Catalysis on Dendrimers

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Polyvalent Catalysts Operating on Polyvalent Substrates: A Model for Surface-Controlled Reactivity

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Dedicated to K. Barry Sharpless on the occasion of his 75th birthday

Abstract: *Unusually fast rates of nucleophilic catalysis of hydrazone ligation were observed when polyvalent anthranilic acid catalysts operating on polyvalent aldehyde substrates were used with PAMAM dendrimers as the common platform. When presented in this way, the catalyst has a strong accelerating effect at concentrations 40–400 times lower than those required for similar monovalent catalysts and displays unique kinetic parameters. We attribute these properties to polyvalent engagement between the dendrimer surface groups, and a potential "rolling" effect leading to fast interparticle kinetic turnover. The phenomenon is sensitive to the density of functional groups on each dendrimer, and insensitive to factors that promote or inhibit nonspecific particle aggregation. These findings constitute a rare experimental example of an underappreciated phenomenon in biological and chemical systems that are organized on interacting surfaces.*

Polyvalent binding is a powerful control element in biology and in laboratory-engineered molecular systems designed to engage biological surfaces.[1–3] Polyvalency may be regarded as a tool for the transfer of molecular information, such as by the induction of cellular signaling events to give a wide spectrum of responses. Chemical catalysis is another mechanism by which polyvalent recognition events can be magnified in their effect. Although polyvalent catalysts have been intensively investigated for practical reasons in synthetic chemistry[4–12]—for example, to increase activity by virtue of high local concentration and recyclability by virtue of easier recovery—they have only rarely been tested as a vehicle for information transfer in model systems.[13]

However, interesting and illustrative examples of "cooperative" or "interfacial" catalysis involving polyvalent substrates do exist (see the Supporting Information). In several of these cases, the importance of the catalyst moving from one substrate to a nearby substrate ("scooting" or "hopping") is highlighted.[14–16] At the risk of oversimplification, these studies have revealed that multiple copies of substrates are operated on by monovalent (solution-phase) catalysts in a manner sensitive to the average two-dimensional "concentration" (density) of the substrate. Polyvalent catalysts, in turn, exhibit the expected properties of high local concentration, which can be profound if the reaction mechanism requires the cooperative action of more than one molecular component for optimal catalytic function. Yet the interaction of polyvalent catalysts with polyvalent substrates seems to have escaped intensive attention so far. Only polynucleotide phosphodiester hydrolysis by gold-nanoparticle- or micelle-supported catalysts has been repeatedly explored from this point of view.[5,17–21] Significant advantages in rate and processivity have been identified, although most quantitative measurements have been reported for a monovalent model substrate.

We describe herein the first exploration of polyvalent catalyst–substrate reactivity in which a bond-forming event, rather than an irreversible cleavage reaction, is monitored. Like others,[11,22] we think it likely that nature takes advantage of the principle in as yet unrealized ways, since living cells are full of surfaces decorated with all manner of functionality.

Figure 1 A shows the overall kinetic scheme that inspired the experiments described below. The initial formation of a catalyst–substrate complex is followed by its dissociation or by capture/conversion to form a catalyst–product complex. We suggest that the overall catalytic rate can be greatly increased if dissociation of the catalyst–product complex (k_{-4}, or off-rate) is relatively slow as compared to the rate of association of an adjacent catalytic site with an adjacent substrate unit (k_5). If this "rolling" process (analogous to the "scooting" of Berg, Jain, and co-workers[23] or the "hopping" of Dawson, Medintz, and co-workers[24]) occurs efficiently, the catalyst and substrate would not be separated, and diffusion limitations would be largely eliminated. If the scaffold is rigid, we expect the rolling effect to be most pronounced when catalytic residues are spaced over similar dimensions as the substrates. If the scaffold is flexible, more than one catalyst–substrate complex could be formed at the same time. This possibility does not invalidate the essential nature of polyvalent–polyvalent catalysis, as simultaneous catalyst–substrate engagement represents an extreme form of rolling.

To create this type of system, we employed poly(amidoamine) (PAMAM) dendrimers as conveniently modifiable polymer scaffolds.[25,26] The condensation of hydrazines (capture reagent) with aldehydes (substrate) under the catalysis of anthranilic acid derivatives[27] (catalyst, Figure 1 B) was chosen as the test reaction because it is capable of generating a chromogenic signal and, at moderate catalyst concentrations, involves rate-limiting Schiff base formation, followed by rapid transimination with the aryl hydrazine to yield the hydrazone product.[28,29] Such a kinetic scheme, as opposed to

