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## Unique Cation Binding Capability of Cyclic Oligo(L-lactic acid) (L-COLA)

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#### ABSTRACT

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Keywords: Cyclic lactic acid Oligomer Macrocyclization Cation binding Size selectivity Cyclic L-lactic acid octamer (L-COLA-8) shows a unique complexing capability towards alkali and alkali earth metal cations in acetonitrile- $d_3$ /chloroform-d (9/1). The valence of the cation affects the stoichiometry of the complexes between L-COLA-8 and the cation; L-COLA-8 forms a 2:1 complex with alkali metal cations, but forms a 1:1 complex with alkali earth metal cations. Additionally, L-COLA-8 shows a binding selectivity for Rb<sup>+</sup> and Ba<sup>2+</sup>, which have a diameter about 3 Å.

Since Pedersen's discovery of the binding capability of crown ethers towards metal cations,<sup>1</sup> the development of host molecules bearing unique molecular recognition capabilities, such as calixarenes,<sup>2,3</sup> cyclodextrins,<sup>4,5</sup> cyclic oligopeptides,<sup>6,8</sup> cucurbiturils,<sup>9,10</sup> and crown ether derivatives<sup>11</sup> have attracted much attention in diverse fields, including biomedical and pharmaceutical fields as well as analytical and separation sciences. Macrocyclization of linear oligomers or polymers with repeating interaction sites for a guest ion or molecule is a powerful approach to construct host molecules with high guest binding capabilities and selectivities. For instance, macrocyclization of oligo(ethylene glycol)s with electrondonating oxygen atoms yields crown ethers with high cation binding capabilities and selectivities through ion-dipole interactions.<sup>11</sup> On the other hand, macrocyclization of maltooligosaccharides produces cyclodextrins bearing unique cavities into which appropriately sized and shaped guest molecules can be selectively incorporated mainly through hydrophobic and van der Waals interactions.4,5

Oligo or poly(lactic acid)s are composed of several or many lactic acid units with an electron-dense carbonyl oxygen. Thus, their macrocyclization should afford unique host molecules with a cation binding capability through ion-dipole interactions. Moreover, they should have wide use in biomedical and pharmaceutical fields due to the potential biodegradability and biocompatibility of the resulting cyclic lactic acids. Except for one report on the crystal structure of a complex between a cyclic lactic acid hexamer and sodium cation,<sup>12</sup> the cation binding capability of a cyclic lactic acid as a

new type of macrocyclic host molecule towards alkali metal and alkali earth metal cations.





Figure 1. Chemical structure of (a) L-COLA-8 and (b) monobenzylated L-LOLA-8.

We chose L-COLA-8, which is composed of eight L-lactic acid units, as the host (Fig. 1a). Alkali metal cations and alkali earth metal cations, including  $Mg^{2+}$  ions, were used as the guest cations. According to a previously reported method, L-COLA-8 was synthesized in ten steps from L-lactide (Scheme S1).<sup>13-15</sup>

Figure 2a shows the changes of the <sup>1</sup>H NMR signals of L-COLA-8 in acetonitrile- $d_3$ /chloroform-d (9/1) upon the addition

