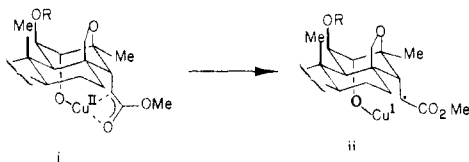


The formation of ring contracted products such as **6** paves the way for a novel entry into the spherandins. Efforts along these lines are currently in progress.

Acknowledgment. This investigation was supported by a Public Health Service Grant (CA 28865) from the National Cancer Institute. The 360-MHz NMR instrument (Nicolet) used in the above studies was purchased in part through funds provided by the National Science Foundation (Grant CHE-81-05004). We are grateful to Professor John K. Stille for insight into the mechanistic aspects of the ring contraction reaction.

(9) A referee has suggested a reasonable alternative mechanism involving formation of a copper(II) enolate via base catalysis followed by electron transfer (cf. i \rightarrow ii).



A Spherand Azophenol Dye: Lithium Ion Specific Coloration with "Perfect" Selectivity

Takahiro Kaneda,* Shin'ichi Umeda, Hisako Tanigawa, and Soichi Misumi*

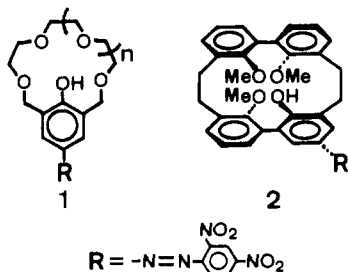
The Institute of Scientific and Industrial Research
Osaka University
Mihogaoka, Ibaraki, Osaka 567, Japan

Yasushi Kai, Hisashi Morii, Kunio Miki, and Nobutami Kasai*

Department of Applied Chemistry
Faculty of Engineering, Osaka University
Yamadaoka, Suita, Osaka 565, Japan

Received March 11, 1985

Designing and synthesizing ligands that can selectively bind a specific metal ion and undergo concomitantly color change are worthwhile subjects in host-guest chemistry. This paper provides such an approach where our attention is focused on lithium.¹ Several macrocyclic ligands have been known as lithium binders, but they also tend to bind other guests.² Recently, we reported ion-selective coloration with crowned (dinitrophenyl)azophenol **1**³ and fluorescent emission with crowned benzothiazolylphenols;⁴



(1) Recently, a colored azo macrocycle with excellent lithium selectivity has been reported: Ogawa, S.; Narushima, R.; Arai, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5760-5762.

(2) (a) Lehn, J. M.; Sauvage, J. P. *J. Chem. Soc., Chem. Commun.* **1971**, 440-441. (b) Dale, J.; Krane, J. *J. Chem. Soc., Chem. Commun.* **1972**, 1012-1013. (c) Kobuke, Y.; Hanji, K.; Horiguchi, K.; Asada, M.; Nakayama, Y.; Furukawa, J. *J. Am. Chem. Soc.* **1976**, *98*, 7414-7419. (d) Olsher, U.; Jagur-Grodzinski, J. *J. Chem. Soc., Dalton Trans.* **1981**, 501-505. (e) Nakamura, H.; Sakka, H.; Takagi, M.; Ueno, K. *Chem. Lett.* **1981**, 1305-1306. (f) Cram, D. J.; Lein, G. M.; Kaneda, T.; Helgeson, R. C.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 6228-6232. (g) Cram, D. J.; Dicker, I. B.; Knobler, C. B.; Trueblood, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 6828-6830.

