

Synthesis of New Macrocyclic Lactones and Their Extraction Study*

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Abstract—New macrocyclic lactones were synthesized by reaction of 3-bromo-5-(5-*tert*-butyl-2-hydroxybenzyl)biphenyl-4-ol with appropriate polyethylene glycol-based dicarboxylic acid dichlorides, and their complexes with $\text{Mg}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$, $\text{Pb}(\text{SCN})_2$, $\text{NaClO}_4 \cdot \text{H}_2\text{O}$, and KClO_4 were prepared. The macrocyclic ligands were evaluated as extractants in the transfer of Li^+ , Na^+ , K^+ , Cu^{2+} , Ni^{2+} , and Hg^{2+} picrates from aqueous to organic phase.

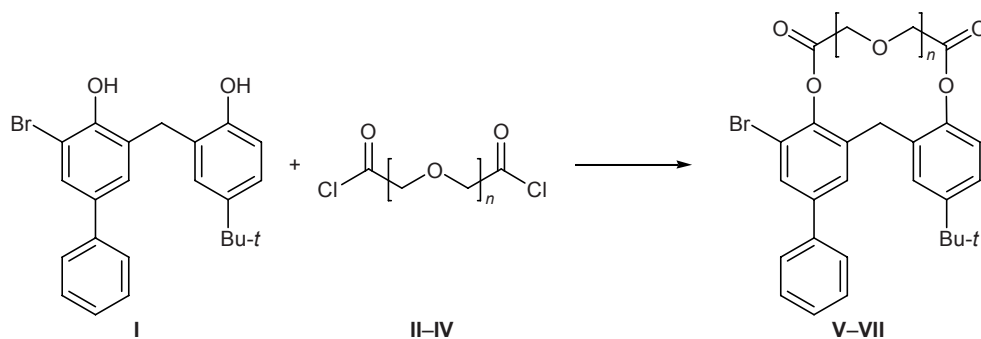
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The importance of macrocyclic ligands continuously increases due to their ability to form complexes with various metal salts [1] and their role in studies on bioprocesses, catalysis, material science, and transport and separation phenomena [2–5]. Macrocyclic polyethers are cyclic compounds in which 4 to 20 heteroatoms are linked through ethylene or propylene moieties. Oxygen [6, 7], nitrogen [8], sulfur [9], and phosphorus may be heteroatoms. A macroring can contain either the same or different heteroatoms. The ability of macrocyclic ligands or polymers based thereon to separate ionic species was reviewed in [10]. It was shown that these compounds are capable of separating Li, Na, and K thiocyanates, as well as such salts as KCl, KBr, KI, and KSCN [11]. Macrocyclic compounds were also used for optical resolution of race-

mates [12, 13]. Though enormous number of lactone and crown ether derivatives and their complexes have already been described, many more interesting systems of this type surely await discovery.

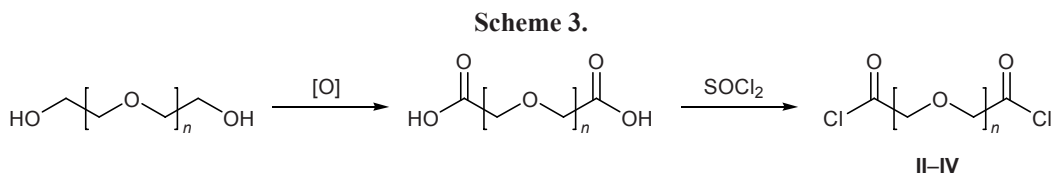
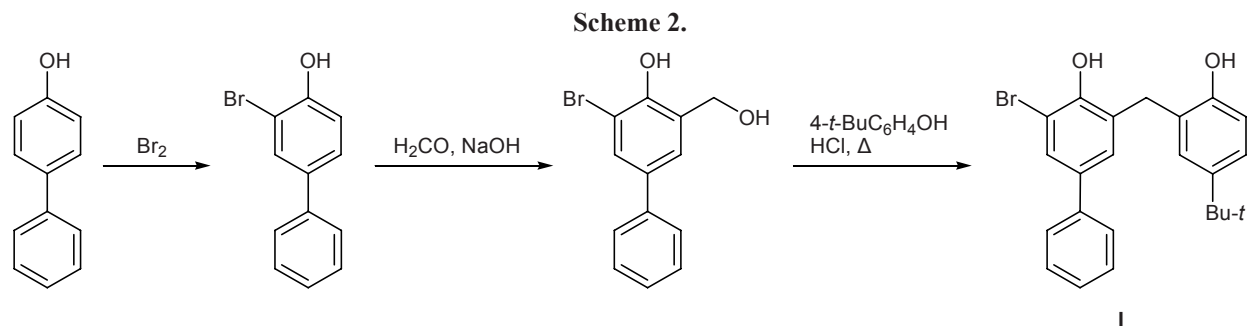
In the present article we report on the synthesis of new macrocyclic ligands and their complexes with metal ions with a view to study their extraction power with respect to metal picrates. Three new macrocyclic lactones **V–VII** differing by the length of the polyether bridge were synthesized as shown in Scheme 1 from 3-bromo-5-(5-*tert*-butyl-2-hydroxybenzyl)biphenyl-4-ol (**I**) and the corresponding dicarboxylic acid dichlorides **II–IV** under the Schotten-Baumann reaction conditions using more dilute solutions to avoid polymerization. Initial compounds **I** and **II–IV** were prepared according to Schemes 2 and 3, respectively. We be-

