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Novel Catalysis in the Internal Nanocavity of Polyamine Dendrimer for Intramolecular Michael Reaction

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Poly(propyleneimine) (PPI) dendrimers functionalized with C_{16} alkyl chains acted as efficient tertiary amine catalysts for an intramolecular Michael reaction. The substrate was accommodated in a reactive conformation within a sterically confined nanocavity consisting of regularly arranged tertiary amino groups of the PPI dendrimers.

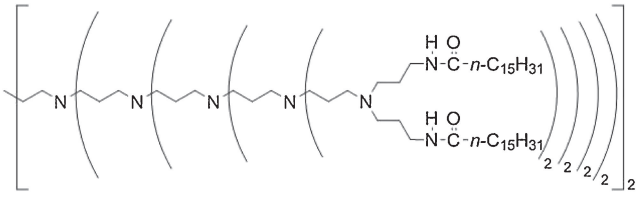
Dendrimers have received considerable attention as promising materials in various research areas[1] because of the following characteristics: 1) tunable chemical and physical properties by changing core, branch, and peripheral units, and 2) internal nanocavities which can encapsulate organic molecules,[2a] metal complexes,[2b,2c] and metal nanoparticles.[2d,2e] In the field of catalysis, dendrimers allow precise design of catalytically active species and reaction environments, exhibiting unique activities and selectivities. To date, various dendrimers have been reported to show positive dendritic effects on catalysis,[3a–3g] such as site-isolation of active species,[3a] locally high concentrations of substrates,[3b,3c] or catalytically active species,[3d] polar/nonpolar reaction environments,[3e] and catalytic pump effects.[3f] However, catalysis due to the steric effect of the confined nanocavities of dendrimers has been rarely investigated.[4]

Herein, we investigated the intramolecular Michael reaction using the alkylated poly(propyleneimine) (PPI) dendrimers as tertiary amine catalysts and found a novel dendritic effect of the internal nanocavity PPI dendrimers.[5,6] The PPI dendrimers accommodated the substrate in a reactive conformation for the intramolecular cyclization within the nanocavity, with the result that the intramolecular Michael reaction proceeded smoothly.

Alkylated PPI dendrimers were synthesized according to a reported procedure.[3f,7,16] Third- to fifth-generation NH_2-terminated PPI dendrimers G_x-NH_2 ($x = 3$, 4, and 5, denoting the generation number of the dendrimer) were treated with palmitoyl chloride to afford alkylated PPI dendrimers, G_x-C_{16} (Scheme 1).

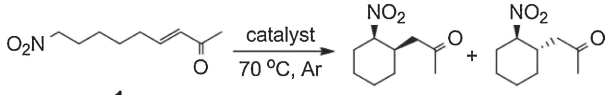
The intramolecular Michael reaction of (*E*)-9-nitro-3-nonen-2-one (**1**) to 1-(2-nitrocyclohexyl)propan-2-one (**2**) was examined using G_x-C_{16} as a catalyst (Table 1). G_5-C_{16} ($pK_a = 10.35$)[8] catalyzed the intramolecular Michael reaction of **1** quantitatively in 2 h (Entry 3). Interestingly, the catalytic activity of G_x-C_{16} increased as the generation of the dendrimer increased (Entries 2, 5, and 6). Triethylamine (TEA, $pK_a = 10.7$),[9] which corresponds to the amine component of the nanocavity of G_5-C_{16}, did not promote this reaction (Entry 12). Other low-molecular-weight amines such as *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (TMPDA, $pK_a = 10.5$),[9] *N*,*N*-dimethyl-4-aminopyridine (DMAP, $pK_a = 9.2$),[9] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, $pK_a = 18.7$)[9] showed lower catalytic activities than G_5-C_{16} (Entry 1 vs. Entries 7, 9, and 11). Even a solvent amount of TEA, with higher amine concentration than the nanocavity of G_5-C_{16},[10] gave a low yield of **2** (Entry 13). The initial reaction rates for the intramolecular Michael reaction of **1** in the presence of G_5-C_{16} and in a TEA solvent were 0.56 and 0.046 μmol s^{-1}, respectively; the catalytic activity of G_5-C_{16} was 12 times greater than that of TEA. When using the poly(ethyleneimine) modified with C_{16} alkyl chains (PEI-C_{16})[16] as an irregularly branched polyamine catalyst, the intramolecular Michael reaction did not proceed efficiently (Entry 14).

