

methyl-2-pentanone and 80% ee for 3,3-dimethyl-2-butanone (entries 11-14). On the other hand, asymmetric reduction of functionalized ketones, such as 2-chloroacetophenone, methyl benzoylformate and 1,1-dimethoxypropanone provided the corresponding (*S*)-alcohols of 58-68% ee (entries 9, 10 and 16). In this case, (*S*)-configurations of product alcohols obtained is due to notations by the sequence rule.

In the asymmetric borane reduction of acetophenone using **1**, a catalytic amount less than 10 mol% of **1** gave the alcohol with lower enantiomeric excess, such as 71% ee with 2 mol% and 73% ee with 5 mol% (entries 1 and 2). When the reaction was carried out at 0 °C, the alcohol of 42% ee was obtained (entry 4). Rapid mixing of all the reagents followed by quenching and workup after 10 min afforded the alcohol with 33% ee (entry 5). Decrease of enantioselectivities at low concentration of **1**, at low temperature or at high concentration of the ketone as described above is attributable to a consequence of competing uncatalyzed reductions by borane itself.

The following procedure is representative. To a mixture of **1** (0.3 M, 0.2 mmol) and BH₃-THF (0.9 M, 1.2 mmol) in THF was added acetophenone (0.5 M, 2.0 mmol) in THF over a period of 1 h *via* a syringe pump at room temperature (*ca.* 25 °C). After 10 min, the reaction mixture was quenched by the addition of 1 N HCl and solvent was removed *in vacuo*. The residue was basified with 1 N NaOH and extracted with ether. The combined extracts were dried over anhydrous MgSO₄. GC analysis showed the formation of 1-phenylethanol in a 98% yield. The solvent was evaporated under reduced pressure and the product alcohol was isolated by bulb-to-bulb distillation *in vacuo*. Optical purity of the product alcohol was determined by capillary GC analysis of (*R*)-MTPA ester using a 50 m methyl silicon column to show 81% ee, *R*.

In conclusion, this is the first example for asymmetric borane reduction of ketones using a new class of chiral oxazaborolidine (**1**) obtained from D-mannitol as a catalyst. The borane asymmetric reduction of several kinds of prochiral ketones with 10 mol% of **1** provided the corresponding alcohols with moderate enantioselectivities of up to 81% ee.

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- The oxazaborolidine **1** was prepared by the reaction of **2** with borane-THF and used without isolation or purification.³
- The erythro β-amino alcohol **2** was prepared from D-mannitol by the known procedure.⁶ **2**: mp 114-115 °C (lit.⁶ 115-116 °C); [α]_D²² 2.38 (*c* 1.0, CHCl₃) (lit.⁷ [α]_D 2.5 ± 0.9 (*c* 1.0, CHCl₃); IR (KBr, cm⁻¹), 3378, 3157, 2988, 1612, 1472, 1379; ¹H NMR (300 MHz, CDCl₃) δ 1.36 (s, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 2.84 (t, 1H, *J*=5.1 Hz), 3.60 (t, 1H, *J*=6.0 Hz), 3.85-4.20 (m, 6H), 4.32 (dt, 1H, *J*=5.1 and 6.6 Hz); ¹³C NMR (75.46 MHz, CDCl₃) δ 109.4, 109.2, 76.7, 76.1, 74.2, 66.9, 66.7, 54.4, 26.7, 26.5, 25.3, 25.2; Anal. Calcd for C₁₂H₂₃NO₅: C, 55.16; H, 8.87; N, 5.36. Found C, 55.34, H, 9.03, N, 5.25.
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Crown Ethers Bearing a Convergent Carboxylic Acid Function: Synthesis of Kemp's Triacid-Capped Crown Ethers and Their Ionophoric Properties

Yeon Hee Cho, Suk-Kyu Chang*, and Jong-In Choe

Department of Chemistry, Chung-Ang University,
Seoul 156-756, Korea

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There has been much recent research interest on the development of the stimuli responsive host systems.^{1,2} The most common tools employed are the changes in pH, along with the thermal, light, and chemical stimuli such as redox reactions. Ionizable crown ethers are one of the most attractive ionophoric systems studied so far for the construction of a functional ionophore system by responding to the changes in pH.³

Kemp's triacid has been widely utilized for the developments of novel host systems by utilizing its unique and rigid U-shaped relationship between carboxylic acid functions.⁴ Some of the ionophoric ligands employing Kemp's triacid structural motif were also reported and their binding properties for the recognition of various metal ions were investi-

gated.⁵⁻⁸ In this case, combination of the Kemp's triacid function with suitable binding site might result in a new host system with high degree of convergency of ligating groups. As a binding site for the ionic recognition of metal cations, well-characterized crown ether moieties were employed,⁹ but no pH-responsive systems was reported. In this work, we have prepared a new pH-responsive ionophoric system of carboxylic acid-capped crown ethers by employing convergent structural characteristics of Kemp's triacid and characterized their ion binding properties.

