Lanthanide(III) nitrobenzenesulfonates and *p*-toluenesulfonate complexes of lanthanide(III), iron(III), and copper(II) as novel catalysts for the formation of calix[4]resorcinarene

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Abstract—Lanthanide(III) salts of *p*-toluenesulfonic acid [lanthanide(III) tosylates, Ln(TOS)$_3$] and nitrobenzenesulfonic acid [Ln(NBSA)$_3$], and *p*-toluenesulfonate complexes of iron(III) and copper(II) were prepared, characterized, and examined as catalysts for the synthesis of resorcinol-derived calix[4]resorcinarenes. The reaction of resorcinol with benzaldehyde yields two isomers, the all-cis isomer (rccc) and the cis-trans-trans isomer (rctt) with the relative isomer ratios depending on the reaction conditions. However, in the reaction of resorcinol with octanal only one isomer, the all-cis isomer, is formed in high yields with less than 0.1 mol % of Yb(TOS)$_3$. Examination of lanthanide(III) tosylates and lanthanide(III) nitrobenzenesulfonates revealed that ytterbium(III) 4-nitrobenzenesulfonate [ytterbium(III) nosylate, Yb(4-NBSA)$_3$] and ytterbium(III) 2,4-dinitrobenzenesulfonate [Yb(2,4-NBSA)$_3$] are the most active catalysts. The catalysts could be easily recovered and reused several times for resorcinarene formation without loss of efficiency. Surprisingly good results were also obtained with iron(III) and copper(II) *p*-toluenesulfonates. Besides optimizing the reaction conditions, new insights into the reaction mechanism were also obtained.
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1. Introduction

Adolf von Baeyer reported already in 1872 that the addition of concentrated sulfuric acid to a mixture of benzaldehyde and resorcinol gave a red-colored product.[1] In 1968, Erdtman finally proved the cyclic tetrameric structure of these condensation products by single crystal X-ray diffraction analysis.[2] As the official IUPAC name of this type of compounds is very complicated, they are commonly called *calixarenes*, referring to the resemblance of the shape of one of the conformers to a type of Greek vase called a calix crater.[3]

Calix[4]resorcinarenes (resorcinarenes), the resorcinol-derived calixarenes, are versatile host compounds for ions, sugars, and organic molecules. Therefore they serve as starting materials for a variety of cavitands and other macrocyclic host compounds.[4] They have also found application as stationary phases in HPLC.[5] Furthermore, they can exhibit liquid-crystalline behavior by appropriate choice of the R groups on the resorcinarene.[6] Resorcinarenes are traditionally prepared by the mineral acid-catalyzed condensation of resorcinol with an aliphatic or aromatic aldehyde.[7]

However, this synthetic procedure requires the use of large quantities of acid, leading to excessive waste streams that are environmentally unfriendly and expensive to deal with. A solvent-free synthesis of resorcinarenes using *p*-toluenesulfonic acid as the catalyst has also been reported.[8] In addition, some conventional Lewis acids like BF$_3$·OEt$_2$, AlCl$_3$, and SnCl$_4$ have been used in the synthesis of aromatic aldehyde-derived resorcinarenes.[9] Although these Lewis acids are usually efficient catalysts, they have several drawbacks: they need to be used in at least stoichiometric amounts, they are easily deactivated by water, and they cannot be recycled or reused. More recently, trifluoromethanesulfonate salts, the so-called triflates, such as ytterbium(III) triflate[10] and bismuth(III) triflate,[11] have been described as efficient catalysts for the synthesis of calix[4]resorcinarenes. An important property of triflate catalysts is their compatibility with water and other protic solvents. After work-up, the catalysts can easily be recycled and reused without significant loss of activity. However, the triflate salts have some major disadvantages including their relatively high cost and the fact that one needs to handle for their preparation the highly corrosive triflic acid.

In a pursuit of lanthanide(III) catalysts, which do not require the use of hazardous or costly compounds, we recently examined lanthanide(III) salts of non-corrosive aromatic

sulfonic acids, such as *p*-toluenesulfonic acid and nitrobenzenesulfonic acids as catalysts for the nitration of aromatic compounds[12–14] and for the acylation of alcohols.[15] The aromatic sulfonic acids are much weaker acids than triflic acid (*p*-toluenesulfonic acid is, for example, about 10^6 times weaker acid than triflic acid),[16] and therefore their complexes with lanthanides are expected to be significantly weaker Lewis acids than the lanthanide(III) triflates. However, our recent studies revealed that their catalytic efficiency was comparable to that of the triflate salts.[12–15] This prompted us to further exploit the inexpensive and convenient lanthanide(III) tosylates and lanthanide(III) nitrobenzenesulfonates as alternatives for the lanthanide(III) triflates. In this study we demonstrate that lanthanide(III) tosylates and lanthanide(III) nitrobenzenesulfonates can be used as efficient, inexpensive, recyclable, and environmentally friendly catalysts for the synthesis of calix[4]resorcinarenes. In addition, we demonstrate that copper(II) and iron(II) complexes of *p*-toluenesulfonic acid also efficiently catalyze formation of calixarenes.

