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COMMUNICATION

Alkali metal ion binding using cyclic polyketones

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Cyclic oligoketones composed of 3,3-dimethylpentane-2,4-diones showed crown ether-like alkali metal ion binding behavior with association constants up to $1.7 \times 10^4 \text{ M}^{-1}$ in chloroform/acetonitrile (v/v, 9/1). The binding properties have been used for catalysis in the Finkelstein reaction in a low-polarity solvent. Furthermore, novel ion-binding hosts were generated by terminal functionalization of linear polyketones.

Macrocyclic molecules that reversibly and selectively bind metal ions have been widely applied as catalysts,¹ ion adsorbers or transporters,² and supramolecular scaffolds.³ Besides crown ethers (**1**; the most representative macrocycles),⁴ many other molecules, including cyclic peptides⁵ and calixarenes,⁶ have been proven to selectively capture various metal ions. As these classical macrocycles are essential for the development of the functional molecular materials required in a sustainable society, finding new molecular motifs for metal ion binding is of high importance in molecular science.

When favorable non-covalent interactions with metal ions are exhibited in a linear molecule, its cyclic counterparts can have better affinity for and selectivity to these ions, as known from the relationship between oligo(ethylene glycol)s and crown ethers.⁷ Based on such an empirical rule, repeating units of known ion-conducting polymers, with which metal ions interact moderately, would be good scaffolds for the generation of novel macrocyclic hosts for metal ions. Poly(3,3-dimethylpentane-2,4-dione)s (**2**)⁸ are recently-reported organic polymers that conduct lithium ions with a high cation transference number.⁹ Their substructures, *i.e.* 1,3- and 1,4-diketones, are well-known to form

chelate complexes with metal ions; thus, the cyclic counterparts of **2**, namely **3–6** (Fig. 1), are expected to show metal ion-binding properties. In addition to the non-hygroscopic nature and good solubility of polyketones, metal ion binding with polyketones is also interesting for synthetic functionalizations. Because many sequence-specific transformations^{8,10} are known, various macrocyclic hosts with different association constants would be produced using the polyketone sequence. Here, we report alkali metal ion-binding properties of cyclic polyketones **3–6** (Fig. 1) with association constants of up to $1.7 \times 10^4 \text{ M}^{-1}$ in chloroform/acetonitrile (v/v = 9:1). As these macrocycles solubilize sodium iodide in low-polarity solvents, the Finkelstein reaction with alkyl bromide was accelerated. The catalytic activities of polyketones are roughly proportional to their binding constants for sodium ion. Whereas interactions of linear polyketone **2** with alkali metal ions were too weak to be observed in solution, synthetic modifications of linear polyketones with pyrene moieties provided a pseudo-cyclic host in which cyclic conformation was induced by π - π stacking. Furthermore, we also investigated the effect of ring size on the modulation of metal ion binding.

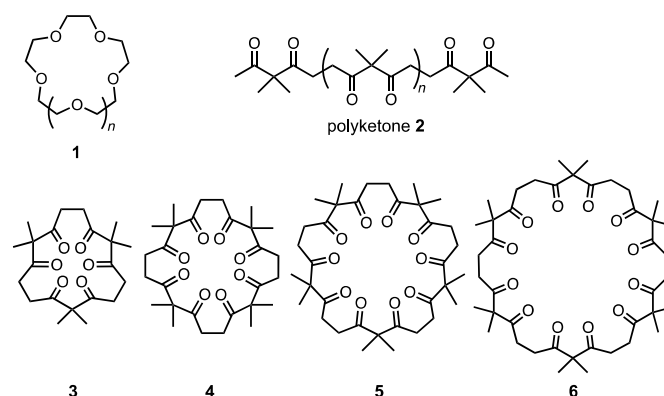


Fig. 1 Structures of linear and cyclic polyketones.

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Cyclic hexaketone **3** was prepared from linear hexaketone according to the procedure we recently reported.¹¹ Other higher homologues **4–6** were derivatized from corresponding calix[*n*]furans through furan ring-opening reactions developed by LeGoff and Williams.¹² Although cyclic dodecaketone **6** has been known for 40 years, its metal ion-binding behavior has not been reported. In fact, ¹H NMR screening of **6** with various MAr₄ salts (M = Li, Na, K) in polar solvents such as methanol, DMF, DMSO, and acetonitrile showed no chemical shift changes, even in the presence of excess amount of metal ions. However, when an NMR titration experiment was conducted in a less-polar mixed solvent, CDCl₃/CD₃CN (v/v, 9:1), the ethylene proton signal of **6** at 2.71 ppm down-shifted slightly in response to the amount of metal salt. Non-linear curve-fitting analysis of the NMR titration results using KB(4-chlorophenyl)₄ gave an association constant of $K = 3.5 \times 10^3 \text{ M}^{-1}$. Job's plot indicated a 1:1 stoichiometry for the complexation between **6** and potassium ion (see ESI).

