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Schiff Base *p-tert*-Butylcalix[4]arenes. Synthesis and Metal Ion Complexation

Ratana Seangprasertkij

Department of Chemistry, Chulalongkorn University, Bangkok 10330, Thailand

Zouhair Asfari, Françoise Arnaud, and Jacques Vicens*

EHICS, URA 405 du CNRS, 1 rue Blaise Pascal, F-67008 Strasbourg, France

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The article describes the synthesis of Schiff base *p-tert*-butylcalix[4]arenes **3a–e** in which the Schiff base unit bridges two opposite hydroxy groups of *p-tert*-butylcalix[4]arene (**1**). The synthesis of **3a–e** have been achieved by refluxing *p-tert*-butylcalix[4]arene 1,3-dicarbaldehyde **2** with appropriate diamino compounds in acetonitrile–methanol. Yields range from 14 to 96%. The complexing properties of **3a–e** toward alkali and alkaline earth cations, transition and heavy metals, and lanthanides are reported.

Introduction

In his 1990 review article sketching the important developments in organic synthesis during the previous 25 years, Seebach[1] stated that "the primary motivations that once induced chemists to undertake natural products syntheses no longer exist and how chemists were drawn to supramolecular chemistry." Supramolecular chemistry involves the development of new synthetic methods directed to research areas such as host–guest chemistry, molecular and ionic recognition, supramolecular catalysis, self-organization, aggregation, signal transfer, allosteric effects, etc. In this respect, attention has been paid to the search for molecular structures that can serve as building blocks for the production of sophisticated molecules by anchoring functional groups oriented in such a way that they delineate a suitable binding site. This was achieved with the development of macrocyclic molecules such as synthetic crown ethers,[2] cryptands,[3] spherands,[4] cyclophanes,[5] and natural cyclodextrins.[6] A relatively new class of synthetic macrocyclic building blocks is emerging: *the calixarenes*. The chemistry of calixarenes is well documented, and several accounts[7] and two books[8] have appeared to date giving an overview of the development and chemistry of these compounds. *p-tert*-Butylcalix[4]arene, **1**, which is the cyclic tetramer of the series, has been shown to be the most important starting building block because (a) it can be produced selectively in large quantities from cheap commerical starting materials,[9] (b) it can easily be chemically modified at the phenolic oxygens (lower rim) and at the *para*-positions (upper rim), and (c) the chemical modifications associated with the conformational properties lead to a large variety of tailor-made receptors.[8]

Since Alfieri et al.[10] reported the synthesis of the first member of a new class of macropolycyclic crown compounds with the *two opposite* OH groups of *p-tert*-butylcalix[4]arene (**1**) bridged by a pentaethylene glycol chain, extensive work has been devoted to the synthesis of preorganized 1,3-bridged calix[4]arene ligands. 1,3-Distal capping of calix[4]arenes at the lower rim has been achieved with poly(oxyethylene) chains, e.g., calix-crown ethers,[7,11] calix-doubly-crowned,[12] double-calix-crown,[13] with terphenyl units (calixspherands),[14] with salophene moieties,[15] with a metallocene unit (metallocene calix[4]arene),[16] with disulfonyl and diacetyl dichlorides,[17] with diaza-crown units (calixcryptand),[18] and with phosphorus atoms (phosphorus polybridged calixarenes).[19] Most of the above ligands complex alkali and alkaline earth cations,

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[1] Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, 1320.

[2] (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495. (b) Izatt, R. M., Bradshaw, J. S., Eds. The Pedersen Memorial Issue. *Adv. Incl. Sci.* **1992**, *7*.

[3] (a) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49. (b) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89.

[4] (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 753. (b) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009.

[5] (a) Vögtle, F.; Neumann, P. *Top. Curr. Chem.* **1974**, *48*, 67. (b) Diederich, F. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH Verlagsgesellschaft: Weinheim, 1990; pp 167–192.

[6] (a) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer Verlag: Berlin, 1978. (b) Szejtli, J. Cyclodextrin Technology. *Topics in Inclusion Science*; Kluwer Academic Publishers: Dordrecht, 1988; Vol. 1.

