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Podand Ionophores Capable of Forming Cation-Binding Cavities through Intramolecular Interactions between the Terminal Groups

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Abstract: A series of podand hosts having suitable cavities for metal cations in virtue of intramolecular interactions between the terminal groups were designed and synthesized. The conformational informations of hosts were obtained by NMR studies including homonuclear NOE difference experiments. Intramolecular interactions between the terminal groups of podand hosts markedly increase binding affinities and selectivities to metal cations.

Acyclic polyethers, podands, are generally considered as poor ionophores for alkali metal cations due to their low binding affinities, compared with the corresponding cyclic analogues such as crown ethers and spherands. This problem can be tackled by forcing the conformations of podands preorganized to be semi-cyclic or cyclic. Still recently illustrated it by applying a conformational locking mechanism to the binding studies of cations with a variety of well-designed acyclic hosts.¹ Alternatively, it may be accomplished by exploiting intramolecular interactions between two terminal groups of podand hosts, as shown in Scheme 1. Only a few examples in this approach have been reported, and most of them are related to an easily ionizable group, carboxylic acid.² Furthermore, the carboxylic group itself was directly coordinated to metal ions as either a neutral or an ionized form. This prevents us to know the precise effects of the conformational preorganization by the terminal group interactions on the affinities and selectivities for binding events.



We report, herein, the new podand hosts possessing a suitable cavity for metal cation as a result of simultaneous hydrogen bonding and π -stacking interactions between the terminal groups. As shown in Scheme 2, syntheses of podand hosts **4a-d**, **5b-c** are straightforward. Diols **1a-d** were sequentially subjected to monotosylations (33-40%), substitutions by *p*-nitrophenol (75-100%), tosylations (64-80%), substitutions by adenine (44-48%),³ and reductions to afford compounds **3a-d**. Couplings of **3a-d** with imide acid chloride **6**⁴ or its N-methyl derivative **7** gave the corresponding podand hosts **4a-d**, **5b-c** in a 75-95% yield, respectively.⁵



Intramolecular hydrogen bonding between adenine and imide moieties, and π -stacking interaction between phenyl and adenine rings in hosts **4a-d** can be easily recognized in the ¹H NMR spectra. Concentration-independent chemical shifts of the imide NHs are summarized in Table 1. The chemical shifts of imide NHs for free and completely complexed forms with adenine were reported to be 7.6 and 13.2 ppm, respectively.⁶ Additionally, the ¹H NMR resonances for the protons of the phenyl and adenine rings in hosts **4a-d** were upfield shifted 0.1 - 0.2 ppm compared with the corresponding to hosts **5b-c** which can not exist in the cyclic forms. The percentages of the cyclic forms were estimated by comparisons of the chemical shifts of the imide NHs.⁷ As ethylene glycol chains are getting longer, the percentages of the cyclic forms are decreasing due to entropic disadvantage.





Watson-Crick Mode

Hoogsteen Mode

host	chemical shift δ (NH, ppm)	% cyclic	% NOE H2:H8	Watson-Crick: Hoogsteen
4a	12.90	95	9.0:2.0	82:18
4b	12.62	90	9.5:2.9	77:23
4 c	12.28	84	6.0:3.4	64:36
4d	11.90	77	3.9:2.9	57:43

In podand hosts 4a-d, two different types of intramolecular hydrogen bonds are possible; Watson-Crick vs Hoogsteen. Preference for each type was explored by the homonuclear NOE difference experiments and the results are also summarized in Table 1. As reported in literatures, 5a, 8 observed NOEs at H₂ and H₈ of adenine upon irradiation of the imide NH in hosts 4a-d may be correlated to the relative populations of Watson-Crick and Hoogsteen hydrogen bonding. It is interesting to find that hydrogen bonding of Watson-Crick type is predominant in hosts 4a and 4b, possessing relatively shorter linkage of ethylene glycol, over that of Hoogsteen type. The degree of preference is, however, getting reduced as the linkage becomes longer. CPK molecular models show that Hoogsteen hydrogen bonding seems to produce more complete cyclic cavities than does Watson-Crick, because the relative orientation of adenine and phenyl rings is different in two conformations. Thus, the Hoogsteen mode generates a better complementary shape of cavity for metal ions. This was confirmed by NOE experiments of the complex of 4b and Na⁺. Podand host 4b dissolved ~ 1 equivalent of sodium picrate in CDCl₃,⁹ while the signal for the imide NH was shifted from 12.6 to 13.2 ppm, corresponding to the completely cyclized form in CDC1₂. Irradiation of the imide NH of the complex 4b Na⁺ gave 5.2% NOE in Hg of the adenine, but not in H₂ at all. This indicates that only Hoogsteen hydrogen bonding exists in the complex 4b Na⁺, in contrast with free host 4b in which Watson-Crick type is much favored as mentioned previously.

