Synthesis and Modification of Novel Iminecalix[4]arene Derivatives

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The synthesis of novel iminecalix[4]arenes and further modification thereafter is described using a synthetic strategy. The reaction of the benzaldehyde derivatives with tetraamine functions on the calix[4]arene easily afforded the pure compounds in 92.4-95.7% yields, regardless of the effect of the substituents on the benzaldehyde derivatives. These compounds were stable under the conditions to obtain their analogue dialkylated in the narrow rim, with 83.2-89.9% yields. Characterization of the newly synthesized iminecalix[4]arene derivatives by spectroscopic methods revealed that all compounds are in the cone conformations.

Key Words : Supramolecular chemistry, Calixarenes, Imines, Receptors, Spectroscopy, Substituent effects

Many macrocyclic compounds have been developed for mimicking several biological processes. Calix[4]arene, one of the noted supramolecular assembly,[1-3] provides a unique cavity capable of recognizing and confining various guest molecules.[4,5]

In search of the deep-cavity calix[4]arenes, researchers had developed the wide and narrow rim modified derivatives.[6-10] One of the approach used was to substitute the wide rim of the calix[4]arene with the Schiff bases. The selective functionalization of the wide rim of the calix[4]arene keeping the narrow rim free for further modifications is very important in the calixarene chemistry. In spite of attempts to substitute the wide rim of the calix[4]arene selectively with tetra Schiff base functions, few research groups had synthesized calix[4]arene with mono or di Schiff base functions.[11] The synthesis of the tetra substituted calix[4]arene Schiff base derivatives was possible only by using the formyl calix[4]arenes or calix[4]arenes pre-alkylated at the narrow rim as precursors.[12] These methods employed calix[4]arenes pre-substituted at the narrow rim, hence the molecules obtained were not feasible for further modifications.[13]

The selective modification of the wide rim of the calix[4]arene with tetra imine functions keeping the narrow rim free for further modifications has been never reported. Herein, we report a high yielding and expedient avenue to synthesize a series of new iminecalix[4]arene derivatives. The 5,11,17,23-tetrakis(amine)-25,26,27,28-tetrahydroxy-calix[4]arene **1** as depicted in Scheme 1 was used as a precursor.[14,15]

As shown in Scheme 1, the reaction of **1** with benzaldehyde derivatives in acetonitrile at room temperature afforded iminecalix[4]arene derivatives **2a-2d** with 92.4-95.7% yields (see the Supplementary Information). This way, the generation of deep cavity and the introduction of tetra imine functions on the wide rim of calix[4]arene happened concomitantly in a one-step process.

The selective modification of the narrow rim, gives flexibility to the calix[4]arene architecture.[16] Therefore, it was
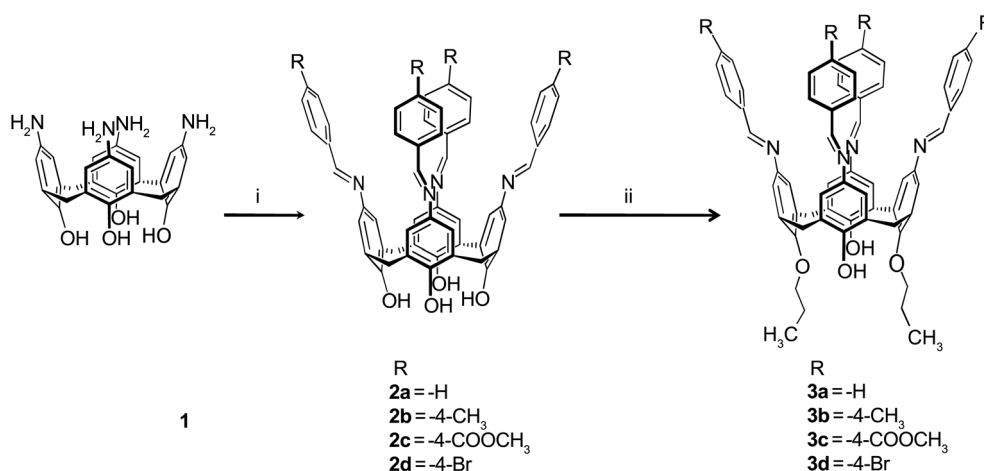
Scheme 1. Reagents and conditions: (i) R-Ph-CHO, CH$_3$CN, N$_2$, 2 h, 92.4-95.7% (ii) Br-CH$_2$CH$_2$CH$_3$, K$_2$CO$_3$, CH$_3$CN, N$_2$, reflux, 12 h, 83.2-89.9%.
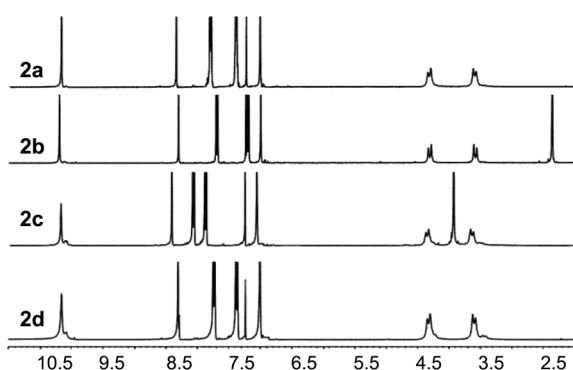
Figure 1. Partial ^{1}H NMR (CDCl$_3$ at 298 K) spectra of compounds **2a-2d**.