[7] (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. (b) Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1. (c) Ungaro, R.; Pochini, A. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Dürr, H., Eds.; VCH Verlagsgesellschaft: Weinheim, 1990; pp 57–81. (d) Arduini, A.; Casnati, A.; Fabbi, M.; Minari, P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. In *Supramolecular Chemistry*; Balzani, V., De Cola L., Eds.; Kluwer Academic Publishers: Dordrecht, 1992; pp 31–50. (e) Asfari, Z.; Weiss, J.; Vicens, J. *Synlett* **1993**, 719.

[8] (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, 1989. (b) Vicens, J.; Böhmer, V. Eds. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Dordrecht, 1991.

[9] Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.

[10] Alfieri, C.; Dradi, E.; Pocchini, A.; Ungaro, R.; Andreetti, G. D. *J. Chem. Soc., Chem. Commun.* **1983**, 1075.

[11] (a) Nijenhuis, W. F.; Buitenhuis, E. G.; de Jong, F.; Sudhölter, J. R.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 7963. (b) King, A. M.; Moore, C. P.; Samankamura Sandayanake, K. R. A.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1992**, 582.

[12] Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; Abu El-Fald, A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979.

[13] (a) Asfari, Z.; Abidi, R.; Arnaud, F.; Vicens, J. *J. Incl. Phenom.* **1992**, *13*, 163. (b) Asfari, Z.; Weiss, J.; Papalardo, S.; Vicens, J. *Pure Appl. Chem.* **1993**, *65*, 585.

[14] (a) Reinhoudt, D. N.; Dijkstra, P. J.; in't Veld, P. J. A.; Bugge, K.-E.; Harkema, S.; Ungaro, R.; Ghidini, E. *J. Am. Chem. Soc.* **1987**, *109*, 4761. (b) Dijkstra, P. J.; Brunink, J. A. J.; Bugge, K.-E.; Reinhoudt, D. N.; Harkema, S.; Ungaro, R.; Ugozzoli, F.; Ghidini, E. *J. Am. Chem. Soc.* **1989**, *111*, 7567.

[15] Nijenhuis, W. F.; van Doorn, A. R.; Reichwein, A. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 3607.

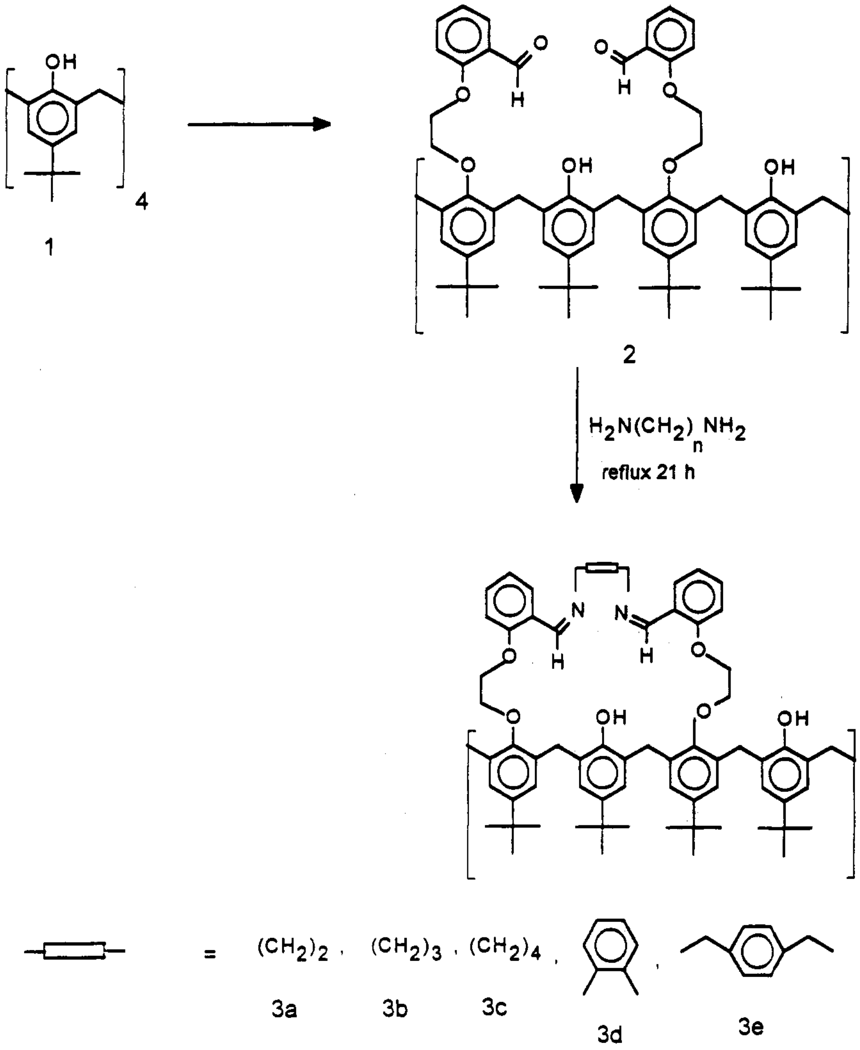
[16] Beer, P. D.; Keefe, A. D. *J. Incl. Phenom.* **1987**, *5*, 499.