The association constants have been determined by metal picrate extraction methods reported by Cram.¹⁰ The results are summarized in Table 2.

Table 2. Association Constants (N -) of Fodald Hosts with Alkan Metal Fictates at 205 ± 1 K.							
host	Li+	Na ⁺	K+	Rb+	Cs+		
4a	5.5 x 10 ⁴	5.5 x 10 ⁴	3.7 x 10 ⁴	1.6 x 10 ⁴	1.4 x 10 ⁴		
4b	1.5 x 10 ⁵	5.4 x 10 ⁵	1.1 x 10 ⁵	2.6 x 10 ⁴	1.8 x 10 ⁴		
4 c	6.1 x 10 ⁴	1.1 x 10 ⁵	2.6 x 10 ⁵	7.9 x 10 ⁴	4.0 x 10 ⁴		
4 d	4.7 x 10 ⁴	7.7 x 10 ⁴	1.3 x 10 ⁵	8.3 x 10 ⁴	6.5 x 10 ⁴		
5b	6.6 x 10 ⁴	4.8 x 10 ⁴	4.0 x 10 ⁴	2.0 x 10 ⁴	1.5 x 10 ⁴		
5c	4.9 x 10 ⁴	2.9 x 10 ⁴	2.3 x 10 ⁴	1.6 x 10 ⁴	1.1 x 10 ⁴		

Table 2. Association Constants (M⁻¹) of Podand Hosts with Alkali Metal Picrates at 293 ± 1 K. *

* Extractions were performed by employing 1.5 mL of host (50 mM in CHCl₃) and 0.3 mL of metal picrate (10 mM in H₂O), in which conditions all of hosts extracted 15 - 60% of metal picrates from aqueous to organic layer. All experiments were triplicated and errors are less than 3% in the extraction percentages.

Two trends are apparent. First, selectivities have been markedly changed and increased in hosts 4b and 4c compared with their N-methyl analogues 5b and 5c which can not exist in the cyclic forms. For example, host 4b, containing pentaethylene glycol linkage, has the highest affinities to Na⁺, and host 4c, containing hexaethylene glycol linkage, to K⁺. It is worthwhile to note that host 4b binds Na⁺ five-fold more strongly than does K⁺. This may simply reflect the complementary sizes of metal ion and cavity, like in the case of crown ethers and cations. Second, the binding affinities of hosts 4b and 4c to cations are much greater than those of the corresponding analogues 5b and 5c. As seen in Table 2, the

association constant of 4b with Na⁺ is ~10-fold higher than that of 5b with Na⁺, and the association constant of 4c with K⁺ is also ~10-fold higher than that of 5c with K⁺. Especially, the association constant (5.5 x 10⁵ M⁻¹) of 4b with Na⁺ is comparable to that (11 x 10⁵ M⁻¹) of a 15-crown-5 derivative¹¹ with Na⁺ reported in this laboratory. The enhancements in affinity and selectivity of our podand hosts must result from preorganization through the intramolecular hydrogen bonding and π -stacking interactions.

In conclusion, we have shown that rationally-designed podand hosts, having the cyclic structures formed by intramolecular interactions between the appropriate terminal groups, can bind metal cations strongly and selectively as well as their cyclic analogues. Nonetheless, our hosts leave room for improvement in stability and selectivity, and we are pursuing this goal by increasing interaction between the terminal groups.

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References and Notes

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- All new hosts were fully characterized by NMR, IR, and MS spectra. Mp.: 4a 101-103 °C; 4b 83-85 °C; 4c 71-73 °C;
 4d 66-69 °C; 5b 61-62 °C; 5c 51-53 °C.
- 7. % cyclic form = 100 x $(\delta_{obsd} \delta_{free}) / (\delta_{complex} \delta_{free}) = 100 x (\delta_{obsd} 7.6) / (13.2 7.6).$
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