Scheme 1.



II, V, n = 1; III, VI, n = 2; IV, VII, n = 3.

* The text was submitted by the authors in English.



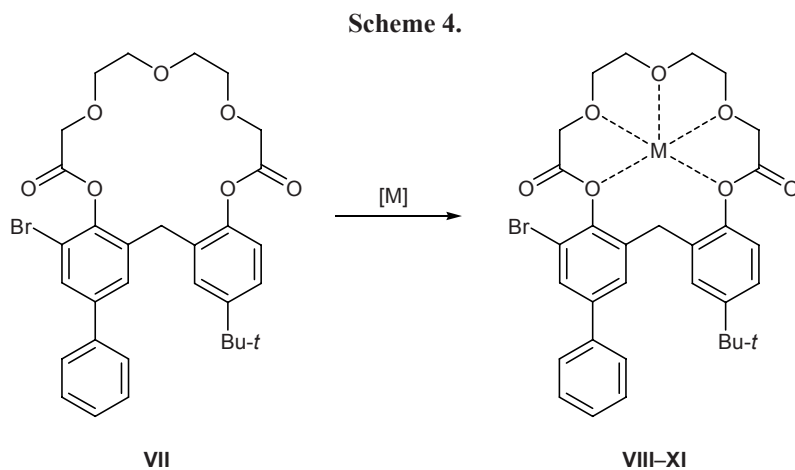
II, $n = 1$; **III**, $n = 2$; **IV**, $n = 3$.

lieved that such macrocyclic lactones should be capable of binding various metal ions via host-guest complexation pattern and separating racemic mixtures.

The structure of compounds **V-VII** was confirmed by the ^1H NMR, IR, and mass spectra and elemental analyses. Macrocyclic lactones **V-VII** showed characteristic carbonyl peaks at $1700\text{--}1760\text{ cm}^{-1}$ and bands typical of aliphatic ether moieties at $1100\text{--}1200\text{ cm}^{-1}$, while no absorption assignable to hydroxy groups was observed in the region $3300\text{--}3500\text{ cm}^{-1}$. These data can be used to monitor the reaction progress. In addition, phenolic hydroxy group usually gives rise to a sharp peak at δ 4–7.5 ppm in the ^1H NMR spectra, so that the absence of signals in the region δ 4–7.5 ppm counts in favor of the reaction completion. If no reaction occurred, the OH signal would be observed at δ 12.0 ppm due to hydrogen bonding with the carbonyl

group of diacid dichloride. Signals from the methylene protons in the polyether fragments of **V-VII** were located at δ 3–4.5 ppm, in keeping with published data. The absence of phenolic hydroxy groups in the products was also confirmed by negative color tests with FeCl_3 . In the fast atom bombardment (FAB) mass spectra of macrocyclic lactones **V-VII**, $[M + \text{H}]^+$ ion peaks were present with m/z values corresponding to those calculated for the assumed structures.

