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Ionic Exchange in *p*-Sulfonatocalix[4]arene-Mediated Formation of Metal–Ligand Complexes

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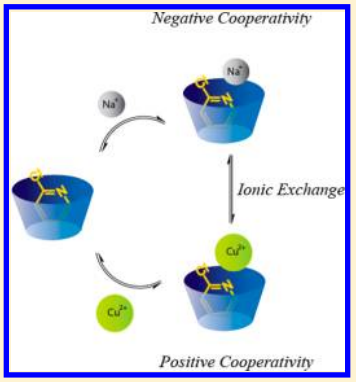
Supporting Information

ABSTRACT: The effect of alkali and transition metal cations in the formation of host–guest complexes with the water-soluble *p*-sulfonatocalix[4]arene (SC4) was studied using 2-chloropyridine and Na^+ and Cu^{2+} as model guest and model cations, respectively. The results obtained from isothermal titration calorimetry and NMR experiments provide evidence for the formation of 1:1:1 ternary complexes for both cations with Cu^{2+} showing positive cooperativity and Na^+ negative cooperativity. The formation of ternary complexes comprising transition metal cations has been scarcely explored but present high potential for devising catalytic systems/models or for enhancing the stability and selectivity of SC4 complexes. Because transition metal cations are usually present in solution together with other SC4 countercations (e.g., Na^+), a general binding model that considers the dynamic formation of all possible complexes (including ionic exchange between ternary complexes) is presented. This model allows the optimization of the conditions required to selectively form target complexes.



INTRODUCTION

p-Sulfonatocalixarenes are a special class of water-soluble macrocycles recognized as potent model receptors for studying noncovalent interactions in aqueous solution with special attention to cation–π, CH, and π–π interactions.[1−10] Besides being very useful models to investigate fundamental aspects of supramolecular chemistry, *p*-sulfonatocalixarenes have proven to be highly attractive building blocks for sensing and supramolecular self-assembly applications including displacement assays for monitoring enzymatic activity, supramolecular polymers, supra-amphiphiles, etc.[11−22] Given the increasing interest and applications of these compounds, detailed knowledge of their binding mechanisms is mandatory for optimization and development of host–guest systems with increased binding affinity and selectivity.

In past years, detailed studies have provided evidence for the, until then ignored, complexation of alkali metal cations by *p*-sulfonatocalix[4]arene (SC4).[23−26] The complexation of such cations, in particular, sodium cations which are always present in solution as SC4 counterions, competes with target guests and affects the apparent thermodynamic parameters that are dependent on the sodium concentration. Obviously, these effects are much more important in the presence of high sodium concentrations (e.g., in buffered solutions), and conclusions derived from that experimental data can be seriously affected.

In additions to competitive effects observed in the presence of metal ions, the formation of ternary complexes between SC4, selected organic guests, and transition metal ions was observed both in solution and in the solid state.[27−29] This behavior presents a parallelism with another feature of SC4: its ability to shift the pK_a of complexed guest molecules.[30] While pK_a shifts are expected due to the ability of this host molecule to preferentially stabilize cationic over neutral forms, the formation of ternary complexes with Lewis acids is more subtle due to the larger size of the cation and geometric requirements for metal–ligand bond formation. In fact, it was demonstrated that the successful formation of such ternary complexes strongly depends on the structure of the guest and on the nature of the metal cation leading to a subtle and interesting interplay between cooperative and competitive binding.[27] Such requirements imply that the formation of the ternary complexes should proceed with high selectivity and, therefore, present high potential to improve the binding ability of SC4 and its applications in catalysis, sensing, and supramolecular self-assembled materials and devices.

In this work, we report the results of a thermodynamic study on the influence of sodium and copper–metal ions on the complexation of a water-soluble calixarene with a selected neutral guest molecule in aqueous solution (Scheme 1). The results present evidence for the formation of ternary complexes in both cases, and a detailed mechanistic model is proposed.

