6874 *Inorg. Chem.* **2010**, *49*, 6874–6882
DOI: 10.1021/ic100097v

Inorganic Chemistry
Article

Cation−π Interaction in Complex Formation Between Tl^+ Ion and Calix[4]crown-6 and Some Calix[4]biscrown-6 Derivatives: Thallium-203 NMR, Proton NMR, and X-ray Evidence

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Received January 17, 2010

Metallocapped complexation of the thallium(I) ion with calix[4]crown-6 (**1**) and three different calix[4]biscrown-6 derivatives (**2**−**4**) has been investigated by a combination of ^{203}Tl and ^{1}H NMR in a $CD_3CN/CDCl_3$ (4:1 v/v) solution. The results clearly revealed the formation in solution of mono- and dithallium(I) complexes in which the metal cations are held in the ligands' cavities close to the calix[4]arene ring. In addition, a solid state mononuclear complex between 1,3-calix[4]bis-*o*-benzo-crown-6 (**3**) and $TlClO_4$ was prepared, and its X-ray crystal structure was determined. The results of the structural data in solution and the solid state suggested that the calix[4]crown-6 derivatives considered provide π cavities as active sites for the complexation of thallium(I) ions.

Introduction

The thallium(I) ion has long been proposed as a suitable mimic of alkali metal ions in biological systems due to its chemical similarity to group 1 metals and favorable size (1.33 Å for K^+ vs 1.40 Å for Tl^+) and dehydration energy (80 kcal mol^{-1} for K^+ vs 82 kcal mol^{-1} for Tl^+) comparison with potassium.[1−3] Because of poor NMR properties of potassium(I) (including natural abundance, gyromagnetic ratio, and chemical shift range) relative to those of thallium(I),

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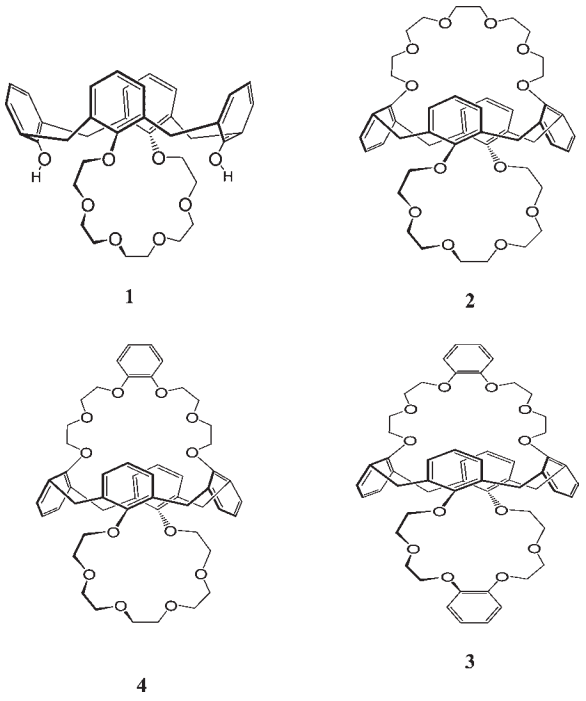
 Published on Web 07/07/2010

many researchers have used thallium(I) NMR instead of potassium(I) NMR for the analysis of binding sites and determination of monovalent cation selectivities.[4,5] Most biomacromolecules including phospholipids,[6−10] carbohydrates,[11−14] proteins,[15,16] and nucleic acids[17−21] possess a structural and/or functional requirement for monovalent cations.

The synthesis of polynuclear complexes that can be studied in solution is an important topic in view of the potential role of such species in multi-metal-centered catalysis in both biological and industrial reactions.[22] Various enzymes, including P1 nuclease, DNA polymerase I, phospholipase C, and alkaline phosphatase, use the synergic action of two metal centers for the hydrolytic cleavage of phosphate ester bonds.[23,24] ^{205}Tl NMR has been previously used as a suitable probe to investigate the binding sites of interaction of the thallium(III) ion with macrobiomolecules like transferrin,[25] yeast pyruvate kinase (yPK),[26] gramicidin,[27] and nucleic acids.[4] Bertini et al. showed that ^{205}Tl NMR is a convenient probe in monitoring the occupancy of the two available binding sites of transferrin, and they characterized the dithallium(III)−transferrin and the monothallium(III) derivatives with bicarbonate as a synergistic ion.[25] Gill et al. used heteronuclear ^{1}H−^{205}Tl NMR and direct ^{205}Tl NMR detection to characterize the binding of Tl^+ to nucleic acid d(G4T4G4)2 in a site-specific manner[4]

Scheme 1. Calix[4]arenes Considered in This Paper



Calixarenes and related macrocycles have received considerable attention for their host−guest chemistry, and their ability to bind metal ions.[28] There is currently increasing interest in the synthesis and structural characterization of new metallocalixarenes.[29] Among calixarene-based ligands, calix[4]biscrown ethers have received particular attention. Thuéry et al. have reported a series of 1:1 and 2:1 complexes of alkali metal ions with a 1,3-calix[4]biscrown ether.[30] In particular, calix[4]biscrown-6's exhibited a high selectivity toward the Tl^+ ion against other monovalent ions such as Ag^+, K^+, Na^+, and Cs^+.[31] In continuation of our research activities on the complexation behavior of thallium(I) ion with different macrocyclic ligands,[32−35] in this work we have used ^{203}Tl and ^{1}H NMR to examine the binding sites of four different calix[4]arene mono- and bis-18-crown-6 derivatives (Scheme 1) with the thallium(I) ion. The resulting data on cation binding clearly revealed the multisite interaction of

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calix[4]crown-6 and three calix[4]biscrown-6 derivatives toward the Tl^+ ion.