interesting to modify compounds **2a-2d** to their analogues dialkylated in the narrow rim. The synthesis of the target compounds **3a-3d** is depicted in Scheme 1. The exchange of proton on distal hydroxyl groups for a propyl function in the reaction of **2a-2d** with 1-bromopropane in the presence of excess K$_2$CO$_3$ gave the desired dialkylated compounds **3a-3d** in 83.2-89.9% yield (see the Supplementary Information). According to the literature, it was presumed that imine bonds are quite unstable.[17] However, we found that, all iminecalix[4]arene derivatives **2a-2d** were stable and successfully converted to their dialkylated analogues following the method described here.

Newly synthesized compounds, as shown in Scheme 1 were characterized by the analysis of their ^{1}H NMR and ^{13}C NMR and MALDI-TOF spectra. For example, the ^{1}H NMR spectra of **2a** showed a typical AB pattern for the methylene bridge protons represented by the two pairs of doublets at δ 3.63 and δ 4.31 ppm for the axial and equatorial protons, respectively. The ^{1}H NMR spectrums of the compounds **2b-2d** showed a similar pattern. As shown in Table 1, the signal for imine protons in **2a** appeared at δ 8.30 ppm in ^{1}H NMR and imine carobons were appeared at δ 157.8 ppm in ^{13}C NMR, revealing the formation of the iminecalix[4]arene.

The tetra substitution in the compound **2a** was confirmed from the close observation of the ^{1}H NMR signals for the Ar-OH (δ 10.15 ppm), -HC=N- (δ 8.30 ppm), calixarene Ar-H (δ 7.00 ppm), and a pair of doublets for the Ar-CH$_2$-Ar (δ

4.30, and δ 3.60 ppm), respectively in a ratio of 1:1:2:1:1. From the ^{1}H NMR spectra of **2a**, the integration pattern for above mentioned protons was found to be 4H: 4H: 8H: 4H: 4H, indicating the successful tetra substitution. Similar patterns of the ^{1}H NMR signals were found in case of compounds **2b-2d** (Figure 1). The tetra substitution was also confirmed from the integration of the ^{1}H NMR signal for 20 aromatic protons, which appeared at δ 7.82-7.78, 7.40-7.38 ppm in compound **2a**, while compounds **2b-2d** showed relevant signals for 16 aromatic protons in their respective ^{1}H NMR spectra.

Figure 1 and Scheme 1 illustrates that the imine[4]calix-arene can be successfully obtained by the reaction of amine-calix[4]arene **1** and benzaldehyde derivatives, irrespective of the electron-donating or electron-withdrawing substituent's on the benzaldehyde moiety. Using benzaldehyde and *p*-tolualdehyde compounds **2a** and **2b** were obtained with the yields of 95.7% and 94.7%, respectively. Whereas, using methyl 4-formylbenzoate and 4-bromobenzaldehyde, the compounds **2c** and **2d** were obtained with good yields of 93.3 and 92.4%, respectively.

It is also important to notice that without any extra purification step, the excess of benzaldehyde was completely removed by the addition of *n*-hexane in the reaction mixture
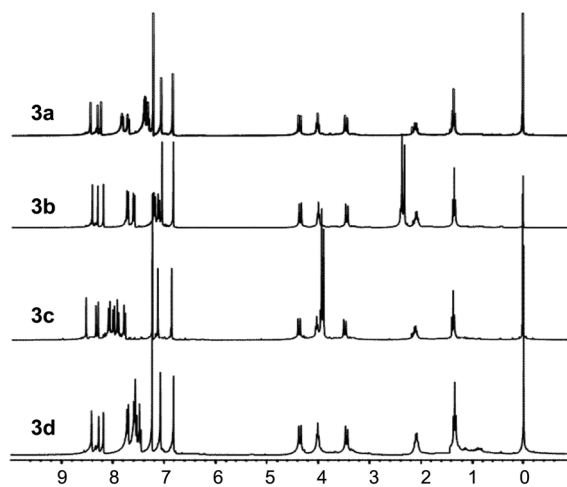

Figure 2. Partial ^{1}H NMR (CDCl$_3$ at 298 K) spectra of compounds **3a-3d**.