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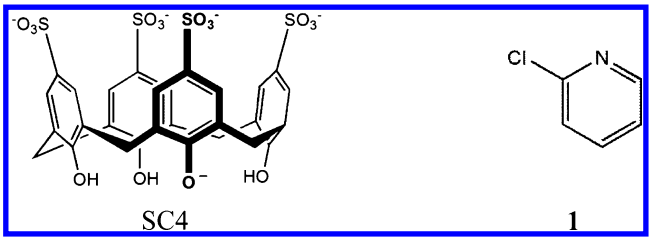
Scheme 1. Structure of *p*-Sulfonatocalix[4]arene and 2-Chloropyridine Guest (1)



RESULTS AND DISCUSSION

2-Cloropyridine **1** was selected as a guest to study the influence of different ions in the host–guest complexation due to its sufficient water solubility to obtain direct information on the binding constant by ITC and ^{1}H NMR experiments but also due its low basicity (pK_a = 0.72),[31] which is sufficiently low to avoid pK_a displacements upon complexation with SC4 in neutral aqueous solution.[30] The apparent binding constant for the 1:1 complex was determined by ITC experiments, and a value for K_{obs} = 175 M^{-1} was obtained (Figure 1). The results

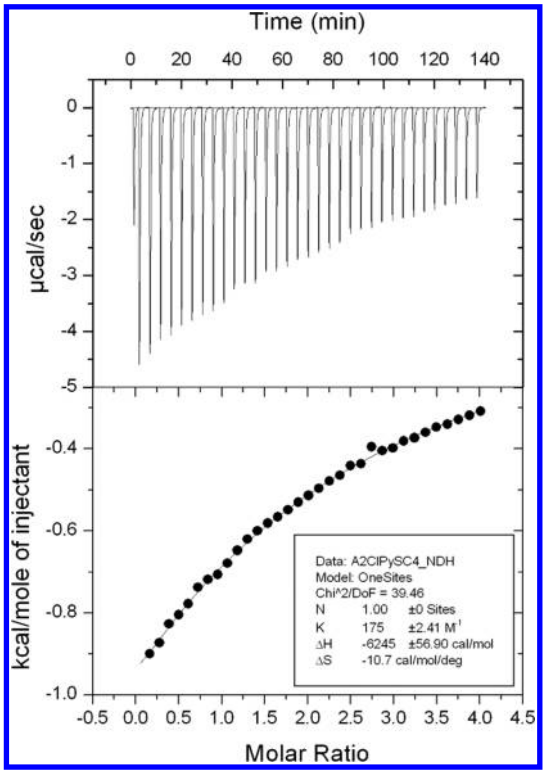


Figure 1. Microcalorimetric titration of **1** with SC4 at 298.15 K: (top) raw data for the sequential 34 injections (8 μL per injection) of **1** solution (20 mM) into SC4 solution (1 mM); (bottom) heat of reaction obtained from the integration of the calorimetric trace after subtracting the dilution heat from the reaction heat and fitted with "one set of binding sites" model at 25 °C.

show that intermolecular complexation between **1** and SC4 is enthalpy-driven accompanied by a negative entropy change, in line with the results obtained for the complex formation at pH 2.0.[7] However, comparing the binding constant for the complex formation obtained at different pH, the value obtained in neutral conditions is about 10-fold lower. This difference is related with the stronger binding abilities at pH 2.0 than at pH 7.0 and is in line with values obtained for others pyridine guests.[3]

^{1}H NMR spectrum of guest **1** in the presence of SC4 (Figure 2) shows upfield single resonances due to fast exchange on the NMR time scale between the free and complexed guest.[2] The absolute value of the complexation-induced chemical shifts increases in the order H4 > H5 > H3 > H6, indicating that the guest molecule should be incorporated into the SC4 cavity by the H4 position, with the N atom located at the upper rim, as also observed at pH 2.0.[7] This structure may enable the formation of ternary complexes with metal ions since the position of the N atom is correctly positioned to allow metal–ligand interactions with cations placed near the sulfonato groups.[27] Therefore, it was decided to investigate the influence of sodium and copper cations in the formation of complexes between **1** and SC4.

We have recently reported the influence of sodium cations, which are always present in aqueous neutral solution as a counterion of SC4, in the complexation of a quaternary ammonium ion by the macrocycle.[25] It was concluded that, in order to obtain the intrinsic binding constant of the guest molecule, a competitive binding model must be employed. In this work, a neutral guest was selected and therefore possible electrostatic repulsions between the positively charged ion and guest molecule are minimized. In fact, as commented above, the particular configuration of the binary complex may allow attractive metal–ligand interactions between the organic guest and the cation.