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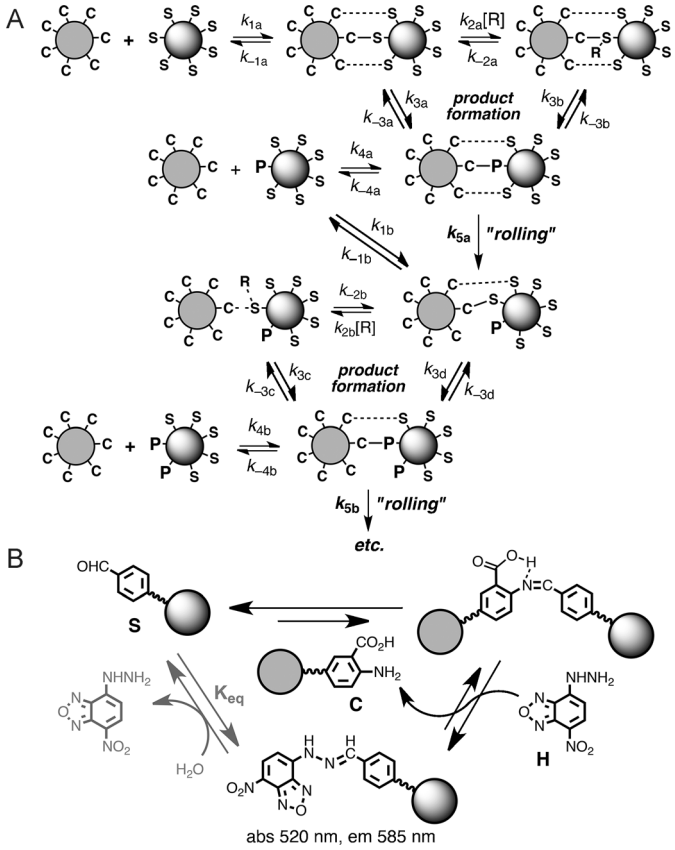

Figure 1. Polyvalent catalysis of polyvalent substrates. A) Overall catalytic scheme. Key: **C** = catalyst; **S** = substrate; **R** = capturing reagent, such as nitrobenzoxadiazole hydrazine in the present case; **P** = product; k_1, k_{-1}: initial association/dissociation rate constant; k_3: product-forming step; k_{-3} = catalyzed product-decomposition step; k_{-4}: escape $\approx k_{-1}$; k_5: polyvalent association rate constant ("rolling" rate). Letter designations (k_{3a}, k_{3b}, etc.) denote the rates of the same fundamental step; these rates may differ in different cycles, probably only slightly at early stages of the reaction. Accelerated substrate transformation may occur if "rolling" (k_5) is much faster than diffusion-controlled steps (k_{-4}, k_1). B) Intermediates in the nucleophilic catalysis of hydrazone formation by monovalent or polyvalent anthranilic acid. In gray is shown the concomitant anthranilate-catalyzed hydrolysis of the hydrazone that establishes K_{eq}.

rate-limiting reagent capture, should be best suited to the generation of a polyvalent catalytic effect. The catalyst accelerates the dehydration step by a combination of nucleophilicity[28,30–33] and intramolecular proton assistance;[27,34,35] the rate of the uncatalyzed reaction is also enhanced by a lowering of the pH value of the reaction medium.[36]

Polyvalent benzaldehyde substrates and anthranilate catalysts based on second-, third-, and fourth-generation amine-terminated PAMAM dendrimers were prepared by a two-step acylation/CuAAC procedure (see the Supporting Information). These fully loaded scaffolds displayed an average of 16, 31, and 61 functional groups, respectively (Figure 2). The latter two values were less than the nominal values of 32 and 64 attachments per dendrimer because commercial PAMAM samples suffer from generational (trailing generations and oligomers) and branching defects (missing arms and intramolecular loops) that are more severe for successive generations.[37]

Besides varying the scaffold size, we changed the surface character of the functionalized G4 dendrimers by the installation of different linkers (propargyl versus tetraglyme) between the triazole and substrate/catalyst moieties to provide particles of different surface polarity proximity. Finally, the average number of substrate or catalyst units per dendrimer (functional-group density) was also varied by mixing functional (aldehyde or anthranilate) and nonfunctional (alcohol) components in the synthetic steps with precise control of the average composition (see the Supporting Information). Monovalent and divalent analogues of the aldehyde substrate (**S**, $\mathbf{S_2}$), anthranilate catalyst (**C**, $\mathbf{C_2}$), and hydrazone (**P**, $\mathbf{P_2}$) were also prepared for comparison (Figure 2).

Reactions with the nitrobenzoxadiazole hydrazine **H**[38] gave rise to chromogenic hydrazone adducts, and reaction progress was monitored by absorbance at 520 nm as a function of time in a microtiter plate reader. Substrate and hydrazine concentrations were in the 25–100 μM range, and the reactions were performed at pH 5, near the optimal pH value for anthranilate catalysis,[27] in 0.1M NaOAc buffer. Hydrazone and oxime ligations at the micromolar level are customarily performed with concentrations of an aniline-derived nucleophilic catalyst of 1 mM or greater, but much lower concentrations of the polyvalent catalysts were required in this study. The observed reaction profiles were fit to the equation derived by Dawson and co-workers that takes into account catalysis of both forward and reverse reactions.[30,31] At the concentrations used, completion was reached at less than 100% conversion of the limiting reagent, corresponding to K_{eq} values in the range of 2×10^4, as expected.[31] Representative data are shown in Figure 3 and Table 1 (see the Supporting Information for detailed experimental methods and results, including all kinetic runs and fits).