Experimental Section

Chemicals. Deuterated acetonitrile and chloroform were purchased from Armar Chemicals. Thallium(I) perchlorate was prepared by treating 1 g of thallium(I) nitrate with 4 mL of 3 M perchloric acid, evaporating to dryness, and recrystallizing three times from water and drying at 120 °C. All other materials were of reagent grade from Merck and used as received. Calix[4]-crown-6 (**1**), 1,3-calix[4]biscrown-6 (**2**), 1,3-calix[4]bis-*o*-benzo-crown-6 (**3**), and 1,3-alternate calix[4]arene-1,3-crown-6;2,4-(1,2-phenylene)-crown-6 (**4**) were prepared and purified as described in our previous publications.[36−38]

Synthesis of [Tl(3)MeCN]ClO_4. Calix **3** (0.03 mmol) was dissolved in acetonitrile−chloroform (4:1 v/v, 3 mL) and treated with an equivalent amount of $TlClO_4$ (0.03 mmol). The slow evaporation of solvent at room temperature, over one week, resulted in well-defined colorless crystals, which were suitable for X-ray crystallography, after their separation and drying under a vacuum.

Thallium-203 NMR Studies. All thallium-203 NMR experiments were performed at 11.7 T (285 MHz ^{203}Tl) on a Bruker DRX-500 pulsed Fourier transform NMR spectrometer. Typical NMR parameters are as follows: a spectral frequency of 285.677 MHz, a spectral width of 150 kHz, a 30° flip angle, a pulse repetition time of 1 s, an acquisition time of 0.039 s, an FID resolution = 12.7 Hz/point, and a number of scans = 128−256. All ^{203}Tl spectra were internally referenced to a capillary tube containing 0.05 M of $TlClO_4$ in D_2O/CD_3OD (2:3 v/v). The complexation behavior of the ligands **1**−**4** toward the thallium(I) ion was studied by adding the ligand into the NMR tube containing 0.01 M thallium(I) perchlorate in a $CD_3CN/CDCl_3$ (4:1 v/v) mixed solvent at 298 K. Stepwise additions of the ligand were made, and the chemical shifts were recorded.

Proton NMR Studies. ^{1}H NMR measurements were recorded at 298 K using a Bruker DRX-500 pulsed Fourier transform NMR spectrometer. Typical operating conditions for routine proton measurements involved a flip angle of 30°, a spectral frequency of 500.133 MHz, a spectral width of 5 kHz, a delay time of 6.0 s, and and acquisition time (AQ) of 1.586 s. Solutions of the ligands **1**−**4** (0.002 M) were prepared in $CD_3CN/CDCl_3$ (4:1 v/v) mixed solvent in a 5-mm NMR tube using the TMS signal as an internal reference.

Caution! *Although we have not encountered any problems, it should be noted that perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled only in small quantities with appropriate precautions.*

X-Ray Crystallography. The single crystal data for [Tl(**3**)-MeCN]ClO_4 were collected at 150 K via ω scans and graphite-monochromated Mo Kα radiation (λ = 0.7107 Å) on an Oxford Diffraction Xcalibur 3 CCD area detector diffractometer equipped with an Oxford Cryosystems open-flow nitrogen cryostat. The data set was corrected for Lorentz polarization effects and for absorption using empirical absorption correction SCALE3 ABSPACK.[39] The structure was solved by direct methods using SIR-2004[40] and refined using SHELXL-97.[41] All non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were introduced at calculated positions and refined using a riding model.

[Tl(3)(MeCN)(H_2O)]ClO_4. $C_{58}H_{65}ClNO_{17}Tl$, M_w = 1287.93, orthorhombic, *Pbca* (No.61), a = 19.171(2), b = 19.282(1), c = 29.746(2) Å, V = 10995.8(15) Å^3, Z = 8, ρ_{calcd} = 1.556 g cm^{-3}, $2\theta_{max}$ = 49.42°, μ ($Mo_{k\alpha}$) = 3.060 mm^{-1}, and colorless prismatic crystals (0.2 × 0.1 × 0.1 mm^3). Empirical absorption corrections (T_{min} = 0.533, T_{max} = 1.000), 28 475 measured reflections, and 8952 unique reflections (R_{int} = 0.0587) of which 5043 had [$I > 2\sigma(I)$]. At final convergence, R_1 [$I > 2\sigma(I)$] = 0.0516, wR_2 (all data) = 0.1343 for 720 refined parameters, S = 0.920, $(\Delta/\sigma)_{max}$ = 0.007, and $\Delta\rho_{max}$ = 1.629 e Å^{-3}.

X-ray crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 772564. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Results and Discussion

Complexation of Tl^+ Ion with Calix[4]crown-6 (1). Thallium-203 NMR Study. In order to investigate the binding sites of the thallium(I) ion inside the calix **1** cavity, the thallium-203 NMR spectra of a 0.01 M Tl^+ solution in $CD_3CN/CDCl_3$ (4:1 v/v) in the presence of varying concentrations of **1** were recorded. As seen, because of the higher flexibility of **1** compared with that of **2**−**4**, the thallium(I) ion possesses a fast exchange rate between the solvated (at −199 ppm) and the 1:1 complexed sites (at −141 ppm), resulting in a population averaged single NMR signal in the entire range of ligand-to-metal molar ratios (R) considered. However, no signal is observed at the molar ratio values of 0.4−0.8, most probably due to broadening of the signal, as a result of fast metal exchange between the free and complexed thallium ion.[42]

Proton NMR Study. It was found that nearly all of the spectral NMR peaks for the skeletal aromatic ring protons and glycolic crown ether protons of ligand **1** shift to lower frequencies upon its complexation with the Tl^+ ion, the magnitude of the shift being significantly different for the various protons of the ligand. The ^{1}H NMR spectra for the aromatic section of calix **1** upon the stepwise addition of Tl^+ to a 0.002 M solution of the ligand in a $CD_3CN/CDCl_3$ (4:1 v/v) mixed solvent are shown in Figure 1A. It is seen that, upon complexation with Tl^+, the largest shifts (upfield or downfield) are observed for the two identical protons of the phenyl−OH protons and the four identical protons of the −CH− aryl groups.

The variations of −OH and *p*-H of aryl chemical shifts versus the Tl^+/calix **1** molar ratio (R') are shown in Figure 1B. The resulting plots clearly indicate the quantitative formation of a complexed species with a 1:1 (Tl^+/calix **1**) stoichiometry.