2. Results and discussion

2.1. Synthesis and characterization of the catalysts

Lanthanide(III) salts of *p*-toluenesulfonic acid, [Ln(TOS)$_3$] with Ln=Yb, La, Nd, Gd, Y, 3-nitrobenzenesulfonic acid, [Yb(3-NBSA)$_3$], 4-nitrobenzenesulfonic acid, [Yb-(4-NBSA)$_3$], and 2,4-dinitrobenzenesulfonic acid, [Yb-(2,4-NBSA)$_3$], (Scheme 1) were prepared by reaction of the acid with the corresponding lanthanide(III) oxide.
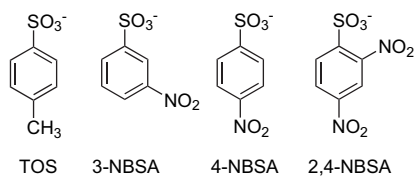
Scheme 1. Aromatic sulfonates used as counterions for lanthanide(III) catalysts.

Single crystal studies of lanthanide(III) tosylates showed that with the exception of the La(III) complex, in which nine water molecules are found in the first coordination sphere, in most of the other lanthanides two tosylate anions

and six water molecules occupy the first coordination sphere, while the third tosylate anion appears in the second coordination sphere.[17] Structural studies on copper(II) tosylate revealed that this complex crystallizes with six molecules of water in the first coordination sphere.[17] To the best of our knowledge, the crystal structure of iron(III) tosylate is not known, but studies on iron(II) tosylate indicate that three tosylate ions bind to iron(II) in a bidentate fashion.[17] Comparison of infrared spectra of iron(II) tosylate and iron(III) tosylate, implied that iron(III) is also six-coordinated by three tosylate anions.

The elemental analysis results of the investigated complexes (see Section 4) indicated that upon drying the crystalline solid at 50 °C in vacuo, some water molecules of crystallization are lost, but the complexes still contain one to four molecules of water. Consequently, infrared spectral data of the complexes showed strong and broad absorption in the region between 3200 and 3600 cm^{-1}, corresponding to the –OH stretching of water molecules.

Since it is known that *p*-toluenesulfonic acid itself is a good catalyst for the formation of calixarenes,[8] it is important to demonstrate the absence of trace amounts of free acid in the lanthanide(III) catalyst. The infrared spectra of lanthanide(III) complexes showed that the broad infrared absorption band between 2400 and 3100 cm^{-1}, typical for the OH stretching mode of protonated benzenesulfonic acid,[18] was absent in all cases. Furthermore, the aqueous solution of lanthanide(III) complexes always had a close-to-neutral pH (pH≈6), which further confirms the absence of free *p*-toluenesulfonic or nitrobenzenesulfonic acid in the isolated lanthanide(III) salts. The absence of free *p*-toluenesulfonic acid in Fe(TOS)$_3$ and Cu(TOS)$_2$ was also confirmed by similar method.

2.2. Formation of resorcinarenes

Herein we report the formation of calix[4]resorcinarenes through lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed condensation of resorcinol with an aromatic or an aliphatic aldehyde (Scheme 2). During this reaction, only the tetrameric resorcinarene and water are formed. The tetrameric nature of the compounds was confirmed by mass-spectrometric analysis. Of the four diastereoisomers formed, we observed the all-cis (rccc) isomer (**3a**) and the cis-trans-trans (rctt) isomer (**4a**) in the reactions with benzaldehyde, with a relative ratio depending on the reaction
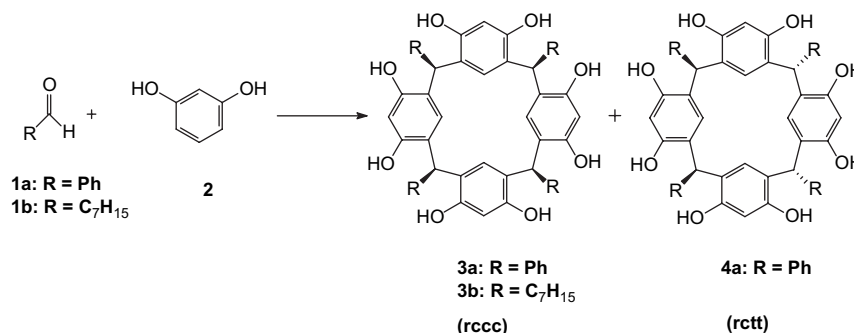
Scheme 2. Formation of calix[4]resorcinarene through lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed condensation of resorcinol with an aromatic or an aliphatic aldehyde.

conditions used. Only in the case of short reaction times (4 h or less) or low catalyst concentration (0.1 mol %), a small amount of a third product is formed. Based on the NMR data this product is likely one of the other possible isomers, however, the exact structure of the product was not further investigated. In the reactions with octanal only the all-cis isomer (**3b**) is formed, although after shorter reaction times, usually 4–12 h, a small amount of a less thermodynamically stable isomer could also be formed. The configuration of the isomers has previously been determined by X-ray diffraction analysis and our NMR spectra are in agreement with the literature data.[4c,19] Although the use of an inert atmosphere is frequently recommended for the formation of resorcinarenes, our experiments indicate that there is no difference in yields or isomer distribution in the reactions performed under argon, nitrogen or in the air atmosphere. Therefore, the reactions can be performed in a simple reflux setup, open to the air.

