Calix[4]arenes with a Lid in their Upper Rims: 1,3-Dipolar Cycloaddition Reactions of Benzonitrile Oxides with 5-Allyl-, 5,11-Dially- and 5,17-Diallylcalix[4]arenes

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The upper rim substituted mono- and diisoxazolinomethylcalix[4]arenes **9-23** are synthesized in good yields from 1,3-dipolar cycloaddition reactions of *para*-substituted phenyl nitrileoxides with 5-allyl-, 5,11-diallyl- and 5,17-diallycalix[4]arenes **5-7**; the structures of **9-23** are consistent with a 'cone' conformation and the 'vase-with-a-lid' structure of **11** was confirmed by a single-crystal x-ray analysis. Preliminary results show that the monoisoxazolinomethylcalix[4]arene can form an inclusion complex with ammonium cation.

INTRODUCTION

Calix[4]arenes have been extensively used as hosts in supramolecular chemistry.[1-3] The cavity of the calix[4]arene alone is small and suitable for small guests only; therefore, considerable effort has been devoted to increasing the apparent size of the cavity by attaching substituents to the calixarene system for inclusion of a larger guest molecule.[1-3] Lower rim modification of calixarenes by various esterification[3] and etherification[4] have been shown to enhance the accommodation ability of these molecules. There are also myriad reports on upper-rim modification of calixarenes;[5-10] among them allyl group substitution has played a special role because it can be further transformed to other functional groups.[10] Many examples of allyl-group transformations have been explored by Gutsche et al., but their work was done primarily on *tetra*-substituted calix[4]arenes.[1, 10]

1,3-Dipolar addition reactions of nitrile oxides and nitrones with alkenes lead to isoxazolines and isoxazoles, respectively.[11] These heterocycles have commonly been used as precursors for many bifunctional groups such as β-aminoalcohols, β-hydroxyketones, α,β-unsaturated ketones, and so on.[12-14] We envision that the calixarenes would become very useful for inclusion complex studies if their cavities are coupled with these heterocycles. Here we report a facile synthesis of calix[4]arene derivatives with mono- and diisoxazolinomethyl groups at their upper rims and their potential application in ammonium ion complexation studies.

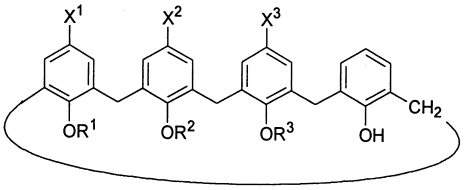
RESULTS AND DISCUSSION

Synthesis of these isoxazolinomethyl-substituted calix[4]arenes **9-23** was started from calix[4]arene **1**.[15a] Recently, in a collaboration with Lin, we have reported an efficient method in synthesizing calix[4]arenes with four different "lower rim" substituents, where a high yield method for monoalkoxycalix[4]arene was discovered.[15b] Treatment of **1** with allylbromide in the presence of sodium methoxide in acetonitrile gave calix[4]arene monoallyl ether **2** in 75% yield.[15b] 25,26-Diallyl ether calix[4]arene **3** and 25,27-diallyl ether calix[4]arene **4** were produced in 50-60% yields when **1** was treated with allylbromide in the presence of NaH in the former and K_2CO_3 in the latter. These allyl ethers **2, 3** and **4** were then converted to the corresponding 5-allylcalix[4]arene **5**, 5,11-diallylcalix[4]arene **6**,[7b] and 5,17-diallycalix[4]arene **7**[7b] in ca. 80% yield through heat-induced Claisen rearrangements (Scheme I). These allylcalix[4]arenes were then reacted with nitrile oxides to form either mono- or diisoxazolinomethyl groups on their upper rims.

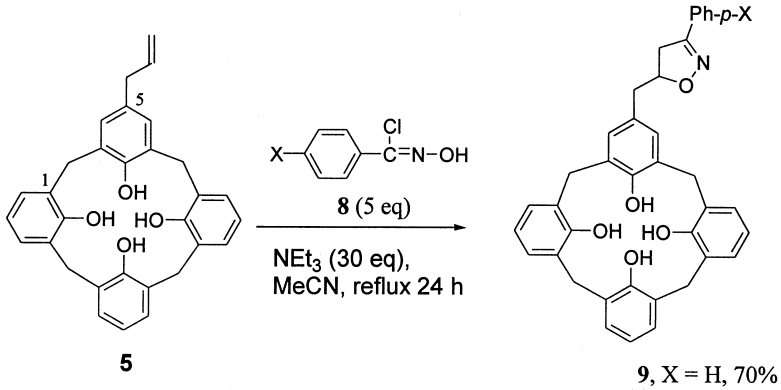
Initially, we were surprised to find that in the syntheses of mono-isoxazolinomethylcalix[4]arenes **9-11**, the reaction did not proceed at all if the ratios of nitrile oxide (prepared in situ from the dehydrochlorination of *para*-substituted benzohydroximoyl chloride **8**-X by NEt_3) to **5** were stoichiometric. When a large excess of nitrile oxide vs. **5** was used, however, the reaction products were mixed with a huge amount of furoxan precipitate. The optimal ratios of **8**-X and NEt_3 to **5**