A close comparison of the $\Delta\delta$ ($\delta_{complex} - \delta_{free\ ligand}$) values of the host protons after complexation with guest ions shows that the phenyl−OH protons give the highest $\Delta\delta$ value of −0.41 ppm, followed by the $-CH_2-$ protons in the bridging group toward the crown loop ($\Delta\delta$ = −0.19 ppm) as well as the $-CH_2-$ protons in the bridging group at the opposite direction of crown loop ($\Delta\delta$ = +0.12 ppm), supporting the fact that the thallium(I) guest ion may penetrate into the calix[4]arene cavity close to the phenyl−OH proton. These observations indicate that the Tl^+ ion, as a soft electron acceptor with strong afinity

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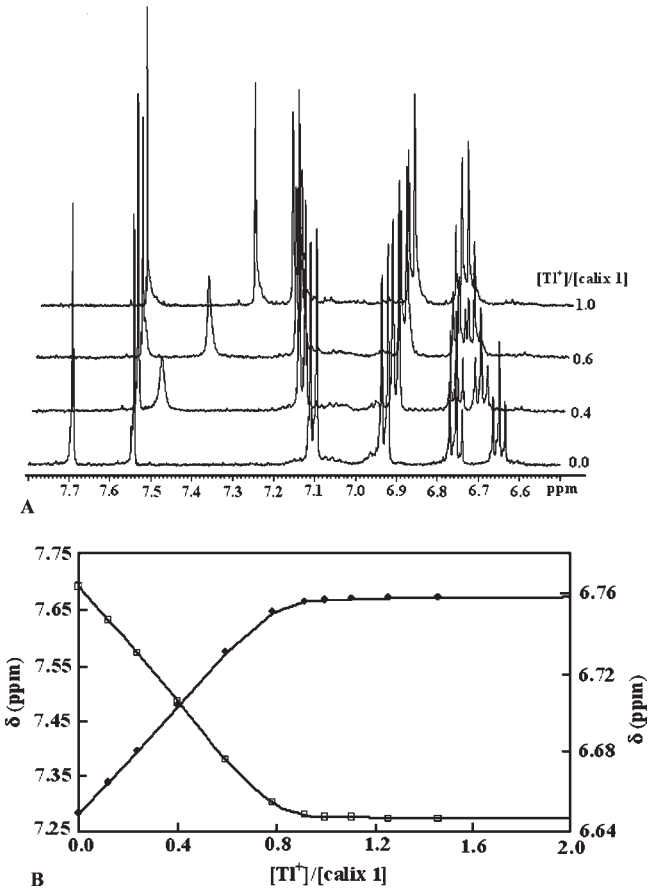


Figure 1. (A) Proton NMR spectra of the aromatic region of calix **1** at various Tl^+/calix **1** molar ratios in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K. (B) The variation of proton chemical shifts for −OH protons (□, left scale) and *p*-H of aryl (●, right scale) as a function of Tl^+/calix **1** molar ratios.

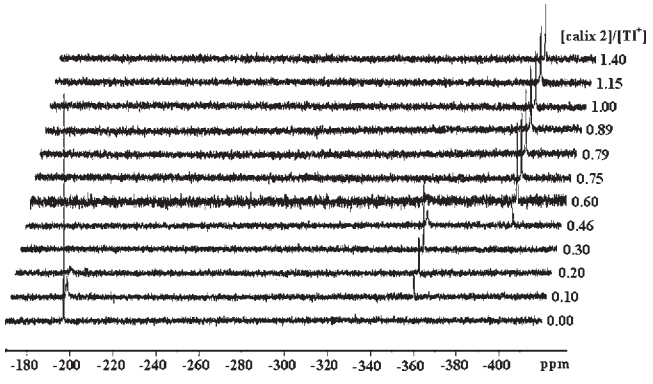


Figure 2. Thallium-203 NMR spectra of calix **2** at various ligand/Tl^+ molar ratios in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K.

toward the π-basic calix[4]arene cavity, may also give cation−π coordination.[43]

Complexation of Tl^+ Ion with 1,3-Calix[4]biscrown-6 (2) and 1,3-Calix[4]bis-*o*-benzo-crown-6 (3). Thallium-203 NMR Study. The thallium-203 NMR spectra of a 0.01 M Tl^+ solution in $CD_3CN/CDCl_3$ (4:1 v/v) in the presence of varying concentrations of calix **2** were recorded, and the results are shown in Figure 2. As is obvious, the thallium-203 NMR signal of the solvated Tl^+ ion shifts appreciably to much higher magnetic fields upon formation of the 1:1 and 2:1 (metal-to-ligand) complexes with calix **2**, revealing the fact that the guest cations can be encapsulated inside the two ligand cavities to form intermolecular complexes, which thus leads to an efficient shielding of the Tl^+ ion.

The spectra shown in Figure 2 revealed two distinct signals at −199 ppm for the free species and at −361 ppm for 2:1 $[Tl_2(\text{calix } \mathbf{2})]^{2+}$ complexed species, at ligand-to-metal ion molar ratios $0 < R \leq 0.2$, emphasizing the occurrence of a slow exchange in the system, on the thallium-203 NMR time scale. Meanwhile, upon further addition of the ligand, to $R > 0.5$, a new signal is observed at −399 ppm for the corresponding mononuclear species $[Tl(\text{calix } \mathbf{2})]^+$ as a result of another slow exchange of the Tl^+ ion between the $[Tl_2(\text{calix } \mathbf{2})]^{2+}$ and $[Tl(\text{calix } \mathbf{2})]^+$ complexed species. The results clearly revealed the formation of stable 2:1 and 1:1 (metal/ligand) complexes with very slow exchange of the cation between these two complexed sites on the NMR time scale.