2.3. Influence of the lanthanide ion

In order to find the most suitable lanthanide(III) ion for the calix[4]resorcinarene formation, a range of lanthanide(III) tosylates were examined as potential catalysts. As can be seen in Table 1, only small differences in yield and isomer distribution are observed for the reaction with benzaldehyde using different lanthanide(III) tosylates. While 93% of resorcinarene is formed after 24 h by using 5 mol % of Yb(TOS)$_3$, and 84% of resorcinarene is formed when using La(TOS)$_3$. In contrast, surprisingly large differences are observed for the reaction with octanal. The use of Yb(TOS)$_3$ leads to 92% of resorcinarene, while only 11% of the product is formed when using La(TOS)$_3$ as the catalyst. This trend over the lanthanide series is consistent with our previous studies involving lanthanide(III) tosylates in the acetylation of alcohols.[15] Solution studies have shown that the solid-state structure, which shows clear structural differences across the lanthanide(III) series,[17,20] was not preserved in acetic acid. In strongly coordinating solvents, such as water, the structures of all lanthanide(III) tosylates are the same since the coordinating solvent displaces the tosylate ligands from the first coordination sphere.[21] Ethanol coordinates strongly enough to the lanthanide ion to displace the tosylate ligands to the second coordination sphere, so that the first coordination sphere around the lanthanide(III) is occupied by ethanol molecules only. In this case, a smaller ionic radius of trivalent lanthanide ion leads to a larger charge-to-size ratio, Z/r, which in turn results in a stronger polarizing power of the lanthanide(III) center, a stronger Lewis acidity, and hence higher reaction yields.

Table 1. Effect of the lanthanide(III) ion on the formation of calix[4]resorcinarene[a]

Ln ion	Benzaldehyde		Octanal
	Yield (%)	rccc:rctt (%)	Yield (%)
La	84	38:62	11
Gd	81	36:64	30
Yb	93	42:58	92
Y	84	33:67	75

[a] Lanthanide(III) *p*-toluenesulfonate (5 mol %), after 24 h, at reflux temperature.

2.4. Influence of the reaction time

Since the screening of the different lanthanide(III) tosylates revealed that the ytterbium(III) complexes are the most powerful catalysts in the lanthanide(III) series, ytterbium(III) nitrobenzenesulfonates were examined as catalysts for the formation of resorcinarenes with benzaldehyde or octanal. When performing the condensation reaction of resorcinol with octanal in the presence of 2 mol % of ytterbium(III) tosylate or nosylate (abbreviation for 4-nitrobenzenesulfonate), the yields are 93–95% after 24 h. The yields and isomer distributions in the reaction of benzaldehyde using ytterbium(III) 3-nitrobenzenesulfonate [Yb(3-NBSA)$_3$], ytterbium(III) 4-nitrobenzenesulfonate [Yb(4-NBSA)$_3$], and ytterbium(III) 2,4-dinitrobenzenesulfonate [Yb(2,4-NBSA)$_3$] are summarized in Table 2. Only minor differences in total yield are observed for the different catalysts. As can be seen in Table 2 and Figure 1, after a certain time the largest amount of rccc isomer is formed when using Yb(4-NBSA)$_3$. Furthermore, the amount of rccc isomer can be increased by increasing the reaction time. This is consistent with the previous findings in which Yb(OTf)$_3$ was used as the catalyst,[10] although this catalyst more efficiently catalyzed the formation of the pure rccc isomer.

Table 2. Effect of the counterion (tosylate and nitrobenzenesulfonate) in function of time on the ytterbium(III) catalyzed formation of resorcinarenes with benzaldehyde[a]

Time (h)	Yield (rccc:rctt) (%)			
	TOS	3-NBSA	4-NBSA	2,4-NBSA
4	90 (32:68)	80 (40:60)	68 (46:54)	86 (40:60)
24	93 (42:58)	87 (45:55)	>98 (61:39)	92 (45:55)
48	95 (51:49)	89 (47:53)	>98 (73:27)	>98 (57:43)
96	96 (64:36)	90 (64:36)	>98 (86:14)	>98 (70:30)
216	96 (86:14)	95 (65:35)	>98 (96:4)	>98 (72:28)

[a] Yb catalyst (5 mol %), at reflux temperature; TOS=*p*-toluenesulfonate, 3-NBSA=3-nitrobenzenesulfonate, 4-NBSA=4-nitrobenzenesulfonate, 2,4-NBSA=2,4-dinitrobenzenesulfonate.
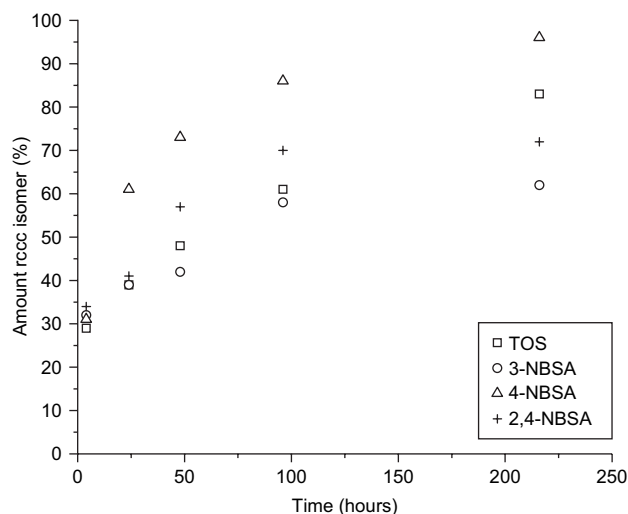
Figure 1. Amount of rccc isomer as a function of the time and the counterion. The amount of rccc (all-cis) isomer is monitored as a function of time for the formation of benzaldehyde-based resorcinarenes with ytterbium(III) catalysts.