[17] van Loon, J.-D.; Kraft, D.; Ankoné, M. J. K.; Verboom, W.; Harkema, S.; Vogt, W.; Böhmer, V.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5176.

[18] Beer, P. D.; Martin, J. P.; Drew, M. G. B. *Tetrahedron* **1992**, *48*, 9917.

0022-3263/94/1959-1741$04.50/0

Scheme 1. Synthetic Pathway to 3a–e



and few studies have been devoted to the complexation of transition and heavy metals and lanthanides.[18]

As part of our work on the synthesis of ligands able to complex transition and heavy metals and lanthanides, we recently reported the synthesis of Schiff base *p-tert*-butylcalix[4]arene **3b** which was observed to complex Cu(II), Pb(II), and Eu(III) with stability constants ranging from 4.8 to 5.0 log units.[20] We undertook the present study in order to gain information on the structural requirements necessary for selective metal ion complexation with Schiff base *p-tert*-butylcalix[4]arenes. The syntheses of Schiff base *p-tert*-butylcalix[4]arene derivatives **3a–e** and their complexing abilities toward alkali and alkaline earth cations, transition and heavy metals, and lanthanides are herein reported.

Experimental Section

Starting Materials for Syntheses. The solvents and all compounds except *p-tert*-butylcalix[4]arene[9] and 25,27-bis[2-[(1-formyl-2-phenyl)oxy]ethyl]-*p-tert*-butylcalix[4]arene[20] were commercial reagents and were used without further purification.

Analytical Procedures. The melting points (mps) were taken on a Büchi 500 apparatus in capillaries sealed under N_2. Elemental analyses were carried out at the Service de Microanalyse of the Institut de Chimie de Strasbourg. The ^{1}H-NMR spectra were recorded at 200 MHz on a Bruker SY200 spectrometer. The FAB mass spectra were obtained on a VG-Analytical ZAB apparatus.

Extraction and Complexation Experiments. The percentage of metallic picrates (2.5×10^{-4} M) extracted from water to dichloromethane containing the calixarene (2.5×10^{-4} M) was determined at 20 °C as previously described.[20] For the most efficient systems, the stability constants in methanol were determined by UV absorption spectrophotometry at 25 °C. The procedure consisted of adding increasing amounts of a metallic salt [$Eu(CF_3SO_3)_3$, $Pb(NO_3)_2$, $Cu(ClO_4)_2 \cdot 5DMSO$] to a solution of the ligand [$C_L = 2.5 \times 10^{-5}$ M (**3c**), 2.5×10^{-4} M (**3d**)]. The resulting spectral changes (Figure 1) were analyzed by the program Letagrop-Spefo.[20]

Syntheses. 25,27-[2,2′-[1,1′-(ethylenediimino)-2,2′-diphenoxy]diethyl]-*p-tert*-butylcalix[4]arene (3a). By means of a procedure previously described by us,[20] 0.17 mL (2.4 mmol) of 1,2-diaminoethane dissolved in 30 mL of methanol was added dropwise into a solution containing 1.95 g (2.1 mmol) of 25,27-bis[2-[(1-formyl-2-phenyl)oxy]ethyl]-*p-tert*-butylcalix[4]arene (**2**) dissolved in 120 mL of acetonitrile/methanol (5:1). The reaction mixture was refluxed under N_2 for 21 h. A white precipitate formed and was washed with methanol: yield 1.13 g (56%); mp 245 °C dec; ^{1}H-NMR ($CDCl_3$) 9.03 (s, 2H), 7.96 (dd, J = 7.7, 1.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.01 (t, J = 7.4 Hz, 2H), 6.99 (s, 4H), 6.87 (d, J = 8.2 Hz, 2H), 6.65 (s, 4H), 6.52 (s, 2H), 4.40 and 3.16 (AB system, J = 13.3 Hz, 8H), 4.43–4.28 (m,

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[19] Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 13.