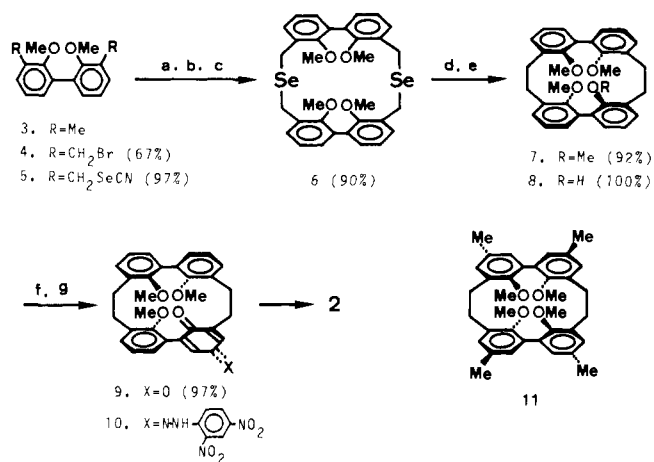


Figure 1. Synthetic scheme. (a) NBS, CCl_4 ; (b) KSeCN , acetone-benzene; (c) **4**, NaBH_4 , THF-EtOH; (d) $h\nu$, $(\text{Me}_2\text{N})_3\text{P}$, THF; (e) Li-AlH_4 , benzene, reflux; (f) PbO_2 , ether- HCOOH ; (g) (2,4-dinitrophenyl)hydrazine, EtOH.

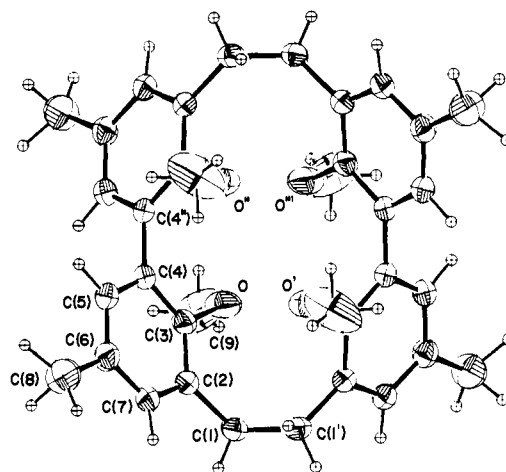


Figure 2. Molecular structure of compound **11** shown by the ORTEP drawing with the thermal ellipsoids at 30% probability level for non-hydrogen atoms and the spheres with radius of 0.1 Å for hydrogen atoms. Compound **11** has a strain-free structure with the dihedral angle of 89.9° between the benzene rings in the biphenyl moiety and the torsional angle of 86.2° around $\text{C}(1)-\text{C}(1')$ bond.

that is, these crown dyes are active toward lithium and calcium salts.^{3b} In order to achieve a much higher level of lithium selectivity, spherand dye **2** has been designed by considering the fact that Cram's spherand⁵ can reject multivalent metal ions perfectly. We describe here the synthesis of **2**, its lithium ion-specific coloration, and the crystal structure of the relevant spherand **11**.

According to our improved method involving photodeselenation which was useful for preparing cyclophanes,⁶ [2.0.2.0]meta-cyclophane **7**⁷ was obtained via seven steps in 30% overall yield

(3) (a) Kaneda, T.; Sugihara, K.; Kamiya, H.; Misumi, S. *Tetrahedron Lett.* **1981**, *22*, 4407-4408. (b) Sugihara, K.; Kaneda, T.; Misumi, S. *Heterocycles* **1982**, *18*, 57-61. (c) Nakashima, K.; Nakatsuji, S.; Akiyama, S.; Kaneda, T.; Misumi, S. *Chemistry Lett.* **1982**, 1781-1782. (d) Nakashima, K.; Yamawaki, Y.; Nakatsuji, S.; Akiyama, S.; Kaneda, T.; Misumi, S. *Chem. Lett.* **1983**, 1415-1418. (e) Nakashima, K.; Mochizuki, N.; Nakatsuji, S.; Akiyama, S.; Kaneda, T.; Misumi, S. *Chem. Pharm. Bull.* **1984**, *32*, 2468-2470.

(4) (a) Tanigawa, I.; Tsuamoto, K.; Kaneda, T.; Misumi, S. *Tetrahedron Lett.* **1984**, *25*, 5327-5330. (b) Nakashima, K.; Nakatsuji, S.; Akiyama, S.; Tanigawa, I.; Kaneda, T.; Misumi, S. *Talanta* **1984**, *31*, 749-751.

(5) Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Lein, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 6752-6754.

(6) Higuchi, H.; Kugimiya, M.; Otsubo, T.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1983**, *24*, 2593-2594.