Macrocyclic lactone **VII** ($n = 3$) was used to obtain complexes with KClO_4 , $\text{NaClO}_4 \cdot \text{H}_2\text{O}$, $\text{Pb}(\text{SCN})_2$, and $\text{Mg}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$. The complexes were prepared by mixing solutions of the ligand and the corresponding metal salt in appropriate solvents as shown in Scheme 4. The IR spectra of the complexes largely resembled the spectrum of the ligand, but the ether band was broadened, indicating coordination of the



VIII, $M = \text{K}$; **IX**, $M = \text{Na}$; **X**, $M = \text{Pb}$; **XI**, $M = \text{Mg}$.

ether oxygen atoms to the metal ion. In addition, the presence of an absorption band at 1090 cm^{-1} typical of ClO_4^- ion suggests that the latter is not coordinated to the metal. Coordination of the ether oxygen atoms to the metal ion implies electron density transfer from the oxygen atoms to the center of the macrocyclic ring, leading to broadening of the ether absorption bands and lowering of the chemical shifts of the corresponding aromatic protons. According to the elemental analyses data, the complexes had 1:1 stoichiometry, i.e., the crown moiety of the ligand accommodates one metal cation via host-guest complexation pattern.

Metal picrate extraction studies were performed using ligands **VI** and **VII** and alkali and transition metal salts. The results are shown in Figs. 1 and 2. The corresponding picrates were prepared from lithium, sodium, and potassium hydroxides and nickel(II), copper(II), and mercury(II) nitrates. The amount of the metal transferred from the aqueous to organic phase was determined by spectrophotometry. The binding properties of the ligands depend upon different factors, such as macrocyclic effect, cavity size, and the nature and number of donor atoms. The results for metal cations of Group IA showed different transporting values according to cavity of the ligand and radius of cation inserted into the crown cavity. Extraction of transition metal picrates was more effective as compared to alkali metals. Presumably, the reason is additional interaction of n -electrons on the carbonyl groups with d -metal ions. Thus, macrocyclic lactones are useful transition metal carriers, which is in agreement with published data [14].

EXPERIMENTAL

The ^1H NMR spectra were obtained using a Varian spectrometer operating at 400 MHz. The mass spectra were measured on Varian 711 and VG Zapspec spectrometers. The elemental analyses were determined using a Leco CHNS-932 analyzer. The IR spectra were obtained on a JASCO FT/IR-300E spectrometer, and the UV spectra were measured on a Shimadzu UV-160A spectrophotometer at the Department of Chemistry, Faculty of Sciences and Arts, University of Selçuk.

All the reagents used in this study were obtained from Merck or Fluka and were used without additional purification. Di-, tri-, and tetraethylene glycols were distilled under reduced pressure over CuSO_4 prior to use. Appropriate dicarboxylic acid dichlorides **II-IV**

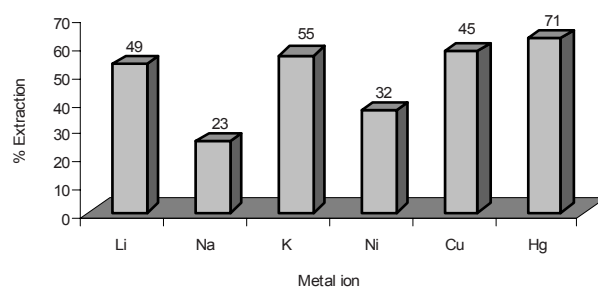


Fig. 1. Extraction of metal picrates from aqueous to organic phase using macrocyclic lactone **VI**.

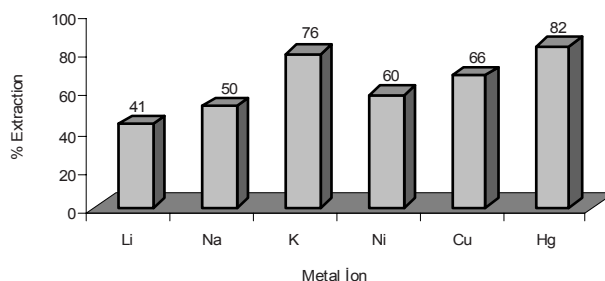


Fig. 2. Extraction of metal picrates from aqueous to organic phase using macrocyclic lactone **VII**.

and macrocyclic ligands **V-VII** were synthesized according to the procedures described in [15-18].

