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Facile synthesis of thiacalix[*n*]arenes ($n = 4$, 6, and 8) consisting of *p*-*tert*-butylphenol and methylene/sulfide alternating linkage and metal-binding property of the $n = 4$ homologue

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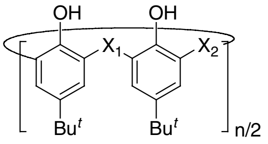
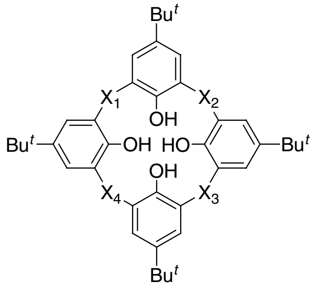
Abstract—2,14-Dithiacalix[4]arene $\mathbf{3}_4$ was conveniently prepared in 16% yield by acid-catalyzed cyclocondensation of 2,2′-thiobis[4-*tert*-butylphenol] with formaldehyde. The present method also afforded the first isolation of the analogues with six and eight phenol units, $\mathbf{3}_6$ (10%) and $\mathbf{3}_8$ (5%), respectively. Solvent extraction showed that $\mathbf{3}_4$ had high selectivity toward Cu^{2+} ion at pH 5.5 by coordination of the bridging sulfur with cooperative donation of the adjacent phenolate oxygens.

2,8,14,20-Tetrathiacalix[4]arene (e.g., $\mathbf{1}_4$), in which all four methylene bridges of the conventional calix[4]arenes (e.g., $\mathbf{2}_4$) are replaced with sulfides, has been described as a new member of the calixarene family.[1] The convenient one-step synthesis of $\mathbf{1}_4$ from phenol and elemental sulfur (Scheme 1)[2] enabled a functional survey to reveal the role of sulfide linkages providing $\mathbf{1}_4$ various intrinsic characteristic features, which are not attainable by conventional calixarene $\mathbf{2}_4$. Among them, especially noteworthy is the binding ability of $\mathbf{1}_4$ class compounds toward soft to intermediate metal ions according to the classification by the ‘hard and soft acids and bases (HSAB) rule’.[3] X-ray structural analysis of several metal complexes of $\mathbf{1}_4$ has clearly elucidated that the bridging sulfide (S) in addition to the phenolate oxygen atoms (O^-) is able to serve as a coordination site to metal ions (Scheme 2).[4] Having the same O^-,S,O^--coordination manner, hexathiacalix[6]arene $\mathbf{1}_6$ was recently shown to have extractability[5] and to form a nano-sized decacopper (II) complex by coordination of the bridging sulfide.[6]



$\mathbf{1}_n$: $X_1 = X_2 = S$; $n = 4, 6, 8$
$\mathbf{2}_n$: $X_1 = X_2 = CH_2$; $n = 4, 6, 8$
$\mathbf{3}_n$: $X_1 = S$; $X_2 = CH_2$; $n = 4, 6, 8$



4: $X_1 = S$; $X_2 = X_3 = X_4 = CH_2$
5: $X_1 = X_2 = S$; $X_3 = X_4 = CH_2$
6: $X_1 = X_2 = X_3 = S$; $X_4 = CH_2$

On the other hand, synthesis of calixarenes, in which part, instead of all, of the methylene bridges of $\mathbf{2}_n$ is replaced by heteroatoms, is, not to say difficult, but more laborious, because the synthetic protocol should be stepwise.[7] In such a trial, Sone et al. reported the synthesis of *p*-*tert*-butylthiacalix[4]arenes, $\mathbf{3}_4$, **4**, **5**, and **6**, in which one to three methylene bridges of $\mathbf{2}_4$ are

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Keywords: thiacalixarenes; complexation; sulfide; extraction.