2.5. Effects of temperature and catalyst loading on the extent of resorcinarene formation

The influence of temperature was studied for the reactions with benzaldehyde and octanal. For the reaction with octanal we could not isolate any resorcinarene when the reaction was performed at room temperature or at 50 °C. However, the reaction with benzaldehyde resulted in resorcinarene formation at room temperature, although with lower yields and less rccc isomer formed. Reaction for 48 h at room temperature leads to 80% of yield with 36% of rccc isomer. In order to further optimize the reaction conditions, we also studied the effect of catalyst amount on both condensation reactions. As can be seen from Table 3, good yields are achieved by using only 0.1 mol % Yb(TOS)$_3$. However, in the reaction of benzaldehyde a small amount of a third isomer was formed when less than 0.1 mol % of Yb(TOS)$_3$ was used. For the condensation with benzaldehyde, an increase to 5 mol % of Yb(TOS)$_3$ resulted also in a larger amount of rccc isomer, but in this case the total yield and amount of rccc isomer are almost not improved when increasing the catalyst load to 10 mol %. Furthermore, in the reaction of octanal with resorcinol, 84% of resorcinarene was formed after 24 h by using 0.1 mol % of Yb(TOS)$_3$ while no resorcinarene could be isolated without using a catalyst. The use of higher catalytic amounts leads to a slight increase in yield: 92% by using 5 mol % under the same reaction conditions.

Table 3. The effect of the ytterbium(III) tosylate loading on the formation of resorcinarenes with benzaldehyde and octanal[a]

Catalyst load (mol %)	Benzaldehyde		Octanal
	Yield (%)	rccc:rctt (%)	Yield (%)
None	2	n.d.	0
0.1	71	32:68	84
1	88	33:67	86
2	88	34:66	92
5	93	42:58	92

[a] After 24 h, at reflux temperature.

2.6. Recovery and reuse of the lanthanide(III) catalyst

After quenching the reaction mixture with water, the resorcinarene was filtered off and washed with water. The catalysts could be easily recovered from the filtrate by evaporating the water under reduced pressure. The ^{1}H NMR spectrum of the recovered Yb(TOS)$_3$ showed a very small amount of impurity compared to the spectrum of the freshly prepared Yb(TOS)$_3$. But as can be seen in Table 4, the presence of this impurity—a few percent of unreacted resorcinol and octanal—has no negative influence on the reactivity of the catalyst in the subsequent runs. Due to this small amount of

Table 4. Recovery and reuse of ytterbium(III) tosylate after the reaction of resorcinol with octanal[a]

Run	Yield (%)	Recovered Yb(TOS)$_3$ (%)
1	95	>98
2	96	>98
3	94	>98

[a] After 24 h, at reflux temperature, the recovered amount of catalyst is each time compared to the initial 5 mol % of Yb(TOS)$_3$ used in the first run.

impurity the weight of the recovered catalyst is somewhat higher than the weight of catalyst used in the first run. In combination with the small catalyst loading required for quantitative reaction, we can conclude that this condensation reaction, catalyzed by lanthanide(III) tosylates and various nitrobenzenesulfonates, is a real catalytic system.

2.7. Use of transition metals and other acidic catalysts

Since copper(II) complexes with some sulfate ligands are also known to be good Lewis acid catalysts,[22] we set out to test the activity of several transition metal tosylates as catalysts for the formation of calixarenes. Iron(III) tosylate is commercially available at relatively low price and copper(II) tosylate was prepared following the procedure applied for the synthesis of lanthanide(III) tosylates. The reactions of resorcinol with octanal and benzaldehyde catalyzed by 5 mol % Cu(TOS)$_2$ and Fe(TOS)$_3$ are shown in Table 5. In all cases nearly quantitative conversion was obtained after 24 h of reaction. Furthermore, remarkably high amount of all-cis isomer was formed in the reaction with iron(III) tosylate. As a comparison, the reported reaction with 8 mol % of ytterbium(III) triflate achieves around 46% of all-cis isomer after 48 h of reaction. This exceptionally high amount of all-cis isomer can probably be explained by a strong Lewis acidity of iron(III) that results from its high charge-to-size ratio. Moreover, in the reaction of resorcinol with octanal the initial reaction rates are higher with copper(II) and iron(III) tosylate compared to lanthanide(III) tosylates. By using copper(II) and iron(III) tosylate 91–94% of resorcinarene was formed after 6 h of reaction while in the case of ytterbium(III) tosylate 18 h of reaction was necessary to obtain the same yield. Furthermore, these catalysts can also be recovered and reused.

The reaction yields obtained by using transition metal and lanthanide tosylates were compared with those when traditional mineral acid such as HCl was used. Nowadays the mineral acid HCl is used in equimolar amounts to promote the formation of resorcinarenes. We compared our results to the one obtained in the reaction of resorcinol with benzaldehyde or octanal in the presence of 500 μL of 37% HCl, which corresponds almost to an equimolar amount compared to the other reactants. As can be seen in Table 5, the reactions promoted by HCl are faster and in the reaction with benzaldehyde more all-cis isomer is formed. On the

Table 5. The effect of the metal ion and its counterion on the formation of calix[4]resorcinarene[a]

Catalyst	Benzaldehyde		Octanal
	Yield (%)	rccc:rctt (%)	Yield (%)
La(TOS)$_3$	84	38:62	11
Cu(TOS)$_3$	91	48:52	93
Fe(TOS)$_3$	95	73:27	96
Yb(TOS)$_3$	93	42:58	95
Yb(3-NBSA)$_3$	87	45:55	91
Yb(4-NBSA)$_3$	>98	61:39	96
Yb(2,4-NBSA)$_3$	>98	57:43	96
HCl[b]	>98/81[c]	100:0/60:40[c]	95

[a] Catalyst (5 mol %), after 24 h, at reflux temperature.
[b] Addition of equimolar amount of HCl.
[c] After 1 h.

other hand, tosylate complexes of transition metals and lanthanides are beneficial for several reasons: they are not required in stoichiometric amounts but in catalytic amounts as small as 0.1 mol % are sufficient, they can be easily recovered and reused several times without loss of activity, and hence they avoid the consumption of strong acids.