3-Bromo-5-(5-tert-butyl-2-hydroxybenzyl)bi-phenyl-4-ol (I) was synthesized according to the procedure reported in [19] (Scheme 2). A solution of 76.3 g of biphenyl-4-ol in 800 ml of chloroform was heated to the boiling point ($55-60^\circ\text{C}$), a solution of 27 ml of bromine in 30 ml of chloroform was added dropwise under stirring, and the mixture was heated under reflux overnight. The resulting dark brown solution was washed with water, dried over MgSO_4 , and evaporated, the residue was treated with petroleum ether, and the white crystals were filtered off. 3-Bromobiphenyl-4-ol thus obtained was treated with 100 ml of 20% aqueous sodium hydroxide and 100 ml of a 37% formaldehyde solution at 50°C over a period of 24 h. The mixture was acidified with acetic acid and was kept for several days. The precipitate was washed with water until the absence of acetic acid odor, heated to 100°C in an oven (the product melted), and cooled to obtain 3-bromo-5-hydroxymethylbiphenyl-4-ol as a glassy material with mp $52-55^\circ\text{C}$. A solution of 40 g (0.2 mol) of 4-tert-butylphenol in 200 ml of xylene was added to 27.9 g (0.1 mol) of 3-bromo-5-hydroxymethylbiphenyl-4-ol, the mixture was heated to 110°C , and 5 ml of hydrochloric acid was added dropwise to the boiling solution. The mixture was stirred for a week at 110°C and cooled to room temperature, and

the precipitate was filtered off. Yield 2.05 g (44.7%), brownish powder, mp 165–168°C. IR spectrum (KBr), ν , cm^{-1} : 3200 (OH), 2800 (CH_2), 1555 ($\text{C}-\text{C}_{\text{arom}}$), 810 ($\text{C}-\text{Br}$). ^1H NMR spectrum (CDCl_3 , 400 MHz), δ , ppm: 1.10 s (9H, *t*-Bu), 3.30 s (2H, CH_2), 5.80 s (2H, OH), 7.15 d.d (4H, H_{arom}), 7.40 m (5H, H_{arom}). Mass spectrum (FAB): m/z 411.087 [$M + \text{H}$] $^+$. Found, %: C 67.12; H 5.63. $\text{C}_{23}\text{H}_{23}\text{BrO}_2$. Calculated, %: C 67.15; H 5.64.

2,2'-Oxydiacetyl chloride (II). Yield 10 g (58.5%), bp 121–123°C. IR spectrum (KBr), ν , cm^{-1} : 2900 (CH_2), 1765 ($\text{C}=\text{O}$), 1155 ($\text{C}-\text{O}$, ether), 760 ($\text{C}-\text{Cl}$). Found, %: C 27.97; H 2.21. $\text{C}_4\text{H}_4\text{Cl}_2\text{O}_3$. Calculated, %: C 28.11; H 2.35.

2,2'-(Ethylenedioxy)diacetyl chloride (III). Yield 14 g (65%), bp 165–180°C. IR spectrum (KBr), ν , cm^{-1} : 2910 (CH_2), 1790 ($\text{C}=\text{O}$), 1160 ($\text{C}-\text{O}$, ether), 760 ($\text{C}-\text{Cl}$). ^1H NMR spectrum, δ , ppm: 3.65 s (4H, $\text{OCH}_2\text{CH}_2\text{O}$); 4.38 s (4H, COCH_2). Found, %: C 33.47; H 3.72. $\text{C}_6\text{H}_8\text{Cl}_2\text{O}_4$. Calculated, %: C 33.50; H 3.74.

3,6,9-Trioxaundecanedioyl chloride (IV). Yield 32.68 g (63%), bp 128–130°C. IR spectrum (KBr), ν , cm^{-1} : 2920–2930 (CH_2), 1765 ($\text{C}=\text{O}$), 1165 ($\text{C}-\text{O}$, ether), 770 ($\text{C}-\text{Cl}$). ^1H NMR spectrum, δ , ppm: 3.75 s (8H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.45 s (4H, COCH_2). Found, %: C 37.05; H 4.68. $\text{C}_8\text{H}_{12}\text{Cl}_2\text{O}_5$. Calculated, %: C 37.09; H 4.67.