Association constants of cyclic ketones **3–6** with lithium, sodium, and potassium ions were determined by NMR titration and are summarized in Table 1. Dodecaketone **6** also bound lithium and sodium ions in CDCl₃/CD₃CN (v/v, 9:1), but their association constants were remarkably smaller than that for potassium ion. Cyclic decaketone **5** showed larger binding constants of $9.2 \times 10^3 \text{ M}^{-1}$ and $1.7 \times 10^4 \text{ M}^{-1}$ for sodium and potassium ions, respectively, whereas the binding constant for lithium ion was more than 10 times smaller than that for the sodium ion. Only weak binding behavior was observed for octaketone **4** when combined with sodium salt. Metal ion binding behavior was not observed for the smallest hexaketone macrocycle, **3**, in the NMR titration experiment.

Table 1 Association constants ($K [\text{M}^{-1}]^a$) of cyclic polyketones **3–6**.

Macrocycle	Li ⁺	Na ⁺	K ⁺
3	— ^b	—	—
4	—	9.8×10^1	—
5	4.7×10^2	9.2×10^3	1.7×10^4
6	2.1×10^2	1.4×10^3	3.5×10^3

^aAssociation constants were determined by ¹H NMR titration experiments in CDCl₃/CD₃CN (v/v, 9:1). Ar₄B[−] anions were used as counterions (Ar = pentafluorophenyl, 3,5-bis(trifluoromethyl)phenyl, and 4-chlorophenyl for Li⁺, Na⁺, and K⁺, respectively) ^bNot determined due to none or trivial chemical shift changes upon addition of metal salts.

The cation-binding mode of macrocycle **5** was determined by single crystal X-ray analysis. Metal ion-free **5** exhibited a rather crumpled ring conformation, and no obvious cavity was found (Fig. 2; ESI).⁸ Potassium complex **5**•K⁺ crystallized from chloroform/acetonitrile revealed that a potassium ion was captured inside the cavity of **5**. The potassium ion was coordinated by five of the ten carbonyl oxygen atoms, with K•••O distances of 2.645–2.725 Å. In addition, one solvent acetonitrile molecule was apically coordinated to the potassium

center. Host **5** was found to have a round conformation in which all the ethylene bridges adopted gauche conformations.

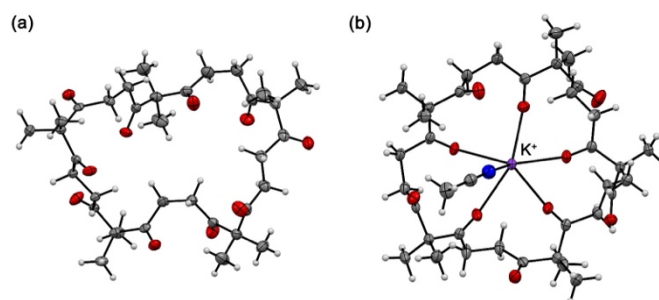


Fig. 2 Crystal structures of (a) **5** and (b) **5**•K⁺. (Thermal ellipsoids are set at the 50% probability level. The counteranion (B(4-chlorophenyl)₄[−]) in (b) is omitted for clarity.)

Metal-free dodecaketone macrocycle **6** was co-crystallized with dichloromethane solvent (ESI). Macrocycle **6** showed a round conformation similar to that of **5**•K⁺, despite the absence of any central metal ion. Although single crystals of potassium ion complex **6**•K⁺ suitable for X-ray analysis were not obtained, an energy-minimized structure for **6**•K⁺ was theoretically obtained from a molecular dynamic simulation with the density-functional tight-binding followed by optimization at the M06/6-311+G(d) level of theory. In the optimized structure, five carbonyl oxygen atoms were placed within 2.740 Å from the potassium ion in a similar fashion to their arrangement in **5**•K⁺. However, ligand **6** no longer took a round shape, but exhibited a folded semilunar shape, presumably because of the overlong chain length. Considering the larger entropy loss upon potassium ion capture with **6**, a higher association constant is reasonable for dodecaketone macrocycle **5**.