Similar results were obtained in the case of calix **3** and interpreted in terms of the formation of dinuclear $[Tl_2(\text{calix } \mathbf{3})]^{2+}$ complexed species when $R \leq 0.5$, with a slow exchange between the solvated thallium(I) ion and its dinuclear complex, and also the occurrence of another slow exchange between the mono- and dinuclear complexes at $0.5 < R < 1$. Table 1 shows all of the chemical shifts for the resulting 1:1 and 2:1 complexes detected in this work. It is worth mentioning that, according to Table 1, while the thallium-203 chemical shifts for the 1:1 complexes of the Tl^+ ion with calix[4]biscrown-6 derivatives **2** and **3** are observed at about −400 ppm, that for the Tl^+−calix **1** system is located at about −140 ppm (i.e., about 160 ppm downfield from the former ones). Such a relatively large chemical shift difference is due to quite different electronic environments of the Tl^+ ion complexed with calix **1** relative to the corresponding complexes with calix derivatives **2** and **3**. First of all, it should be noted that the calix[4] cavity in the case of the calix **1** derivative is in con-conformation, while those in calix derivatives **2** and **3** are 1,3-alternative conformers, which results in different π−cation interactions. The large shift of −0.41 ppm, from 7.69 to 7.28 ppm in ^1H NMR spectra, was observed for the -OH signal of calix **1** upon complexation with the Tl^+ ion, reflecting the strong interaction of the Tl^+ ion with the hydroxyl groups of the ligand and, consequently in the different electronic environment of the complexed Tl^+ ion. Moreover, our crystallographic studies of the 1:1 Tl^+−calix **3** complex (see the following sections and Figure 7) revealed that the second cavity defined by calix **3** is partially occupied by an acetonitrile molecule, the methyl group of which interacts with one of the aromatic rings bearing the polyoxa chain coordinated to the Tl^+ ion, which can also affect the electronic environment of the complexed Tl^+ ion.

Proton NMR Study. The ^1H NMR spectra of the aromatic region of calix **2** at various Tl^+/ligand molar ratios (R') in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K are shown in Figure 3A. It should be noted that the corresponding ^1H NMR spectra of calix **3** showed a more or less similar trend, and thus it is not shown here. As is obvious from Figure 3A, the signals of the free calix **2** split into two distinct signals which shifted and broadened upon addition of the cation; for example, the doublet centered at 7.13 ppm due to the *m*-H of aryl for the free **2** ($R' = Tl^+$/calix **2** = 0) is split

Table 1. Thallium-203 NMR Chemical Shift (ppm) of Different Complexes of Thallium−Calixarenes

		Tl^+/calix			
code	name	1:1		2:1	
calix **1**	calix[4]crown-6	−141.3			
calix **2**	1,3-calix[4]biscrown-6	−399.1		−359.6	
calix **3**	1,3-calix[4]bis-*o*-benzo-crown-6	−401.6		−363.8	
calix **4**	calix[4]arene-1,3-crown-6;2,4-(1,2-phenylene)-crown-6	−367.4	−415.2	−312.2	−361.5

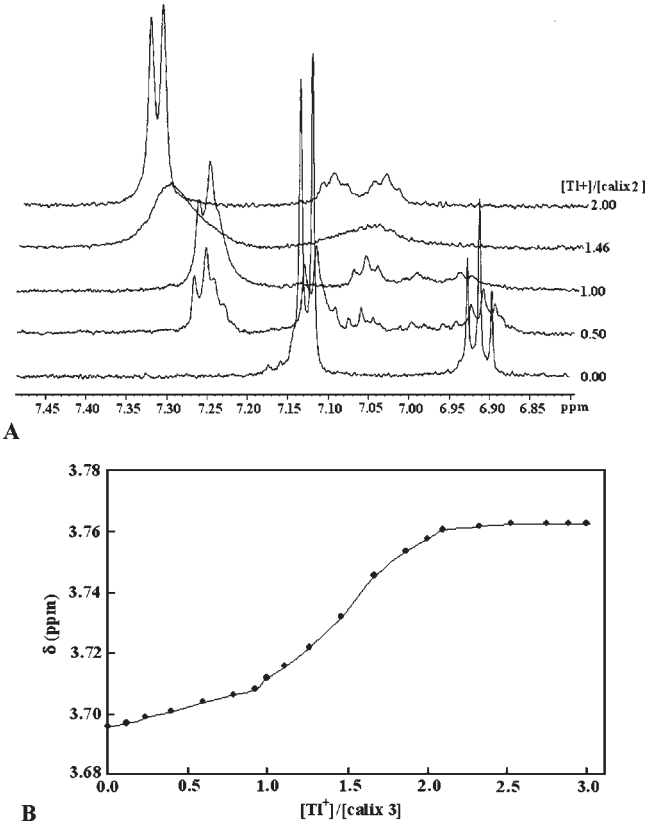


Figure 3. (A) Proton NMR spectra of the aromatic unit of calix **2** at various Tl^+/ligand molar ratios in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K. (B) The variation in chemical shift of the $O-CH_2-CH_2-O$ proton of calix **3** as a function of the Tl^+/ligand molar ratio.

into two distinct doublets at $R' = 0.5$ centered at δ 7.12 and 7.26 ppm corresponding to the empty and filled cavities of the unsymmetrical mononuclear $[Tl(\text{calix } \mathbf{2})]^+$ species, respectively. Similar ^1H NMR results have also been reported by Thuéry et al.[30] for the complexation of the Cs^+ ion with 1,3-calix[4]biscrown-6 at $0 < R' < 1$, which was related to the occurrence of a slow exchange between the free and complexed host.

Figure 3B shows the variation in chemical shift of $O-CH_2-CH_2-O$ protons of the benzo-18-crwon-6 substituent of calix **3** (Figure 3B) as a function of the Tl^+/ligand molar ratio (R'). As can be seen, the molar ratio plots show two distinct regimes: the first is in the range of $R' = 0-1$, and the second is in the range of $R' = 1-2$, with two clear inflection points at metal-to-ligand molar ratios of 1 and 2, emphasizing the successive and quantitative formation of the two complex species $[Tl(\text{calix } \mathbf{3})]^+$ and $[Tl_2(\text{calix } \mathbf{3})]^{2+}$.

Since the mononuclear complexes of $[Tl(\text{calix } \mathbf{3})]^+$ and $[Tl(\text{calix } \mathbf{2})]^+$ are formed quantitatively at around $R' = 1$, one can expect to observe at least two separate ^1H NMR signals for all of the protons corresponding to the empty and filled cavities of such unsymmetrical mononuclear species. However, according to the corresponding ^1H NMR spectra for aromatic (Figure 3A) and glycolic (not shown) regions at $R' = 1$, the signals are quite broad, and no distinct separate signals are observed for unsymmetrical mononuclear species. One easy hypothesis for this observation is that the Tl^+ ion can intramolecularly alternate rapidly on the NMR time scale between the two crown cavities by migrating through the π-basic hole of the calix[4]arene moiety in calix **2** and calix **3** (Scheme 2). In fact, it could be postulated that the complexation of the Tl^+ ion with calix **2** at $R' < 1$ is a three-site exchange system and at $R' = 1$ a two-site exchange system, as illustrated in Scheme 2. Meanwhile, as can be seen from Figure 3A, further addition of the thallium(I) ion to reach $R' > 1$ will result in a stepwise decoalescence of most proton signals, due to the stepwise occupation of the two crown sites of calix **2** and the consequent reduction of the intramolecular exchange rate.

