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The Catalytic Activity of Ionophoric Calix[4]arene Analog

Yukihiro OKADA, Yuji SUGITANI, Yoshinori KASAI, and Jun NISHIMURA*
Department of Chemistry, Gunma University, Tenjin-cho, Kiryu 376

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Synopsis. Calix[4]arene analog (**2**) having 2-[2-(2-methoxyethoxy)ethoxy]ethyl groups was prepared in 92% yield. Compound **2** showed the extraction of alkali metal ions as an ionophore and the catalytic activity for some S_N2 reactions.

The chemistry of calix[*n*]arene gathers some attentions in many interesting applications such as the binding of organic molecules and inorganic ions.[1,2] Accordingly, the modifications of calixarene and its derivatives are widely investigated to explore the new aspects in this chemistry. Calix[4]arene analog **1** was formed by the dimerization of a metacyclophane and paraformaldehyde, and its derivatives exhibited the interesting ionophoric properties.[3] The selectivity of **1** for metal ions appeared for large metal ions as same as calix[6]arene,[4] although the structure of **1** resembles calix[4]arene.[5] By using the property, the derivatives of **1** would become a phase-transfer catalyst for the nucleophilic substitution reaction. So we were prompted to evaluate the catalytic activity of **2** having triethylene glycol units on the S_N2 reaction such as ester synthesis, Williamson ether synthesis, and Finkelstein reaction and to compare the results with those of the corresponding calix[*n*]arene derivatives. In this note, we would like to report the synthesis, extraction of alkali metal ions, and catalytic activity of **2** (Eq. 1).

Experimental

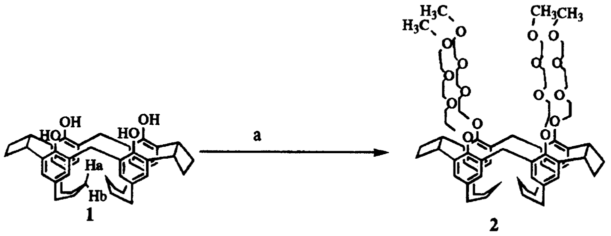
Measurements. Elemental analysis was performed at the Microanalytical Center of Gunma University. NMR spectra were recorded with a Varian Gemini-200 FT NMR and JEOL JNM-PMX 60 SI spectrometer. IR spectra were recorded with a Hitachi 270-50 infrared spectrophotometer. Mass spectrum was obtained with a JEOL-DX302 mass spectrometer. The reaction temperatures were controlled by a thermoregulator. The rate constants were obtained by the pseudo-first-order kinetics. The product yields were determined by ^{1}H NMR spectra. Each reaction was examined at the stage of more than 50% conversion of the starting material.

Synthesis. Tetrakis[2-[2-(2-methoxyethoxy)ethoxy]ethyl] Ether of Calix[4]arene Analog 2. Calix[4]arene analog **1** (400 mg, 2.5×10^{-3} mol) was dissolved in dry THF (10 cm^3) at room temperature under N_2. The solution was treated with NaH (2 equiv, 60wt%) and 2-[2-(2-methoxyethoxy)ethoxy]ethyl bromide (2 equiv) at 60—65 °C for 12 h under N_2.[3] After acidic extraction with $CHCl_3$ (300 cm^3), the solution was dried over Na_2SO_4 and evaporated. The residue was separated with column chromatography (SiO_2, benzene/ethyl acetate) to give **2** in 92% yield; liquid. Found: C, 67.26; H, 8.43%. Calcd for $C_{72}H_{104}O_{16}\cdot3H_2O$: C, 67.58; H, 8.66%. IR ν (neat) 2864, 1456, 1216, 1110, and 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta=-0.03$ (2H, bq-like), 0.64—0.88 (2H, m), 1.33—1.60 (4H, m), 1.64—1.93 (4H, m), 2.27—2.58 (12H, m), 2.58—2.80 (4H, m), 2.97 (2H, d, $J=7.0$ Hz), 3.38 (12H, s), 3.43—3.96 (48H, m), 4.31 (2H, d, $J=7.0$ Hz), 4.49 (4H, bt-like), 6.87 (4H, d, $J=1.7$ Hz), and 7.04 (4H, d, $J=1.7$ Hz).