Table 2 Finkelstein reactions^a catalysed by polyketones **3–6**.

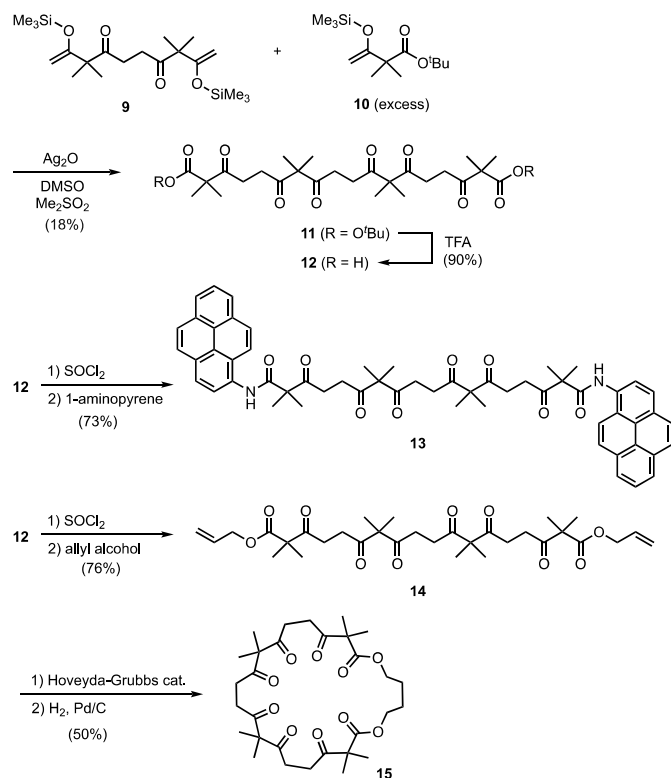
entry	catalyst	yield of 8
1	none	n.d.
2	3 (10 mol%)	n.d.
3	4 (10 mol%)	18%
4	5 (10 mol%)	98%
5	6 (10 mol%)	78%
6	6 (5 mol%)	41%
7	6 (20 mol%)	95%

^aReaction conditions: NaI 1.2 equiv., refluxed for 48 h; yields were determined by ¹H NMR spectroscopy using an internal standard.

Alkali ion-binding hosts **4–6** exhibited catalytic activity for the Finkelstein reaction¹³ that correlates with their association constants for cations. Sodium iodide, a frequently used iodide source, is virtually insoluble in low-polarity solvents; therefore,

a reaction between 1-bromooctane (**7**) and sodium iodide does not proceed in a solution of chloroform/acetonitrile (v/v = 19/1).¹⁴ However, in the presence of cyclic decaketone **5** (10 mol%), octyl iodide (**8**) was quantitatively obtained after refluxing for 48 h (Table 2). Under the same conditions, **6** also gave iodide **8** in good yield (78%), but the smaller macrocycles **3** and **4** were less active. The reaction yield decreased when the amount of catalyst **6** was reduced to 5 mol% (entry 6), while use of 20 mol% catalyst gave **8** in 95% yield (entry 7). The observed positive correlation between catalytic activity and sodium ion binding constants indicated that cyclic polyketones worked as solubilizing agents for inorganic salts in low-polarity organic solvents by capturing hard sodium cations.

Although interactions of linear polyketones **2** (for example, $n = 2$) with alkali metal ions were not detected by NMR spectroscopy, terminal functionalization altered their binding properties. The octaketone analogue **11** substituted with terminal *tert*-butoxy carbonyl groups was synthesized through a silver(I) oxide-mediated cross-coupling reaction between tetraketone analogues **9** and **10** in 18% yield. After hydrolysis of the *tert*-butyl ester, dicarboxylic acid **12** was converted to acid chloride and then two 1-aminopyrene moieties were introduced to give **13** in 73% yield (Scheme 1). A probe molecule **13** exhibited dual fluorescence emission at 387 and 485 nm in CHCl₃/CH₃CN (v/v, 9:1) solution, assignable to pyrene monomer and excimer states, respectively. This observation indicated that **13** can adopt both linear and pseudo-cyclic conformations in which two pyrene moieties are well-separated and π -stacked, respectively (Fig. 3).¹⁵



Scheme 1 Synthesis of linear and cyclic ketone analogues **13**, **14**, and **15**.