In the absence of a catalyst, the reaction of monovalent aldehyde **S** with **H** under these conditions proceeded at a rate of approximately $0.14\,\mathrm{M^{-1}s^{-1}}$. The presence of a monovalent catalyst at a low concentration of either 25 or 100 μM increased the reaction rate by a factor of approximately 3. Aldehydes displayed on dendrimers were better substrates than others: In the absence of an added catalyst, background rates of $1.3–6.6\,\mathrm{M^{-1}s^{-1}}$ were observed, depending on which dendrimer scaffold was used. This effect is probably due to the high local concentration of aldehyde groups on these structures, but other examples of anomalous reactivity have been described.[39] Again, a monovalent catalyst at 25 or 100 μM improved these reactions very little, increasing the rates threefold at most.

In contrast, the use of the dendrimer-supported polyvalent catalysts resulted in much faster reactions with polyvalent, but not monovalent, substrates (Table 1). Rate constants of approximately $30–400\,\mathrm{M^{-1}s^{-1}}$ were observed for the G2, G3, and G4 dendrimer systems, corresponding to 13–28-fold rate enhancements relative to the rate of hydrazone formation from a polyvalent substrate with a monovalent catalyst, and approximately 90–1300-fold relative to the

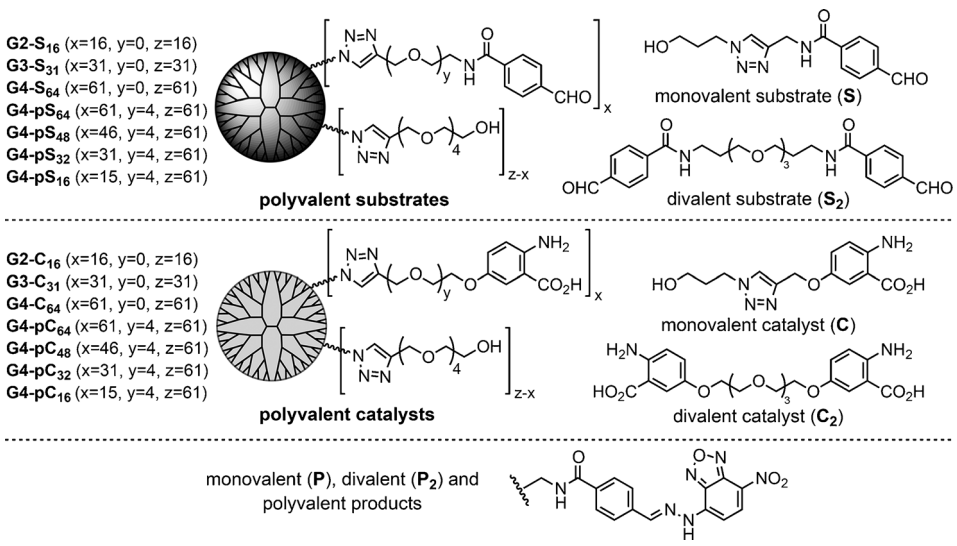

Figure 2. Monovalent and dendrimer-based polyvalent substrates and catalysts. Functionalized dendrimers are designated by the following code: G#-$X_{valence}$, where G# is the dendrimer generation (G2, G3, or G4); X is the functional unit displayed (S is the benzaldehyde substrate with the short propargylamide linker from **2a**, pS is the benzaldehyde substrate with the longer tetraglyme-based linker from **2b**, C is anthranilate with the short propargyl linker from **3a**, and pC is anthranilate with the longer tetraglyme-based linker from **3b**); "valence" is the approximate number of substrate or catalyst units attached per dendrimer.

Table 1: Rate constants derived from the plots shown in Figure 3A–D. [**H**] = 25 μM for all experiments.

Figure no.	Substrate[a]	Catalyst[a]	k_{obs} [$M^{-1}s^{-1}$]	Rate ratio 1[b]	Rate ratio 2[c]
3A	**G2-S$_{16}$**[d]	**G2-C$_{16}$**[e]	66.5 ± 3.3	511.5	25.6
	G2-S$_{16}$[d]	**C**[f]	3.2 ± 0.16	24.6	1.2
	G2-S$_{16}$[d]	none	2.6 ± 0.13	20.2	1.0
	S	**G2-C$_{16}$**[e]	1.1 ± 0.05	8.5	0.8
	S	**C**[f]	0.41 ± 0.02	3.2	0.3
	S	none	0.13 ± 0.01	1.0	0.1
3B	**G3-S$_{31}$**	**G3-C$_{31}$**	391.0 ± 15.0	2607	59.2
	G3-S$_{31}$	**C**	14.0 ± 0.7	93.3	2.1
	G3-S$_{31}$	none	6.6 ± 0.3	44.0	1.0
	S	**G3-C$_{31}$**	8.1 ± 0.4	54.0	1.2
	S	**C**	0.3 ± 0.02	2.0	0.05
	S	none	0.15 ± 0.02	1.0	0.02
3C	**G4-S$_{61}$**	**G4-C$_{61}$**	30.1 ± 1.5	231.5	20.1
	G4-S$_{61}$	**C**	2.3 ± 0.11	17.7	1.5
	G4-S$_{61}$	none	1.5 ± 0.08	11.5	1.0
	S	**G4-C$_{61}$**	0.63 ± 0.03	6.0	0.4
	S	**C**	0.32 ± 0.02	3.2	0.2
	S	none	0.13 ± 0.01	1.0	0.09
3D	**G4-pS$_{61}$**	**G4-pC$_{61}$**	29.1 ± 1.5	223.8	22.3
	G4-pS$_{61}$	**C**	1.76 ± 0.09	13.5	1.4
	G4-pS$_{61}$	none	1.30 ± 0.08	10.0	1.0
	S	**G4-pC$_{61}$**	0.59 ± 0.04	4.5	0.5
	S	**C**	0.32 ± 0.02	2.5	0.2
	S	none	0.13 ± 0.01	1.0	0.1