Dedicated to the memory of the late Professor Ta-shue Chou ( )

Scheme I



1 $R^{1-3} = X^{1-3} = H$
2 $R^1 = -CH_2-CH=CH_2$, $R^{2,3} = X^{1-3} = H$
3 $R^1 = R^2 = -CH_2-CH=CH_2$, $R^3 = X^{1-3} = H$
4 $R^1 = R^3 = -CH_2-CH=CH_2$, $R^2 = X^{1-3} = H$
5 $R^{1-3} = H$, $X^1 = -CH_2-CH=CH_2$, $X^{2,3} = H$
6 $R^{1-3} = H$, $X^1 = X^2 = -CH_2-CH=CH_2$, $X^3 = H$
7 $R^{1-3} = H$, $X^1 = X^3 = -CH_2-CH=CH_2$, $X^2 = H$



5

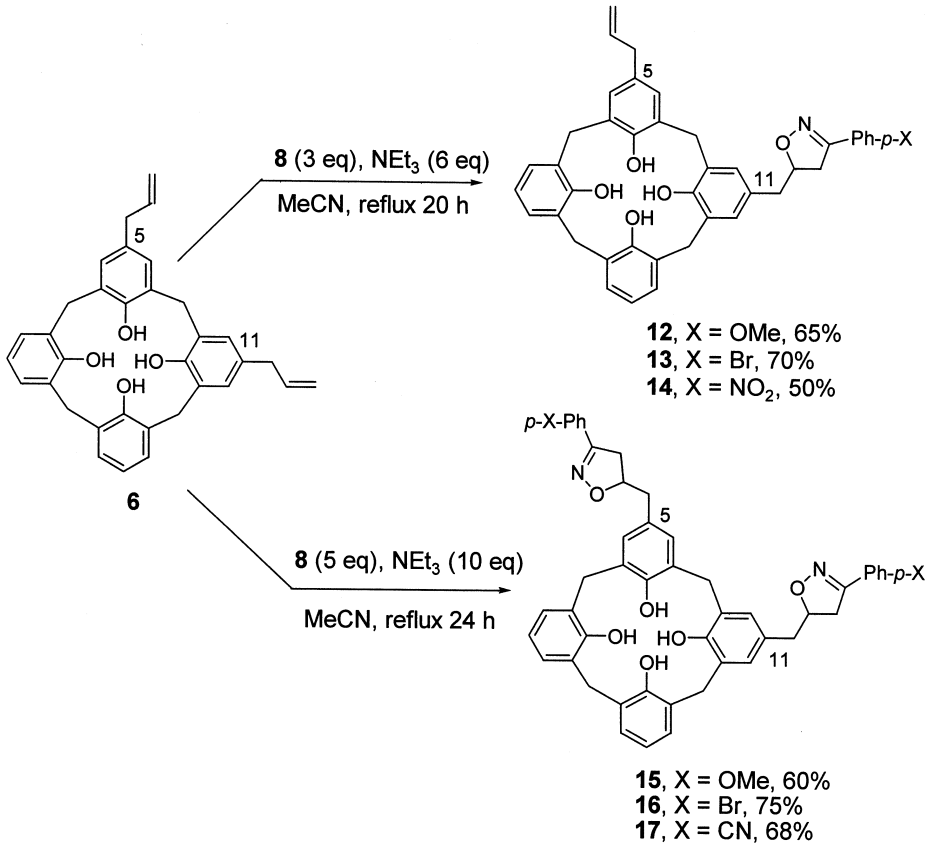
9, X = H, 70%
10, X = OMe, 78%
11, X = CN, 68%

were found to be ca. 5 and 30, respectively, which gave the mono-adducts **9-11** in 68~78% isolated yields (Scheme I). Latter, in the selective syntheses of 5-allyl-11-isoxazolinomethylcalix[4]arenes **12-14** or 5,11-diisoxazolinomethylcalix[4]arenes **15-17** from 5,11-diallylcalix[4]arene **6**, we found again that excess nitrile oxide was needed. When 3 equiv. of hydroximoyl chloride **8** (6 equiv. base) was added to a dilute solution of **6** in acetonitrile, the mono-adducts **12-14** were produced in 50~70% yields, concomitantly with a small amount (<5%) of bis-adducts **15-17**. The yields of bis-adducts **15-17** were optimal when 5 equiv. of **8**-X with 10 equiv. NEt_3 and a more concentrated solution condition were used (Scheme II).

