the relative difference in reactivity and selectivity between **G1(N:)** and **G2(N:)**. Catalyst **G1(N:)** has a small and potentially selective array of hydrogen bond donors capable of selecting a specific product. Catalyst **G2(N:)** possesses many more hydrogen bond donors capable of interacting with the product in a less selective way (i.e., interactions within the dendritic branches rather than at the core), perhaps leading to the lack of *syn:anti* selectivity. These multiple hydrogen bonding groups could speed up the reaction, however, by generating a favorable polar microenvironment (as in the control experiment using acetamide as an additive).

It should be noted that diastereoselective recognition within chiral dendrimers has been previously reported.[18,19] For example, we reported chiral dendroclefts that exhibited diastereoselective monosaccharide binding.[18] In this case, it was reported that the extent of branching controlled the diastereoselectivity of the recognition process as a consequence of the dendritic branches forming secondary hydrogen bond interactions with the bound monosaccharide, a possible parallel to factors involved with dendritic catalysts **G1(N:)** and **G2(N:)**.

Further work is in progress to confirm the mode of action of this dendritic effect and to assess the molecular recognition properties of these dendrimers. Results of these studies will be reported in due course. It is, however, worthwhile to point out that the proposed mode of action of the dendritic shell mimics the role played by an enzyme/protein superstructure in influencing catalysis/binding at the active site. It is well-known that steric and hydrogen bonding interactions are of importance in the operation of a vast range of different enzymes and proteins.

We have therefore generated a "dendritic active site" in which a deeply encapsulated, catalytically active tertiary amine has its catalytic properties modified by the presence of the surrounding superstructure. This indicates the potential of dendritic encapsulation to mimic some of the effects of biological encapsulation. These systems perhaps merit Brunner's description of such dendritically encapsulated catalysts as "dendrizymes".[8a]

It is desirable in the future for dendritic catalysts to ally strongly altered reaction selectivities with significantly enhanced rates. Such studies will require a suitable combination of steric and electronic factors, and work in such a direction is in progress in our laboratories.

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(19) For diastereoselectivities in dendritic growth processes, see: P. K. Murer, P. K.; Lapierre, J.-M.; Greiveldinger, G.; Seebach, D. *Helv. Chim. Acta* **1997**, *80*, 1648−1681.