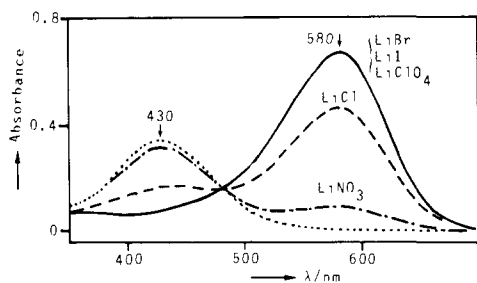


Figure 3. Visible spectra of spherand-metal salt-piperidine systems in CHCl_3 , (---) salt free, LiF , Li_2SO_4 , MX ($\text{M} = \text{Na}, \text{K}, \text{Rb}, \text{Cs}; \text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}, \text{ClO}_4, \text{NO}_3, \text{SO}_4$), BeCl_2 , MX_2 ($\text{M} = \text{Mg}, \text{Ca}, \text{Sr}, \text{Ba}; \text{X} = \text{Cl}, \text{Br}, \text{ClO}_4$), MX_2 ($\text{M} = \text{Mn}, \text{Co}, \text{Ni}, \text{Zn}, \text{Cd}, \text{Sn}, \text{Hg}; \text{X} = \text{Cl}, \text{Br}$), MCl_3 ($\text{M} = \text{Al}, \text{Cr}, \text{Fe}, \text{Sb}, \text{Cr}, \text{Bi}$), $\text{Pb}(\text{OAc})_2$, AgClO_4 .

from *o*-cresol (Figure 1). By comparison of ^1H NMR data,^{7,8} this cyclophane was assigned to spherand **7** which has the same geometry as that of crystallographically defined tetramethyl derivative **11**⁷ (described below). Demethylation of **7** was carried out by boiling with LiAlH_4 in benzene to afford exclusively monodemethylated product **8**⁷ in quantitative yield.⁹ Oxidation of **8** with PbO_2 ¹⁰ gave quinone **9**. Treatment of this quinone with (2,4-dinitrophenyl)hydrazine deposited orange crystals of the desired azophenol **2**⁷ in quantitative yield, which was derived by tautomerization of the first-formed hydrazone **10**.

The molecular structure of **11** determined by X-ray diffraction method is shown in Figure 2.¹¹ As the structure has crystallographic D_2 symmetry, only a quarter of the molecule is independent. The distance from the oxygen atom of a methoxy group

(7) Carbon and hydrogen analyses were within 0.30% of theory, and ^1H NMR (Bruker WM 360, CDCl_3) and mass spectra were consistent with the structural assignments. **2**: reddish orange needles (MeCN), mp 257–260 °C; UV (CHCl_3) λ_{max} ($\log \epsilon$ 4.39). **7**: colorless prisms (hexane), mp 232–232.5 °C; ^1H NMR δ 7.18 (dd, $J = 7.4, 1.8$ Hz, 4 H, Ar H), 7.02 (dd, $J = 7.4, 1.8$ Hz, 4 H, Ar H), 6.94 (t, $J = 7.4$ Hz, 4 H, Ar H), 3.01 (s, 12 H, OMe), 3.0–2.8 (m, 8 H, Ar CH_2). **8**: white needles (MeOH), mp 168–169 °C. **11**: colorless columns (CHCl_3 - MeOH), mp 277–277.5 °C (sealed tube); ^1H NMR δ 7.00 (d, $J = 1.8$ Hz, 4 H, Ar H), 6.81 (d, $J = 1.8$ Hz, 4 H, Ar H), 2.97 (s, 12 H, OMe), 2.9–2.7 (m, 8 H, Ar CH_2), 2.27 (s, 12 H, Ar Me).

(8) The ^1H NMR signals due to the methoxy protons of **7** appeared at higher field by 0.44 ppm than those of biphenyl derivative **3**. Such an upfield shift can be expected with the shielding of two faced benzene rings in the structure. A similar upfield shift, 0.40 ppm, was also observed for **11**.

(9) The reaction has been successfully applied to demethylation of an anisole unit in a variety of cyclic polyether systems using THF as a solvent, which gave frequency better yield than benzene. The following literature encouraged us to use LiAlH_4 as demethylating agent: Carroll, J. F.; Kulkowit, S.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1980**, 507–508.

(10) De Jonge, C. R. H. I.; van Dort, H. M.; Vollbracht, L. *Tetrahedron Lett.* **1970**, 1881–1884.