Crown ethers containing Kemp's triacid moiety were prepared by the reaction of a well mixed 1:1 mixture of suitable aminomethyl crown ethers and Kemp's triacid in neat at 200 °C under argon atmosphere as shown in Scheme.¹⁰ The crude reaction products were purified by the column chromatography (silica gel, solvent; CH₂Cl₂:MeOH=9:1, v/v), and light yellow colored products were obtained in good yield (80-85%).¹¹

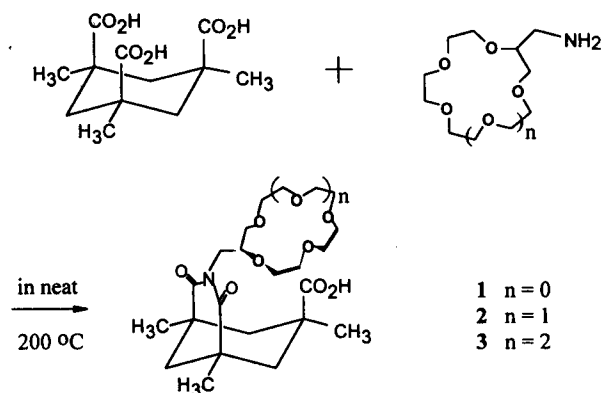
The preliminary ionophoric properties of the prepared ligands were investigated by the competitive solvent extraction experiments. The aqueous phase (buffered at pH=9 with Tris-HCl buffer), which contains 1.0 mM of alkali metal or alkaline earth metal cation mixture, was extracted with CHCl₃ solution containing 5.0 mM of ligand. The separated organic phase was back-extracted with 0.1 M HCl solution,¹² and the amount of the back-extracted metal cation was determined by inductively coupled plasma (ICP) atomic absorption analysis (Table 1). The extraction experiment was performed under competitive condition to assess the real discrimination characteristics of the ligand toward individual metal cation among the alkali or alkaline earth metal cation mixture.

As can be seen from the Table 1, compounds 1-3 exhibit efficient and selective extraction behaviors for the alkali metal cation. For example, 1 and 2 showed prominent selectivity toward Na⁺, while 3 exhibited selectivity toward K⁺ ion among alkali metal cations. The compounds 1-3 are capable of discriminating the metal guest ions by utilizing the crown ether moiety, in addition to the neutralization process of the carboxylic acid function that is convergent toward crown ether and functions as a pH responding site. However, for alkaline earth metal cations as guests, the extraction efficiency is much inferior as expected from the formation of charged complexes, by the combination of a carboxylate and a doubly charged alkaline earth metal cation. That is, the complexes formed with the alkaline earth metal cation are still singly charged and need extra counterion to maintain the electroneutrality for the efficient extraction into organic

Table 1. Competitive Extraction of Alkali and Alkaline Earth Metal Cations

Ligand	Extractability (%)						
	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Sr ²⁺	Ba ²⁺
1	2.7	12.1	1.6	2.2	4.3	<1.0	2.6
2	4.5	27.9	3.7	3.8	10.1	<1.0	<1.0
3	1.1	19.4	24.9	1.3	4.0	1.1	1.1

Aqueous phase: mixture of metal chlorides in Tris buffer (pH=9, each in 1.0 mM, 2.0 mL). Organic phase: 5.0 mM of the ligand in CHCl₃ (2.0 mL). At 25 °C. Determined by ICP.



Scheme 1.

solvent, while for alkali metal cation the complex formed is neutral itself with the carboxylate function acting both as a ligand and counterion for the singly charged guest ion.¹³ Furthermore, the selectivity pattern is less pronounced for the alkaline earth metal cations. However, interesting thing is that all of the tested ligands showed moderate selectivity toward Ca²⁺, irrespective of the ring size of the crown moiety. This observation suggests that in the case of alkaline earth metal cations, the carboxylate moiety plays a key role in binding the metal cations, and crown moiety seems to participate less significantly in the binding process.

To have further insight into the ionophoric behavior of the ligands, competitive transport experiments were performed (Table 2).¹⁴ Competitive transport of alkali or alkaline earth metal cation mixtures from slightly alkaline solution (pH 9, buffered with a Tris-HCl buffer) into acidic receiving phase (0.1 M HCl solution) through chloroform liquid membrane (containing 5.0 mM of the carrier) was conducted. The transport experiments were performed with a U-tube apparatus at 25 °C with constant stirring for 24 h and the amount of transported guest ions was determined by ICP method. The transport experiments showed that the ligands have unique selectivity toward alkali metal cations. The 15-crown-5 and 18-crown-6 analogs of the series exhibited particularly selective transport behavior. That is, 2 and 3 exhibited significant selectivity for Na⁺ and K⁺ ion, respectively, corresponding to their best fitting crown ether ring size. For example, the selectivity ratio of 2 for the transport of Na⁺ over Li⁺ and K⁺ was 18 and 83, respectively. For 3, the transport selectivity toward K⁺ over Li⁺ and Na⁺ was reached about

Table 2. Competitive Transport of Alkali and Alkaline Earth Metal Cations through Chloroform Liquid Membrane

Carrier	Transport rate (×10 ⁸ mol/h)						
	Li ⁺	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺	Sr ²⁺	Ba ²⁺
1	0.43	2.94	6.78	0.56	7.62	1.28	3.97
2	2.31	43.2	0.52	0.62	7.74	2.83	1.94
3	0.51	9.15	60.3	0.37	8.43	5.64	3.56

Transport conditions: source phase; a mixture of metal chlorides each in 0.1 M (pH=9.0, Tris buffer, 5.0 mL), membrane; 5.0 mM of the carrier in CHCl₃ (15.0 mL), receiving phase; 0.1 M of HCl (5.0 mL). At 25 °C. Determined by ICP.