Extraction of Alkali Metal Ions. Compound **2** (2.5×10^{-4} mol dm^{-3}) was dissolved in CH_2Cl_2 and picric acid (2.5×10^{-4} mol dm^{-3}) and metal hydroxide (0.1 mol dm^{-3}) were dissolved in water. The solution (5.0 cm^3) of **2** was shaken for 10 min with the picrate solution (5.0 cm^3) at 22 °C. After the extraction, the combined solution was separated by a centrifuge for 10 min (3000 rpm). The % extraction was repeatedly measured by the absorbance of picrate in CH_2Cl_2.[3,4] Experimental error was estimated to be less than 2%.

Results and Discussion

Ionophore **2** was synthesized along Equation 1. A 2-[2-(2-methoxyethoxy)ethoxy]ethyl unit was chosen as a binding site, because it is a stable substituent under neutral and basic conditions. Calix[*n*]arenes (*n*=4 and 6) having the same substituent were prepared by the reported methods for the references.[6] The structure of **2** was determined by ^{1}H NMR spectroscopy, including COSY, NOESY, DEPT, and ^{13}C experiments. The spectroscopic findings on the structure determination are as follows: 1) the cyclobutane methine protons of **2** appear at nearly the same position ($\delta=4.49$) to that of **1** ($\delta=4.56$).[3] 2) The inner Ha protons of pentamethylene bridges shift from $\delta=-0.22$ for **1**[3] to $\delta=-0.03$ for **2** reflecting a small conformational change by the substitution. 3) The methylene bridge protons for **2** appear at $\delta=2.97$ and 4.31 to demonstrate the cone conformation, although those for **1** appear at $\delta=3.28$ and 3.97.[3]

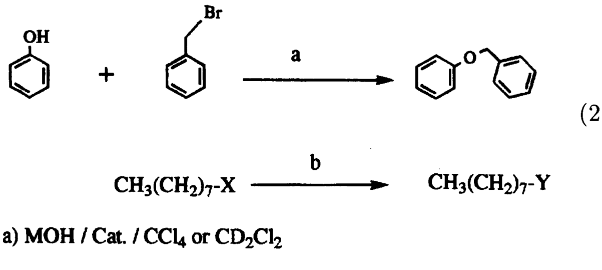


a) $CH_3(OCH_2CH_2)_3Br$ / NaH / THF

(1)

The ionophoric behavior of **2** was examined by the extraction of alkali metal pictates. The extraction experiments were performed with equal molar (2.5×10^{-4} mol dm^{-3}) of **2** in CH_2Cl_2 and alkali metal picrate in water.[5] The typical features are as follows: i) **2** shows the sufficient extractability for alkali metal ions. ii)

The order of the selectivity and extractability is Rb^+ (27.5%)>K^+ (25.3%)>Cs^+ (13.8%)>Na^+ (8.4%)>Li^+ (1.9%).

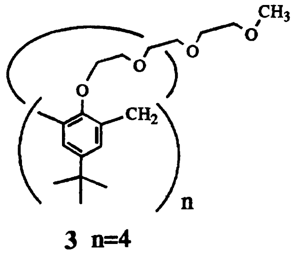


(2)

(3)

The results of ion extraction experiments suggest a possibility that **2** might display a catalytic activity for a nucleophilic substitution reactions with inorganic reagents in organic media. Accordingly, we investigated the catalytic activity of **2** on some S_N2 reactions (Eqs. 2 and 3) and compared the results with those of calix[*n*]arene derivatives (n=4 and 6 for **3** and **4**) (Chart 1).[6] The reaction was followed by ^1H NMR and the rate was estimated as a psuedo-first-order rate constant k (s^{-1}) for the increase of product. Firstly, we examined the esterification with metal acetate, benzyl bromide, and catalyst **2**, **3**, or **4**. The reaction proceeded in the presence of these catalysts, but not in the absence of them. Therefore, their catalytic activity is apparent. The rate constants remained in the same range with small ion (K^+) and large ion (Cs^+) for each catalyst. And moreover, the reaction was slow ($k=10^{-6}$—10^{-7}) because of the low nucleophilicity of acetate ion. Since the substitution by acetate did not give much information on their catalytic activity, we chose the Williamson ether synthesis with phenol, benzyl bromide, metal hydroxide, and catalyst, because phenolate has high nucleophilicity and hydrophobicity.[6] In fact, the difference of their catalytic activities clearly appeared in this case as shown in Table 1. Catalysts made the reaction markedly faster than that without them. In carbon tetrachloride as a nonpolar solvent, the catalytic activity of **2** remarkably increased when larger ions were used and maximum rate constant was recorded in RbOH system. This behavior of **2** was similar inclination to that of calix[6]arene derivative **4** because of the same affinity both **2** and **4** for large ions. The other experiments were performed in dichloromethane as a polar solvent. The rate constant in this solvent increased by around 2—8 times as compared to that in CCl_4, probably due to the increment of the solubility of ion-catalyst complex and activity of nucleophile. The increasing order of rate constant, when **2** was used, can be explained by the selectivity of the catalyst for binding the alkali metal ion and solubilizing the metal hydroxide; K^+ and Rb^+ are suitable for the complexation with **2**, but Cs^+ ion is too large to fit the binding site of **2** effectively.[3,5] By the addition of a little water to make two-phase system, the rate became larger, but the order of enhancement by the catalysts did not change. This experimental result shows that the present catalysts can be used as phase-transfer catalysts. The order of catalytic activity for ether synthesis is **3**<**2**≤**4**.