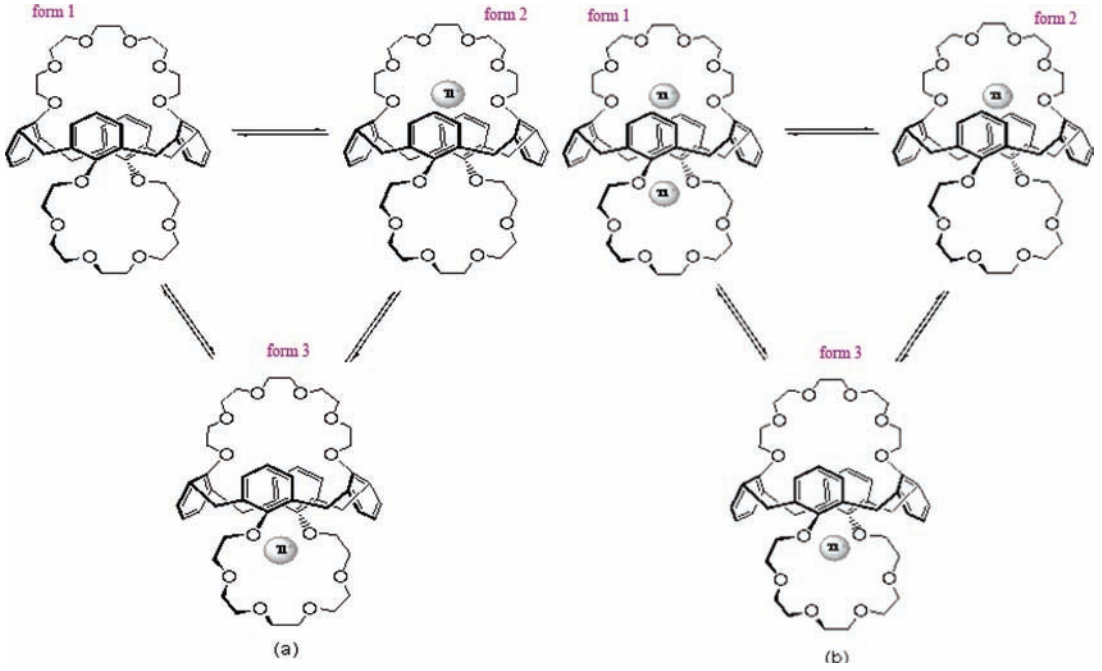
There is also a three-site exchange system for $1 < R' < 2$, with two available sites for mononuclear intramolecular exchange as well as a possible exchange between mononuclear and dinuclear complexes (Scheme 2b).

As is obvious from Figure 3A, at a molar ratio of $R' = 2$ (corresponding to the formation of a $[Tl_2(\text{calix } \mathbf{2})]^{2+}$ complex), a well resolved doublet is observed for aromatic protons (*m*-H of aryl in the calix cavity) in the ^1H NMR spectrum of the 2:1 symmetrical dinuclear complex. Accordingly, it can be concluded that the thallium(I) ions stand on the main symmetry axis of the $[Tl_2(\text{calix } \mathbf{2})]^{2+}$ complex. Similar results have been obtained in the case of the calix **3** complex and interpreted in terms of the formation of unsymmetrical mononuclear species at a molar ratio of $R' \leq 1$, with slow intermolecular and fast intramolecular exchange of the cation between the two crown sites of calix **3**. A rapid exchange between mono- and binuclear species and also intramolecular exchange between mononuclear complexes was also observed when the molar ratio was $R' > 1$.

Variable Temperature ^1H NMR Study. In order to further elucidate the inter- and intramolecular Tl^+ complexation behavior shown in Scheme 2, the variable temperature ^1H NMR was carried out in a $CD_3CN/CDCl_3$ (4:1 v/v) solution at different metal ion to calix **2** molar ratios. Figure 4 depicts the representative proton NMR spectra of a Tl^+/calix **2** system of metal/ligand molar ratios, R', of 1.0, 1.3, 1.5, and 2.0 at five different temperatures in the range of 223−293 K. The spectra show two groups of signals: (i) signals at chemical shifts of 6.85−7.15 ppm composed of triplets due to the *p*-H and (ii) those at chemical shifts 7.15−7.35 ppm composed of doublets related to the *m*-H of aryl groups of the calix cavity.

As is obvious from Figure 4, at $R' = 1$ and at the highest temperature of 293 K, a broadened *m*-H doublet is observed

Scheme 2. Multisite Exchange Equilibria between Calix **2** and Thallium(I) Ion: (a) Tl^+/Calix **2** Molar Ratio ≤ 1 and (b) Tl^+/Calix **2** Molar Ratio ≥ 1



at about 7.20−7.27 ppm, which becomes sharper and shifts to some extent to higher frequencies at lower temperatures. Such a broad single doublet insists the occurrence of a fast exchange between forms 2 and 3 depicted in Scheme 2a. It is interesting to note that, as the temperature decreases, the exchange rate decreases and, consequently, the single doublet begins to split into two doublets, each of which belonging to the *m*-H of aryl groups of the calix cavity in the two 1:1 complex conformers given by forms 2 and 3 in Scheme 2a. A more or less similar temperature effect is observed for *p*-H triplets of the aryl groups of the calix cavity, over a chemical shift range of 6.85−7.15 ppm.