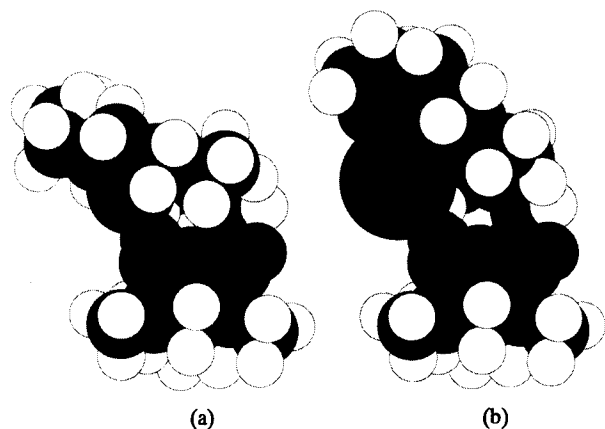


Figure 1. MM+ optimized structures of (a) $2 \cdot \text{Na}^+$ and (b) $2 \cdot \text{K}^+$ complexes.

120 and 6.6, respectively. These results suggest that the transport rate is largely governed by the nature of the crown ether moiety for alkali metal cations, implying again the strong participation of the crown moiety in the complex formation. The transport efficiency and the selectivity of Kemp's triacid based carriers toward the alkaline earth metal cations are not so prominent, but all showed moderate selectivity toward Ca^{2+} ion.

The selectivity pattern of the ionophores **1-3** toward alkali metal cations was attempted to interpret by the molecular modeling studies using HyperChem package.¹⁵ The representative MM+ geometry optimized structures of the complex for **2**, with AM1 calculated charges, are given in Figure 1 for Na^+ and K^+ ion as guest. The optimized structure of the complex suggests that the crown ether moiety and carboxylate function are converging each other toward metal cationic guest. In case of Na^+ ion, the metal ion sits snugly on the compact pseudo-cavity comprising the crown ring and the appended carboxylate function, interacting efficiently with both sites. On the other hand, with K^+ ion as a guest, the ligand **2** does not provide sufficient space for the complete accommodation of the guest ion, results in having somewhat opened and perching structure. That might be one of the reasons for the less efficient ionophoric interaction with K^+ guest compared with Na^+ ion.

All these observations suggest that the crown ethers bearing Kemp's triacid moiety has suitable structural and ionophoric properties for the ionic recognition of alkali metal cations, by combining suitably crown ether moiety as a recognition site and ionizable carboxylic acid group as a pH-responder site.

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11. Representative procedure. A stoichiometric solution of aminomethyl-3n-crown-n ether ($n=4-6$) and Kemp's triacid was made in CH_2Cl_2 to attain a homogeneous mixture of the two reactants. The solvent was evaporated under reduced pressure and the solid mixture was allowed to react under argon atmosphere at 200 °C. After 2 h, the reaction mixture was dissolved in CH_2Cl_2 , and purification by the chromatography on silica gel (CH_2Cl_2 : MeOH=9:1, v/v) afforded desired oily products, which solidified on standing. Selected spectral data. **1**: 85%, low melting solid, IR (NaCl, neat) 3390, 1675, 1116 cm^{-1} ; ^1H NMR (CDCl_3) 9.0 (br s, 1H), 4.0-3.4 (m, 17H), 2.7 (d, $J=14$ Hz, 2H), 1.9 (d, $J=14$ Hz, 1H), 1.1-1.4 (m, 12H); FAB-MS: m/z (rel intensity) for $\text{C}_{21}\text{H}_{33}\text{NO}_8$, calcd 427.2, found 428 (58). **2**: 80%, low melting solid, IR (NaCl, neat) 3323, 1528, 1122 cm^{-1} ; ^1H NMR (CDCl_3) 7.9 (br s, 1H), 3.9-3.4 (m, 21H), 2.7 (d, $J=14$ Hz, 2H), 1.9 (d, $J=14$ Hz, 1H), 1.1-1.4 (m, 12H). FAB-MS: m/z (rel intensity) for $\text{C}_{23}\text{H}_{37}\text{NO}_9$, calcd 471.2 found 472 (21). **3**: 85%, low melting solid, IR (NaCl, neat) 3308, 1625, 1558, 1117 cm^{-1} ; ^1H NMR (CDCl_3) 3.9-3.4 (m, 25H), 2.7 (d, $J=14$ Hz, 2H), 1.9 (d, $J=14$ Hz, 1H), 1.4-1.0 (m, 12H) FAB-MS: m/z (relative intensity) for $\text{C}_{25}\text{H}_{41}\text{NO}_{10}$, calcd 515.3, found 516 (28).
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