

5.27 (dd, $J=1.8, 7.5$ Hz, 1H), 4.64 (t, $J=5.2$ Hz, 1H), 2.78 (m, 1H), 1.87-1.47 (series of m, 6H), 1.07 (s, 3H). $[\alpha]_D^{23} = -30.9^\circ$ (c 1.16, CHCl_3). mp 56-57 °C. **9**: ^1H NMR (200 MHz, CDCl_3) δ 5.56 (m, 2H), 5.04 (s, 1H), 4.89 (m, 1H), 3.64 (s, 3H), 2.68 (t, $J=9.8$ Hz, 1H), 2.04-1.31 (series of m, 6H), 1.18 (s, 3H), 1.12 (s, 9H). $[\alpha]_D^{24} = +27.0^\circ$ (c 1.13, CHCl_3). **10**: ^1H NMR (200 MHz,

CDCl_3) δ 4.70 (dt, $J=4.5, 10.6$ Hz, 1H), 3.71 (s, 3H), 3.51 (m, 2H), 2.05 (m, 2H), 1.83-1.49 (series of m, 6H), 1.23 (m, 1H), 1.20 (s, 9H), 1.16 (s, 3H). **1**: ^1H NMR (200 MHz, CDCl_3) δ 4.93 (dt, $J=4.4, 10.5$ Hz, 1H), 2.45 (m, 1H), 2.19-1.58 (series of m, 9H), 1.22 (m, 1H), 1.19 (s, 9H), 0.94 (s, 3H); IR (CHCl_3 , cm^{-1}) 1737 (s), 1720 (s). $[\alpha]_D^{24} = +57.9^\circ$ (c 1.04, CHCl_3). mp 54 °C.

Cation- π Interaction between Synthetic Hosts and Alkali Metal Cations

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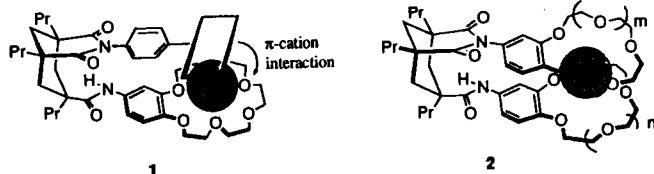
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Received December 7, 1996

Among noncovalent binding forces, the cation- π interaction has recently received considerable attention because it plays an important role in biological systems such as acetylcholine-binding sites and ion channels.¹ A number of theoretical and experimental studies have been reported on the cation- π interaction between aromatic surfaces and quaternary ammoniums, or alkali metal cations.²⁻⁵ Based on the computational calculations, Dougherty³ and Kollman⁴ described the nature and magnitude of the cation- π interactions between alkali metal cations and benzene. Experimentally, Shinkai⁵ and Ungaro⁶ have nicely demonstrated that two benzene rings of the 1,3-alternate calix[4]arenes can participate as π -donors in the complexation with metal cations, and thus increase the binding affinities and selectivities toward a particular metal cation.

We here report the synthesis and binding properties of the aryl-containing hosts **1** for evaluation of the cation- π interactions in the complexation with alkali metal cations in a water-saturated CH_2Cl_2 .

The interaction between an alkali metal cation and aromatic surface alone is too weak in solution to be measured accurately. Therefore, the hosts **1** designed here are composed of two metal-binding sites, the benzo-18-crown-6 as a main binding site and the π -donor aromatic unit as an additional site. Two binding sites must be placed in a proper way to participate simultaneously in the complexation with metal cations. In addition, they must be conformationally independent of each other and thus the cation- π interactions could be deduced from the direct comparisons of the binding affinities of the reference host and aryl-containing analogues. For these purposes, tripropyl Kemp's triacid **4**^{9,10} is an ideal spacer molecule in which carboxylic groups are separated ~ 3 Å from each other with U-shaped relationship.

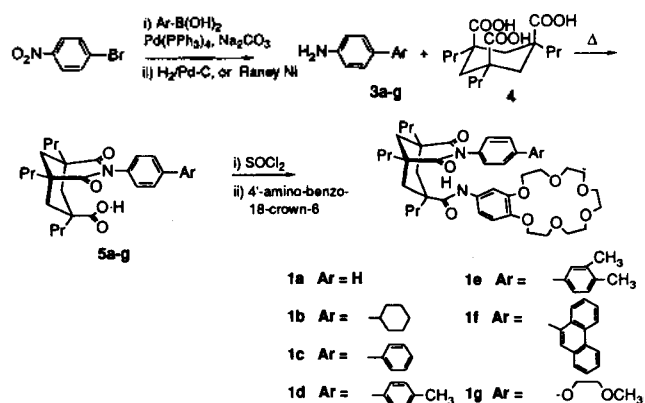


Utilizing this structural feature of Kemp's triacid **4**, we recently reported several bis(crown ether) hosts **2** in which two crown ethers could bind cooperatively alkali metal cations through intramolecular 1:1 sandwich-type complexes.^{10a}

