CHEMISTRY LETTERS, pp. 1289-1292, 1989.

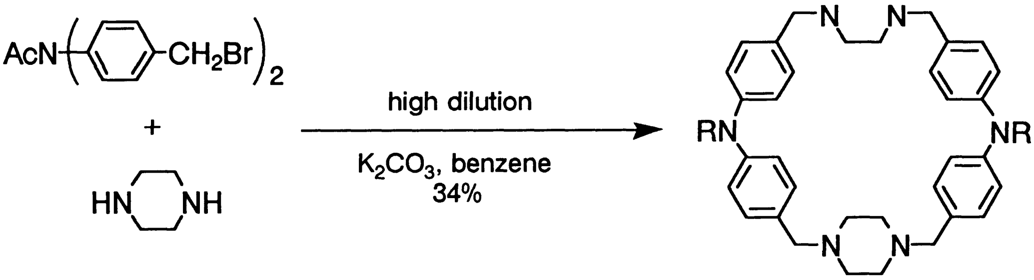
Lithium Selective Complexation by a Novel Cyclophane-type Macrocyclic Ligand

Nobuhiro KIHARA, Kazuhiko SAIGO,* Yoshio KABATA,
Mami OHNO, and Masaki HASEGAWA
Department of Synthetic Chemistry, Faculty of Engineering,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

A novel cyclophane consisting of diphenylamine and piperazine skeletons was synthesized by their direct 2:2 condensation using benzene as a template. The cyclophane was a very effective ligand for alkaline metal and ammonium cations, and showed highly selective extractability for lithium cation.

Multidentate macrocyclic ligands are effective co-receptors to catalyze various reactions or to transport cations between two phases.[1] For the catalytic reaction and the transportation, the hydrophobicity of the macrocyclic ligand around the cation plays a significant role. Lariat ethers can improve the hydrophobicity of a macrocyclic *hole* by the modification of the side-arm(s).[2] Calixarenes are macrocyclic ligands having a deep hydrophobic cavity with reasonable binding ability.[3] But, there is no report on the synthesis and complexation of a macrocyclic ligand with binding sites at the center of a deep hydrophobic cavity except for Lehn's cyclophanes, by which, however, only anion binding was examined.[4] We report here the first example of the complexation of a cyclophane-type macrocyclic ligand with cations.

To achieve cation binding by such a macrocycle, a novel cyclophane **1** having diphenylamine skeletons and piperazine moieties was designed and synthesized with the expection that four aromatic rings of the dipheylamine skeletons and two piperazine moieties offer a hydrophobic pocket[5] and an electrostatic field in the center of the cavity, respectively.



1a : R=Ac
1b : R=H

From the reaction mixture of 2:2 direct condensation of N,N-bis(4-bromomethylphenyl)acetamide[6)] and piperazine in ethanol/tetrahydrofuran/benzene under high dilution conditions, cyclophane **1a** was isolated in 34% yield as a benzene complex by addition of a large amount of benzene. The precipitate contained an equimolar amount of benzene, and the benzene could not be removed from **1a** under reduced pressure. The phenomenon indicates that a hydrophobic cavity was introduced in **1a** and that a strong complex was formed by hydrophobic interaction between the cavity and the benzene molecule. The absence of benzene in the solvent for the condensation resulted in lower yield (20%). This means that benzene acts as a template in the high dilution condensation. It should be noted that the template effect by a neutral molecule, such as benzene, is very rare except for our previous result.[7)]

Reductive deacetylation of cyclophane **1a** was achieved by treatment of **1a** with lithium aluminium hydride in tetrahydrofuran to give cyclophane **1b**. Cyclophane **1b** was soluble in acidic water (below pH 3), and the presence of a hydrophobic cavity in **1b** was confirmed by NMR[8)] and fluorescence spectra.[9)]

The binding property of cyclophane **1** toward cations at 25 °C in chloroform, saturated with water, was determined by the extraction method developed by Cram *et al.*[10)] Since the solubility of the complex of cyclophane **1b** with alkaline metal picrates in chloroform was rather low, the complexation of cyclophane **1a** was performed. The association constant (*K*a) and free energy ($\Delta G°$) for the complexation are summarized in Table 1. These values were reproducible, and the standard deviations are also shown in Table 1.

Table 1. Equilibrium and Free Energy Parameters for the Association between Cyclophane **1a** and Picrates in $CHCl_3$ at 25 °C Calculated from Aqueous Layer and Organic Layer (in parentheses)

Cation	$Ka/10^6$ l·mol^{-1}		Standard Deviation		$-\Delta G°$/kcal·mol^{-1}	
Li^+	114	(95)	13	(7.0)	11.0	(10.9)
Na^+	4.4	(4.7)	0.78	(0.76)	9.1	(9.1)
K^+	4.6	(4.8)	0.51	(0.47)	9.1	(9.1)
Cs^+	2.3	(1.9)	0.36	(0.34)	8.7	(8.6)
NH_4^+	3.6	(3.1)	0.24	(0.15)	9.0	(8.9)
$MeNH_3^+$	0.11	(0.17)	0.057	(0.0038)	6.8	(7.1)
t-$BuNH_3^+$	0.013	(0.014)	0.0044	(0.0009)	5.6	(5.7)

Cyclophane **1a** formed stable complexes with alkaline metal and ammonium picrates. Surprisingly, the cyclophane formed the most stable complex with lithium cation, and *K*a value of the complex was greater by a factor >20 than any other complex. It is known that ligands, which are able to form a complex with lithium cation selectively, have a cavity fitting closely to the diameter of lithium cation (1.36 Å).[1a,11] But, the examination using CPK molecular models showed that the cavity of **1a** is too large to include lithium cation with well size-fitting as shown in Fig. 1. Therefore, the selective complexation of **1a** with lithium cation may not come from the size fitting between the cavity and naked lithium cation.