[20] Seangprasertkij, R.; Asfari, Z.; Arnaud, F.; Weiss, J.; Vicens, J. *J. Incl. Phenom.* **1992**, *14*, 141.

[21] van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.

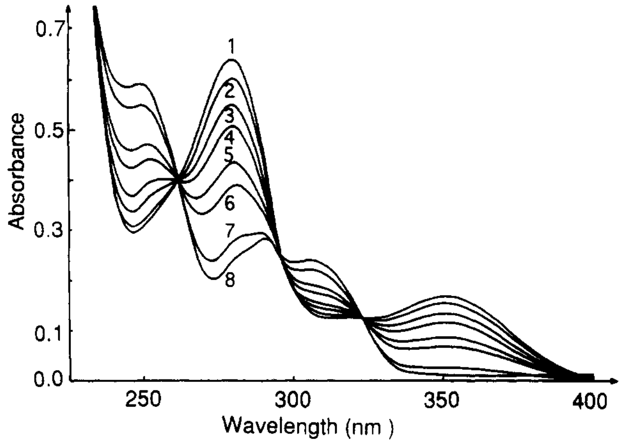

Figure 1. Spectra of ligand **3c** upon addition of $Eu(CF_3SO_3)_3$ in methanol: $C_L = 2.5 \times 10^{-5}$ M. Spectra 1–8 correspond to $0 \leq C_{Eu}/C_L \leq 6$.

8H), 3.64 (s, 4H), 1.28 (s, 18H), 0.84 (s, 18H); FAB positive 969.6. Anal. Calcd for $C_{64}H_{76}O_6N_2$: C, 79.29; H, 7.91. Found: C, 79.22; H, 7.68.

25,27-[2,2′-[1,1′-(1,3-Propylenediimino)-2,2′-diphenoxy]diethyl]-*p-tert*-butylcalix[4]arene (3b). The synthesis of **3b** in 19% yield has already been published.[20] The yield was improved to 86% by means of the procedure described for **3a**. Compound **2** (2.88 g, 3.1 mmol) and 0.28 mL (3.4 mmol) of 1,3-diaminopropane produced a white solid, which was washed with methanol: yield 2.43 g (86%); mp 300 °C dec (lit.[20] mp 301–303 °C).

25,27-[2,2′-[1,1′-(1,4-Butylenedimino)-2,2′-diphenoxy]diethyl]-*p-tert*-butylcalix[4]arene (3c). By means of the procedure described for **3a**, 2.88 g (3.1 mmol) of **2** and 0.34 mL (3.4 mmol) of 1,4-diaminobutane were allowed to react. No precipitation occurred. After the reaction was complete the solvents were evaporated to dryness. The residue was dissolved in the smallest possible amount of chloroform and precipitated by the addition of methanol. The white precipitate was filtered and washed with methanol: yield 1.64 g (54%); mp 289 °C dec; ^{1}H-NMR ($CDCl_3$) 8.83 (s, 2H), 7.92 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.05 (s, 4H), 6.97 (t, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.64 (s, 4H), 6.47 (s, 2H), 4.46 and 3.23 (AB system, *J* = 13.3 Hz, 8H), 4.35 (s, broad, 8H), 3.18 (m, 4 H), 1.49 (m, 4H), 1.31 (s, 18H), 0.85 (s, 18H); FAB positive 997.2. Anal. Calcd for $C_{66}H_{80}O_6N_2 \cdot CH_3OH$: C, 78.16; H, 8.23. Found: C, 78.38; H, 8.46.

25,27-[2,2′-[1,1′-(*o*-Phenylenediimino)-2,2′-diphenoxy]diethyl]-*p-tert*-butylcalix[4]arene (3d). By means of the procedure described for **3c**, 1.00 g (1.1 mmol) of **2** and 0.14 g (1.2 mmol), of 1,2-phenylenediamine were allowed to react; no precipitation occurred. The solvents were evaporated to dryness. The residue was recrystallized from ether/methanol: yield 0.15 g (14%); mp 192 °C dec; ^{1}H-NMR ($CDCl_3$) 7.78 (m, 2H), 7.37–6.35 (m, 20H), 4.57–3.60 (m, 12H), 3.50–3.14 (m, 4H), 1.26 (s, 18H), 0.89 (s, 18H); FAB positive 1017.5. Anal. Calcd for $C_{68}H_{76}O_6N_2$: C, 80.27; H, 7.53. Found: C, 80.25; H, 7.49.