The synthesis of hosts **1a-1g** is outlined in Scheme 1. The various arylamines **3c-3f** were prepared by the Pd(0)-catalyzed coupling of 1-bromo-4-nitrobenzene with the corresponding boronic acids,⁷ and followed by reduction with $\text{H}_2/\text{Raney Ni}$ or Pd-C. A finely ground mixture of the arylamine **3** and tripropyl triacid **4** was heated at ~ 180 °C for 2 h under argon atmosphere to give N-aryl imide acids **5a-5g** (45-90%). After treating with SOCl_2 , the acids were reacted with 4'-aminobenzo-18-crown-6 to afford the various hosts **1a-1g** (38-65%).⁸







The binding abilities of the hosts **1a-1g** toward alkali metal cations were determined by two phase (water/ CH_2Cl_2) picric acid extractions. The extraction experiments were performed at 26 ± 0.2 °C by employing 5.0 mL of hosts (0.20 mM) in CH_2Cl_2 and 5.0 mL of picric acid (0.10 mM) and MOH (0.10 M) in deionized water, and the results are summarized in Table 1.

The host **1a** (Ar=H) has been studied as a reference



Scheme 1.

Table 1. Extraction Percentages of Alkali Metal Cations by Hosts 4a-4g

Entry	Host	Ar	Na ⁺	K ⁺	Rb ⁺	Cs ⁺
1	4a	H	5.7	61	42	24
2	4b		6.1	58	40	20
3	4c		8.5	67	46	27
4	4d		8.7	70	50	28
5	4e		8.8	72	52	31
6	4f		10	72	52	33
7	4g		11	69	53	36

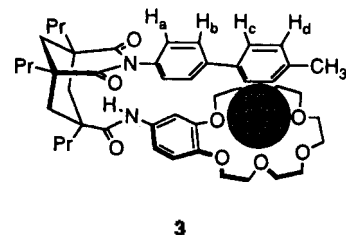
*The extraction values were determined by measuring changes in absorbances of picrate anions in aqueous layer in 373 nm. All extractions have been at least triplicated and errors in extraction percentages are within 1%.

molecule that can not exert any cation- π interaction. The hosts 1c-1f, however, contain the additional aryl moieties that could participate as π -donors in the complexation with alkali metal cations. The CPK molecular modelling studies indicate that the additional aryl units in 1c-1f are placed in the just above the crown ring and can be cooperatively involved in the binding of metal cations.

The host 1c (Ar=Ph) containing an additional phenyl group exhibits higher extractabilities of alkali metal cations by 3-6% than does the reference host 1a, while the host 1b containing a cyclohexyl group shows slightly decreased extractabilities. The increments of extractabilities by the host 1c are probably ascribed to the cation- π interaction between an additional phenyl surface and metal cations. To increase the contribution of the cation- π interaction to the complexation, we have synthesized the hosts 1d and 1f which contain more electron-rich aryl surfaces by introduction of the methyl group(s). Addition of each methyl group increases the extraction percentages up to 2-3%. The host 1e, therefore, extracts 11% (K⁺), 10% (Rb⁺), and 7% (Cs⁺) more than does the host 1a. The host 1f containing the largest aryl surface, shows highly similar extractabilities of metal cations with the host 1e. The forgoing trend of extractabilities by the hosts 1a-1f consistently demonstrates the participation of the cation- π interaction in the complexation.

The existence of the cation- π interaction can be realized by ¹H NMR study. As a representative example, the signals for the aryl protons (H_a-H_d in complex 3) of the host 1d in the presence of one equivalent of alkali metal salts are either upfield- or downfield-shifted (± 0.00 -0.03 ppm), and the magnitude and direction of the shifts depend on the nature of both cations and counteranions.

The changes in the chemical shifts for the protons, H_a-H_b, might arise mainly from the conformational rearrangement of the aryl group in the adjacent benzo-18-crown-6. The signal for the proton H_d is always downfield-shifted (~ 0.02 ppm) upon complexation, while that for H_c is negligibly shifted (< 0.01 ppm). Since the proton H_d is far away from



the aryl and carbonyl groups, the downfield shifts may result mainly from a decrease in the π -electron density of the aryl ring resulting from the M⁺...Ar interaction.

Finally, we prepared the host 1g containing two additional oxygens that could interact with metal cations, for comparisons of relative complexation properties. The host 1g shows a similar extractability with the aryl-containing hosts 1e and 1f. This result suggests that the CH₃OCH₂CH₂O- group in 1g and the aryl surfaces (dimethylphenyl and phenanthryl) in 1e and 1f provide a comparable binding energy ($\Delta\Delta G = -0.25 \sim -0.40$ kcal/mol)¹¹ in the complexation with alkali metal cations.

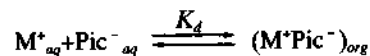
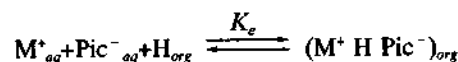
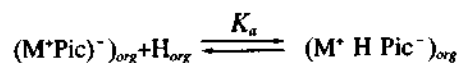
In conclusion, we have synthesized the aryl-containing hosts for binding of alkali metal cations and evaluated the cation- π interactions in water-saturated CH₂Cl₂ by a systematic manipulation of the hosts. Compared with the reference host 1a, the hosts 1c-1f show higher extractabilities of alkali metal cations up to 11% due to the additional interactions between the aryl surfaces and metal cations. This study may provide an experimental evidence for the importance of the cation- π interactions in biological system such as ion channels.