Upon stepwise addition of NaBAR₄ salt (Ar = 3,5-bis(trifluoromethyl)phenyl), the intensity of the fluorescence emission of **13** gradually decreased. In particular, the attenuation of low-energy emission band was more remarkable than that of the monomer emission band (Fig. 3b). These spectral changes indicated that pseudo-cyclic conformation of **13** was selectively consumed by formation of sodium complex which is a none or less fluorescent species. Despite the acyclic structure, pyrene-terminated **13** showed a higher binding constant ($K = 6.4 \times 10^2 \text{ M}^{-1}$) for sodium cation than did macrocycle **4** bearing the same number of carbonyl groups. The optimized structure for **13**•Na⁺ suggested that five C=O...Na⁺ coordination bonds stabilizes pseudo-cyclic conformation in which two pyrene moieties are no longer π -stacked (ESI). This structure also supported the significant attenuation of excimer fluorescence upon complexation with sodium ions.

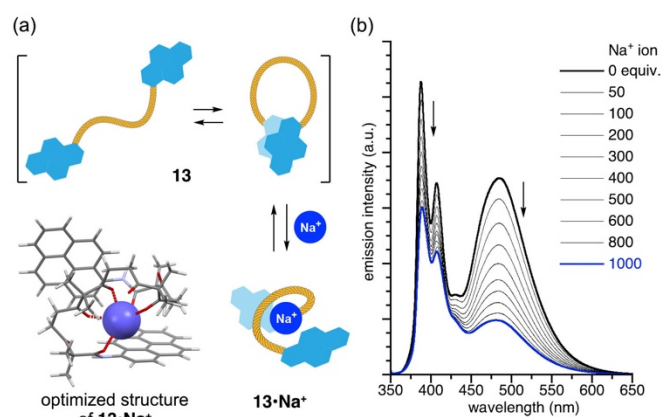


Fig. 3 (a) Equilibrium between **13** and its sodium cation complex **13**•Na⁺. (b) Fluorescence emission spectra ($\lambda_{\text{ex}} = 342 \text{ nm}$) of **13** in CHCl₃/CH₃CN (v/v, 9:1) after the addition of 0–1000 equivalents of NaBAR₄ salt.

Linear polyketone analogues are also advantageous for the synthesis of cyclic polyketones with controlled ring size. When allyl ester-terminated **14** was subjected to ring-closing metathesis using the Hoveyda–Grubbs catalyst,¹⁶ cyclic polyketone **15** was obtained in 50% yield after hydrogenation of the C=C double bond. Macrocycle **15** has eight carbonyl groups, as does compound **4**, but its ring size is 4 atoms larger than the ring size of **4**. Although precursor **14** did not show cation binding behavior, macrocycle **15** bound sodium ion with an association constant of $K = 4.1 \times 10^2 \text{ M}^{-1}$ in CHCl₃/CH₃CN (v/v, 9:1). The ring size expansion based on linear polyketone functionalization resulted in a remarkable increase in the binding constant, compared with that of **4**.

In summary, we have demonstrated that cyclic polyketones composed of 3,3-dimethylpentane-2,4-dione units act as alkali metal ion-binding hosts in low-polarity solvents. Single crystal X-ray analysis and theoretical calculations revealed that the formation of multiple coordination bonds with carbonyl oxygen atoms is important for strong binding. Such binding properties of cyclic polyketones **4–6** were used for solubilization of an inorganic sodium salt in a low-polarity organic solvent.

Furthermore, terminal functionalization strategies using linear polyketones enable precise control of ring size that can widely vary their cation binding constants. Although some well-known ion-binding hosts, such as crown ethers and cyclic peptides, are hygroscopic or less soluble in common organic solvents, the present polyketones are stable solids with good solubility in most organic solvents. These properties should guarantee the development of polyketone-based functional materials in the near future.

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There are no conflicts to declare.

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- When the Finkelstein reaction between **7** and NaI was conducted in chloroform/acetonitrile (v/v = 9/1), the reaction proceeded even in the absence of catalyst owing to partial solubility of NaI. We thus selected a lesser polar solvent to rule out the background reaction.
- At the measuring concentration range (0.1–5 μ M for **13**), the relative intensity of excimer emission to monomer emission was virtually independent of the concentration (Fig. S1), which indicates that emission at 485 nm derives from intramolecularly stacked pyrene moieties.
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