[a] The substrate and catalyst were used at a concentration of 100 μM, unless otherwise noted. [b] Ratio (k_{cat}/k_{uncat}) of the rate of the polyvalent reaction to that of the reaction [**S** + **H**]. [c] Ratio (k_{cat}/k_{uncat}) relative to the reaction [polyvalent substrate + **H**]. [d] Concentration: 50 μM. [e] Concentration: 12.5 μM. [f] Concentration: 25 μM.

reaction involving a monovalent substrate with a monovalent catalyst. The same pattern was also observed at pH 6; although the absolute rates of all the reactions decreased relative to those at pH 5, the polyvalent display of the catalyst and substrate afforded the same kinetic advantage (see Figures S4 and S8 in the Supporting Information).

Similar levels of acceleration (approximately 70-fold) have been reported with monovalent catalysts operating on monovalent substrates, but far higher concentrations of aniline[30] or 5-methoxyanthranilic acid[27] were required (10 and 1 mM, respectively). The use of either of these known catalysts at 25 μM gave similar results to those described above for monovalent **C** (data not shown). Substrate and catalyst concentrations are described here in terms of the functional groups; for example, when substrate **G4-pS$_{61}$** was used at an aldehyde concentration of 25 μM, the concentration of the fully functionalized dendrimer was 25/61 = 0.4 μM. Thus, in terms of the concentration of reactive particles, the observed reaction rates are far in excess of any reported so far.

Although G2, G3, and G4 dendrimer substrates and catalysts all showed strong rate acceleration in reactions with each other, the relative rates did not track with size. The G3 dendrimer imparted enhanced reactivity in all cases as compared to the G2 and G4 platforms (Figure 3B, Table 1), including as a polyvalent substrate reacting in the absence of a catalyst (6.6 versus 2.6 or 1.5 $M^{-1}s^{-1}$), in the presence of monovalent catalyst (14.0 versus 3.2 or 2.3 $M^{-1}s^{-1}$), and as a polyvalent catalyst with the monovalent substrate (8.1 versus 1.1 or 0.63 $M^{-1}s^{-1}$). As expected from these results, the G3 polyvalent–polyvalent combination was the fastest reaction measured in this study, with a rate constant of 391 $M^{-1}s^{-1}$ in the presence of 100 μM catalyst (3.2 μM of the polyvalent G3 catalyst particle).

Several lines of evidence were inconsistent with nonspecific aggregation being the key factor in the observed acceleration of hydrazone formation, rather than a structure-based polyvalent catalytic effect of the type described in Figure 1A: 1) No aggregates were observed by dynamic light scattering for dendrimers bearing the catalyst and the substrate under the reaction conditions; only at concentrations approximately 100 times greater were aggregates detected. The minimum aggregate size detected by our instrumentation is approximately 5 nm. 2) G4 dendrimers with and without a tetraglyme spacer between the triazole and the aldehyde groups (designated **G4-S$_{61}$** and **G4-pS$_{61}$**) were

