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Nucleobase dendrimer as a multidentate ligand for a rare-earth metal ion

Masahide Tominaga, Jun Hosogi, Katsuaki Konishi* and Takuzo Aida*

Fields and Reactions, Precursory Research for Embryonic Science and Technology, Japan Science and Technology Corporation, and Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan. E-mail: aida@macro.t.u-tokyo.ac.jp

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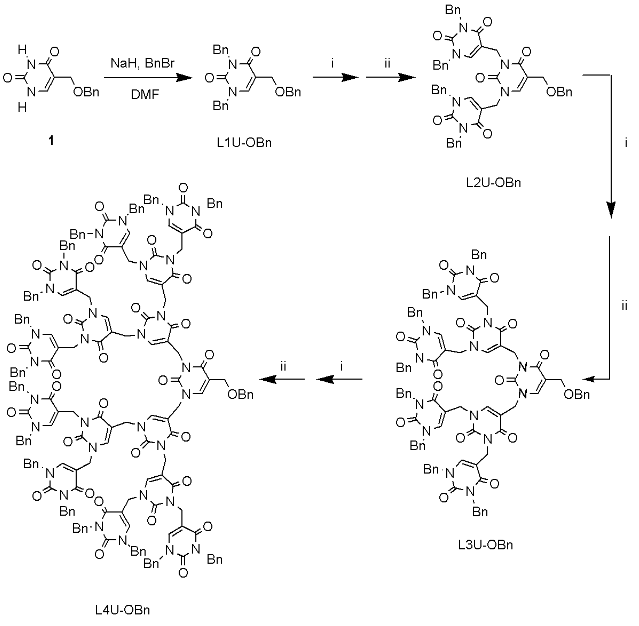
Novel dendritic macromolecules consisting of uracil units (L*n*U-OBn) with the numbers of the nucleobase layers (*n*) of 2–4 were synthesized; L3U-OBn and L4U-OBn both formed 1 : 1 complexes with La^{3+}, where the L4U-OBn–La^{3+} complex, in particular, was highly robust towards methanolysis.

Dendrimers are hyperbranched, three-dimensional macromolecules with a pseudo network structure,[1] and have a potential for trapping of guest molecules.[2] In particular, dendritic molecules bearing binding sites for metal ions have attracted great attention.[3–5] Herein, we report the synthesis of the first dendritic polynucleobase, and highlight its very high activity for multidentate ligation with lanthanum ion.[6]

For the synthesis of the dendritic architecture, we chose uracil as a building block. Synthesis of the dendritic polyuracils (L*n*U-OBn; *n* = number of the nucleobase layers) was carried out by the convergent approach (Scheme 1) starting from (i) bromination of 1,3-dibenzyl-5-benzyloxymethyluracil (L1U-OBn) with HBr–AcOH,[7] followed by (ii) an alkaline-mediated coupling reaction of the resulting 5-bromomethyl derivative (L1U-Br) with 5-benzyloxymethyluracil **1**, to give L2U-OBn. Repetition of these two steps allowed formation of higher-generation L*n*U-OBn (*n* = 3, 4).[8] The absence of structural defects in L*n*U-OBn (*n* = 2–4) was confirmed by ^1H NMR, MALDI-TOF-MS and SEC analyses. For example, L*n*U-OBn (*n* = 2–4) all showed a single MALDI-TOF-MS peak due to $[M + Na]^+$ [Fig. 1(a) (I)–(III)] and a unimodal SEC chromatogram [Fig. 1(b)]. L*n*U-OBn (*n* = 2–4) were highly soluble in common organic solvents such as CH_2Cl_2, $CHCl_3$, benzene, acetone, MeCN and DMF, but scarcely soluble in protic solvents such as MeOH and water. In the electronic absorption spectra in MeCN, L*n*U-OBn (*n* = 2–4) showed an absorption band due to the uracil units at 274.8–275.6 nm, which is red-shifted from that of non-dendritic L1U-OBn (270.0 nm), indicating some intramolecular electronic interactions among the dendritic uracil units.