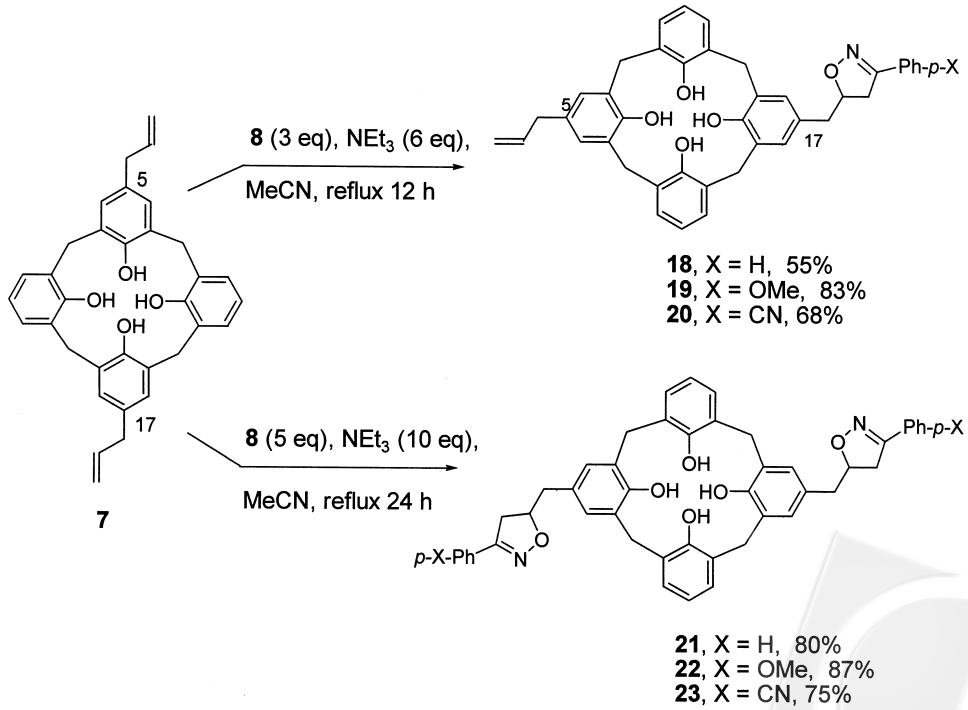
Our results show that the amount of base and **8** used is crucial for selective syntheses of either mono- or bis-isoxazolino adducts. The excess base needed is attributed to the inherent acidity of calix[4]arenes, which may neutralize themselves with the base NEt_3.[16] To expand the scope of the hosts, we further carried out the 1,3-dipolar reactions of 5,17-diallylcalix[4]arene **7** with **8**-X, which gave selectively either the 5-allyl-17-isoxazolino-methyl- **18-20** or 5,17-diisoxazolinomethylcalix[4]arenes **21-23** in 55-87% yields, if an appropriate amount of nitrile oxide is added and the concentration controlled (Scheme III).

All the products are identified by spectroscopic data including ^{1}H- and ^{13}C-NMR, FAB-MS and elemental analysis. Taking the mono-isoxazolinomethylcalix[4]arene **10** (X = -OMe) for example, its FAB-MS is consistent with the expected M+1 (*m/z* = 614). The incorporation of the isoxazolino group to **5** is shown by the appearance of two new pairs of doublets (δ 7.67 and 6.97) in **10**, which represent the four AA'XX' protons of the aryl group in phenylisoxazoline. Furthermore, the multiplet signals of the methine proton ($CH_2C\underline{H}=CH_2$) in starting material **5** are shifted from δ 5.8 to 4.9 (H-5' of the isoxazoline). The disappearance of ^{1}H-NMR signals of the terminal methylene of allyl-group in δ 5~5.1 and the emerging of two new signals in δ 2.6-2.7 and δ 2.8-2.9 also supports the formation of the isoxazoline-ring. The patterns of ^{1}H-NMR spectra of 5,11-diisoxazolino-adducts **15-17** and 5,17-diisoxazolino-adducts **21-23** are almost identical to those of corresponding mono-isoxazolinoadducts **9-11** except for different relative peak area ratios. Accordingly, the forma-

Scheme II



Scheme III



tion of 5-allyl-11-isoxazolinomethylcalix[4]arenes **12-14** and 5-allyl-17-isoxazolinoethylcalix[4]arenes **18-20** can be determined by judging ^{1}H-NMR signals from the characteristic pattern of isoxazoline described above as well as the remaining ally group. All the resonance signals arising from the bridge methylene carbons of **9-23** fall in the range of δ 31.8±0.3, which are consistent with a prediction of *syn* orientation for all aryl groups. [17]

An x-ray crystallographic investigation was studied on the monoisoxazolino-methylcalix[4]arene **11**, which reveals an interesting structure feature of the cavity (Fig. 1 and Table 1). Unlike its starting material 5,17-diallylcalix[4]arene **7**[18a] and other examples in the literature in upper-rim substituted calix[4]arenes,[18] the structure of **11** shows that the isoxazolino-group tends to bend toward the cavity of the calix[4]arene in solid state. Due to this upper-rim-substitution and the self-inclusion of the aryl group of isoxazoline, the calix[4]arene cavity is extended and covered with a "lid" (Fig. 2).