Figure 3 shows the influence of sodium ions in the complexation of **1** by SC4 in neutral aqueous solution carried out by ITC and fitted with the "one set of binding sites" model (see Supporting Information). As can be observed, the binding constants decrease as the concentration of Na$^+$ increases, suggesting a competitive binding phenomena as previously reported for quaternary ammonium cation.[25] However, Figure 3 (right) shows a plot of the inverse of K_{obs} against NaCl concentration, where the absence of a linear dependence puts into evidence that the competitive model does not apply in the present case.[25] Simulation of K_{obs} assuming a competitive binding model (dashed curve in Figure 3) shows that, contrary to what is observed, K_{obs} should approach zero at high NaCl concentrations in spite of the comparable binding affinities of the two guests (**1** and Na$^+$). In this way, an alternative binding model that accounts for the formation of a ternary complex between SC4, Na$^+$, and **1** was proposed (Scheme 2).

According to this scheme, it can be shown that the observed binding constant is given by

$$K_{obs} = \frac{K_1 + K_1 K_{T1}[Na^+]_0}{1 + K_{Na}[Na^+]_0} \quad (1)$$

Moreover, due to the cyclic nature of Scheme 2, K_{T2} can be calculated according to the following relation:

$$K_{T2} = \frac{K_{T1} K_1}{K_{Na}} \quad (2)$$

Fitting the experimental data to eq 1 yields the following binding constants K_1 = 268 ± 25 M^{-1}, K_{T1} = 54 ± 6 M^{-1}, and K_{T2} = 80 ± 14 M^{-1} while K_{Na} was kept constant and equal to 183 M^{-1} in order to obtain more reliable values for the previous binding constants.[26] While K_{T1} measures the affinity of Na$^+$ for the binary **1**@SC4 complex, K_{T2} measures the affinity of **1** for Na@SC4. As can be observed, the obtained values are lower

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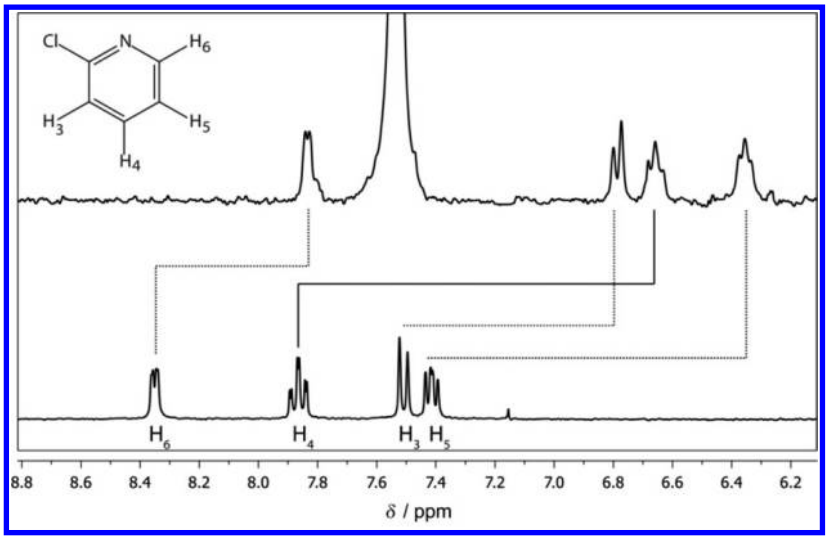


Figure 2. ^{1}H NMR spectra of **1** (1 mM) in D_2O at 25 °C: (bottom) in absence of SC4, (top) in the presence of 2.5 mM of SC4.