(11) X-ray structure analysis of **11**. Crystal data: $\text{C}_{36}\text{H}_{40}\text{O}_4$, FW = 536.7, orthorhombic, $Ccca$, $a = 20.080$ (1) Å, $b = 18.929$ (1) Å, $c = 8.076$ (1) Å, $V = 3069.8$ (3) Å³, $Z = 4$, $D_c = 1.161$, $D_m = 1.12$ g cm^{-3} . The X-ray diffraction data were collected on a Rigaku four-circle diffractometer using nickel-filtered $\text{Cu K}\alpha$ radiation by θ - 2θ scan up to $2\theta = 120^\circ$. The crystal structure was solved by direct methods and was refined by block-diagonal least squares using a total of 1116 reflections. The nonhydrogen atoms were refined anisotropically together with the hydrogen atoms with the fixed isotropic temperature factors taken from the attached carbon atoms in the final stage of their isotropic refinement. The final R index is 0.071.

to the center of the molecule is 2.078 Å. The radius of the cavity (0.68 Å) is obtained by subtracting the Pauling's van der Waals radius of oxygen (1.40 Å) from this distance. The four methoxy oxygens are at the corners of a tetrahedron. The size of the cavity is comparable with the ionic radius of Li^+ (0.60¹² or 0.73 Å¹³) and is smaller than that of Na^+ (0.95¹² or 1.16 Å¹³). The large thermal amplitudes of the methoxy methyl group show the conformational flexibility of the group.

On neutralization in ethanol with a series of alkali metal hydroxides and tetramethylammonium hydroxide, the weak acid **2** gave colored salts with an absorption maximum at 615 nm, independent of the species of cations.¹⁴ This finding suggests that the phenoxide anion from **2** interacts with the solvated cations or forms solvent-separated ion pairs in the protic solvent.

In chloroform, no phenolate anion of **2** was detected even in the presence of excess piperidine as a base. However, addition of crystalline lithium salts to this mixture gives rise to changes in absorption spectra, indicating the formation of the phenolate (Figure 3).¹⁵ A dramatic color change from yellow to violet took place rapidly when the lithium salts were added, except for nitrate, fluoride, and sulfate. No tendency for interaction was observed with any of the other 58 salts listed in Figure 3.

In the hydrophobic solvent, the lithium ion of the colored species is believed to be encapsulated in the hydrophilic cavity of the counteranion on the basis of the following facts: (1) the cavity is expected to be small¹⁶ but able to accommodate the guest; (2) the coloration takes place only when the specimen is in contact with lithium salts; (3) the monodemethylation of spherands **7** and **11**¹⁷ occurs exclusively in aprotic solvent such as benzene even in the presence of excess LiAlH_4 ; (4) no cation exchange between Li^+ and Ca^{2+} or Ba^{2+} was observed. The observed perfect lithium selectivity under the given conditions is described in terms of binding the guest ion by coulombic attractive force and ion-dipole interactions and rejecting larger or multivalent cations¹⁸ by steric effects caused by the narrow entrances to the small cavity in the spherand dye.

Supplementary Material Available: Tables of final atomic parameters and interatomic bond distances for **11** (2 pages). Ordering information is given on any current masthead page.

(12) Pauling, L. "The Nature of the Chemical Bond", 3rd ed.; Cornell University Press: New York, 1960.

(13) (a) Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr., Sect. B* **1969**, *B25*, 925–946. (b) Shannon, R. D. *Acta Crystallogr., Sect. A* **1976**, *A32*, 751–767.

(14) In contrast to this, cation dependence was observed for crown dye system **1**.

(15) The visible spectra were measured as follows. After a spoonful of crystalline salt (ca 10^{-4} mol) was added to a stock solution (1.6×10^{-5} M, 2.5 mL) of **2** containing piperidine (50 μL , 50 mmol), the resulting mixture was well shaken for 1 min in a cell and then the spectra were recorded within 5 min.

(16) Extraordinarily large pK_a for **2**, 13.5 in 10% water-dioxane at 25 °C, is compatible with this small cavity because of the unstability of the resulting anion due to a large electronic repulsive force.

(17) No evidence for complexing lithium with this spherand was obtained by both picrate salt extraction and NMR spectroscopic techniques.

(18) It is quite likely that the effective size of multivalent cations becomes larger than that of naked ones by interactions with counteranions under the experimental conditions.