Table 1. Yields and spectral data of iminecalix[4]arene derivatives

Compounds	Δδppm (^{1}H NMR) (Ar-CH$_a$H$_e$-Ar)	δppm (^{13}C NMR) (Ar-CH$_2$-Ar)	δppm (^{1}H NMR) (Ar-H)	δppm (^{1}H NMR) (-CH=N-)	δppm (^{13}C NMR) (-CH=N-)	% yield
2a	0.76	32.47	7.01	8.34	159.3	**95.7**
2b	0.72	32.48	7.00	8.31	159.2	**94.7**
2c	0.73	32.39	7.05	8.41	157.8	**93.3**
2d	0.72	32.41	7.00	8.30	157.7	**92.4**
3a	0.91	32.10	6.86, 7.09	8.47, 8.33	159.9, 157.3	**89.9**
3b	0.91	32.17	6.84, 7.06	8.43,8.32	159.9, 157.4	**88.1**
3c	0.91	32.05	6.86, 7.13	8.54, 8.31	156.6, 155.7	**83.2**
3d	0.91	32.10	6.82, 7.08	8.42, 8.20	158.5, 155.8	**86.5**

a- axial proton, e- equatorial proton

while isolating the final compounds **2a-2d**. The complete removal of benzaldehyde is indicated by the absence of aldehyde peak at δ 9.90-10.10 ppm in the respective ^{1}H NMR spectra of compounds **2a-2d**. Hence, the tetra substituted compounds **2a-2d** were obtained easily keeping the narrow rim hydroxyl groups free for further modifications. The alkylation of the narrow rim hydroxyl groups on the distal positions in the compounds **2a-2d** gave compounds **3a-3d**.

Analysis of the ^{1}H and ^{13}C NMR spectra of the narrow rim modified compound **3a**, established the alkylation of hydroxyl groups in distal positions. Similar to that of the compound **2a**, compound **3a** also showed the typical AB pattern for the methylene bridge protons represented by two pairs of doublets at δ 3.35 and δ 4.35 ppm for the axial and equatorial protons, respectively.

As shown in the Figure 2 and Table 1, the singlet's for the imine protons and the calix[4]arene aromatic protons in the compound **2a** were split into the two pair of singlet's, each for the imine protons and the calix[4]arene aromatic protons after the *o*-alkylation to obtain the compound **3a**. Moreover, phenyl aromatic protons also followed the trend. The bridging of the aromatic rings by the imine bonds in the iminecalix[4]arene, results into a long π-electron conjugation system. The effect of this long π-electron conjugation is reflected in the ^{1}H NMR spectra of compound **3a**. The signal for four imine protons in compound **3a**, split's into two singlet's for two protons each, one due to the unsubstituted hydroxyl group and the other due to the substituted hydroxyl group at δ 8.47, 8.33 ppm, respectively. As shown in the Table 1, the ^{13}C NMR signals for four imine protons in compound **3a**, split's into two singlet's for two protons each, one due to the unsubstituted hydroxyl group and the other due to the substituted hydroxyl group at δ 159.9, 157.3 ppm, respectively. A marked upfield shift was observed for the protons of the unsubstituted hydroxyl groups. The signal for the four phenolic hydroxyl group protons at δ 10.15 ppm in the compound **2a**, was found to be shifted to δ 8.26 ppm for two protons of the phenolic hydroxyl group in the compound **3a**. Compounds **3b-3d** also showed the similar patterns as compound **3a** in their respective ^{1}H NMR and ^{13}C NMR spectra. It has now been established that analysis of ^{1}H NMR and ^{13}C NMR spectrums can be effectively employed for conformational analysis of calix[4]arenes.[18] As shown in Table 1, the methylene bridge carbons in compounds **2a-2d** and **3a-3d** appeared between δ 32.48-32.39 ppm, which noticeably validated that all compounds are in the cone conformations.

In conclusion, we have shown that the new iminecalix[4]arenes with the cone conformation can be synthesized in high yield at room temperature. Our strategy has proven that the iminecalix[4]arenes with the narrow rim free for further modification can be easily obtained. The narrow rim hydroxyl groups of the iminecalix[4]arene derivatives were successfully dialkylated with high yields. The method used here is highly applicable to produce a series of various iminecalix[4]arenes and their narrow rim modified derivatives. The synthesis and application of the iminecalix[4]arene derivatives is under investigation.

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