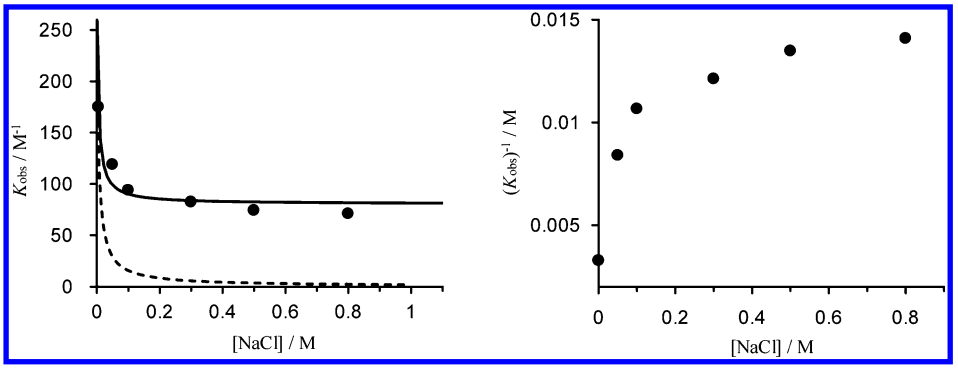
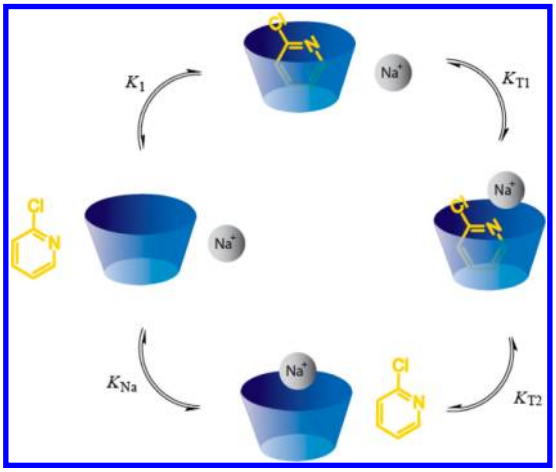


Figure 3. Influence of NaCl concentration in K_{obs} (left) and $1/K_{obs}$ (right) for the complex formation of **1** with SC4. The K_{obs} was obtained by microcalorimetric titration and fitted to the "one set of binding sites" model. The lines (left) represent the fit according to eq 1. The dashed line was calculated assuming a competitive binding model with K_{Na} = 180 M^{-1} and K_1 = 270 M^{-1}.

Scheme 2



than their counterparts for the formation of binary complexes, thus indicating negative cooperativity in contrast with the results obtained for the formation of ternary complexes with bicyclic azoalkane guests and transition metal ions.[27]

The complexation of nitrogen-containing guests with SC4 results in the preferential stabilization to the cationic guest−proton or guest−metal adducts, and as a consequence, the acid−base or metal−ligand equilibrium is displaced toward the formation of the adduct. However, in the present case, **1** does not interact with Na^+ in competitive aqueous solutions, and therefore, the formation of the ternary complex cannot be simply interpreted as a result of an equilibrium displacement but as the formation of a true ternary complex that only takes place within the cavity of SC4.

Despite the negative cooperativity observed for the present system, the molar fraction of the ternary complex in solution can be significant, especially in the presence of sodium-containing buffers or SC4 concentrations above the millimolar range. Figure 4 (left) shows the molar fraction distribution of binary and ternary complexes with increasing concentration of **1** in the presence of low Na^+ concentration (only as SC4 counterions) and in the presence of 0.1 M of Na^+ a concentration of sodium buffer commonly used in titrations involving SC4 as a macrocyclic host.[26] As can be observed, in the presence of low Na^+ concentration, the formation of the binary complex dominates, but in the presence of 0.1 M of Na^+, the main species formed is the ternary complex showing that the type of complexes can be switched by addition of sodium salts to the solution. It is also interesting to simulate the distribution of complexes when the concentration of the guest is kept constant and the concentration of SC4 varies. Because SC4 has five Na^+ counterions at neutral pH, the concentration of binary complex predominates at low SC4 concentration and the ternary complex predominates at high host concentration.

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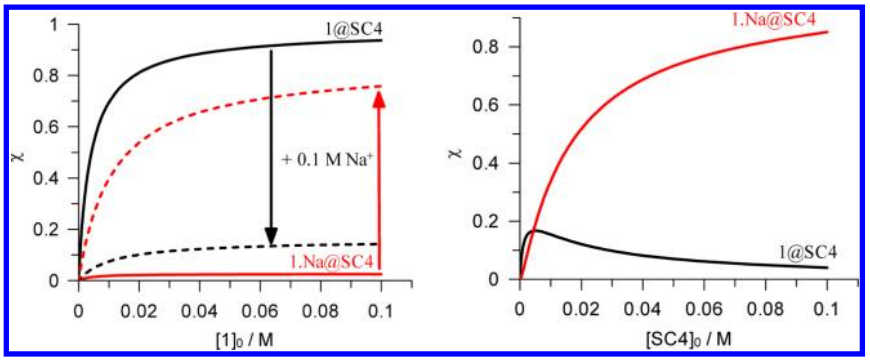

Figure 4. (Left) Molar fraction distribution of the **1**@SC4 (black) and **1**·Na@SC4 complexes (red) as a function of the concentration of **1** with 0.1 mM of SC4 and 0.5 mM of Na^+ (solid lines) and 100 mM Na^+ (dashed lines). (Right) Molar fraction distribution of **1**@SC4 (black) and **1**·Na@SC4 complexes (red) as a function of the concentration of SC4 with 1 mM of **1**.