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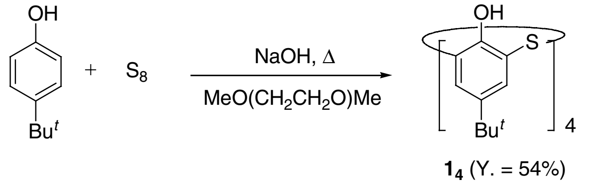
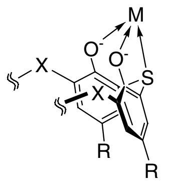


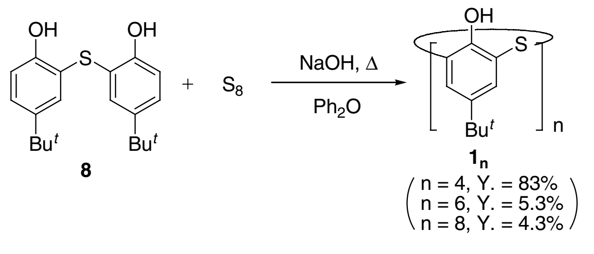
Scheme 1. One-step synthesis of **1**$_4$.



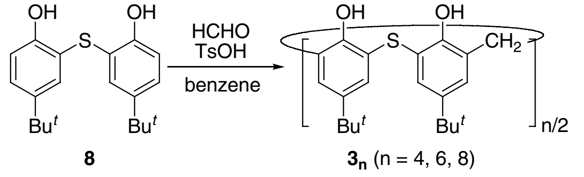
Scheme 2. Coordination manner of thiacalix[*n*]arenes (**1**$_n$ or **3**$_4$). For clarity, part of calixarene is drawn.

replaced by sulfur bridges, by stepwise joining of *p-tert*-butylphenol followed by eventual cyclization under high dilution condition to give them in low yields (0.3–4.0% from *p-tert*-butylphenol).[8] Furthermore, synthesis of their larger analogues with six or eight phenol units (e.g., **3**$_6$ and **3**$_8$) has been unprecedented. Although such partially sulfur-bridged calix[*n*]arenes are an attractive platform for ligands as well as supramolecular building blocks, improvement of the synthetic protocol is a key to survey such studies.

Very recently, we reported an improved synthetic method of **1**$_n$ ($n = 4$, 6, 8) by NaOH-catalyzed condensation of an acyclic dimer (2,2′-thiobis[4-*tert*-butylphenol], **8**), instead of *p-tert*-butylphenol, with elemental sulfur (Scheme 3).[9] This dimer method gave rise to the idea that the cyclocondensation of dimer **8** with formaldehyde should give thiacalix[*n*]arenes **3**$_n$ with sulfide-methylene alternate bridges (Scheme 4). According to this strategy, here we report the convenient synthesis of **3**$_4$ and the first isolation of the larger ring analogues **3**$_n$ ($n = 6$, 8). Obtainment of an appreciable amount of **3**$_4$ prompted us to study its metal-binding ability, revealing the high selectivity toward Cu^{2+} ion.



Scheme 3. Synthesis of **1**$_n$ via dimer **8**.



Scheme 4. Synthesis of **3**$_n$ from sulfur-bridged dimer of phenol (**8**).

The dimer **8** was prepared by the reaction of *p-tert*-butylphenol with SCl_2 according to a reported procedure.[10] The preparation of **3**$_n$ was first attempted by base-catalyzed reaction of **8**: The reaction of **8** with 37% HCHO in the presence of equimolar amount of NaOH in xylene gave a mixture of thiacalix[4]arenes containing not only **3**$_4$ but also **5** and **6**, which were identified by the reported spectral data.[8] Separation of each thiacalix[4]arene by chromatography on silica gel and recrystallization from various solvents was intractable because of the resemblance of their structural and physicochemical properties. From the peak areas of the NMR spectrum of the mixture, the yields of **3**$_4$, **5**, and **6** were estimated to be 5.5%, 1.4%, and 7.3%, respectively. It is known that the sulfide bond of 2,2′-thiobisphenol cleaves to give a mixture of 2,2′-, 2,4′-, and 4,4′-regioisomers of thiobisphenol in the presence of a base.[11] Therefore, the scrambling of the S-bridging positions among X_1–X_4 of thiacalix[4]arenes is attributed to the cleavage of sulfide bonds of **8** and/or the intermediary oligomers, indicating that control of the reaction products is essentially difficult in the base-induced reaction.

It has been assumed that the acid-catalyzed condensation of *para*-substituted phenols with formaldehyde gives acyclic oligomers as major products.[12] Recently, however, Gutsche et al. reported synthesis of **2**$_n$ ($n = 4$–20) by acid-catalyzed condensation of *p-tert*-butylphenol with formaldehyde.[13] Their results turned our attention from the base-catalyzed condensation of **8** to acid-catalyzed condensation (Scheme 4). The results under various reaction conditions are shown in Table 1.