25,27-[2,2′-[1,1′-(*p*-Xylenediimino)-2,2′-diphenoxy]diethyl]-*p-tert*-butylcalix[4]arene (3e). By means of the procedure described for **3c**, 2.88 g (3.1 mmol) of **2** and 1.25 g (9.2 mmol) of *p*-xylenediamine provided a white solid which was washed with ether/methanol: yield 3.05 g (96%); mp 240 °C dec; ^{1}H-NMR ($CDCl_3$) 8.75 (s, 2H), 7.98 (d, *J* = 6.0 Hz, 2H), 7.32 (m, 2H), 7.05 (s, 2H), 6.99 (s, 2H), 7.04–6.63 (m, 4H), 6.64 (s, 4H), 6.47 (s, 2H), 4.73 (s, 4H), 4.37–4.16 (m, 8H), 4.34 and 3.23 (AB system, *J* = 13.1 Hz, 8H), 1.30 (s, 18H), 0.85 (s, 18H); FAB positive 1045.5. Anal. Calcd for $C_{70}H_{80}O_6N_2$: C, 80.41; H, 7.72. Found: C, 80.70; H, 7.46.

Results and Discussion

Schiff base *p-tert*-butylcalix[4]arenes **3a–e** were constructed as shown on Scheme 1 via 25,27-bis[2-[(1-formyl-2-phenyl]oxy]ethyl]-*p-tert*-butylcalix[4]arene (**2**) in the cone conformation or cone-1,3-dialdehyde. Cone-1,3-dialdehyde **2** was obtained from the reaction of *p-tert*-butylcalix[4]arene **1** with 2-(2′-bromoethoxy)benzaldehyde under conditions leading to 1,3-distal-selective alkylations of hydroxyl groups.[20] Compound **2** was refluxed with 1–3 equiv of the appropriate diamino compounds in acetonitrile–methanol for 21 h. After the workup, pure products **3a–e** were either simply filtered and washed with methanol or crystallized from chloroform–methanol or ether–methanol. The respective yields were 56%, 86%, 54%, 14%, and 96%. The high yield of **3e** was probably due to its insolubility in acetonitrile/methanol. All the products were white powders except **3d**, which was bright yellow. All melted with decomposition at temperatures ranging from 192 to 300 °C. They were all characterized by ^{1}H-NMR, FAB MS, and elemental analysis (see Experimental Section). From their ^{1}H-NMR spectra, **3a–e** were deduced to be 1,3-bridged *p-tert*-butylcalix[4]arene derivatives because of the presence of only two singlets for the *tert*-butyl groups (0.84 and 1.28 ppm for **3a**, 0.85 and 1.31 ppm for **3c**, 0.89 and 1.26 ppm for **3d**, and 0.86 and 1.30 ppm for **3e**, values that match those found for **3b** (0.88 and 1.31 ppm).[20] That **3a–e** exist in a cone conformation was deduced from the presence of characteristic AB systems at 3.16 and 4.40 ppm (*J* = 13.3 Hz) for **3a**, 3.23 and 4.46 ppm (*J* = 13.3 Hz) for **3c**, and 3.23 and 4.34 ppm (*J* = 13.1 Hz) for **3e**, values that match those found for **3b** (3.27 and 4.46 ppm with *J* = 13.7 Hz).[20] The chemical shift and the coupling constant for the AB system of **3d** could not be measured because of its complex spectrum. On the basis of the spectrometric evidence the transformations of **2** into **3a–e** occur with retention of the cone conformation of the *p-tert*-butylcalix[4]arene moiety.

Two-Phase Solvent Extraction. Solvent extraction and transport of metal cations by calix[*n*]arenes were first investigated by Izatt et al. with calix[*n*]arenes (*n* = 4, 6, and 8)[22] that showed selectivity for the Cs^+ ion. Subsequently, highly preorganized ligands such as polyether receptors derived from calix[4]arenes were observed to be selective for the K^+ ion,[11–13] and calixspherands[14] were observed to be selective for the Rb^+ ion.