Two-dimensional ROESY and ^{23}Na DOSY NMR experiments provide further evidence for the formation of the ternary complex. ROE cross peaks observed between the aromatic protons of SC4 and H3, H4, H5 protons of **1** (Figure 5) in the

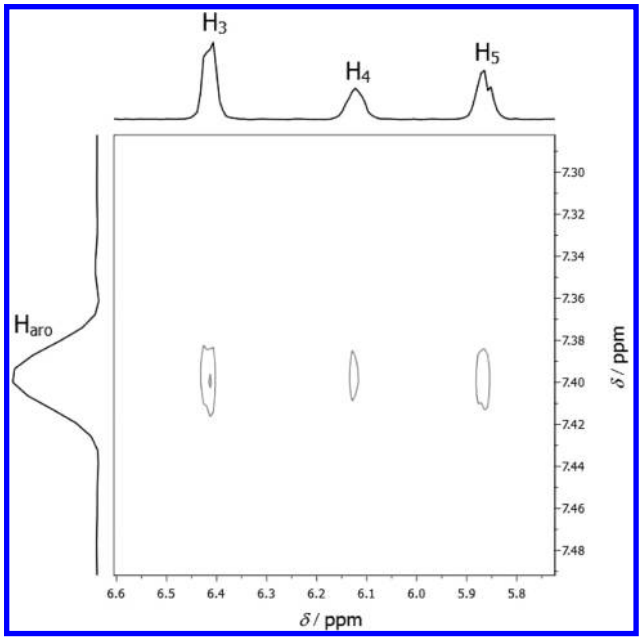

Figure 5. Two-dimensional ROESY NMR spectra of **1** (4 mM) with SC4 (8 mM) in the presence of 140 mM of Na^+ in D_2O with a mixing time of 500 ms at 25 °C.

presence of 140 mM of NaCl are consistent with the inclusion of **1** in the SC4 cavity and suggest that the guest is not competitively displaced to the bulk solution by Na^+ cations.

^{23}Na DOSY NMR experiments were used to obtain the diffusion coefficient of Na^+ cations (D_{obs}) in a solution containing 10 mM of SC4. In these conditions, about 88% of SC4 is complexed with Na^+ cations (assuming that K_{Na} = 183 M^{-1}). Figure 6 shows the influence of the addition of **1** in the D_{obs} of a solution containing 10 mM of SC4. The results previously obtained for benzyltrimethylammonium ion (BTA) are also plotted for comparison purposes.[25] As can be observed, the addition of increasing amounts of BTA leads to an increase in the D_{obs} to values close to that observed for free Na^+ in bulk solution, confirming that the alkali cation is displaced from the SC4 cavity to the bulk due to the competitive complexation of BTA. In the case of **1**, the D_{obs} reaches a plateau in value much

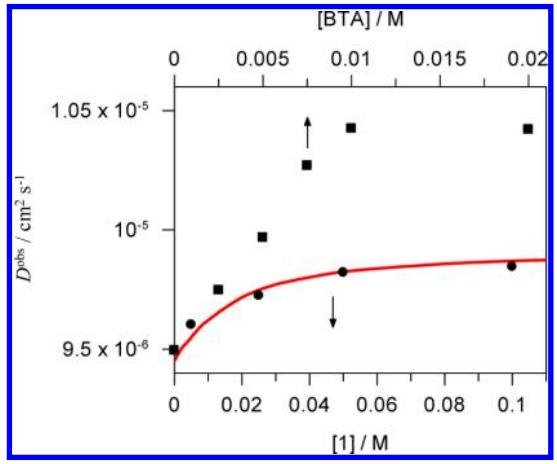

Figure 6. Influence of **1** (circles) and benzyltrimethylammonium ion (squares) (data from ref 16) in the diffusion coefficient of Na^+ for a solution of SC4 (10 mM) in D_2O at 25 °C. The solid red line represents the fitting to eq 3.