4-Bromo-14-*tert*-butyl-2-phenyl-16*H*-dibenzo[*h,k*][1,4,7]trioxacyclododecine-6,10(7*H*,9*H*)-dione (V). A five-necked flask equipped with two dropping funnels, mechanical stirrer, gas-inlet tube, and reflux condenser was charged with 1 l of anhydrous benzene and 3.1 ml (3.16 g, 0.04 mol) of anhydrous pyridine. One dropping funnel was filled with a solution of 8.22 g (0.02 mol) of 3-bromo-5-(5-*tert*-butyl-2-hydroxybenzyl)biphenyl-4-ol in 250 ml of benzene, and the other, with a solution of 7.55 g (0.02 mol) of 2,2'-oxydiacetyl chloride in 250 ml of benzene. The mixture was heated to the boiling point under vigorous stirring while continuously bubbling nitrogen, and both dropping funnels were opened simultaneously to add the reactants over a period of 16 h. When the reaction was complete, pyridine hydrochloride was filtered off, the solvent was distilled off, and the viscous residue was washed with a 2% solution of sodium hydroxide and aqueous methanol (1:1) and extracted into chloroform. The extract was dried over sodium sulfate, evaporated to a volume of 20–30 ml, and added to 10–15 ml of methanol, the mixture was left to stand for

2 days, and the fawn crystals were filtered off. Yield 2.5 g (25%), mp 208–209°C. IR spectrum (KBr), ν , cm^{-1} : 3090 ($\text{C}-\text{H}_{\text{arom}}$), 2990–2960 (CH_2), 1730 ($\text{C}=\text{O}$), 1290 ($\text{C}-\text{O}$, ester), 1145–1155 ($\text{C}-\text{O}$, ether), 810 ($\text{C}-\text{Br}$). ^1H NMR spectrum (CDCl_3 , 400 MHz), δ , ppm: 1.27 s (9H, *t*-Bu), 3.30 s (2H, CH_2), 4.28 s (4H, CH_2OCH_2), 6.65 d (3H, H_{arom}), 7.10–7.20 d.d (4H, H_{arom}), 7.36 m (3H, H_{arom}). Mass spectrum (FAB): m/z 509.073 [$M + \text{H}$] $^+$. Found, %: C 63.70; H 4.91. $\text{C}_{27}\text{H}_{25}\text{BrO}_5$. Calculated, %: C 63.65; H 4.95.

4-Bromo-17-*tert*-butyl-2-phenyl-9,10-dihydro-19*H*-dibenzo[*k,n*][1,4,7,10]tetraoxacyclopentadecine-6,13(7*H*,12*H*)-dione (VI) was synthesized in a similar way from 8.22 g (0.02 mol) of 3-bromo-5-(5-*tert*-butyl-2-hydroxybenzyl)biphenyl-4-ol (I) and 8.44 g (0.02 mol) of 2,2'-(ethylenedioxy)diacetyl chloride. Yield 2.8 g (28%), mp 221–222°C. UV spectrum (CHCl_3): λ_{max} 304 nm. IR spectrum (KBr), ν , cm^{-1} : 3110 ($\text{C}-\text{H}_{\text{arom}}$), 2960–2860 (CH_2), 1745 ($\text{C}=\text{O}$), 1638 ($\text{C}-\text{C}_{\text{arom}}$), 1295 ($\text{C}-\text{O}$, ester), 1055–1140 ($\text{C}-\text{O}$, ether), 800 ($\text{C}-\text{Br}$). ^1H NMR spectrum (CDCl_3 , 400 MHz), δ , ppm: 1.15 s (9H, *t*-Bu), 3.95 s (2H, CH_2), 4.25 s (4H, COCH_2), 6.65 d (3H, H_{arom}), 7.30 d.d (4H, H_{arom}), 7.45 m (3H, H_{arom}). Mass spectrum (FAB): m/z 553.117 [$M + \text{H}$] $^+$. Found, %: C 63.02; H 5.26. $\text{C}_{29}\text{H}_{29}\text{BrO}_6$. Calculated, %: C 62.94; H 5.28.