Table 1. The acid-catalyzed cyclocondensation of **8**

Entry	Catalyst (0.3 equiv)	Methylene source (1.2 equiv)	Yields (%)[a]		
			3$_4$	**3**$_6$	**3**$_8$
1	TsOH	37% HCHO	16	10	5
2	TsOH	*s*-Trioxane	11	5	2
3	TsOH	$(CH_2O)_n$	13	2	2
4[b]	AcOH	37% HCHO	0	0	0
5	MsOH	37% HCHO	7	0	0

[a] Isolated yield based on **8**.

[b] Starting material **8** was recovered.

The reaction of **8** with 37% HCHO in the presence of 0.3 equiv of TsOH as an acid catalyst in benzene afforded the desired $\mathbf{3}_4$, $\mathbf{3}_6$, and $\mathbf{3}_8$ as isolable products in 16%, 10%, and 5% yield, respectively (Table 1, entry 1).[14] Each cyclic product was, in turn, conveniently separated by preferential precipitation by using a combination of solvents such as CH_2Cl_2 and benzene. Each cyclic oligomer was identified by spectral data including NMR, FAB MS spectra, and elemental analyses. Especially, the m/z values of $\mathbf{3}_4$ (684), $\mathbf{3}_6$ (1027), and $\mathbf{3}_8$ (1369) are direct evidence of the formation of a tetramer, hexamer, and octamer, respectively. It should be noted that the total yield of $\mathbf{3}_4$ from dimer **8** by the reported stepwise method is only 4.4%.[8] Considering the obtainable yield, labor and times hitherto spent until the attainment of $\mathbf{3}_4$, it can be said that the present method is more simple and efficient for synthesis of $\mathbf{3}_4$.[15]

The reactions of **8** with other methylene sources such as paraformaldehyde and *s*-trioxane instead of 37% HCHO gave preferential formation of $\mathbf{3}_4$ over $\mathbf{3}_6$ and $\mathbf{3}_8$, but the yields of $\mathbf{3}_4$ were somewhat lower than that of the reaction with 37% HCHO (Table 1, entries 2 and 3). The yields of cyclic products also depended on the acid catalysts. The use of AcOH, the acidity of which ($pK_a = 12.6$ in DMSO)[16] is lower than that of TsOH ($pK_a = 0.9$ in DMSO),[16] resulted in quantitative recovery of the starting material, indicating that the activation of the reaction by AcOH is very poor (Table 1, entry 4). On the contrary, the reaction with MsOH ($pK_a = 1.6$ in DMSO)[16] selectively gave $\mathbf{3}_4$, but in only 7% yield (Table 1, entry 5). Although the detailed mechanism of the present reaction must await further investigation, it might be conceivable that a stronger acid gives higher activation of electrophiles to promote the linear and cyclic condensation of **8**. Variation of other reaction conditions such as concentration of **8** and temperature did not give higher yields of $\mathbf{3}_n$ than ones of entry 1 (Table 1).[17]

Table 2 summarizes the spectral data for OH groups of $\mathbf{3}_n$ along with those of $\mathbf{1}_n$[9,18] and $\mathbf{2}_n$[19] obtained by ^{1}H NMR in $CDCl_3$ solution and IR in KBr powder, indicating the existence of intramolecular hydrogen bonds between the OH groups of $\mathbf{3}_n$. Comparison of the data of $\mathbf{3}_n$ with those of $\mathbf{1}_n$ and $\mathbf{2}_n$ suggests that the strength of the hydrogen bonding of $\mathbf{3}_n$ is intermediate between $\mathbf{1}_n$ and $\mathbf{2}_n$. This is reasonable because the increase in the number of the sulfide bonds should enlarge the calix skeleton to separate the neighboring OH groups further.