lower than what would be expected in the case of competitive binding. If D_{obs} is expressed by the mole fraction averaged of the diffusion coefficients of all sodium species (eq 3)[32] and, as an approximation, the diffusion coefficient of the complexes Na@SC4 and **1**·Na@SC4 are considered to be similar to that of SC4 (D_{SC4}), eq 3 can be used to fit the data presented in Figure 6. Using this procedure, values of $D_{SC4} = 0.34 \times 10^{-5}$ $cm^2\ s^{-1}$ and $D_{Na} = 1.09 \times 10^{-5}$ $cm^2\ s^{-1}$ were obtained, in good agreement with those previously reported and more importantly supporting the model proposed in Scheme 2 against the competitive binding model.[24]

$$D_{obs} = \chi^{free} D_{Na} + \chi^{Na@SC4} D_{Na@SC4} + \chi^{\mathbf{1}\cdot Na@SC4} D_{\mathbf{1}\cdot Na@SC4}$$
$$= \chi^{free} D_{Na} + (\chi^{Na@SC4} + \chi^{\mathbf{1}\cdot Na@SC4}) D_{SC4} \quad (3)$$

The addition of transition metal, such as Zn^{2+}, Co^{2+}, and Mn^{2+} to an inclusion complex formed between SC4 and bicyclic azoalkanes was already explored by Nau and coworkers.[27,28] The formation of interesting ternary complexes exhibiting positive cooperative binding behavior found in that approach and the negative cooperativity founded here with Na^+ cations, motivated the study of the binary system **1**@SC4 in the presence of a divalent transition metal cation. In this way, the influence of the addition **1** into SC4 was studied in the

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presence of Cu^{2+} cations by ITC (see Supporting Information for a representative titration curve).

Figure 7 shows the dependence of the apparent binding constant of **1** with SC4 against the concentration of Cu^{2+}. As

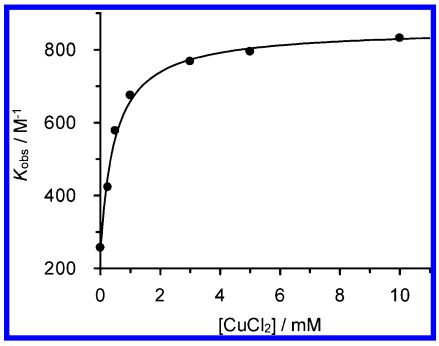
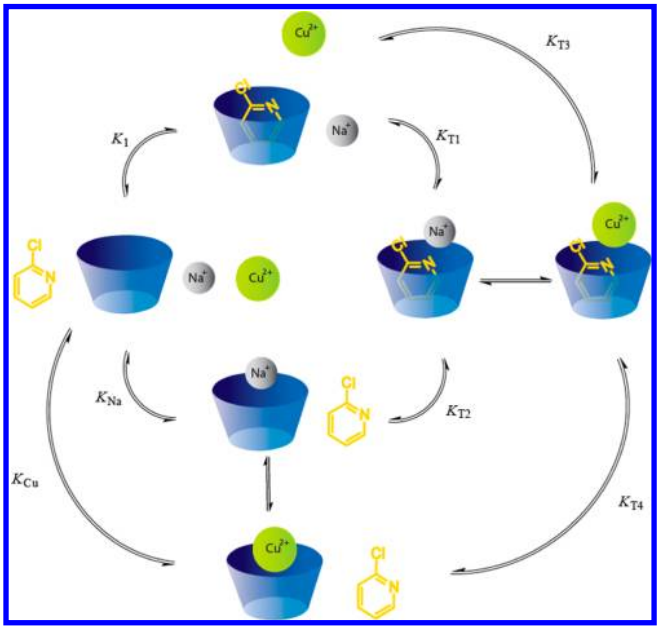


Figure 7. Dependence of the apparent binding constant with the concentration of $CuCl_2$. The K_{obs} was obtained by microcalorimetric titration and fitted to the "one set of binding sites" model. The line represents the fit according to eq 4.

can be observed, the presence of increasing concentrations of Cu^{2+} leads to an increase in the apparent binding constant. In order to exclude the possibility of **1**·Cu^{2+} complex formation as being responsible for this augment in the binding constant, control experiments were performed. The results revealed that the addition of the same metal ion to an aqueous solution of **1** did not give rise to a significant heat effect in the ITC experiments (see Supporting Information), which is in line with the complexation of other transition metal ions by bicyclic azoalkanes and suggests that the complex formation between **1** and Cu^{2+} cations has a very low binding constant.