Preliminary results from ^{1}H-NMR ($CDCl_3$) titration studies indicate that possible inclusion complexes are formed between the isoxazolinomethylcalix[4]arene **10** and tetrabutylammonium bromide (TBAB) (see Fig. 3 and 4).[19] Substantial up-field shifts and broadened signals of all the aromatic-ring protons (δ 6.6-7.1) and the disappearance of the phenol hydroxy signal (δ 10.2) of **10** were observed when various amounts of TBAB existed in 5% (v/v) aqueous $CDCl_3$ (Fig. 3c-3h). Upon a 1:1 stoichiometry of **10** to TBAB (Fig. 3g and 4f) the spectra reached a maximum change in chemical shifts (Δδ = ~0.08 ppm). However, no change in ^{1}H NMR of **10** was found when 1 eq. of TBAB was added without water (Fig. 3b), which implies that water assisted hydrogen bonding

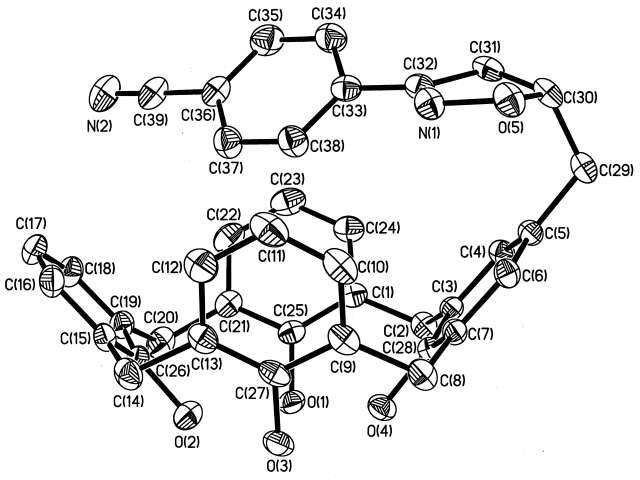


Fig. 1. The ORTEP of *para*-cyano-phenyl-isoxazolino-methylcalix[4]arene **11**, thermal ellipsoids drawn at the 30% probability level.

Table 1. Selected Bond Lengths (Å) and Bond Angles (deg) of **11**

O(1)-C(25)	1.388(3)	O(2)-C(26)	1.385(3)
O(3)-C(27)	1.391(3)	O(4)-C(28)	1.382(3)
O(5)-N(1)	1.412(3)	O(5)-C(30)	1.464(4)
N(1)-C(32)	1.279(4)	N(2)-C(39)	1.141(4)
C(1)-C(25)	1.395(4)	C(1)-C(24)	1.396(4)
C(1)-C(25)	1.520(4)	C(2)-C(3)	1.518(4)
N(1)-O(5)-C(30)	108.8(2)	C(32)-N(1)-O(5)	108.7(3)
C(25)-C(1)-C(24)	116.9(3)	C(25)-C(1)-C(2)	123.2(3)
C(24)-C(1)-C(2)	119.9(3)	C(3)-C(2)-C(1)	114.9(2)
C(28)-C(3)-C(4)	117.4(3)	C(28)-C(3)-C(2)	121.4(3)
C(4)-C(3)-C(2)	121.2(3)	C(5)-C(4)-C(3)	122.5(3)
C(6)-C(5)-C(4)	117.6(3)	C(6)-C(5)-C(29)	119.8(3)
C(4)-C(5)-C(29)	122.6(3)	C(5)-C(6)-C(7)	122.5(3)
C(6)-C(7)-C(28)	118.3(3)	C(6)-C(7)-C(8)	120.9(3)
C(28)-C(7)-C(8)	120.7(3)	C(7)-C(8)-C(9)	109.8(2)

may have played an important role for ammonium ion complexation. On the other hand, the chemical shifts of methylene signals of TBAB are down-field shifted by ca. 0.05 ppm in the presence of 1 eq. **10** (Fig. 4). The inclusion of TBAB within the cavity of **10** can explain both the high field shifts of the aromatic ^{1}H NMR signals of **10** and the downfield shift of the methylene protons of TBAB. Similar results in the inclusion of ammonium ions by other calix[4]arene systems have been reported by Gutsche et al.[20] Finally, a Raney-nickel catalyzed hydrogenation was attempted to hydrolyze the *para*-isoxazolinomethly group on the calix[4]arenes to β-hydroxy-ketones. The reaction did proceed but their products tend to form strong complexes with the nickel ion which made their identification by NMR difficult.[21] Although it seems difficult to purify the ring-opened products of these isoxazolino-methylcalix[4]arenes, MS and IR data[21] reveal that they are quite promising for nickel ion complexation.

In summary, we have developed a facile synthesis of a series of mono- and/or di-*para*-substituted-phenylisoxazolinomethylcalix[4]arenes **9-23**. Since the isoxazolines are well known to be convertible to many other bifunctional groups, we have work in progress in this aspect and are ex-

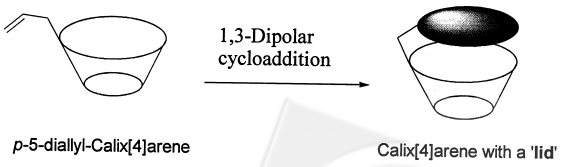


Fig. 2. An illustration that delineates the structural features of **7** and **11**.