However, upon increasing the [Tl^+]/[calix **2**] molar ratio from 1.0 to 1.3 and 1.5 (Figures 4B and C, respectively), a new doublet signal begins to show up, at higher chemical shifts than that for the 1:1 complex, for the *m*-H aryl groups of the calix **2** cavity, which becomes sharper at lower temperatures, expectedly. Such an observation implies that there are two exchangeable forms corresponding to the binuclear and mononuclear species in solution. It is worth mentioning that the relative area of these two doublets is proportional to the corresponding molar ratios at lower temperatures. The observed behavior is in support of the multisite exchange equilibria between calix **2** and the thallium(I) ion shown in Scheme 2b.

On the other hand, the observation of at least three triplets for the *p*-H's of the aryl groups of the calix **2** cavity, at lower temperatures, not only confirms the exchange between the 2:1 and 1:1 Tl^+−calix **2** complexed species but also reveals the fact that, in both 1:1 and 2:1 forms, the para-hydrogen atoms of the aryl groups have different magnetic environments (see below the crystallographic structure of [Tl(**3**)(MeCN)(H_2O)]$^+$).

Finally, at a [Tl^+]/[calix **2**] molar ratio of 2 (Figure 4 D), both crown sites of the calix molecule are occupied by two thallium(I) ions so that all *m*-H aryl groups possess similar magnetic environments, which result in a single doublet at all temperatures studied. However, the existence of two different triplets for the *p*-H protons of the aryl groups, at all temperatures studied, revealed the fact that in the 2:1 complex formed the four *p*-H's are divided into two groups, one close to the Tl^+ ions and one far away from them. This is most probably due to the fact that, upon complexation with the metal ions, each of the crown ether moieties of calix **2** adopts a kind of boat-shaped configuration to conveniently encapsulate the thallium(I) ion (see the crystallographic structure shown in Figure 7). It is interesting to note that at $1 \leq R' < 2$ (Figure 4A−C), there are three different triplets present in the 6.85−7.15 ppm region of the corresponding ^{1}H NMR spectra for the *p*-H's of the aryl groups of calix **2**, one due to the unoccupied crown site of the ligand and two others for the occupied site, as mentioned above for the case of the [Tl_2(calix **2**)]$^{2+}$ complex.

Complexation of Tl^+ Ion with 1,3-Alternate Calix[4]-arene-1,3-(18-crown-6;2,4-(1,2-phenylene)-18-crown-6 (Calix 4). Thallium-203 NMR Study. The thallium-203 NMR spectra of a 0.01 M Tl^+ solution in $CD_3CN/CDCl_3$ (4:1 v/v) in the presence of varying concentrations of calix **4** were recorded, and the results are shown in Figure 5. As can be seen, at molar ratios $R < 0.5$, the thallium-203 NMR spectra of the inclusion complexes of calix **4** with the thallium(I) ion normally show three distinct signals for the free and complexed guest species, one signal for the solvated (at −199 ppm) and two upfield signals for the 2:1 [Tl_2(calix **4**)]$^{2+}$ complex (at −312 and −362 ppm), indicating a very slow exchange of the Tl^+ ion between the solvated and complexed sites, within the thallium-203 NMR time scale. Obviously, upon the addition of calix **4** to the thallium(I) ion solution at $R = 0.5$, both crown units of the host molecule will be occupied; in them, the two Tl^+ ions will possess a more or less different electronic environment. It is worth mentioning that, in a recent publication, Matthews et al. have reported the ability of using the thallium-205 NMR to observe the intermediate species in solution, in which a small change in electronic

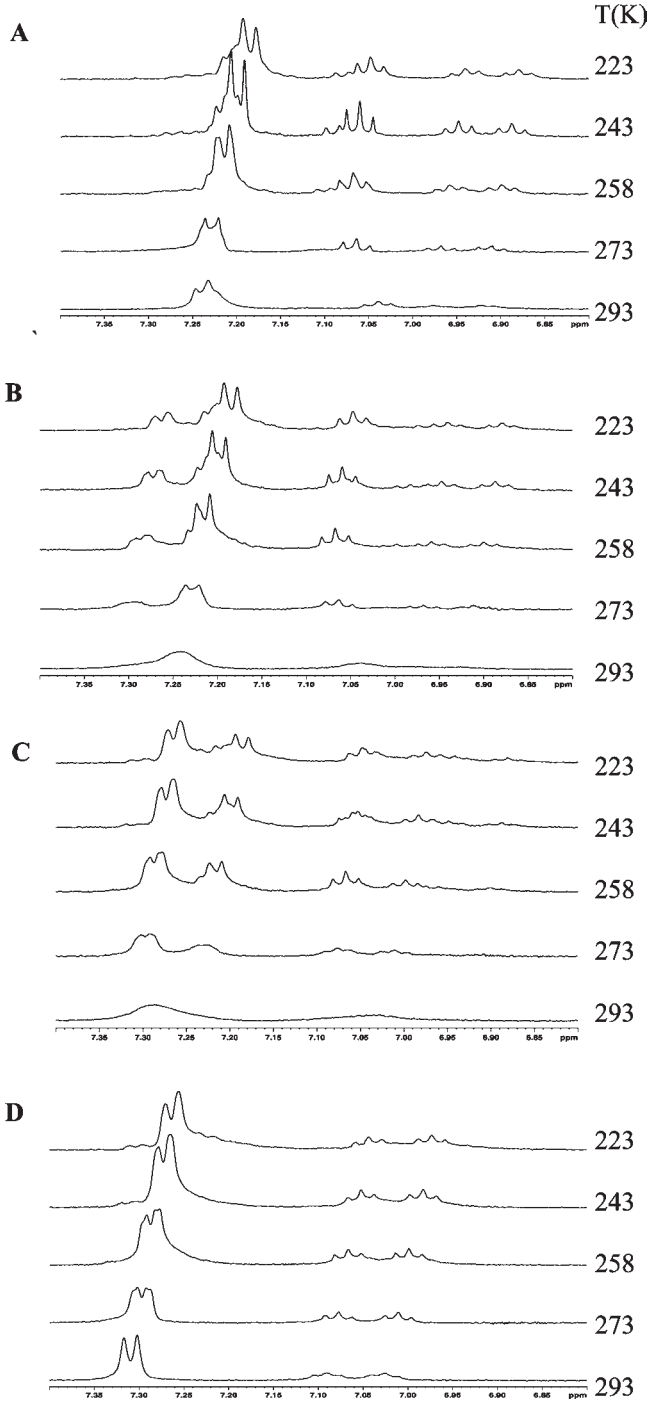


Figure 4. Proton NMR spectra of the aromatic unit of calix **2** at various Tl^+/ligand molar ratios and different temperatures in $CD_3CN/CDCl_3$ (4:1 v/v): (A) $R' = 1.0$; (B) $R' = 1.3$; (C) $R' = 1.5$; (D) $R' = 2.0$.

environment would greatly affect the thallium(I) resonance, so that a clear and direct observation of the complexation process can be made.[5] Here, because of some asymmetry in the structure of the two crown units of calix **4**, the resulting $[Tl_2(\text{calix } \mathbf{4})]^{2+}$ complex gives two thallium(I) resonances related to binding of a Tl^+ ion in each of the two different crown units of the ligand, which can be observed separately in a slow exchange regime on the thallium-203 NMR time scale.