In order to analyze the data in Figure 7, we propose a complexation model identical to Scheme 2, but adding Cu^{2+} complexes (Scheme 3). According to this scheme, the observed binding constant is given by eq 4:

Scheme 3



$$K_{obs} = \frac{K_1 + K_{Na}K_{T2}[Na]_0 + K_{Cu}K_{T4}[Cu]_0}{1 + K_{Na}[Na]_0 + K_{Cu}[Cu]_0} \quad (4)$$

Fitting K_{obs} data presented in Figure 7 with eq 4 allows the determination of K_{Cu} = 2500 M^{-1} (which compares with K_{Cu} = 5650 M^{-1} previously determined)[26] and K_{T4} = 860 M^{-1}, and from these two, K_{T3} = 7150 M^{-1}. These values indicate that **1** is more effectively complexed by SC4 in the presence of Cu^{2+} due to the formation of the metal−ligand bond in the ternary complex, as previous observed for bicyclic azoalkanes.[27,28] This is in contrast with behavior observed for Na^+, where the formation of the ternary complex is less favored in comparison with the respective binary complexes as a result of the very low **1**·Na^+ interactions that are not effective enough to overcome the repulsive interactions associated with the formation of the ternary complex.

Scheme 3 is an interesting example of a small dynamic library of five different complexes that can be pushed toward the selective formation of one species by adjusting the concentration of the reactants. In order to analyze the phenomena with more clarity, the molar fraction of the complexes can be simulated using a numerical procedure (see Supporting Information). As can be observed in Figure 8, when SC4 is titrated with **1** in the presence of 5 mM of Cu^{2+}, the ternary **1**·Cu@SC4 complex is the main species formed, demonstrating that under appropriate conditions high selectivity can be obtained. However, the reverse experiment, where **1** is titrated with SC4, shows a completely different picture. In this case, because the concentration of sodium cations changes with the concentration of SC4, the **1**·Cu@SC4 complex predominates for low SC4 (and therefore low Na^+) concentration reaching a maximum value. After this point, the **1**·Cu@SC4 concentration decreases due to the augment of Na^+ in solution and the equilibrium shifts toward the formation of the **1**·Na@SC4 complex due to the Na^+−Cu^{2+} ionic exchange process. It is important to stress that simple competitive Na^+ effect does not account for this product distribution. To give an example, this behavior can have important implications in envisaged catalytic applications since under these conditions a maximum catalytic activity could be expected at ca. 6 mM of SC4, and above this concentration, autoinhibition due to the Na^+−Cu^{2+} exchange could be expected. Taking inspiration from metalloenzymatic systems, combinations of transition metal ions and water-soluble macrocyclic hosts, such as calixarenes, cyclodextrins, and cucurbiturils, are frequently used to accelerate, catalyze, and/or alter the product distribution of organic reactions.[33−36] We believe that the mechanistic model present here and its implications can be expanded to other systems and, therefore, help in their interpretation and optimization.

CONCLUSIONS

In conclusion, NMR and ITC techniques have been employed to demonstrate the ability of SC4 to form ternary complexes comprising a suitable organic guest and inorganic cations, and a quantitative complexation model was proposed. While the formation of ternary complexes was previously described for divalent metal cations, their occurrence with Na^+ cations was not reported before. In contrast with Cu^{2+}, the formation of Na^+ ternary complexes presents negative cooperativity probably due to the absence of significant stabilization by metal−ligand bond. Despite the observed negative cooperativity, the results presented here are of special importance due to the omnipresence of Na^+ cations in SC4 solutions. Therefore,