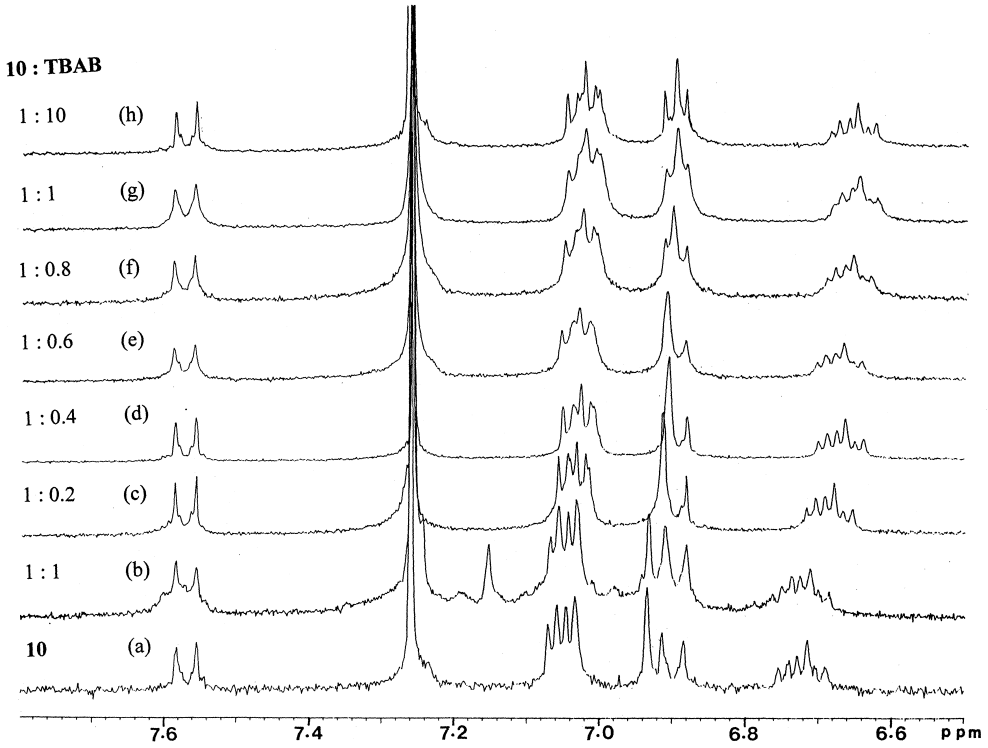


Fig. 3. ^{1}H NMR spectra of the phenolic and aromatic regions of compound **10** (1.7 mM) in $CDCl_3$ at 25 °C (a), and spectrum (b) in the presence of a 1:1 ratio of tetrabutylammonium bromide (TBAB), and (c)-(h) in the presence of various amount (1:0.2 to 1:10) of TBAB in 5% (v/v) water.

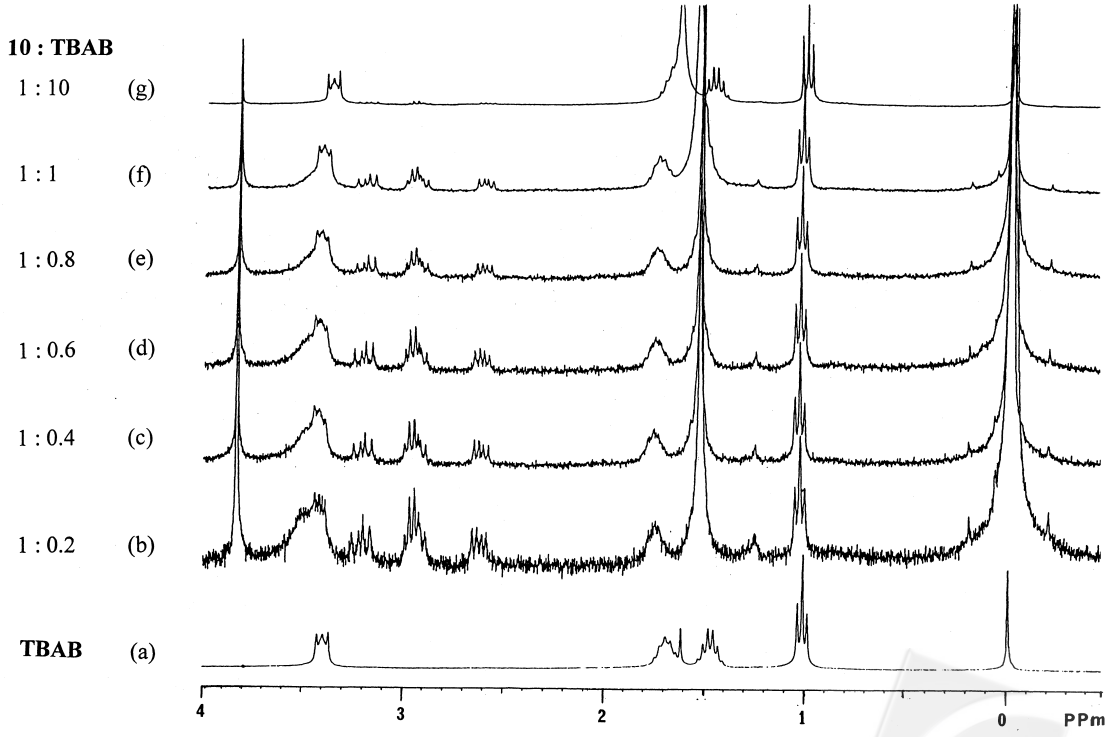


Fig. 4. ^{1}H NMR spectra of tetrabutylammonium bromide (TBAB) and the aliphatic regions of compound **10** (fixed at 1.7 mM) in $CDCl_3$ at 25 °C (a), and spectrum (b)-(g) in the presence of various amounts (1:0.2 to 1:10) of TBAB in 5% (v/v) aqueous $CDCl_3$.

ploring their use in metal ion extractions. The results will be reported in due course.