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#### Tetrahedron

of K<sup>+</sup>. Adding K<sup>+</sup> shifts both the methine and methyl proton signals of L-COLA-8. Similarly, adding Na<sup>+</sup>, Rb<sup>+</sup>, or Cs<sup>+</sup> shifts the proton signals of L-COLA-8, whereas adding Li<sup>+</sup> only slightly shifts these proton signals. These observations suggest L-COLA-8 forms a complex with Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, and Cs<sup>+</sup>, but complexation with Li<sup>+</sup> is negligible. Job plots for the complexes of L-COLA-8 with Na<sup>+</sup>, K<sup>+</sup>, and Rb<sup>+</sup> using an NMR method show a maximum at a [L-COLA-8]/[cation] ratio of 2:1, indicating that L-COLA-8 forms a 2:1 complex with these cations in acetonitrile $d_3$ /chloroform-d (9/1) (Fig. 3, S19, S20). In the case of the complex between L-COLA-8 and Cs<sup>+</sup>, it is difficult to determine the stoichiometry by the Job plots because the shift of the proton signals of L-COLA-8 upon adding one or less equivalent of Cs<sup>+</sup> is only a little. On the other hand, in the ESI-MS spectrum of a mixture of L-COLA-8 ( $1.0 \times 10^{-4}$  M) and CsClO<sub>4</sub> ( $1.0 \times 10^{-3}$  M) in acetonitrile/chloroform (9/1), a strong peak corresponding to the 2:1 complex ([2COLA + Cs]<sup>+</sup>, m/z = 1286) is observed along with a slight peak corresponding to the 1:1 complex ([COLA + Cs]<sup>+</sup>, m/z = 709) (Fig. S22). This observation strongly suggests that L-COLA-8 forms a 2:1 complex with Cs<sup>+</sup>, similar to the complexes with Na<sup>+</sup>, K<sup>+</sup>, and Rb<sup>+</sup>.







**Figure 3.** Job plot for the complex between L-COLA-8 and KClO<sub>4</sub> in acetonitrile- $d_3$ /chloroform-d (9/1) at 25 °C.

Table 1 shows the binding constants (*K*) between two COLA molecules and one alkali metal cation in acetonitrile-

 $d_3$ /chloroform-d (9/1) at 25 °C estimated from the <sup>1</sup>H NMR spectral changes of L-COLA-8 upon adding alkali metal cations. The binding capability of L-COLA-8 increases in the following order: Li<sup>+</sup> << Na<sup>+</sup> < Cs<sup>+</sup> < K<sup>+</sup> < Rb<sup>+</sup>. This trend differs from those of 18-crown-6 (Li<sup>+</sup> < Na<sup>+</sup> < Cs<sup>+</sup> < Rb<sup>+</sup> < K<sup>+</sup>), <sup>16</sup> 21-crown-7 (Li<sup>+</sup> < Na<sup>+</sup> < K<sup>+</sup> < Rb<sup>+</sup> < Cs<sup>+</sup>), <sup>16</sup> and dibenzo-24-crown-8 (K<sup>+</sup> < Rb<sup>+</sup> = Cs<sup>+</sup>)<sup>17</sup> in methanol. Additionally, L-COLA-8 (host : guest = 2 : 1) and these crown ethers (host : guest = 1 : 1) form complexes with different stoichiometries, suggesting that they have different coordination modes with the alkali metal cations.

**Table 1.** Binding constants (*K*) between L-COLA-8 and alkali metal cations in acetonitrile- $d_3$ /chloroform-d (9/1) at 25 °C.



Figure 4, S10, and S11 shows the <sup>1</sup>H NMR spectral changes of L-COLA-8 upon the addition of alkali earth metal cations. Upon adding Ca<sup>2+</sup>, Sr<sup>2+</sup>, or Ba<sup>2+</sup> ions, the proton signals of L-COLA-8 shift remarkably. In contrast, adding Mg<sup>2+</sup> ion hardly induces a shift. These results indicate that L-COLA-8 has a negligible binding capability towards Mg<sup>2+</sup> as well as Li<sup>+</sup> in acetonitrile- $d_3$ /chloroform-d (9/1). In addition, the results imply that unlike crown ethers, which have a more flexible ring structure that allows binding with the smaller cations,<sup>20</sup> L-COLA-8 has a rigid ring structure.



**Figure 4.** <sup>1</sup>H NMR spectral changes observed for L-COLA-8  $(1.0 \times 10^{-4} \text{ M})$  in acetonitrile-*d*<sub>3</sub>/chloroform-*d* (9/1) upon the addition of (a) Ba(ClO<sub>4</sub>)<sub>2</sub> and (b) Mg(ClO<sub>4</sub>)<sub>2</sub> at 25 °C.