Dendritic polyuracils bear many heteroatoms and are expected to show potential for trapping of multi-coordinate metal ions. La^{3+} was chosen as a substrate, which is characterized by the largest ionic radius among rare-earth metal ions, and its preference to adopt a high coordination number (up to 12).[9] Typically, upon titration of an MeCN solution of L3U-OBn (10 μM) with $La(OTf)_3$ at 25 °C, the absorption band of the uracil units red-shifted from 275.2 to 281.4 nm with clear isosbestic points at 248.4 and 275.0 nm (Fig. 2, inset). Plots of the absorbance at 296.6 nm *vs.* $[La(OTf)_3]_0$ showed a clear inflection point at a mole ratio $[L3U\text{-}OBn]_0/[La(OTf)_3]_0$ of unity (Fig. 2). Job plots of ΔA at 296.6 nm also exhibited a maximum at a mole ratio $[L3U\text{-}OBn]_0/[La(OTf)_3]_0$ of unity. Furthermore, MALDI-TOF-MS spectrometry of a mixture of L3U-OBn and $La(OTf)_3$ (1 : 2) showed a peak at 2133 due to $[L3U\text{-}OBn\text{–}La(OTf)_2]^+$ (calc. *m/z* 2134) in addition to that of a Na^+ adduct [Fig. 1(a) (ii)]. These observations indicate a strong one-to-one complexation between L3U-OBn and La^{3+} with an association constant $> 10^7$ M^{-1}.[10] Likewise, titration of one-generation larger L4U-OBn with $La(OTf)_3$ (Fig. 2) showed a similar red shift (275.6 to 281.0 nm) with two isosbestic points (246.8, 271.8 nm), and a Job plot again indicated a 1 : 1 complexation of L4U-OBn with La^{3+}. Furthermore, a MALDI-TOF-MS peak due to the one-to-one adduct $[L4U\text{-}OBn\text{–}La(OTf)_2]^+$ (calc. *m/z* 3847) was observed [Fig. 1(a) (iii)].

An MeCN solution of L3U-OBn (2.5 mM) at 25 °C showed two C=O stretching vibrational bands at 1708 [C(2)=O] and 1665 cm^{-1} [C(4)=O] [Fig. 3(a)].[11] On the other hand, when $La(OTf)_3$ (5.0 mM) was added to the solution, a new IR band at 1609 cm^{-1}, assignable to the coordinated C=O functionality,



Scheme 1 Synthetic approach to dendritic polyuracils L*n*U-OBn (*n* = 2–4). *Reagents and conditions*, i, HBr, AcOH, dioxane, r.t., 12 h; ii, **1**, K_2CO_3, DMF, r.t., 12 h.

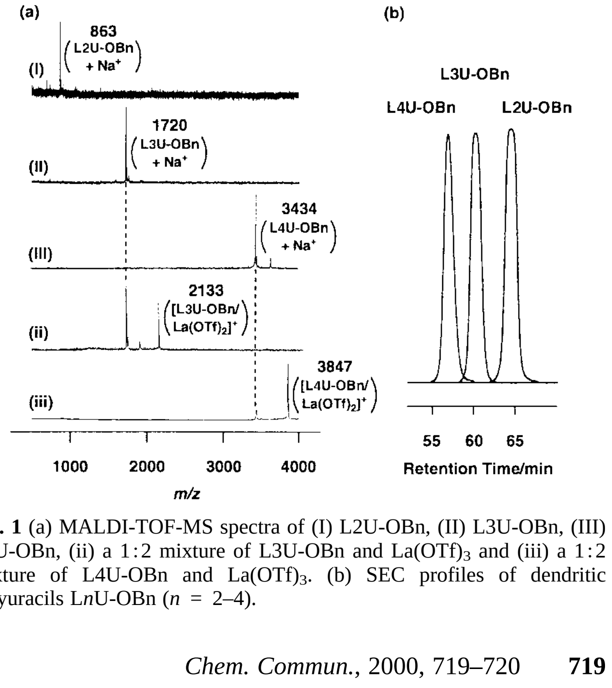


Fig. 1 (a) MALDI-TOF-MS spectra of (I) L2U-OBn, (II) L3U-OBn, (III) L4U-OBn, (ii) a 1 : 2 mixture of L3U-OBn and $La(OTf)_3$ and (iii) a 1 : 2 mixture of L4U-OBn and $La(OTf)_3$. (b) SEC profiles of dendritic polyuracils L*n*U-OBn (*n* = 2–4).

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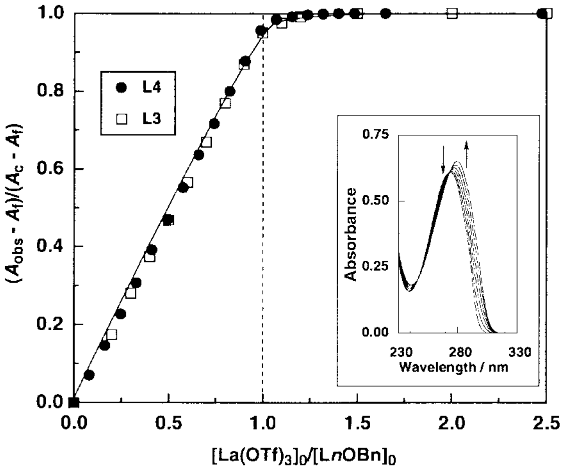

Fig. 2 Spectroscopic titration of MeCN solutions of L*n*U-OBn (10 μM) (*n* = 3 [□], 4 [●]) with $La(OTf)_3$ at 25 °C monitored at 296.6 nm. Plots of $(A_{obs} - A_f)/(A_c - A_f)$ *vs.* $[La(OTf)_3]_0/[LnU\text{-}OBn]_0$. A_{obs} represents the observed absorbance, while A_f and A_c denote the absorbances of free and complexed uracil units, respectively. Inset: absorption spectral change.