2.8. Postulated mechanism for the lanthanide(III) tosylate and nitrobenzenesulfonate catalyzed formation of calix[4]resorcinarenes

Barrett and co-workers proposed in their study on Yb(OTf)$_3$-catalyzed formation of resorcinarenes that once the resorcinarene is formed, it (reversibly) binds to Yb(OTf)$_3$, thus generating a complex, which liberates triflic acid, or is itself acidic enough to promote protodealkylation and hence isomerization.[10] Although the above work clearly demonstrates the Brønsted acid nature of the isomerization of resorcinarenes, it is not clear how the initial resorcinol–aldehyde bond formation is initiated.

We performed in situ infrared experiments to gain more insight into the initial interactions between the aldehyde and Yb(TOS)$_3$. Octanal could be monitored following the carbonyl absorption band at 1721 cm^{-1}. Unfortunately, it was not possible to follow the formation of resorcinarene with in situ infrared spectroscopy, since the vibration bands of the C–C bonds in the resorcinarene, such as, for example, the band at 1603 cm^{-1}, fall in the same region as the vibration bands of the C–C bonds in resorcinol, leading to strong overlapping. Figure 2 shows the most interesting part of recorded in situ infrared spectra, which shows the step-by-step addition of octanal, Yb(TOS)$_3$, and resorcinol to an ethanolic solution. By addition of 5 mol % of Yb(TOS)$_3$, the intensity of carbonyl absorption band of octanal at 1721 cm^{-1} strongly decreased. This cannot originate from a full coordination of ytterbium to octanal since Yb(TOS)$_3$ was present in only 5 mol %. Rather, Yb(TOS)$_3$-catalyzed acetal formation can be expected (Scheme 3, step A). The ability of Sc(OTf)$_3$ to catalyze the acetal formation at an early reaction stage has been described in the Friedel–Crafts alkylation of aromatics with arenecarbaldehydes in the presence of 1,3-propanediol.[23] Since the lanthanide(III) tosylates have

similar catalytic properties as triflate salts, it can be expected that tosylates also can catalyze the acetal formation in the presence of an excess of ethanol. Furthermore, a new absorption band that appeared at 1011 cm^{-1} is consistent with the C–O single bond absorption characteristic of acetals. The intensity of this absorption band increases upon addition of Yb(TOS)$_3$, consistent with the Yb(TOS)$_3$-catalyzed formation of the acetal.

The catalytic reaction followed by proton NMR spectroscopy was recorded in deuterated ethanol at 65 °C (Fig. 3). Addition of octanal to an ethanolic solution of resorcinol resulted in formation of a small peak around 4.5 ppm, consistent with acetal formation (Scheme 3, step A). Upon addition of 5 mol % of Yb(TOS)$_3$ the proton signal of the aldehyde group nearly completely disappeared while the signal around 4.5 ppm that can be attributed to the CH-proton of the acetal strongly increases. Furthermore, peaks of the remaining octanal are broadened upon addition of Yb(TOS)$_3$, which indicates coordination of the carbonyl group to paramagnetic ytterbium(III) ion (Scheme 3, step B). Unfortunately, it was not possible to follow the disappearance of acetal peak as the reaction proceeded, due to overlap with the peak of water that is formed in the course of reaction. The spectrum shown in Figure 3c corresponds to the reaction mixture after 11 h of reaction. As it can be seen in the aromatic NMR region at this stage of the reaction several calixarene isomers are formed, however, after 24 h of reaction only the all-cis isomer is present in solution.