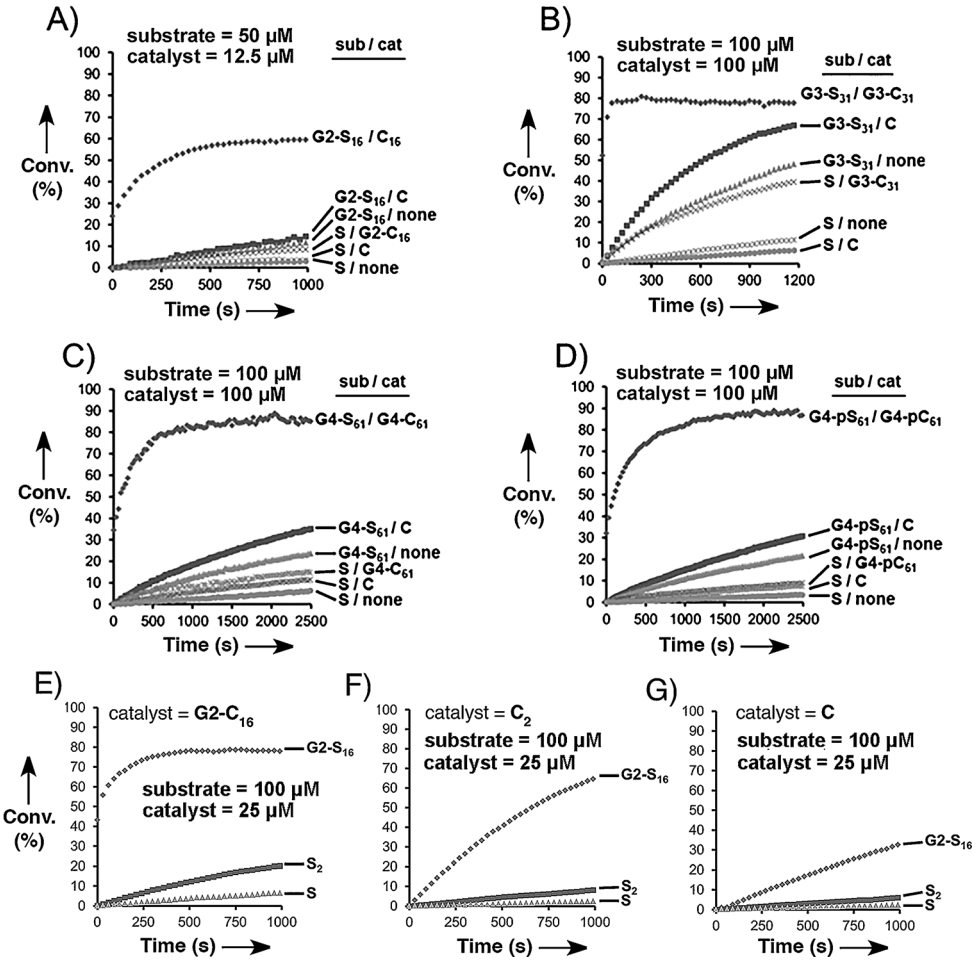

Figure 3. Representative data for reactions of species shown in Figure 2. A–D) Reactivity profiles of fully loaded G2/short linker, G3/short linker, G4/short linker, and G4/long linker polyvalent catalysts and substrates in the presence of hydrazine **H**. E–G) Reactions of monovalent, divalent, and G2-polyvalent substrates with monovalent, divalent, and G2-polyvalent versions of the catalyst. All reactions were performed with 25 μM hydrazine **H**; the concentrations of aldehyde and anthranilate groups are indicated in each panel.

prepared with the expectation that they should differ significantly in their tendency to aggregate in aqueous solution. These scaffolds gave virtually identical results (Figure 3C versus D, Table 1), thus suggesting that hydrophobicity of the dendrimer surface had little effect on polyvalent catalysis.[18] 3) The presence of unreactive hydrophilic or hydrophobic dendrimers added in excess had no effect on reaction kinetics (see Figure S10). If nonspecific aggregation were important, one or both of these added dendrimers would be expected to change the reaction rate.

To gain a better appreciation of the roles of intramolecular association versus polyvalency, we prepared a divalent substrate and catalyst as the simplest tethered components. Figure 3E–G shows comparisons of reactions with monovalent, divalent, and G2-based polyvalent reactants. Pairwise comparisons of rate (see Figures S20 and S21) showed that multivalency had a consistently greater effect for the substrate than for the catalyst. Thus, the divalent catalyst operated on various substrates only 1.5–2.7 times faster than the monovalent catalyst, but the divalent substrate reacted 3.8–4.6 times faster than its monovalent counterpart in the presence of different catalysts. Similarly, the rate acceleration for the polyvalent versus divalent substrate (6.5–26.1-fold) was much greater than for the polyvalent versus divalent catalyst (3.3–7.4-fold).

We suggest that these results reflect two beneficial effects of substrate polyvalency: enhanced initial binding to the catalyst (an advantage that can be described in terms of effective molarity[40,41]) and enhanced processivity, or "rolling" (Figure 4). Polyvalent catalysts should benefit from the first but not the second. Overall, the intersection of a polyvalent catalyst and a polyvalent substrate is highly effective, especially since the concentrations of catalyst- and substrate-bearing particles are much less than those of the lower-valent species used in these comparisons.

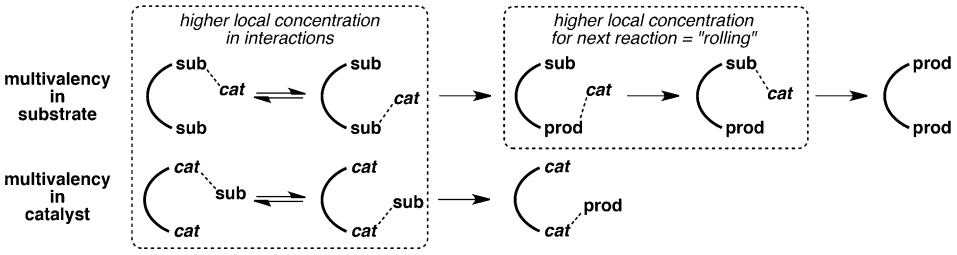

Figure 4. Schematic representation of two different types of polyvalent advantage in catalysis. "sub" = substrate (aldehyde), "cat" = catalyst (anthranilate), "prod" = product (hydrazone).