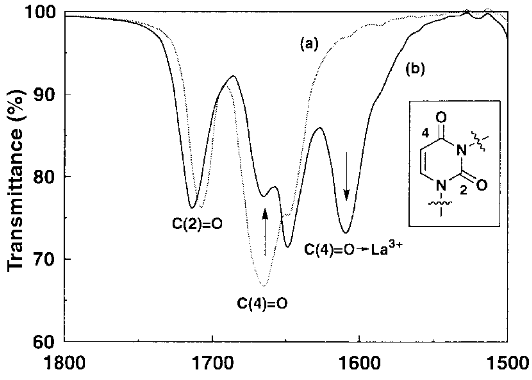

Fig. 3 IR spectra of (a) L3U-OBn (2.5 mM) and (b) a 1 : 2 mixture of L3U-OBn and $La(OTf)_3$ (2.5, 5.0 mM) in MeCN at 20 °C.

appeared at the expense of the non-coordinated C(4=O band [Fig. 3(b)]. Considering also a small shift due to the C(2)=O frequency (1708 to 1714 cm^{-1}), the C(4)=O functionality is likely involved predominantly in the complexation with La^{3+}.[12] As estimated from the decrease in integral area of the free C(4)=O band at 1665 cm^{-1},[13] an La^{3+} ion accommodates four out of seven C(4)=O groups in L3U-OBn for complexation. On the other hand, in the complexation with higher-generation L4U-OBn having fifteen C(4)=O groups, seven C(4)=O groups were estimated to coordinate to a La^{3+} ion.

From the above results, it is expected that La^{3+} ion is trapped by L4U-OBn more strongly than lower-generation L3U-OBn. In fact, the L4U-OBn–La^{3+} complex was highly robust towards methanolysis: when an MeCN solution of a mixture of L3U-OBn (10 μM) and $La(OTf)_3$ (20 μM) was titrated with MeOH (Fig. 4), the absorption spectral change at 296.6 nm showed a complete dissociation of La^{3+} from L3U-OBn at a MeOH content of 40%. On the other hand, the L4U-OBn–La^{3+} complex showed a spectral profile of only 30% dissociation under the same conditions (Fig. 4).

The high activity of L*n*U-OBn for the complexation with La^{3+} is considered to take great advantage of the multidentate coordination characteristics of the dendritic polyuracil architecture, since non-dendritic L1U-OBn did not show any substantial spectral changes upon mixing with $La(OTf)_3$. Spectral changes were also small when L*n*U-OBn (*n* = 3, 4) were mixed (1 : 1 mol ratio; in MeCN) with metal ions such as Na^+, K^+, Zn^{2+}, Cu^+, Cu^{2+} or Ag^+ (triflate salts) having a preference for lower coordination numbers.

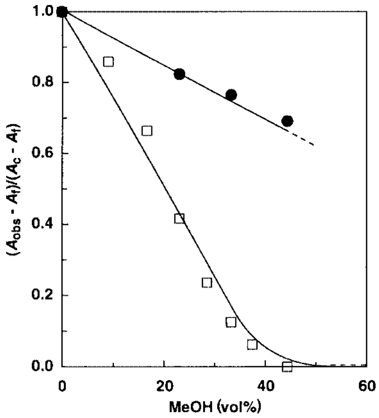

Fig. 4 Spectroscopic titration of an MeCN solution of a 1 : 2 mixture of L*n*U-OBn (10 μM) (*n* = 3 [□], 4 [●]) and $La(OTf)_3$ (20 μM) with MeOH at 25 °C monitored at 296.6 nm. Plots of $(A_{obs} - A_f)/(A_c - A_f)$ *vs.* vol.% of MeOH.

Dendrimer complexes of lanthanide ions have attracted attention as luminescent materials[4] and have also been applied as MRI contrast agents.[5] On the other hand, a nucleobase complex of a transition metal such as platinum has been studied for biomedical applications.[14] The new metal-ligating nucleobase dendrimer consisting of uracil units may therefore have good potential for a variety of applications in materials science and medicinal chemistry.

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