A preliminary evaluation of the binding efficiencies of **3a–e** was carried out by solvent extraction of metal picrates into dichloromethane under neutral conditions. The results are summarized in Table 1. Compound **3a** was observed to extract less than its homologues containing three and four carbons in the Schiff base moiety **3b** and **3c**. Alkali and alkaline earth cations are very poorly extracted by ligands **3a–c**. However, the better extraction of Li^+ and Na^+ ions with **3c** may be explained by the greater flexibility of its bridge which is due to an additional carbon that allows the chain to adopt a more convenient geometry for complexation. In the transition metal series, Fe^{2+} and Cu^{2+} ions were extracted more efficiently. Heavy metal cations are extracted with a higher preference for Pb^{2+} ion. In the lanthanide series, there is an extraction selectivity for Nd^{3+} and Eu^{3+} ions with **3b** and for Eu^{3+} ion with **3c**.

The most efficiently extracted metal ions have been tested with aromatic ligand **3d**, which showed a good

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(22) (a) Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782. (b) Izatt, S. R.; Hawkins, R. T.; Christensen, J. J.; Izatt, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 63.

(23) Shannon, R. D.; Prewitt, C. T. *Acta. Crystallogr.* **1970**, *B20*, 1076.

Table 1. Percentage Extraction, %*E*, of Metal Picrates (2.5 × 10^{-4} M) by Ligands 3a–d (2.5 × 10^{-4} M) from Water into Dichloromethane

	% extraction			
	3a	**3b**[a]	**3c**	**3d**
Li^+	4	8	10	
Na^+	3	6	11	
K^+	4	7	9	
Rb^+	3	9	9	
Cs^+	3	7	5	
Mg^{2+}	4	5	6	
Ca^{2+}	2	4	3	
Sr^{2+}	3	4	6	
Mn^{2+}	2	3	4	
Fe^{2+}	0	9	19	10
Co^{2+}	3	6	8	
Ni^{2+}	2	9	9	
Cu^{2+}	7	21	19	24
Cd^{2+}	2	8	8	
Pb^{2+}	3	15	18	6
Y^{3+}	1	8	3	
Pr^{3+}	1	6	4	
Nd^{3+}	1	12	5	
Eu^{3+}	0	13	14	5
Gd^{3+}	1	5	6	
Yb^{3+}	1	9	6	

[a] Taken from ref 20.

extracting power for Cu^{2+} ion only. The extracting property of **3e** has not been tested because of its low solubility in dichloromethane.

Complexation in Methanol. The more effective extraction systems (i.e., **3b–d** with Eu^{3+} ion, **3b** and **3c** with Pb^{2+} ion, and **3c** with Cu^{2+} ion) were examined. The slow complexation kinetics for **3b** and **3d** with Cu^{2+} ion, which showed the best extraction data, prevented any reliable determination of the stability constant.

Table 2. Stability Constants in Methanol at 25 °C

		log *K*		
cations	ionic radii[23] (Å)	**3b**[a]	**3c**	**3d**
Cu^{2+}	0.73	*b*	4.3 ± 0.1	*b*
Pb^{2+}	1.18	5.0	3.8 ± 0.3	≤1
Eu^{3+}	0.95	4.8	4.11 ± 0.04	3.7 ± 0.2

[a] Taken from ref 20. [b] Slow complexation kinetics.

The spectrum of ligand **3c** after the addition of Eu($(CF_3SO_3)_3$), given in Figure 1 as an example, shows two new bands of high intensity at 277.5 and 348 nm and three isobestic points at 254.6, 296.2, and 319.8 nm. The spectra were numerically interpreted assuming the presence of 1:1 complexes. The values of the corresponding stability constants are given in Table 2 (as log *K*). With Pb^{2+} ion and **3d**, the spectral changes were almost nonexistent, and in this case only an upper limit of 1 log unit can be given.

The variation of p (average number of protons bound per mole of ligand) vs pH suggests that ligand **3c** only loses its two protons at higher pH (pK_1 and $pK_2 > 12$). It is unlikely that the complexes formed under our experimental conditions (pH ≈ 8) would involve the participation of the phenolic oxygen as phenoxide ions.

The binding ability depends on the length of the Schiff base bridge. Ligand **3b**, which contains a bridge of three carbon atoms, forms the more stable complexes. This ligand presents the optimal cavity size for Eu^{3+} ion and for the larger Pb^{2+} ion. The stability of the complexes decreases for the longer bridged ligand **3c** and also for the more rigid aromatic ligand.

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