EXPERIMENTAL SECTION

General

Melting points were determined on a Yanaca MP-500D melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz NMR, ^{13}C and DEPT were recorded at 75.4 MHz, and the chemical shifts are reported in parts per million (δ) in values relative to $CDCl_3$ (δ = 7.25 for proton and 77 ppm for carbon) or tetramethylsilane as internal standard. Coupling constants are reported in hertz (Hz). Mass spectra were recorded on a VG-Trio 2000 spectrometer. High-resolution mass spectra were recorded on a Joel JMS-HX110 or a Joel JMS-SX/SX 102A spectrometer of the instrument center of National Tsing-Hua and National Chung-Hsin University. The matrix used for FAB mass spectra was *m*-nitrobenzylalcohol. C,H,N combustion analyses were determined on a Heraeus analyzer and all analyzed compounds are within ±0.4% of the theoretical value unless otherwise indicated. Column chromatography was performed on silica gel 70-230 mesh or 230-400 mesh from E. Merck; thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F_{254} from E. Merck.

General procedure for the preparation of 5-[3'-(*para*-X-phenyl)-4',5'-dihydro-Δ^2-isoxazolino-methyl]-25,26,27,28-tetra-hydroxycalix[4]arenes (9-11)

To a well stirred solution of 0.50 g (1.1 mmol) of monoallylcalix[4]arene 5[15] and 0.84 g (5.4 mmol) of *para*-substituted-benzohydroximoyl chloride[11] **8**-X in CH_3CN (50 mL) was added an excess of Et_3N (3.33 g, 32.7 mmol). The mixture was stirred at reflux for 24 h, washed with water, and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified on a silica gel column by elution with *n*-hexane/chloroform (gradient from 4:1 to 1:1 v/v) to give the desired 5-isoxazolinomethylcalix[4]arene **9-11**. The isolated yields based on 1 are as follows: **9** (X = H) 70%, **10** (X = OMe) 78%, **11** (X = CN) 68%.

9 (X = H): colorless solid; mp 239-240 °C ; ^{1}H-NMR ($CDCl_3$): δ 10.09 (s, 4 H), 7.51 (d, 2 H, *J* = 3.5 Hz), 7.24 (s, 3 H), 6.93-6.95 (m, 6 H), 6.77 (s, 2 H), 6.61-6.62 (m, 3 H), 4.76-4.78 (m, 1 H), 4.14 (bs, 4 H), 3.42 (bs, 4 H), 3.28-3.08 (m, 1 H), 2.79-2.88 (m, 2 H), 2.58-2.51, (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 157.07 (C_q), 149.37 (C_q), 149.31 (C_q), 148.11 (C_q), 131.14 (C_q), 130.52 (C_q), 130.23 (CH), 129.51 (CH), 129.18 (CH), 128.98 (C_q), 128.80 (C_q), 128.72 (C_q), 127.17 (CH), 122.83 (CH), 82.42 (CH), 40.67 (CH_2), 39.93 (CH_2), 32.23 (CH_2); FAB-MS *m/z*: 584 (M^++1). Anal. Calcd for $C_{38}H_{33}O_5N$: C, 78.22; H, 5.66; N, 2.40. Calcd for $C_{38}H_{33}O_5N \cdot 1/2\ CH_3CN$: C, 77.55; H, 5.72; N, 3.48. Found: C, 77.76; H, 5.70; N, 3.12.

10 (X = OMe): pale pink solid; mp 207-209 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 4 H), 7.67 (d, 2 H, *J* = 8.5 Hz), 7.14 (d, 6 H, *J* = 7.5 Hz), 7.04 (s, 2 H), 6.97 (d, 2 H, *J* = 8.5 Hz), 6.85-6.79 (m, 3 H), 4.95-4.89 (m, 1 H), 4.34 (bs, 4 H), 3.84 (s, 3 H), 3.61 (bs, 4 H), 3.32-3.20 (m, 1 H), 3.08-2.97 (m, 2 H), 2.78-2.69 (m, 1 H); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 161.49 (C_q), 156.66 (C_q), 149.36 (C_q), 149.32 (C_q), 148.06 (C_q), 131.32 (C_q), 130.36 (CH), 129.51 (CH), 128.96 (C_q), 128.81 (C_q), 128.72 (CH), 122.82 (CH), 114.60 (CH), 82.16 (CH), 55.80 (CH), 40.69 (CH_2), 40.22 (CH_2), 32.22 (CH_2); FAB-MS *m/z*: 614 (M^++1). Anal. Calcd for $C_{39}H_{35}O_6N$: C, 76.35; H, 5.71; N, 2.28. Calcd for $C_{39}H_{35}O_6N \cdot 1/4$ n-Hexane: C, 76.60; H, 6.07; N, 2.21. Found: C, 76.90; H, 5.82; N, 2.47.