Interestingly, the Job plots (Fig. 5, S21) and the ESI-MS spectrum (Fig. S23)<sup>21</sup> indicate that the stoichiometry of the complexes between L-COLA-8 and alkali earth metal cations is 1:1, in sharp contrast to the complexes between L-COLA-8 and alkali metal cations, which have a 2:1 stoichiometry. Table 2 summarizes the binding constants between L-COLA-8 and alkali earth metal ions. L-COLA-8 shows a binding selectivity for Ba<sup>2+</sup>, and the increasing order of the binding constants (Mg<sup>2+</sup> << Ca<sup>2+</sup> < Sr<sup>2+</sup> < Ba<sup>2+</sup>) is consistent with that of the complex between dibenzo-24-crown-8 and alkali earth metal cations,<sup>22</sup> although the stability constants for the former are lower.



**Figure 5.** Job plot for the complex between L-COLA-8 and Ba( $ClO_4$ )<sub>2</sub> in acetonitrile- $d_3$ /chloroform-d (9/1) at 25 °C.

**Table 2.** Binding constants (*K*) between L-COLA-8 and alkali earth metal cations in acetonitrile- $d_3$ /chloroform-d (9/1) at 25 °C.



Linear oligo(ethylene glycol)s that are composed of several oxyethylene units have a cation binding capability, but their binding constants are much lower than those of the corresponding macrocyclic crown ethers. For instance, heptaethylene glycol dimethyl ether forms complexes with alkali metal cations in methanol. The binding constants with Na<sup>+</sup>, K<sup>+</sup>, and Cs<sup>+</sup> are 47, 741, and 257 M<sup>-1</sup>, respectively.<sup>23</sup> Thus, we compared the cation binding capability between L-COLA-8 and the corresponding linear lactic acid octamer (L-LOLA-8). Similar

to L-COLA-8, an NMR titration method was used to evaluate the cation binding capability of L-LOLA-8.



**Figure 6.** <sup>1</sup>H NMR spectral changes for monobenzylated L-LOLA-8 (1.0 ×  $10^4$  M) in acetonitrile- $d_3$ /chloroform-d (9/1) upon the addition of (a) RbClO<sub>4</sub> and (b) Ba(ClO<sub>4</sub>)<sub>2</sub> at 25 °C.

Figure 6 shows the <sup>1</sup>H NMR spectral change of monobenzylated L-LOLA-8 upon the addition of Rb<sup>+</sup> or Ba<sup>2+</sup> in acetonitrile- $d_3$ /chloroform-d (9/1). Even upon adding eight-times the molar amounts of these cations, the proton signals of monobenzylated L-LOLA-8 are not shifted, indicating that L-LOLA-8 hardly forms a complex with these cations. These results clearly demonstrate that the macrocyclic structure is necessary for the cation binding by oligo(lactic acid)s.

In conclusion, cyclic L-lactic acid octamer (L-COLA-8) effectively forms a complex with alkali and alkali earth metal ions in acetonitrile-*d*<sub>3</sub>/chloroform-*d* (9/1). L-COLA-8 forms a 2:1 complex with alkali metal cations, but forms a 1:1 complex with alkali earth metal cations. L-COLA-8 selectively binds to metal cations with a diameter about 3 Å, such as Rb<sup>+</sup> and Ba<sup>2+</sup>. In sharp contrast to L-COLA-8, the linear oligo(L-lactic acid)s, L-LOLA-8, hardly forms a complex with these metal cations. These results confirm that macrocyclization is important to prepare a cation-binding host molecule from oligo(L-lactic acid)s. It is expected that various combinations of L- and D-lactic acids will realize cyclic oligo(lactic acid)s with higher cation binding capabilities and selectivities. Further studies along these lines are now in progress in our laboratory.

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#### Supplementary Material

Supplementary data associated with this article can be found, in the online version, at------ Experimental details, spectral data, titration curves for complex formation, and Job plots for complexes.

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