As is obvious from Figure 5, upon further addition of the ligand at molar ratios of $R > 0.5$ to the thallium(I) ion

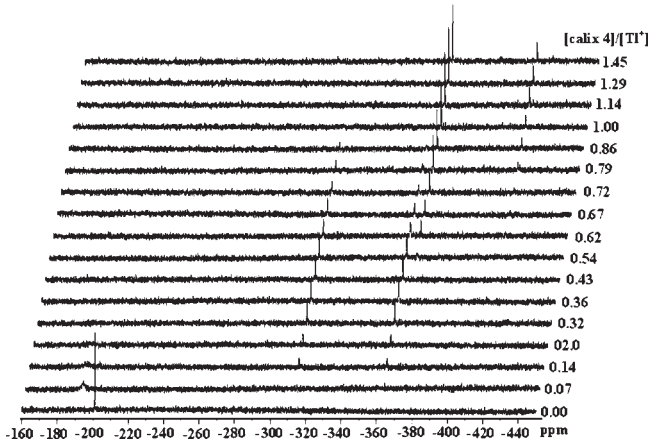


Figure 5. Thallium-203 NMR spectra of calix **4** at various ligand/Tl^+ molar ratios in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K.

solution, two new distinct signals at −367 and −415 ppm, due to the formation of the 1:1 $[Tl(\text{calix } \mathbf{4})]^+$ begin to grow at the expense of the signals at −312 and −362 ppm of the complex $[Tl_2(\text{calix } \mathbf{4})]^{2+}$. As is obvious from Figure 5, at molar ratios of $R = 1$ or greater, the thallim-203 NMR spectra only shows the two NMR signals corresponding to the 1:1 $[Tl(\text{calix } \mathbf{4})]^+$ complex. One easy interpretation of the observations is that the calix **4** ligand possesses two binding sites with different binding abilities for the thallium(I) ion.[44] This interpretation is also supported by ^1H NMR studies described below. The two signals observed for the 1:1 $[Tl(\text{calix } \mathbf{4})]^+$ complex at −367 and −415 ppm are most possibly related to the Tl^+ ion located in 18-crwon-6 and benzo-18-crown-6 units of calix **4**, respectively.

It is interesting to note that, according to the thallium-203 NMR spectra shown in Figure 5, the relative intensity of the −367 ppm signal-to- −415 ppm signal is also 3:1, which implies that the ionophoricity of the former cavity (i.e., cavity related to the −367 ppm signal) is 3 times larger than that of the latter cavity (i.e., cavity related to the −415 ppm signal). These observations demonstrate the ability of thallium-203 NMR to distinguish the Tl^+ ion binding sites in macromolecules and to investigate how specific the monovalent sites respond to the ligand binding.

Proton NMR Study. Figure 6 shows the ^1H NMR spectra of the aromatic region of calix **4** at various Tl^+/ligand molar ratios (R') in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K. Because of the asymmetry of calix **4** with respect to calix **2** and **3**, its ^1H NMR pattern is more complicated; however, from the ^1H NMR spectra of calix **4**, some results similar to those for calix **2** and **3** can be obtained. From Figure 6, it seems that at a molar ratio of $R' = 2$, one of the doublet of triplets for the *p*-H of aryl (corresponding to $[Tl_2(\text{calix } \mathbf{4})]^{2+}$) is overlapped with protons of the benzo group at the top of the 18-crown-6 loop.

The inset of Figure 6 shows ^1H NMR spectra of the *p*-H of aryl of calix **4** at a molar ratio of $R' = 3$ decoupled with ^{203}Tl. Because of a lesser abundance of ^{203}Tl relative to ^{205}Tl (i.e., 29.5% to 70.5%), the decoupling cannot be applied quantitatively. This observation can help to prove the hypothesis of the presence of two types of aryl protons in the resulting 1:1 and 2:1 complexs. The tallium(I) ion

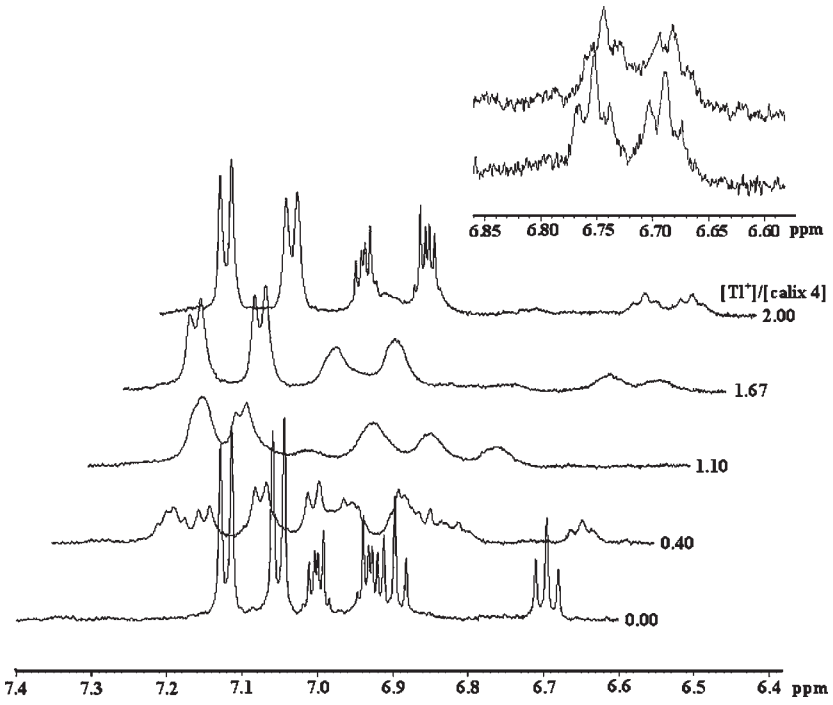


Figure 6. Proton NMR spectra of the aromatic region of calix **4** at various Tl^+/ligand molar ratios in $CD_3CN/CDCl_3$ (4:1 v/v) at 298 K. Inset shows the ^1H NMR spectrum of the *p*-H of the aryl region of calix **4** at a Tl^+/ligand molar ratio of 3.0: (top) ^{203}Tl decoupled NMR; (bottom) ^1H NMR ^{203}Tl coupled for comparison.