11 (X = CN): light blue solid; mp 254-256 °C; ^{1}H-NMR ($CDCl_3$): δ 10.09 (s, 4 H), 7.48-7.56 (m, 4 H), 6.93-7.01 (m, 6 H), 6.86 (s, 2 H), 6.70-6.58 (m, 3 H), 4.84-4.94 (m, 1 H), 4.17 (bs, 4 H), 3.45 (bs, 4 H), 3.20-3.10 (m, 1 H, *J* = 16.7 Hz), 2.79-2.91 (m, 2 H), 2.68-2.60 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 155.20 (C_q), 148.79 (C_q), 148.65 (C_q), 147.68 (C_q), 133.90 (C_q), 132.30 (CH), 129.91 (C_q), 128.94 (CH), 128.81 (CH), 128.46 (C_q), 128.18 (C_q), 128.05 (C_q), 126.91 (CH), 122.20 (CH), 118.34 (C_q), 113.12 (C_q), 82.66 (CH), 39.89 (CH_2), 38.63 (CH_2), 31.63 (CH_2); FAB-MS *m/z*: 609 (M^++1). Anal. Calcd for $C_{39}H_{32}O_5N_2$: C, 76.97; H, 5.26; N, 4.61. Calcd for $C_{39}H_{32}O_5N_2.1/2\ H_2O$: C, 75.85; H, 5.35; N, 4.54. Found: C, 76.02; H, 5.34; N, 4.71.

X-ray Structural Analysis of 11

A light blue crystal of $C_{39}H_{32}O_5N_2$ was crystallized from 25% chloroform in hexane. Its structure was determined by means of single-crystal x-ray analysis on a Siemens *SMART CCD* diffractometer with λ = 0.71073 Å, radiation at 295±2 K, and reflections were controlled using three different φ setting angles; each setting was scanned by 0.3° ω between frames. The crystals are orthorhombic, with space group *Pbca* and unit cell dimensions *a* = 17.8131(2) Å, *b* = 16.6211(2) Å, *c* = 20.9856(2) Å, α = β = γ = 90°, *V* = 6213.28(12) Å^3, *Z* = 8, ρ_{calcd} = 1.301 g cm^{-3}, crystal size (mm) 0.40 x 0.35 x 0.03, absorption coefficient = 0.086 mm^{-1}, 24066 reflections, 5470 independent reflections, 4892 with I > 3.00σ(I) and with 416 parameters. The non-hydrogen atoms were refined *anisotropically*. Hydrogen atoms were fixed at calculated positions and refined using a riding mode. The model was finally refined by the full-matrix least-square methods with ω =

$1/[\sigma^2(F_0)]$ to final R values of 0.0585 and $R_w = 0.1207$.

General procedure for the preparation of 5-allyl-11-[3'-(*para*-X-phenyl)-4',5'-dihydro-Δ^2-isoxazolinomethyl]-25,26,27,28-tetrahydroxy-calix[4]arenes (12-14)

To a well-stirred solution of 0.31 g (0.6 mmol) of 5,11-diallylcalix[4]arene 6[7b] and 0.28 g (1.8 mmol) of *para*-substituted-benzohydroximoyl chloride **8**-X in CH_3CN (50 mL) was added 0.36 g (3.6 mmol) of Et_3N. The mixture was stirred at reflux for 20 h, cooled to rt, washed with water, and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified on a silica gel column by elution with *n*-hexane/chloroform (gradient from 4:1 to 1:2 v/v) to give the desired 5-allyl-11-isoxazolinomethyl-calix[4]arene **12-14**. Small amounts (<5%) of bis-adducts **15-17** were isolated. The isolated yields based on **6** are as follows: **12** (X = OMe) 65%, **13** (X = Br) 70%, and **14** (X = NO_2) 50%.

12 (X = OMe): light pinkish solid; mp 191-193 °C; ^{1}H-NMR ($CDCl_3$): δ 10.18 (s, 4 H), 7.58 (d, 2 H, *J* = 8.7 Hz), 7.07-6.69 (m, 12 H), 5.91-5.81 (m, 1 H), 5.07-5.00 (m, 2 H), 4.86-4.80 (m, 1 H), 4.24 (bs, 4 H), 3.83 (s, 3 H), 3.55 (bs, 4 H), 3.28-3.16 (m, 3 H), 3.00-2.89 (m, 2 H), 2.68-2.60, (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 160.94 (C_q), 156.03 (C_q), 148.83 (C_q), 148.72 (C_q), 147.55 (C_q), 146.97 (C_q), 137.41 (CH), 133.57 (C_q), 130.62 (C_q), 129.76 (CH), 128.93 (CH), 128.88 (CH), 128.41 (CH), 128.26 (CH), 128.23 (C_q), 128.16 (CH), 128.10 (CH), 128.04 (CH), 122.25 (CH), 122.12 (CH), 115.69 (CH_2), 114.03 (CH), 81.62 (CH), 55.28 (CH_3), 40.14 (CH_2), 39.65 (CH_2), 39.31 (CH_2), 31.71 (CH_2); FAB-MS *m/z*: 654 (M^++1).