In the intramolecular Michael reaction of **1**, a diastereomeric mixture of **2a** and **2b** with a *syn*:*anti* ratio of 45:55 was obtained (Entries 1 and 8). In the case of G_5-C_{16}, isomerization of **2a** to



Scheme 1. Structure of G_5-C_{16} dendrimer.

Table 1. Intramolecular Michael reaction of **1** using various amine catalysts[a]



1 **2a** (*syn*) **2b** (*anti*)

Entry	Catalyst	Time	Conv. /%[b]	Yield /%[b]	*syn*:*anti*[b]
1	G_5-C_{16}	15 min	69	68	43:57
2	G_5-C_{16}	1 h	85	84	44:56
3	G_5-C_{16}	2 h	99	98 (89[c])	43:57
4	G_5-C_{16}	24 h	99	98	25:75
5	G_4-C_{16}	1 h	72	70	42:58
6	G_3-C_{16}	1 h	62	60	41:59
7	DBU	15 min	60	58	20:80
8	DMAP	5 min	13	12	44:56
9	DMAP	15 min	30	29	34:66
10	DMAP	8 h	99	98	10:90
11	TMPDA	1 h	7	3	—
12	TEA	1 h	N. R.	—	—
13	TEA[d]	1 h	17	15	43:57
14	PEI-C_{16}	1 h	13	12	41:59

[a]Reaction conditions: **1** (0.2 mmol), catalyst (tertiary N atom: 30 μmol), toluene (2 mL). [b]Determined by ^{1}H NMR using an internal standard. [c]Isolated yield. [d]TEA (2 mL) was used instead of toluene.

the thermodynamically stable *anti*-isomer **2b** did not occur to a significant extent until complete conversion of **1** had taken place (Entries 1–4). On the other hand, when using DMAP, the isomerization reaction proceeded simultaneously with the intramolecular Michael reaction (Entries 8–10).

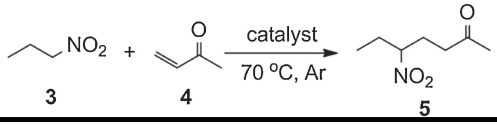
Furthermore, in the intramolecular Michael reaction of (*E*)-8-nitro-3-octen-2-one, G_5-C_{16} showed higher catalytic activity than DMAP; G_5-C_{16} afforded 1-(2-nitrocyclopentyl)propan-2-one in 99% yield for 30 min, while DMAP gave 22% yield of the cyclization product (Table S3).[11,16]

The intramolecular Michael reaction generally occurs via nucleophilic attack of a carbanion generated by deprotonation of a donor part to a distant acceptor part and subsequent protonation of the corresponding enolate intermediate.[12] Noting the positive generation effect observed for G_x-C_{16} and the low catalytic activity of PEI-C_{16}, it was suggested that the efficient intramolecular Michael reaction using G_5-C_{16} proceeds through substrate orientation within the sterically confined nanocavity consisting of regularly arranged tertiary amino groups of G_5-C_{16}; the encapsulated substrate **1** is deprotonated by the tertiary amino group to form the corresponding carbanion species **1a** together with a quaternary ammonium cation. Next, the acceptor part of **1a** is oriented toward the distant donor part of **1a** by a sterically confined nanocavity consisting of the core and branch units of G_5-C_{16}. This conformation allows an electrostatic interaction between the quaternary ammonium cation of the nanocavity and the carbonyl group of **1a**,[13] resulting in facile nucleophilic attack of the donor part of **1a** to form a cyclized enolate intermediate. Subsequent protonation of the enolate intermediate furnishes the product **2**. The sluggish isomerization of **2a** to **2b** during the intramolecular Michael reaction may be due to the preferential accommodation of **1** over **2** into the nanocavity of G_5-C_{16}. After complete conversion of **1**, the isomerization of **2a** to **2b** occurs.