We also examined the Finkelstein reaction of octyl halide involving a conversion from bromide to iodide or from iodide to bromide.[7] The results are summarized in Table 2. The Finkelstein reaction still proceeded without any catalysts, because halide salts are soluble in various solvents. But, when catalyst was combined in this system, the rate was enhanced clearly by 1.5—2



3 n=4
4 n=6

Chart 1.

Table 1. Rate Constant of the Reaction between Phenoxide and Benzyl Bromide[a)]

Base	Solvent	k ($10^7 s^{-1}$)			
(MOH)		None	**2**	**3**	**4**
NaOH	CCl_4	4.2	62	50	67
KOH	CCl_4	6.1	79	56	70
RbOH	CCl_4	5.6	160	60	180
NaOH	CD_2Cl_2	8.4	120	90	140
NaOH	sat. CD_2Cl_2[b)]	17	590	120	390
KOH	CD_2Cl_2	15	520	480	600
RbOH	CD_2Cl_2	18	760	420	990
CsOH	CD_2Cl_2	28	320	220	710

a) Phenol : benzyl bromide : base : catalyst = 1 : 1 : 3.5 : 0.029 (molar ratio); phenol, 0.43 mol dm^{-3}; temp, 32±1 °C. Experimental error was ±10%. b) Saturated with D_2O.

Table 2. Rate Constant of the Finkelstein Reaction[a)]

Substrate	Reagent	Solvent[b)]	Temp[c)]	k ($10^7 s^{-1}$)			
	(MY)		°C	None	**2**	**3**	**4**
n-$C_8H_{17}Br$	KI	A	50	27	42	28	31
	RbI	A	50	22	41	24	24
	CsI	A	50	14	24	18	20
	KI	B	50	—	39	20	28
	RbI	B	50	—	36	17	25
	CsI	B	50	—	31	14	20
n-$C_8H_{17}I$	KBr	B	75	9.2	15	12	13
	RbBr	B	75	—	14	10	11
	CsBr	B	75	—	12	8.0	9.7

a) Substrate : reagent : catalyst = 1 : 5 : 0.05 (molar ratio); substrate, 0.24 mol dm^{-3}. Experimental error was ±10%. b) A: CD_3COCD_3, B: CD_3CN. c) ±2 °C.

times (see Table 2). In the case involving a conversion of octyl bromide to iodide, **2** showed the maximum rate for KI and RbI in acetone or acetonitrile, indicating that the complexation with the alkali metal ion is an important factor for acceleration of this reaction. Note that **2** has the largest rate constant among the catalysts for all metal iodides examined in this reaction.

In the other case involving a conversion of octyl iodide to bromide, **2** also showed the maximum rate for K^+ and Rb^+ salts, although the reaction of iodide to bromide is difficult. Furthermore, **2** is again the best catalyst for all metal bromides. These results suggest that the cylindrical structure of **2** gives a favorable environment for this Finkelstein reaction.

In conclusion, **2**, which was derived from calix[4]arene analog **1**, was easily obtained in 92% yield and acted as an ionophore for alkali metal ions. Interestingly, **2** showed an effective catalytic activity for some S_N2 reactions in several media.

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