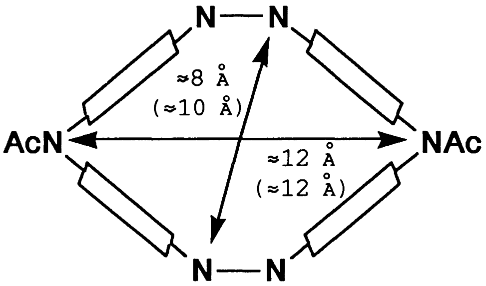


Fig. 1. The size of the cavity of **1a** estimated using CPK molecular models. The piperazines were put in chair or boat form (in parentheses).

To explain the high selectivity of cyclophane **1a** toward lithium cation, the following reasons can be considered: (1) The cyclophane formed complexes with hydrated cations as observed in some crown ethers,[1a,12] and the selectivity appeared by the combination of the acidity of the metal cations and the size fitting between the cavity and the hydrated cations. Lithium cation, the most acidic cation in alkaline metal cations, may highly polarize the coordinating waters to form the most stable complex with basic piperazine moieties. Furthermore, the examination using CPK molecular models showed that $Li(OH_2)_6^+$ could fit well to the cavity of **1a** by forming hydrogen bonds between piperazine moieties and two molecules of the waters coordinating arround lithium cation. (2) The hydrophobic field of the cyclophane influenced the complexation and the selectivity by a subdominant hydrophobic interaction between the cavity and the trinitrophenyl group in ion-contacted metal picrates. The hardest counter cation (Li^+) would result in the lowest electron density of the trinitrophenyl group, thus, the interaction between the electron-accepting trinitrophenyl group and the electron-donating benzene rings in the cyclophane increased, resulting in the formation of the most stable complex.

Cyclophane **1a** also formed complexes with ammonium picrates. The complexes may be formed with hydrated ammonium picrates as well as metal picrates, since the cavity of **1a** is also rather large for naked ammonium picrates. The hydrophobicity of the substituents of the ammonium picrates did not enlarge *Ka*, but *Ka* decreased in order scale with enlarging the substituent of the ammonium salts. Therefore, the selectivity of **1a** to ammonium picrates can be clearly explained by steric repulsion. Such phenomena were reported for ligands having no hydrophobic cavity such as spheraplex.[13] It should be emphasized, however, that the recognition ability of **1a** for alkyl substituent in ammonium picrates was considerably higher than that of the known ligands.

Further investigations for the selective recognition to lithium cation and for the application of 1 as a co-receptor are in progress.

References

1) a) "Host-Guest Complex Chemistry I," ed by F. Vögtle, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo (1981); b) "Host-Guest Complex Chemistry II," ed by F. Vögtle, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo (1982); c) "Host-Guest Complex Chemistry III," ed by F. Vögtle and E. Weber, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo (1984).
2) K. A. Arnold, A. M. Viscariello, M. Kim, R. D. Gandour, F. R. Fronczek, and G. W. Gokel, Tetrahedron Lett., 29, 3025 (1988).
3) C. D. Gutsche, M. Iqbal, and I. Alam, J. Am. Chem. Soc., 109, 4314 (1987).
4) J. Jazwinski, J.-M. Lehn, R. Meric, J.-P. Vigneron, M. Cesario, J. Guilhem, and C. Pascard, Tetrahedron Lett., 28, 3489 (1987).
5) Diphenyl methane skeleton is effective to introduce a hydrophobic cavity to a cyclophane. K. Odashima and K. Koga, "Cyclophane," ed by P. M. Keehn and S. M. Rosenfeld, Academic Press, New York (1983), Vol. 2, Chap. 11, pp. 629-678.
6) M. Wakselman and M. Dome, Bull. Soc. Chim. Fr., 1975, 571.
7) K. Saigo, R.-J. Lin, M. Kubo, A. Youda, and M. Hasegawa, J. Am. Chem. Soc., 108, 1996 (1986).
8) Up-field shifts of the chemical shifts of aromatic compounds such as phenols were observed in the presence of **1b** in 1.27 mol·l^{-1} DCl.
9) Fluorescence (λ_{max} = 485 nm, excited at 350 nm) of 8-anilino-1-naphthalenesulfonic acid (ANS) was observed in 1 mol·l^{-1} HCl in the presence of **1b**.
10) R. C. Helgeson, G. R. Weisman, J. L. Toner, T. L. Tarnowski, Y. Chao, J. M. Mayer, and D. J. Cram, J. Am. Chem. Soc., 101, 4928 (1979). The method can be performed only for the case of 1:1 ligand-cation stoichiometry. In our cases, calculated *Ka* values were independent on the concentration of picrates, indecating 1:1 stoichiometry of the complexes.
11) J.-M. Lehn, Acc. Chem. Res., 11, 49 (1978); D. J. Cram and G. M. Lein, J. Am. Chem. Soc., 107, 3657 (1985).
12) M. Czulger, J. Chem. Soc., Chem. Commun., 1981, 472.
13) D. J. Cram, Angew. Chem., Int. Ed. Engl., 25, 1039 (1986).

(Received May 2, 1989)