To support this suggested substrate orientation in the intramolecular Michael reaction, preliminary kinetic studies of the intramolecular Michael reaction of **1** were carried out using G_5-C_{16}, TEA, and PEI-C_{16} (Table S4[16]). The activation entropies $\Delta S^{\ddagger}$ of G_5-C_{16}, TEA, and PEI-C_{16} were −266, −249, and −243 $J\,K^{-1}\,mol^{-1}$, respectively. The smaller $\Delta H^{\ddagger}$ value of G_5-C_{16} confirms that the transition state for cyclization is more restricted by steric effects when this catalyst is used compared to the case of TEA and PEI-C_{16}.[14] The activation enthalpies $\Delta H^{\ddagger}$ were obtained as 16.4, 29.0, and 30.6 $kJ\,mol^{-1}$ for G_5-C_{16}, TEA, and PEI-C_{16}, respectively, showing that the nanocavity of G_5-C_{16} lowered the barrier for intramolecular nucleophilic attack by stabilizing the transition state. The activation energy E_a of G_5-C_{16} (20.0 $kJ\,mol^{-1}$) was much lower than that of TEA and PEI-C_{16} (31.7 and 33.3 $kJ\,mol^{-1}$, respectively).

The catalytic activities of G_x-C_{16} and other amines were examined in the *intermolecular* Michael reaction of 1-nitropropane (**3**) and methyl vinyl ketone (**4**) to 5-nitroheptan-2-one (**5**) (Table 2).[15] The catalytic activities of G_5-C_{16} and a solvent amount of TEA were almost the same in terms of yield (Entry 1 vs. Entry 7) and initial reaction rate (1.43 and 1.58 $\mu mol\,s^{-1}$ for G_5-C_{16} and TEA, respectively), which was in sharp contrast to the results obtained for the intramolecular Michael reaction of **1** (Table 1, Entry 2 vs. Entry 13). Further, the difference of the catalytic activity between G_5-C_{16} and PEI-C_{16} was smaller in the intermolecular Michael reaction than that in the intramolecular Michael reaction (Table 1, Entry 3 vs. Entry 14, and Table 2, Entry 1 vs. Entry 8). These remarkably different results between *intramolecular* and *intermolecular* Michael reaction support the occurrence of specific substrate orientation for intramolecular cyclization of **1** within the internal nanocavity of G_5-C_{16}.

Table 2. Intermolecular Michael raction of **3** and **4** to **5**[a]



3 4 5

Entry	Catalyst	Conv. of **3**/%[b]	Yield of **5**/%[b]
1	G_5-C_{16}	47	45
2[c]	G_5-C_{16}	85	70
3	G_4-C_{16}	25	24
4	G_3-C_{16}	14	12
5	TMPDA	8	6
6	TEA	4	3
7	TEA[d]	45	43
8	PEI-C_{16}	24	22

[a]Reaction conditions: **3** (0.2 mmol), **4** (0.5 mmol), catalyst (tertiary N atom: 30 µmol), toluene (2 mL), 24 h. [b]Determined by GC using an internal standard. [c]48 h. 1-(5-Ethyl-2-hydroxy-2-methyl-5-nitrocyclohexyl)ethanone was obtained in 13% yield by consecutive reaction of **5** (see ref. 15). [d]TEA (2 mL) was used instead of toluene.

In conclusion, the alkylated PPI dendrimer G_5-C_{16} acted as an organocatalyst and showed a novel dendritic effect in the intramolecular Michael reaction based on substrate orientation within its internal nanocavity. The sterically confined nanocavity consisting of regularly arranged amino groups of G_5-C_{16} could accommodate the substrate in a reactive conformation for intramolecular cyclization. We believe that such substrate orientation within the internal nanocavities of dendrimers may be applicable not only to the intramolecular Michael reaction but also to other cyclization reactions.

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10 Dynamic light scattering (DLS) measurement of G_5-C_{16} in toluene revealed that G_5-C_{16} was an unimolecular micelle with an average diameter of 8.0 ± 1.5 nm. We assumed that the diameter of the PPI unit of G_5-C_{16} was ca. 4 nm based on its molecular modeling. The concentration of tertiary amino groups in the internal nanocavity of G_5-C_{16} was calculated as 3.3 mol dm^{-3} which value is lower than that of a solvent amount of TEA (7.2 mol dm^{-3}).

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