In summary, the in situ infrared and proton NMR measurements established that lanthanide(III) tosylates and nosylates catalyze acetal formation in the reaction between the aldehyde and ethanol. Once the acetal is formed, the reaction proceeds similarly to the build-up sequence postulated by Weinelt and Schneider for the acid-catalyzed condensation reaction between resorcinol and acetaldehyde in methanol/HCl.[24] The acid-catalyzed condensation has frequently been interpreted in terms of cationic intermediates and electrophilic aromatic substitution,[3] but our experiments indicate that the lanthanide(III) catalyst is responsible for more than simple coordination to the aldehyde. In fact, if ethanol is used as a solvent, the lanthanide ion plays a dual
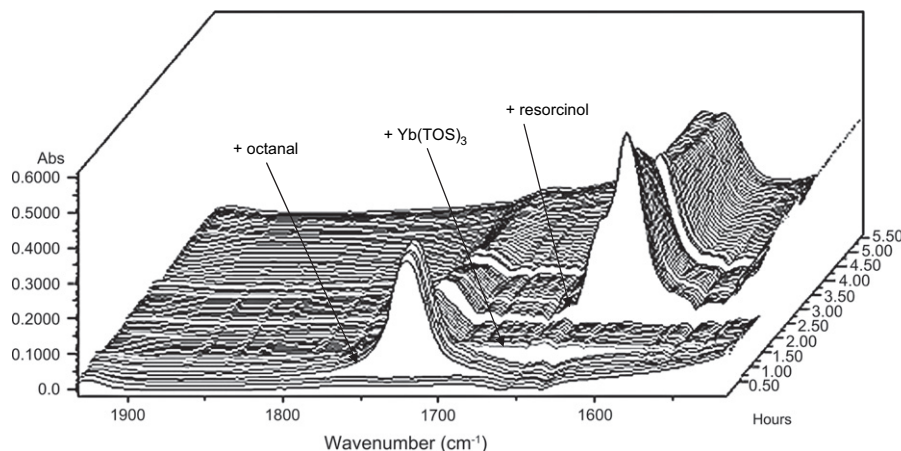
Figure 2. In situ infrared spectra of the Yb(TOS)$_3$-catalyzed reaction of octanal and resorcinol in the presence of an excess of ethanol. Only the part giving information on the initial interaction of Yb(TOS)$_3$ is depicted. At the addition of Yb(TOS)$_3$ catalyst, an immediate decrease in absorbance of the C=O absorption of octanal (1721 cm^{-1}) is observed.
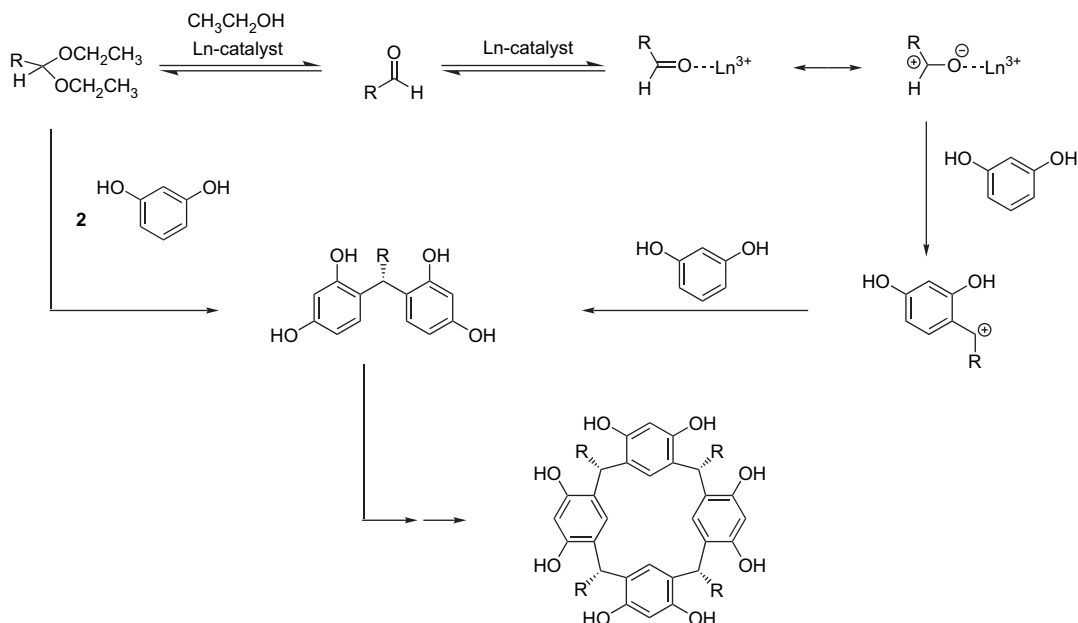
Scheme 3. Postulated mechanism for the lanthanide catalyzed formation of calix[4]resorcinarenes.
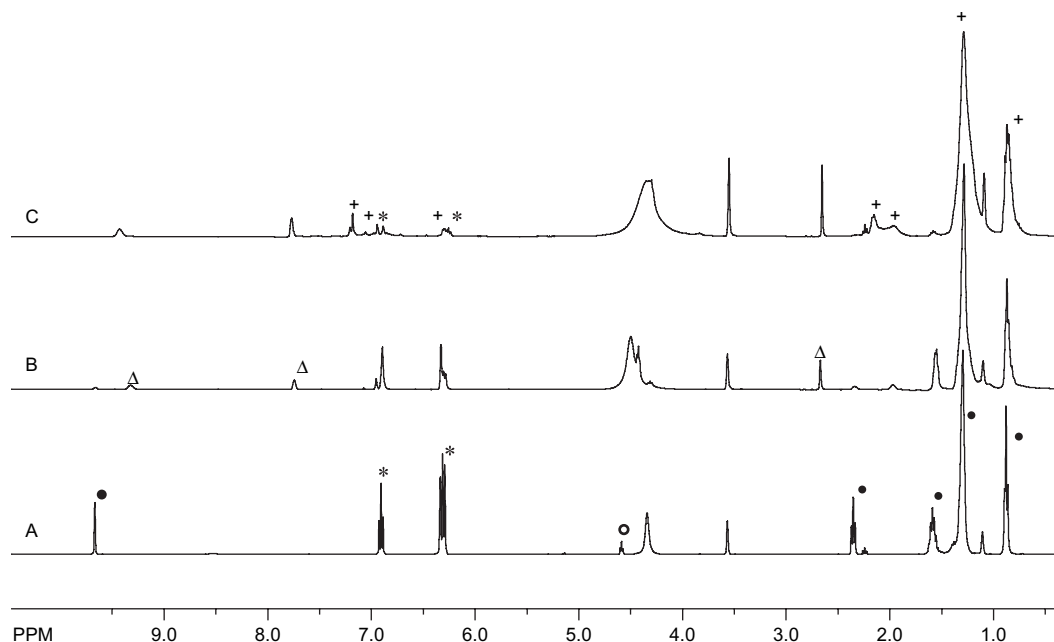
Figure 3. Proton NMR spectra of formation of calix[4]resorcinarenes at 65 °C. The peaks at 1.11, 3.57, and 4.40 ppm are due to ethanol and water (A): resorcinol (stars) and octanal (black circles) in CD_3CD_2OD result in formation of small amount of acetal (white circles), (B): after addition of 5 mol % of Yb(TOS)$_3$ (white triangles) more acetal is produced and, (C): after 11 h of reaction different isomers of calix[4]resorcinarene are present in the solution (plus signs).