can coordinate to four arene rings at a time, and if these ligands can support two Tl^+ ions at one time in distinct coordination environments, then both Tl^+ ions cannot both interact with all four arene rings.

X-Ray Crystal Structure of [Tl(3)(MeCN)(H_2O)]ClO_4. The crystal structure consists of discrete [Tl(**3**)(MeCN)-(H_2O)]$^+$ cations and perchlorate anions. Figure 7 shows the [Tl(calx **3**)(MeCN)]$^+$ cation with atom labeling.

Due to the two polyoxa chains, the calixarene adopts a 1,3-alternate conformation. As shown in Figure 7, two CH$\cdots\pi$ interactions are formed between the aromatic rings of the calixarene and the catechol rings of the polyoxa chains. In fact, the C6 atom is 3.633(8) Å from the plane defined by the nearest catechol ring (3.103(7) Å for C13) and 4.63(1) Å from its centroid (4.38(1) Å for C13). This disposition of the calix[4]arene moiety and of the two polyoxa chains defines two cavities located on opposite sides of the calix[4]arene rim.

As shown in Figure 7, one of these cavities is occupied by a thallium(I) ion which is coordinated by three oxygen atoms from the polyoxa chain and by a water molecule. The Tl−O distances range from 2.739(9) Å to 2.949(4) Å, as expected for this kind of bond.[45] The coordination sphere is completed by the two aromatic rings bearing the polyoxa chain not coordinated to the metal. Each aromatic ring interacts with the metal center via π− cation interactions involving three of the six carbon atoms, with metal to carbon distances falling in the range 3.095−3.317 Å.

Included cations forming polyhapto aromatic interactions are very common in calixarene complexes, mainly in the case of alkali metal cations,[46] but to the best of our knowledge, only one crystal structure was previously reported containing calixarene, including a thallium(I) ion π-interacting with the aromatic rings of the calixarene

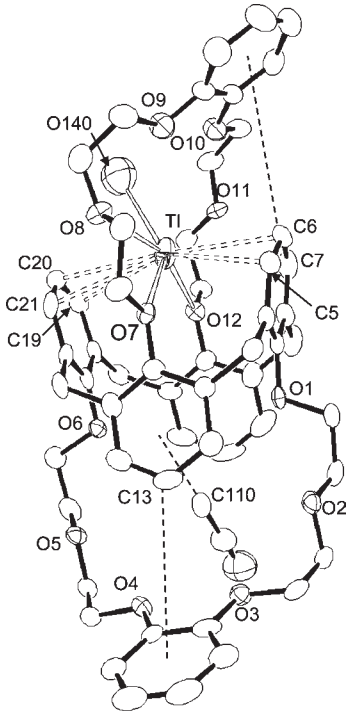


Figure 7. ORTEP drawing of the [Tl(**3**)(MeCN)(H_2O)]$^+$ cation with labeling scheme adopted. H atoms and counteranions are omitted for clarity. Selected bond distances: Tl−O12 = 2.945(4), Tl−O7 = 2.949(4), Tl−O8 = 2.926(5), Tl−O140 = 2.739(9), Tl$\cdots$C5 = 3.310(7), Tl$\cdots$C6 = 3.155(8), Tl$\cdots$C7 = 3.259(8), Tl$\cdots$C19 = 3.319(7), Tl$\cdots$C20 = 3.095(7), Tl$\cdots$C21 = 3.273(7) Å.

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moiety.[5] Also in that structure, the Tl···C distances were about 3.2−3.3 Å. Due to the similarity of Tl^+ and K^+ cations, a close comparison can be done between the Tl···C distances found in these crystal structures and the K···C distances observed in analogous complexes of the potassium ion, which are slightly longer and generally fall in the range 3.2−3.6 Å.[47] Additional information could also be obtained by analyzing the Tl···C distances in complexes featuring Tl^+ ions involved in poly hapto aromatic interactions with phenyl or cyclopentadienyl groups. Actually, a search of the CSD database has evidenced that most of the metal to carbon distances in complexes where the Tl^+ is located near the normal to an aromatic ring (angle between the Tl-centroid vector and the normal to the aromatic plane being less than 20°) are about 3.2−3.3 Å, in good agreement with distances observed in the crystal structure of $[Tl(\mathbf{3})(MeCN)(H_2O)]^+$.[45]

As shown in Figure 7, the second cavity defined by the ligand is partially occupied by a MeCN molecule. Actually, the methyl group of the MeCN interacts with one of the aromatic rings bearing the polyoxa chain coordinated to the Tl^+ cation, giving rise to carbon to plane and carbon to centroid of the ring distance values of 3.229(6) and 3.68(1) Å, respectively.

Conclusion

We have used ^1H NMR and direct detection of ^{203}Tl NMR to characterize the binding of Tl^+ to some calix[4]arene crown ether derivatives **1**−**4** in a site-specific manner. The power of direct detection ^{203}Tl NMR is demonstrated by the observation of a previously unobserved complexity in the association of monovalent cations with the calixarene systems. Also, successive formation of mononuclear and dinuclear species, alternation of thallium(I) between two binding sites of calix derivatives **2**−**4** by migration through the π-basic hole.

Acknowledgment. This work has been supported by grants from the Tarbiat Modares University Research Council, which is hereby gratefully acknowledged.

Supporting Information Available: Crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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