Rates of hydrazone formation with G4 dendrimers bearing different numbers of substrate and catalyst units were measured, with the total concentration of substrate and catalyst moieties kept constant at 100 μM. Thus, particles

bearing fewer functional units were used in larger amounts. The observed reaction rate constants were found to be highly sensitive to the functional-group density on the scaffold (Figure 5). Relatively small decreases in rate were observed when the occupancy of the substrate or catalyst was cut to three-quarters (61–46 per dendrimer), but a much greater loss was observed in going from three-quarters to half (46–31 per dendrimer; Figure 5 A,B). The simultaneous variation of both substrate and catalyst loading produced a dramatic drop in catalytic rate at both the first and second dilution in functional-group density (Figure 5 C). Furthermore, polyvalent reactions involving 16 and 31 functional units on each scaffold were highly dependent on the scaffold size (Table 2). Thus, the reaction of **G2-S$_{16}$** mediated by **G2-C$_{16}$** was much faster than all reactions involving a similar number of reactive groups on the larger G4 scaffold (**G4-pS$_{15}$** + **G4-pC$_{61}$**; **G4-pS$_{61}$** + **G4-pC$_{15}$**; **G4-pS$_{15}$** + **G4-pC$_{15}$**). Similarly, **G3-S$_{31}$** + **G3-C$_{31}$** was a much faster reaction than reactions involving **G4-pS$_{31}$** or **G4-pC$_{31}$**. In contrast, reactions between any of the fully loaded dendrimers were all within a factor of 4 of each other (see Figures S4, S6, and S8 and Tables S1–S3).

Table 2: Comparison of reactions involving similar numbers of substrate and catalyst units on different-sized dendrimer scaffolds. Aldehyde and anthraniliate concentration: 100 μM, unless noted otherwise.

Figure no.	Substrate	Catalyst[a]	k_{obs} [$M^{-1}s^{-1}$]	Rate incr.[b]
5 A	**G4-pS$_{15}$**	**G4-pC$_{61}$**	1.7 ± 0.09	1.1
5 B	**G4-pS$_{61}$**	**G4-pC$_{15}$**	3.7 ± 0.19	2.5
5 C	**G4-pS$_{15}$**	**G4-pC$_{15}$**	1.5 ± 0.08	1.0
S4 F	**G2-S$_{16}$**	**G2-C$_{16}$** (50 μM)	143.9 ± 7.2	95.9
5 A	**G4-pS$_{31}$**	**G4-pC$_{61}$**	3.3 ± 0.17	1.8
5 B	**G4-pS$_{61}$**	**G4-pC$_{31}$**	4.8 ± 0.24	2.7
5 C	**G4-pS$_{31}$**	**G4-pC$_{31}$**	1.8 ± 0.09	1.0
3 B	**G3-S$_{31}$**	**G3-C$_{31}$**	391.0 ± 19.6	217.2

[a] The catalyst was used at a concentration of 100 μM, unless noted otherwise. [b] Factor by which the rate constant increased relative to the slowest reacting polyvalent scaffolds bearing a similar number of reactive substrates and catalysts.

This observed sharp and nonlinear dependence of reaction rate on functional-group density is significantly different from that of "cooperative" catalysts, in which two or more functional groups on the same scaffold combine to produce a much more effective catalyst than if the functional groups are on different molecules. In such a case, for example, a two-armed catalytic assembly would be revealed by a constant second-order dependence of rate on the density of catalyst–component groups on the scaffold.[11,42] Figure 5 shows a different scenario in which the magnitude of rate acceleration varies across the range of functional-group densities, thus implicating a structure-dependent phenomenon such as "rolling". A simple aggregation effect would be expected to produce a steadier drop in rate as the putative aggregates were diluted by the addition of more dendrimers bearing fewer functional groups.

The concentrations of polyvalent catalysts and polyvalent substrates were independently varied to survey the reaction-rate dependence on these factors (Figure 6). For all three scaffolds, the rate was found to increase with increasing catalyst concentration, although in a nonlinear manner (Figure 6 A–C). In contrast, for G4 and G3, but not G2 dendrimers, high substrate concentrations relative to the catalyst were inhibitory (Figure 6 D–F).