role (Scheme 3). Most of the octanal is conversed to the acetal by lanthanide catalyzed acetal formation and the remaining octanal coordinates to the lanthanide ion to form a cationic electrophilic species, which attacks the resorcinol to form the calix[4]resorcinarene.

It is reasonable to assume that once some calix[4]resorcinarene is formed, it binds to the lanthanide(III) tosylate or nitrobenzenesulfonate in a way similar as proposed in the study on Yb(OTf)$_3$-catalyzed formation of resorcinarenes. Barrett and co-workers suggest that this complex liberates the

associated acid, or is itself acidic enough to promote protodealkylation and hence isomerization.[10] In order to determine whether the complex itself or the liberated acid catalyzes the isomerization, the following experiment was performed. Benzaldehyde-derived calix[4]resorcinarene (1 g) with a known isomer distribution was left to react with the respective catalyst in 10 mL of ethanol just beneath the reflux temperature. After 120 h, the calix[4]resorcinarene was isolated in the usual way and the isomer distribution was determined from the ^1H NMR spectrum. As can be seen in Table 6, the degree of isomerization strongly depends on

Table 6. Influence of the tosylate and nitrobenzenesulfonate counterion on the isomerization of all-cis calix[4]resorcinarene (rccc), formed from benzaldehyde and resorcinol, to cis-trans-trans calix[4]resorcinarene (rctt)[a]

Catalyst	rccc:rctt	pK_a of the acid
Yb(TOS)$_3$	45:55	−6.56
Yb(3-NBSA)$_3$	55:45	−7.25
Yb(4-NBSA)$_3$	55:45	−7.23
Yb(2,4-NBSA)$_3$	54:46	N.A.
Er(OTf)$_3$	71:29	≤−12

[a] Benzaldehyde-based calix[4]resorcinarene of 1 g (44% rccc, 56% rctt), 10 mol % of hydrated lanthanide catalyst, 10 mL ethanol, 120 h at reflux temperature.

the counterion. If the lanthanide-resorcinarene complex would itself promote protodealkylation we expect no difference between the various counterions. Moreover, during this experiment a clear decrease in pH was noticed. Thus, we can assume that the liberated acid catalyzes the isomerization and hence the extent of isomerization depends on the acidity of the respective sulfonic acid formed. Since *p*-toluenesulfonic acid (pK_a=−6.56),[16] *p*-nitrobenzenesulfonic acid (pK_a=−7.23), and *m*-nitrobenzenesulfonic acid (pK_a=−7.25)[25] are much weaker acids than triflic acid (pK_a< −12),[26] they do not really catalyze the isomerization of the all-cis isomer (rccc) to the cis-trans-trans isomer (rctt). As shown in Table 2 and Figure 1, the smallest amounts of rccc isomer was formed when using Yb(3-NBSA)$_3$ or Yb(2,4-NBSA)$_3$. The lower efficiency of these two catalysts may be contributed to the steric effect of the substituents on the aromatic ring, which may form more crowded environment around the lanthanide(III) ion.

As these latter experiments indicate that calixarene formation results in a lanthanide–calixarene complex with concomitant liberation of the associated Brønsted acid, it is evident that further formation of calixarene can also occur autocatalytically by this liberated acid. For comparison, the reaction between benzaldehyde and resorcinol was also carried out in the presence of 5 mol % of *p*-toluenesulfonic acid monohydrate and after 24 h of reflux in ethanol nearly complete conversion was obtained (83% rccc isomer and 17% rctt isomer).

3. Conclusions

We have demonstrated that lanthanide(III), copper(II), and iron(III) *p*-toluenesulfonates and the lanthanide(III) salts of nitrobenzenesulfonic acids are efficient catalysts for the condensation reaction of resorcinol with benzaldehyde or octanal to form calix[4]resorcinarenes. Moreover, in the reactions with benzaldehyde, the amount of each isomer can be tuned not only by varying the reaction time but also by appropriate choice of the metal ion. Although *p*-toluenesulfonic and nitrobenzenesulfonic acids are about 10^6 times weaker than triflic acid, their lanthanide(III) salts are strong Lewis acids, which are able to catalyze the formation of resorcinarenes. Good reaction yields are obtained after 24 h with only 0.1 mol % of catalyst. The initial formation of acetals as key intermediates has been confirmed. The use of *p*-toluenesulfonic acid and nitrobenzenesulfonic acids over triflic acid for the preparation of lanthanide(III)

catalysts is both environmentally and economically advantageous. These catalysts can easily be recovered after reaction and reused several times without loss of efficiency.