Table 2. ^{1}H NMR chemical shifts and IR stretching frequencies for OH of $\mathbf{1}_n$, $\mathbf{2}_n$, and $\mathbf{3}_n$

Calixarene	δ_{OH}/ppm ($CDCl_3$)	ν_{OH}/cm^{-1} (KBr)	Reference
$\mathbf{1}_4$	9.60	3324	18
$\mathbf{2}_4$	10.35	3164	19
$\mathbf{3}_4$	9.93	3210	This work
$\mathbf{1}_6$	9.18	3279	18
$\mathbf{2}_6$	10.53	3127	19
$\mathbf{3}_6$	10.04	3209	This work
$\mathbf{1}_8$	8.68	3327	9
$\mathbf{2}_8$	9.64	3258	19
$\mathbf{3}_8$	9.28	3315	This work

Since the number of bridging sulfides, rather than the cyclic or acyclic form, has recently been revealed to have distinct effect on the extractability of sulfur-bridged oligomers of phenol,[20] the easy access to $\mathbf{3}_4$ by the dimer method prompted us to study its binding ability toward first transition metal ions (Cu^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}) and Mg^{2+} ion by solvent extraction.[21] The pH of the aqueous phase was varied in the range where precipitation of the metal hydroxides did not form. The percent extraction, $E\%$, for metal ions by $\mathbf{3}_4$ was calculated by Eq. 1,

$$E\% = ([\mathrm{Metal}]_{\mathrm{aq,init}} - [\mathrm{Metal}]_{\mathrm{aq}})/[\mathrm{Metal}]_{\mathrm{aq,init}} \qquad (1)$$

where $[\mathrm{Metal}]_{\mathrm{aq,init}}$ and $[\mathrm{Metal}]_{\mathrm{aq}}$ are the concentrations of metal ions in aqueous phase before and after extraction, respectively. The pH dependence of $E\%$ (Fig. 1) showed that at lower pH (= 3–5), $\mathbf{3}_4$ has almost no extraction ability ($E\% < 10$). In contrast at higher pH, the $E\%$ value of transition metal ions rose, suggesting that $\mathbf{3}_4$ released the phenolic protons to bind to those metal ions by ligation with O^-. The $E\%$ values increased rapidly from pH around 6 for Co^{2+} and Ni^{2+} and moderately for Zn^{2+}. For Cu^{2+} ion, $E\%$ value increased sharply at more acidic pH (= 5) and reached 95% at pH 6, showing that $\mathbf{3}_4$ is a selective extractant to Cu^{2+} over Co^{2+}, Ni^{2+}, and Zn^{2+} around pH 5.5. Although the $E\%$ for Cu^{2+} decreased in a more basic region due to complex formation with OH^-, $\mathbf{3}_4$ extracted Cu^{2+} quantitatively around pH 6.5–7.0.

It should be noted that the selectivity of dithiacalix[4]arene $\mathbf{3}_4$ toward Cu^{2+} ion over Co^{2+} and Zn^{2+} ions is more pronounced than that of tetrathia $\mathbf{1}_4$;[20] there is only a small difference in the half extraction pH

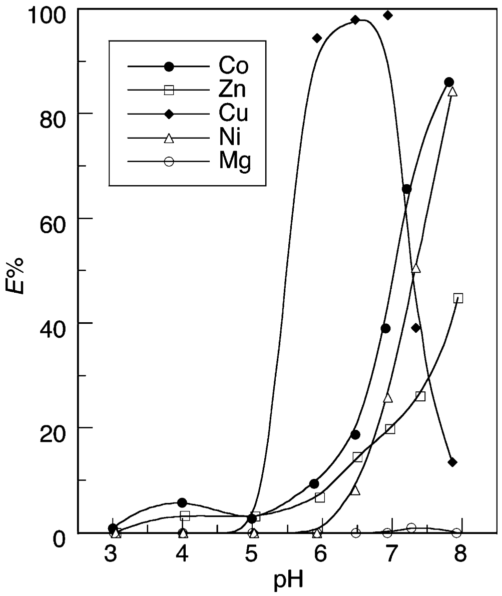


Figure 1. The pH dependence of $E\%$ for Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, and Mg^{2+}. Aq (10 mL): 1.0×10^{-4} M metal ion, 0.05 M buffer, Org (10 mL): 5.0×10^{-4} M $\mathbf{3}_4$.