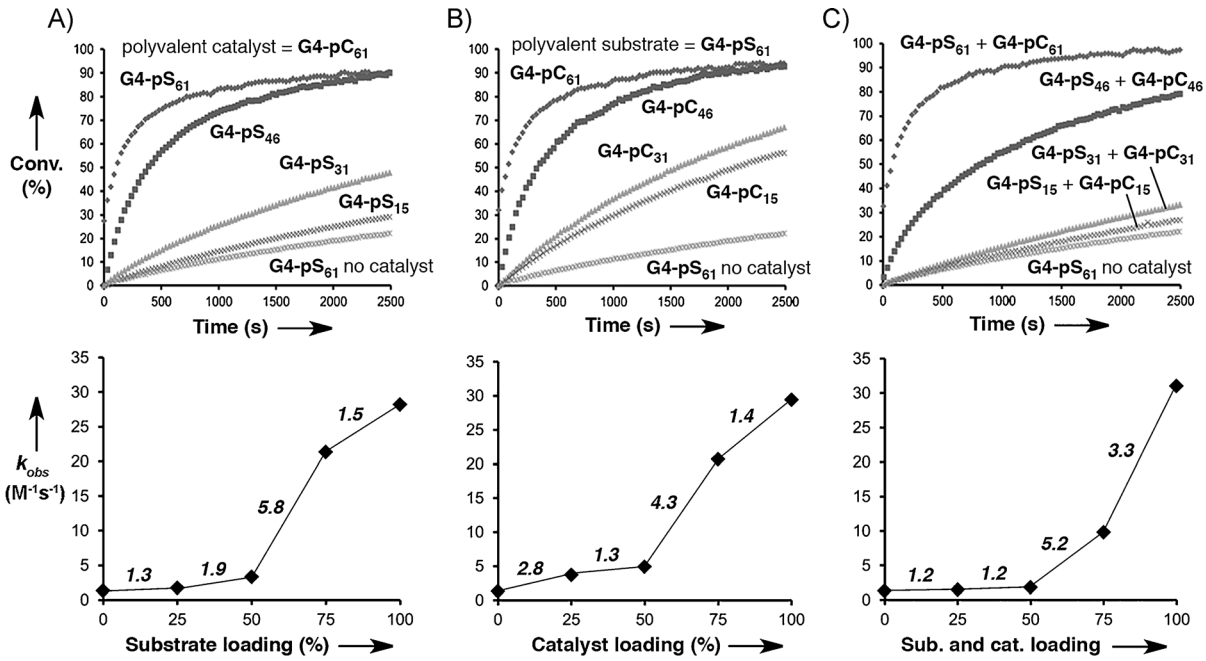

Figure 5. Exploration of rate versus density of the substrate and catalyst on PAMAM scaffolds. A) Variation in substrate loading, B) variation in catalyst loading, C) simultaneous variation in substrate and catalyst loading. Plots of rates derived from these reactions are shown on the right; values in italics are the ratios of the rate of each reaction to that of the next reaction in the series with lower functional-group density. All reactions were performed with 100 μM total substrate, 100 μM total catalyst, and 25 μM hydrazine **H**. Similar results were observed in analogous experiments with 25 μM catalyst (see Figure S16).

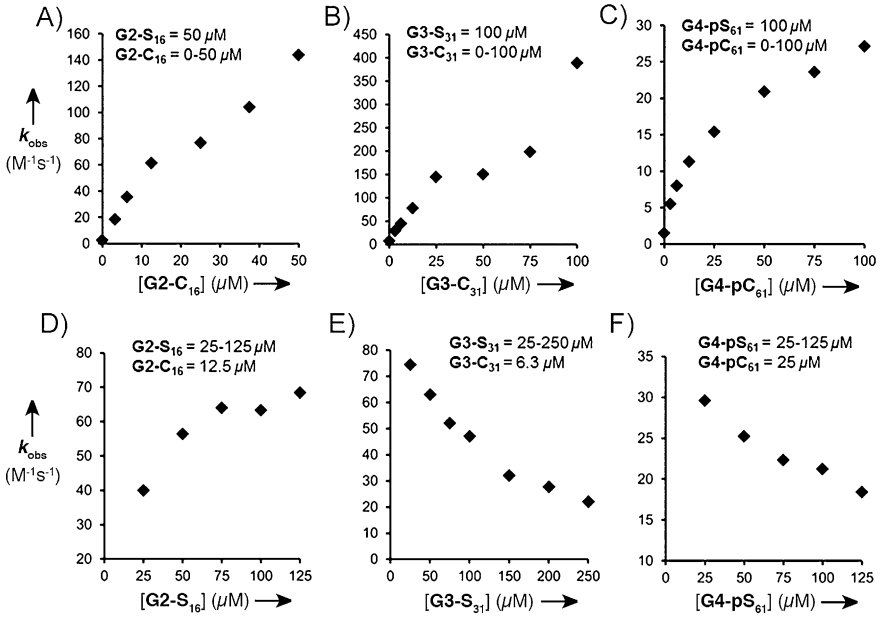

Figure 6. Plots of observed rate constant versus concentration of the fully loaded polyvalent catalyst (A–C) or substrate (D–F), with G2/short linker, G3/short linker, and G4/long linker dendrimers. All reactions were performed with 25 μM hydrazine **H**.