Acknowledgment. This work was financially supported by the Non-directed Research Fund, Korea Research Foundation (1995, 01-D-0623).

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8. Yields were not optimized and all new hosts were fully characterized by ^1H NMR, ^{13}C NMR, IR and elemental analysis. Mp: **1a** 130-131 °C; **1b** 114-116 °C; **1c** 101-103 °C; **1d** 162-164 °C; **1e** 290-293 °C; **1f** 142-144 °C; **1g** 130-132 °C.
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11. The cation- π energy ($\Delta\Delta G$) has been calculated by assuming 1:1 complexes and employing the equations shown below.



Here, K_a (stability constant) = K_e (extraction constant) / K_d (distribution constant) and $\Delta\Delta G = \Delta G(\text{host } \mathbf{1e}) - \Delta G(\text{host } \mathbf{1a}) = -RT \ln\{K_a(\mathbf{1e})/K_a(\mathbf{1a})\}$. Since the distribution constant (K_d) must be identical under the same extraction conditions except the host (0.2 mM), $K_a(\mathbf{1e})/K_a(\mathbf{1a}) = K_e(\mathbf{1e})/K_e(\mathbf{1a})$ and thus $\Delta\Delta G = -RT \ln [K_e(\mathbf{1e})/K_e(\mathbf{1a})]$, where $K_e = [\text{M}^+ \cdot \text{H} \cdot \text{Pic}^-]_{\text{org}} / [\text{M}^+]_{\text{aq}} [\text{Pic}^-]_{\text{aq}} [\text{H}]_{\text{org}}$ at equilibrium. Therefore, the cation- π interaction in the host **1e** is -0.29 (Na⁺), -0.35 (K⁺), -0.28 (Rb⁺), and -0.24 kcal/mol (Cs⁺), respectively. The same treatments can be applied in the other hosts.

An Unusually Low Diastereoselectivity in the Photocyclization of *Ortho*-2,2,2-trifluoroethoxybenzophenone

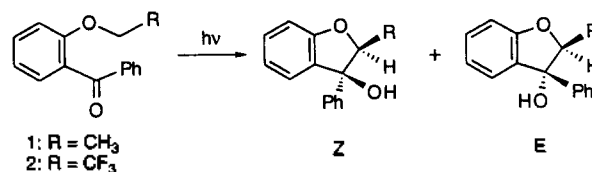
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Received December 17, 1996

The Yang reaction,¹ which produces cyclic alcohols via intramolecular hydrogen abstraction by excited ketones, has received a lot of attentions in both synthetic² and mechanistic³ aspects. Since it can give diastereomeric mixtures of the cyclic alcohols, many recent studies on the reaction have been oriented toward understanding the factors controlling diastereoselectivities in the photocyclization of various ketones.⁴ Recently Wagner has studied several ketones to give 1,5-biradical intermediates which then couple to form cyclic alkanols in varied diastereomeric ratios.⁵ The results have been analyzed in terms of conformational preferences that pre-exist in the biradicals and entropic factors related to intersystem crossing during the product formation. One system that they have looked at is *o*-alkoxybenzophenone, among which *o*-ethoxybenzophenone, **1**, gives diastereomeric dihydrobenzofuranols in an 11:1 *Z/E* ratio in benzene. In our lab, we have recently investigated the photoreactivity of *o*-2,2,2-trifluoroethoxybenzophenone, **2**, which is structurally related to **1**, and found a strikingly different ratio in the diastereomeric dihydrobenzofuranols. The result is described below (Scheme 1).

The starting ketone was prepared by stirring *o*-hydroxybenzophenone (1 eq.) and potassium carbonate (1.5 eq.) with excess amounts of 2,2,2-trifluoroethyl iodide (3 eq.) in DMF at 40 °C. After purification by column chromatography over silica gel using hexane and ethyl acetate



Scheme 1.

(10 to 1) as eluents, an oily product was obtained in 65% yield.⁷ The ketone was dissolved into 0.5 ml of benzene- d_6 and transferred to an NMR tube (0.2 M). After degassing by bubbling argon through for 10 minutes, the sample was subjected to photolysis using a Hanovia 450 W medium pressure mercury lamp with a Pyrex filter. After 50 minute irradiation, the reaction was completed and the formation of two isomeric products was apparent from its ^1H NMR spectrum (Figure 1).

Each product was confirmed by the usual spectroscopic methods and by comparing it with that of photoproduct from **1**.⁸ Assignment of stereochemistry of each isomer was made on the basis of the same criteria used for photoproducts from **1**, in which the chemical shifts of groups cis to a phenyl were more upfield than the one trans to it.

The ratio of *Z*- to *E*-2-trifluoromethyl-3-phenyldihydrobenzofuran-3-ol turned out to be 2 to 1 (by NMR in-