Table 3. Half extraction pH of metal ions by $\mathbf{1}_4$ and $\mathbf{3}_4$

Calixarene	Co^{2+}	Cu^{2+}	Zn^{2+}	Reference
$\mathbf{1}_4$	5.9	5.4	6.1	20
$\mathbf{3}_4$	7.0	5.5	>8.0	This work

($pH_{1/2}$)[22] for Cu^{2+} between $\mathbf{1}_4$ and $\mathbf{3}_4$, whereas $pH_{1/2}$ for Co^{2+} and Zn^{2+} obtained by $\mathbf{3}_4$ is larger by 1 and 2 pH units, respectively, than that obtained by $\mathbf{1}_4$ (Table 3). Thus, decreasing the number of sulfide bridges from four to two diminishes the extractability toward Co^{2+} and Zn^{2+} but little affects the extractability toward Cu^{2+}, resulting in higher selectivity of $\mathbf{3}_4$ toward Cu^{2+} ion. In the case of Mg^{2+} ion, the extraction by $\mathbf{3}_4$ was not observed within pH range of 3–8. The fact that dithiacalix[4]arene $\mathbf{3}_4$ has extraction ability toward 'soft' to 'intermediate' metal ions, especially Cu^{2+}, but no ability toward 'hard' Mg^{2+} ion suggests the coordination of the bridging sulfur, which determines the metal-ion selectivity. Thus, it may be concluded that $\mathbf{3}_4$ coordinates to metal ions by O^-,S,O^- donor sets, which has been exemplified by metal complexes of $\mathbf{1}_4$ (Scheme 2).[4,20] Although the number of the donor sets of $\mathbf{3}_4$ is less than that of $\mathbf{1}_4$, two seems to be enough for $\mathbf{3}_4$ to maintain coordination ability toward Cu^{2+} ion.

In conclusion, 2,14-dithiacalix[4]arene ($\mathbf{3}_n$) can be conveniently obtained by acid-catalyzed condensation of 2,2′-thiobis[4-*tert*-butylphenol] **8** with formaldehyde. Notably, the dimer protocol afforded analogues with larger ring members, $\mathbf{3}_6$ and $\mathbf{3}_8$ for the first time. The ready availability of $\mathbf{3}_4$ allowed an extraction study, revealing that $\mathbf{3}_4$ is a highly selective extractant toward Cu^{2+} ion at pH 5.5 by coordination of the O^-,S,O^- donor sets. The preparations and structural characterization of metal complexes of $\mathbf{3}_4$ as well as $\mathbf{3}_6$ and $\mathbf{3}_8$ are now underway in our group.

Acknowledgements

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14. A mixture of **8**[10] (3.0 g, 9 mmol), 37% HCHO (0.9 g, 11 mmol), and $TsOH{\cdot}H_2O$ (0.51 g, 3 mmol) in benzene (50 mL) was heated at reflux under nitrogen atmosphere for 3 days in a 100-mL flask equipped with a Dean and Stark water collector. The reaction mixture was cooled to ambient temperature, to which was added 2 M HCl. The organic phase was separated and then removed under reduced pressure. Dilution of the residue with CH_3CN caused precipitation of a white solid comprising $\mathbf{3}_n$ where $n = 4$, 6, and 8 as evidenced by ^1H NMR spectrum. To the precipitate, in turn, was added CH_2Cl_2 to dissolve $\mathbf{3}_4$ and $\mathbf{3}_6$, leaving $\mathbf{3}_8$ as the insoluble part. From the CH_2Cl_2-soluble part were recovered $\mathbf{3}_6$ as the less soluble component by addition of benzene, and then $\mathbf{3}_4$ as the more soluble one. Each separated crude cyclic product was recrystallized from $CHCl_3$–CH_3CN to give $\mathbf{3}_4$ (510.2 mg, 15.9% yield), $\mathbf{3}_6$ (322.3 mg, 10.1% yield) and $\mathbf{3}_8$ (160.4 mg, 5.0% yield). All spectral data of $\mathbf{3}_4$ coincided with those of the previous report.[8] $\mathbf{3}_6$: mp >339.5 °C (dec); IR (KBr): 3209 (OH), 2963 (CH) cm^{-1}; FAB MS *m/z* 1027 (M^+, 100%); ^1H NMR ($CDCl_3$) δ 10.04 (s, 6H, OH), 7.52, 7.53 (d, 6H, $J = 2.4$ Hz, Ar), 7.25, 7.26 (d, 6H, $J = 2.4$ Hz, Ar), 3.95 (br s, 6H, CH_2), 1.24 (s, 54H, Bu^t); ^{13}C NMR ($CDCl_3$) δ 151.4, 144.5, 132.5, 129.6, 127.0, 120.8 (Ar), 34.1 (Bu^t), 33.2 (CH_2), 31.4 (Bu^t). Anal. Calcd for $C_{63}H_{78}O_6S_3{\cdot}1/2H_2O$: C, 73.00; H, 7.68; S, 9.28. Found:

C, 73.26; H, 7.54; S, 9.18. $\mathbf{3}_8$: mp >360 °C (dec); IR (KBr): 3315 (OH), 2959 (CH) cm^{-1}; FAB MS m/z 1369 (M^+, 100%); ^1H NMR ($CDCl_3$) δ 9.28 (s, 8H, OH), 7.55, 7.56 (d, 8H, $J = 2.4$ Hz, Ar), 7.27, 7.28 (d, 8H, $J = 2.4$ Hz, Ar), 3.96 (br s, 8H, CH_2), 1.24 (s, 72H, Bu^t); ^{13}C NMR ($CDCl_3$) δ 151.0, 144.6, 132.4, 129.0, 127.5, 121.8 (Ar), 34.1 (Bu^t), 32.8 (CH_2), 31.4 (Bu^t). Anal. Calcd for $C_{84}H_{104}O_8S_4 \cdot CH_3CN$: C, 73.20; H, 7.64; S, 9.09. Found: C, 72.91; H, 7.56; S, 8.80.

15. Sone's method consists of hydroxymethylation of dimer **8**, the condensation to tetramer, the hydroxymethylation, and cyclization to $\mathbf{3}_4$ (totally four steps). In each step, the desired product needs to be isolated by use of both column chromatography and recrystallization. Also, the eventual cyclization must be carried out under highly dilute condition to avoid polymerization. See Ref. 8.
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17. The initial concentration of **8** in entry 1 (Table 1) was 6 (w/v)%. On the other hand, using 1.2 (w/v)% of **8**, the obtainable yield of $\mathbf{3}_n$ was 12% ($\mathbf{3}_4$), 1.2% ($\mathbf{3}_6$), and trace ($\mathbf{3}_8$). Also, 15 (w/v)% of **8** gave 2.5% ($\mathbf{3}_4$), 0.6% ($\mathbf{3}_6$), and 0.2% ($\mathbf{3}_8$). Use of refluxing toluene and xylene did not give any detectable amount of cyclic products, suggesting that fragmentation of sulfide bonds might take place. In addition, the FAB-MS spectrum of the residue after removal of cyclic products $\mathbf{3}_n$ from a reaction mixture of entry 1 showed only small peaks for linear oligomers containing more than six phenol units, suggesting the difficulty of formation of $\mathbf{3}_6$ and $\mathbf{3}_8$.
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21. The procedure for solvent extraction is as follows. To a vial tube was pipetted an aqueous solution (10 mL) containing metal ion ($[\mathrm{Metal}]_{\mathrm{aq,init}} = 1.0 \times 10^{-4}$ M), Me_4NCl (0.1 M) for $\mathbf{3}_4$ as well as a pH buffer (0.05 M) and a 10 mL of $CHCl_3$ solution of $\mathbf{3}_4$ (5.0×10^{-4} M). The mixture was shaken for 24 h at 300 strokes/min at 23 ± 2 °C. After the aqueous phase was separated by centrifugation, the total concentration of the metal species remaining in the aqueous phase, $[\mathrm{Metal}]_{\mathrm{aq}}$, was measured by inductively coupled plasma atomic emission spectrophotometer (ICP–AES). The pH of the aqueous phase was adjusted with glycine–HNO_3 (2.5–3.5), succinic acid–NH_3 (4.0–5.0), MES–NH_3 (5.5–6.0), PIPES–NH_3 (6.3–7.0), Tris–HNO_3 (7.5–8.5), and CHES–NH_3 (9.0–10.0).
22. Half extraction pH, $pH_{1/2}$, is defined to be pH, at which $E\% = 50\%$. The $pH_{1/2}$ value of $\mathbf{3}_4$ in Table 3 was estimated from the curves in Figure 1. For Ni^{2+}, $pH_{1/2}$ value of $\mathbf{3}_4$ was estimated to be 7.3. The $pH_{1/2}$ value of Ni^{2+} by $\mathbf{1}_4$ was not obtained due to slow extraction rate,[3a,20] hence comparison for Ni^{2+} ion was not attempted here.