4-Bromo-20-*tert*-butyl-2-phenyl-9,10,12,13-tetrahydro-22*H*-dibenzo[*n,q*][1,4,7,10,13]pentaoxacyclooctadecine-6,16(7*H*,15*H*)-dione (VII) was synthesized in a similar way from 4.11 g (0.01 mol) of 3-bromo-5-(5-*tert*-butyl-2-hydroxybenzyl)biphenyl-4-ol and 4.66 g (0.01 mol) of 3,6,9-trioxaundecanedioyl chloride. Yield 1.56 g (37%), mp 201–203°C. UV spectrum (CHCl_3): λ_{max} 304 nm. IR spectrum (KBr), ν , cm^{-1} : 3020 ($\text{C}-\text{H}_{\text{arom}}$), 2900–2990 (CH_2), 1720 ($\text{C}=\text{O}$), 1595 and 1638 ($\text{C}-\text{C}_{\text{arom}}$), 1270 ($\text{C}-\text{O}$, ester), 1120–1150 ($\text{C}-\text{O}$, ether), 810 ($\text{C}-\text{Br}$). ^1H NMR spectrum (CDCl_3 , 400 MHz), δ , ppm: 1.35 s (9H, *t*-Bu), 3.45 s (2H, PhCH_2Ph), 4.15 s (4H, COCH_2), 6.60 d (3H, H_{arom}), 7.15 d.d (4H, H_{arom}), 7.45 m (3H, H_{arom}). Mass spectrum (FAB): m/z 597.141 [$M + \text{H}$] $^+$. Found, %: C 62.14; H 5.41. $\text{C}_{31}\text{H}_{33}\text{BrO}_7$. Calculated, %: C 62.32; H 5.55.

Complex VIII. A 0.1 M solution of compound VII in hot alcohol, 4 ml, was mixed with a 0.1 M solution of KClO_4 in water, 4 ml, and the mixture was kept for 24 h. The precipitate was filtered off, washed with methanol, and dried. Yield 0.115 g (42%), mp 278–280°C (decomp.). IR spectrum (KBr), ν , cm^{-1} : 1715 ($\text{C}=\text{O}$), 1590 ($\text{C}-\text{C}_{\text{arom}}$), 1120–1095 ($\text{C}-\text{O}$, ether).

Found, %: C 58.35; H 5.11. $C_{31}H_{33}BrKO_7$. Calculated, %: C 58.47; H 5.23.

Complex IX. A 1 M solution of compound VII in hot alcohol, 8 ml, was mixed with a 1 M solution of $NaClO_4 \cdot H_2O$ in alcohol. The mixture was heated to the boiling point and was left to stand for 2 days. The precipitate was filtered off, washed with cold methanol, and dried. Yield 2.44 g (45%), mp 285–292°C (decomp.). IR spectrum (KBr), ν , cm^{-1} : 1722 (C=O), 1586 (C–C_{arom}), 1100–1095 (C–O, ether). Found, %: C 60.33; H 5.21. Calculated $C_{31}H_{33}BrNaO_7$. Calculated, %: C 60.01; H 5.36.

Complex X. A 1 M solution of compound VII in hot ethyl acetate, 4 ml, was mixed with a 1 M solution of $Pb(SCN)_2$ in hot water, 4 ml. The precipitate was filtered off, washed with 50% aqueous alcohol, and dried. Yield 0.70 g (20%), mp 305–310°C (decomp.). IR spectrum (KBr), ν , cm^{-1} : 1755 (C=O), 1120 (C–O, ether). Found, %: C 46.11; H 3.96. $C_{31}H_{33}BrO_7Pb$. Calculated, %: C 46.27; H 4.13.

Complex XI. A 1 M solution of compound VII in hot ethyl acetate, 4 ml, was mixed with a 1 M solution of $Mg(ClO_4) \cdot 6H_2O$ in hot water, 4 ml. The precipitate was filtered off, washed with 50% aqueous alcohol, and dried. Yield 0.15 g (10%), mp 300–307°C (decomp.). IR spectrum (KBr), ν , cm^{-1} : 1735 (C=O), 1100 (C–O, ether). Found, %: C 60.01; H 5.33. $C_{31}H_{33}BrMgO_7$. Calculated, %: C 59.87; H 5.35.

Metal picrate extraction study. The detailed procedure is given in [20–23]. A 1×10^{-3} M solution of ligand I–III in chloroform and a solution of picric acid (2×10^{-5} M) and the corresponding metal nitrate (or metal hydroxide for Group IA cations) (1×10^{-2} M) in water were prepared. A 50-ml container was charged with 10 ml of each solution, the container was capped, and the mixture was shaken for 3 h and left to stand for phase separation. The concentration of metal picrate in the aqueous phase was measured by spectrophotometry, and the extraction percentage was calculated using the equation

$$\% \text{ Extraction} = (A_0 - A)/A_0 \times 100,$$

where A_0 is the absorbance of metal picrate in the aqueous phase prior to extraction, and A is the absorbance of metal picrate in the aqueous phase after extraction.

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