These varying outcomes in the rate dependence on catalyst and substrate concentration would not be observed if each catalyst and substrate moiety was acting independently as in free solution. Furthermore, the inhibitory behavior of higher concentrations of the larger substrate dendrimers is consistent with a potentially deleterious consequence of polyvalent interactions. As represented in Figure 1, multiple catalyst and substrate groups on interacting scaffolds can engage with each other simultaneously. It is possible that some of the resulting imines may not be processed efficiently, since not all will be equally accessible to the hydrazine. Such an inhibitory effect would be expected to be more severe for larger dendrimers, which should be more prone to simultaneous binding over large surface areas. The counterbalancing of this phenomenon with rate acceleration by rolling should produce an optimal formulation, represented in this preliminary study by the significantly faster reactivity of the G3–G3 poly–poly pair compared to G2–G2 and G4–G4.

Rates of hydrazone formation were also measured at different temperatures for polyvalent systems versus monovalent analogues (see Figure S13 and Table S5). Most of these reactions, as well as the reaction of a polyvalent substrate without a catalyst, slowed down at increased temperatures, as previously observed by Bane and co-workers, and ascribed by them to the more favorable formation of imine intermediates at lower temperature.[43] [A similar inverse temperature dependence and formal negative enthalpy of activation have been reported for a different organocatalytic reaction (thiourea-catalyzed Mannich alkylation of imines) in association with the formation of key hydrogen bonds in the activated complex.[44]] In contrast, the very fast processing of polyvalent substrates in the G2 and G3 series was invariant with changes in temperature between 25 and 45 °C (see Figure S13 A,E).

This striking difference was reflected in kinetic parameters obtained by standard Eyring analysis, albeit over a limited temperature range (see Figures S13 and S14). Reactions involving polyvalent substrates with polyvalent catalysts showed substantially diminished entropic costs (less negative values of activation entropy), as expected for polyvalent assistance. Apparent entropy–enthalpy compensation was also observed. Although the compensation is unlikely to be statistically significant,[45,46] this case is uniquely interesting: Few studies of compensation have involved true catalysis (rather than the binding of catalysts), and none have examined activation parameters versus variations in the valency of substrates and catalysts.

Finally, the relationship between solution viscosity and reaction rate was explored by measuring the rates of reactions of the polyvalent **G3-S$_{31}$** substrate with hydrazine **H** in the presence of different catalysts (**G3-C$_{31}$**, **C$_2$**, **C**), in mixtures of a buffer and glycerol (up to 50 %) to increase solution viscosity.[47] Although all observed rates were inversely dependent on the glycerol content (see Figure S23), the polyvalent catalyst was significantly less sensitive to increasing viscosity than the divalent or monovalent catalyst. The significant participation of a "rolling" interaction that does not require the diffusion-induced collision of separated particles would be expected to produce such a result.

The interaction of polyvalent surfaces in a catalytic bond-forming function was shown herein to be distinctive. It enabled very rapid anthranilate-catalyzed hydrazone formation when both the substrate and the catalyst were displayed in a polyvalent manner, even though particle concentrations were low. Most interestingly, this type of process was found to be sensitive to functional-group density, reaction-mixture viscosity, and temperature in unusual ways, consistent with the processive "rolling" of catalyst- and substrate-bearing particles with respect to each other. These findings illustrate a relatively simple way to enhance surface-based catalytic reactivity, and suggest the existence of a complex kinetic landscape with elements of homogeneous and heterogeneous catalytic features. We believe that additional examples await the construction of such systems in the laboratory and the discovery or appreciation of membrane- or biopolymer-arrayed catalysts and substrates in biology.

Keywords: dendrimers · hydrazone formation · kinetics · polyvalent catalysts · polyvalent substrates

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[39] For example, Dawson reported a rather fast uncatalyzed reaction of benzaldehyde with a peptidic hydrazine at pH 4.5 ($k_{obs} \approx 2.6\,M^{-1}s^{-1}$; Ref. [30]), whereas Kool described a slower uncatalyzed reaction of hydrazine **H** with *p*-nitrobenzaldehyde ($0.52\,M^{-1}s^{-1}$ at pH 4.5; $0.06\,M^{-1}s^{-1}$ at pH 5.5; Ref [27]). Since *p*-nitrobenzaldehyde should be a much more reactive electrophile than the 4-formylbenzamides, the PAMAM dendrimer, and the peptide used by Dawson, may accelerate the reaction in other ways.

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Communications

Catalysis on Dendrimers

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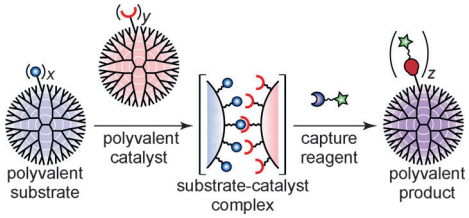
Polyvalent Catalysts Operating on Polyvalent Substrates: A Model for Surface-Controlled Reactivity



Roll and rock: Fast nucleophilic catalysis of hydrazone ligation was observed with polyvalent anthranilic acid catalysts operating on polyvalent aldehyde substrates with a common dendrimer platform. The rapid catalysis and unique kinetic parameters observed are attributed to polyvalent engagement between the dendrimer surface groups and a potential "rolling" effect that promotes fast interparticle kinetic turnover (see picture).