4. Experimental

4.1. Materials and methods

Reagents were obtained from Aldrich Chemical Co. Inc., Acros Organics or Rhodia Electronics and Catalysis, and were used without further purification. Iron(III) tosylate was purchased from Aldrich and copper(II) tosylate was prepared in the same way as the lanthanide(III) tosylates. ^{1}H NMR spectra were run on a Bruker Avance 300 spectrometer, operating at 300 MHz. Elemental analysis was performed on a CE Instruments EA-1110 elemental analyzer. Mass spectra were recorded on a Thermo Electron mass spectrometer, type LCQ, with an electrospray ionization source (ESI). In situ infrared spectra were obtained using a ReactIR 1000 IR (Applied Systems Inc., Mettler Toledo).

4.2. General procedure for the synthesis of Ln(TOS)$_3$ and Ln(NBSA)$_3$ complexes

The lanthanide(III) salts were synthesized by reaction of 1.1 equiv of the corresponding lanthanide(III) oxide and 6 equiv of *p*-toluenesulfonic acid in water. After stirring the solution in boiling water for 30 min, the excess of oxide was removed by filtration. The filtered solution was evaporated to dryness and the resulting solid was dried in a vacuum oven at 50 °C over night. Copper(II) tosylate was prepared from copper(II) oxide and *p*-toluenesulfonic acid and the lanthanide(III) nitrobenzenesulfonates are prepared in a similar way from the respective nitrobenzenesulfonic acid.

4.3. Elemental analysis results for Ln(TOS)$_3$·xH$_2$O and Ln(NBSA)$_3$·xH$_2$O

Yb(TOS)$_3$·H$_2$O (C$_{21}$H$_{23}$S$_3$O$_{10}$Yb) Calcd (found): C, 35.75 (35.63); H, 3.29 (3.69)%. Yb(3-NBSA)$_3$·2H$_2$O (C$_{18}$H$_{16}$S$_3$O$_{17}$N$_3$Yb) Calcd (found): C, 26.51 (26.47); H, 1.98 (2.06); N, 5.15 (5.41)%. Yb(4-NBSA)$_3$·3H$_2$O (C$_{18}$H$_{18}$S$_3$O$_{18}$N$_3$Yb) Calcd (found): C, 25.94 (25.57); H, 2.18 (2.34); N, 5.04 (5.52)%. Yb(2,4-NBSA)$_3$·4H$_2$O (C$_{18}$H$_{17}$S$_3$O$_{25}$N$_6$Yb) Calcd (found): C, 21.91 (21.52); H, 1.74 (1.65); N, 8.52 (8.57)%. La(TOS)$_3$·3H$_2$O (C$_{21}$H$_{27}$S$_3$O$_{12}$La) Calcd (found): C, 35.70 (35.68); H, 3.85 (3.76)%. Gd(TOS)$_3$·3H$_2$O (C$_{21}$H$_{27}$S$_3$O$_{12}$Gd) Calcd (found): C, 34.76 (34.60); H, 3.75 (3.70)%. Y(TOS)$_3$·H$_2$O (C$_{21}$H$_{23}$S$_3$O$_{10}$Y) Calcd (found): C, 40.65 (40.56); H, 3.74 (4.08)%. Cu(TOS)$_2$·H$_2$O (C$_{14}$H$_{16}$S$_2$O$_7$Cu) Calcd (found): C, 39.66 (39.71); H, 3.88 (4.78)%.

4.4. General procedure for the lanthanide catalyzed formation of calix[4]resorcinarenes

To a stirred solution of the nonahydrated lanthanide(III) catalyst (5 mol %, 0.318 mmol) in absolute ethanol (10 mL) were added the resorcinol (6.36 mmol, 699 mg) and benzaldehyde (6.36 mmol, 645 μL). This solution was heated till just beneath the reflux temperature. After a given period of time the solution was cooled and poured into

distilled water (20 mL). The precipitated resorcinarene was filtered on a dry weighed crucible and washed with water (3×10 mL). After drying the resorcinarene to constant weight (after about 48 h in a vacuum oven at 90 °C) the crucible was weighed again giving the amount of formed resorcinarene. To obtain the isomer distribution, a small amount of resorcinarene was dissolved in deuterated DMSO and a ^{1}H NMR spectrum was recorded. The ratio was obtained by integration of the signals at δ=5.64 (4H, benzylic hydrogens of rccc isomer) versus the signals at δ=5.54 (4H, benzylic hydrogens of rctt isomer) and δ=5.57 (2H, *ortho* to OH in rctt isomer). Electron spray ionization mass spectrometry was performed to prove the tetrameric structure: *m/e* (ESI$^+$)=793 (M+1)$^+$, 1608 (2M+Na+1)$^+$. CHN-analysis was performed after drying the calix[4]resorcinarene for 48 h at 50 °C in a vacuum oven: $C_{52}H_{40}O_8 \cdot 3H_2O$ Calcd (found): C, 73.74 (73.89); H, 5.47 (5.56)%.

The procedures for the reactions with octanal were identical with the only difference that these reactions were performed at reflux temperature. CHN-analysis was also performed after drying the calix[4]resorcinarene for 48 h at 50 °C in a vacuum oven: $C_{56}H_{80}O_8 \cdot 3H_2O$ Calcd (found): C, 71.91 (71.51); H, 9.27 (9.35)%.

Acknowledgements

References and notes

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