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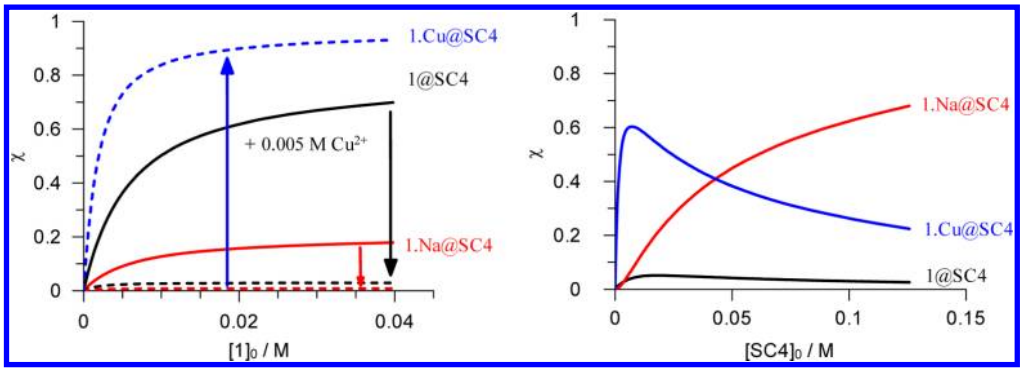

Figure 8. (Left) Molar fraction distribution of the **1**@SC4 (black), **1**·Na@SC4 complexes (red), and **1**·Cu@SC4 (blue) as a function of the concentration of **1** with 1 mM of SC4 and 5 mM of Na^+ (solid lines) and the same conditions upon addition of 5 mM Cu^{2+} (dashed lines). (Right) Molar fraction distribution of **1**@SC4 (black), **1**·Na@SC4 (red), and **1**·Cu@SC4 (blue) complexes as a function of the concentration of SC4 with 1 mM of **1** and 5 mM of Cu^{2+}.

and in addition to competitive binding, the possibility of ternary complex formation should also be considered in future studies concerning the complexation of organic guests with SC4.

EXPERIMENTAL SECTION

NaCl from Fluka (assay ≥99.5%), $CuCl_2{\cdot}2H_2O$ (assay ≥99%), and 2-chloropyridine (assay ≥99%) from Sigma-Aldrich were used without further purification. *p*-Sulfonatocalix[4]arene (SC4) was prepared using a procedure described in a previous work.[25] All solutions were prepared with Mili-Q water.

Microcalorimetry. The microcalorimetric titrations were performed on an isothermal titration microcalorimeter (VP-ITC) from Microcal Co. (Northampton, MA) at atmospheric pressure and 25 °C. In each run, a solution of guest in a 0.270 mL syringe was sequentially injected with stirring at 459 rpm into a solution of host in the sample cell (1.459 mL volume). Each solution was degassed and thermostated by using a ThermoVac accessory before titration. In each titration, the reference cell was filled with the same sample as in the sample cell.

NMR Spectroscopy. ^{1}H NMR spectra were recorded in a 300 MHz instrument while 2D NOESY (nuclear Overhauser effect spectroscopy) was obtained in a 500 MHz instrument. DOSY NMR spectra were recorded at 25 °C on a Varian Inova 500 spectrometer by using DSS as an external reference and equipped with a 5 mm 1H/X indirect probe with Z-shielded gradients. The NMR experiments were processed with MestreC v.3.9 software (Mestrelab Inc.). ^{1}H and ^{23}Na diffusion spectra were acquired with the Hahn spin−echo based PGSE pulse sequences.[37] In both cases, rectangular shaped pulsed gradients (G) were applied with a power level linearly incremented from 4 to 65 G cm^{-1} in 32 steps. The duration of the pulse field gradients (δ) applied to encode and decode the diffusion was set to 1 ms for ^{1}H and 3 ms for ^{23}Na. The diffusion delay period Δ of the experiment was optimized to 100 ms for ^{1}H and 40 ms for ^{23}Na. Such an optimized Δ value provided a convenient sampling of the exponential decay of the signal intensity during the diffusion experiment, and this was essential to achieve accurate results for the determined diffusion coefficients.[38] Calibration of the absolute gradient strength was provided by the spectrometer, and the particular probe was calibrated with the actual diffusion pulse sequence by using a compound of known diffusion as a reference. The reference sample for the ^{1}H diffusion experiments was 99% D_2O at 25 °C (D) 1.87 × 10^{-5} cm^2 s^{-1}) and for the ^{23}Na diffusion experiments was 2 M NaCl solution in 10% D_2O in H_2O at 25 °C (D = 1.14 × 10^{-5} cm^2 s^{-1}). As expected, both reference samples provided the same gradient strength with an error of less than 1%.

ASSOCIATED CONTENT

Supporting Information

NMR spectra, representative microcalorimetric titrations, and numerical procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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