13 (X = Br): light yellowish solid; mp 110-112 °C; ^{1}H-NMR ($CDCl_3$): δ 10.18 (s, 4 H), 7.53-7.46 (m, 4 H), 7.06-7.02 (m, 4 H), 6.92 (s, 2 H), 6.87 (s, 2 H), 6.76-6.69 (m, 2 H), 5.91-5.82 (m, 1 H), 5.07-5.02 (m, 2 H), 4.91-4.85 (m, 1 H), 4.24 (bs, 4 H), 3.51 (bs, 4 H) 3.26-3.17 (m, 3 H), 3.00-2.87 (m, 2 H), 2.69-2.62, (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 155.66 (C_q), 148.85 (C_q), 148.73 (C_q), 147.67 (C_q), 146.97 (C_q), 137.40 (CH), 133.58 (C_q), 131.85 (CH), 130.29 (C_q), 128.96 (CH), 128.92 (CH), 128.63 (C_q), 128.50 (C_q), 128.28 (C_q), 128.23 (C_q), 128.19 (C_q), 128.12 (C_q), 128.07 (CH), 128.03 (CH), 124.20 (C_q), 122.23 (CH), 122.14 (CH), 115.72 (CH_2), 82.22 (CH), 40.06 (CH_2), 39.31 (CH_2), 39.15 (CH_2), 31.72 (CH_2), 31.68 (CH_2); FAB-MS *m/z*: 704 (M^+ + 1). Calcd for $C_{41}H_{36}O_5NBr$-1/ 2 MeOH: C, 69.37; H, 5.29; N, 1.95. Found C, 69.27; H, 5.66; N, 2.35.

14 (X = NO_2): light yellowish solid; mp 174-177 °C; ^{1}H-NMR ($CDCl_3$): δ 10.18 (s, 4 H), 8.23 (d, 2 H, *J* = 8.7 Hz), 7.77 (d, 2 H, *J* = 8.7 Hz), 7.06-7.02 (m, 2 H), 6.93-6.68 (m, 8 H), 5.88-5.82 (m, 1 H), 5.08-4.94 (m, 3 H), 4.22 (bs, 4 H), 3.50 (bs, 4 H) 3.30-3.16 (m, 3 H), 3.04-2.92 (m, 2 H), 2.74-2.66, (m, 1 H); FAB-MS *m/z*: 670 (M^+ + 2). Calcd for $C_{41}H_{36}N_2O_7$-1/ 2 NEt_3: C, 73.48; H, 6.05; N, 4.87. Found C, 73.22; H, 6.08; N, 4.57.

General procedure for the preparation of 5,11-di-[3'-(*para*-X-phenyl)-4',5'-dihydro-Δ^2-isoxazolino-methyl]-25,26,27,28-tetra-hydroxycalix-[4]arenes (15-17)

To a well-stirred solution of 0.31 g (0.6 mmol) of 5,11-diallylcalix[4]arene **6**[7b] and 0.46 g (3.0 mmol) of *para*-substituted-benzohydroximoyl chloride **8**-X in CH_3CN (25 mL) was added 0.61 g (6.0 mmol) NEt_3. The mixture was stirred at reflux for 24 h, cooled to rt then washed with water, and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified on a silica gel column by elution with *n*-hexane/chloroform (gradient from 4:1 to 1:3 v/v) to give the desired 5,11-diisoxazolinomethylcalix[4]arene **15-17**. The isolated yields based on **6** are as follows: **15** (X = OMe) 60%, **16** (X = Br) 75%, and **17** (X = CN) 68%.

15 (X = OMe): light pinkish solid; mp 202-203 °C; ^{1}H-NMR ($CDCl_3$): δ 10.17 (s, 4 H), 7.57 (d, 4 H, *J* = 8.7 Hz), 7.05 (d, 4 H, *J* = 7.2 Hz), 6.95 (s, 4 H), 6.90 (d, 4 H, *J* = 8.7 Hz), 6.71 (t, 2 H, *J* = 7.7 Hz), 4.87-4.81 (m, 2 H), 4.22 (bs, 4 H), 3.83 (s, 6 H), 3.52 (bs, 4 H), 3.29-3.20 (m, 2 H), 2.98-2.90 (m, 4 H), 2.68-2.61, (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 160.97 (C_q), 156.04 (C_q), 148.82 (C_q), 147.55 (C_q), 130.77 (C_q), 129.85 (CH), 128.95 (C_q), 128.35 (C_q), 128.32 (CH), 128.20 (CH), 128.12 (CH), 122.23 (CH), 122.20 (CH), 114.05 (CH), 81.59 (CH), 81.56 (CH), 55.31 (CH_3), 40.20 (CH_2), 39.72 (CH_2), 31.70 (CH_2); FAB-MS *m/z*: 803 (M^++1).

16 (X = Br): ivory white solid; mp 195-197 °C; ^{1}H-NMR ($CDCl_3$): δ 10.16 (s, 4 H), 7.50-7.43 (m, 8 H), 7.07-7.04 (m, 4 H), 6.94-6.93 (m, 4 H), 6.71 (t, 2 H, *J* = 7.7 Hz), 4.90-4.86 (m, 2 H), 4.23 (bs, 4 H), 3.52 (bs, 4 H), 3.24-3.19 (m, 2 H), 2.97-2.87 (m, 4 H), 2.70-2.63 (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 155.61 (C_q), 148.75 (C_q), 147.55 (C_q), 131.76 (CH), 130.39 (C_q), 129.76 (CH), 128.93 (CH), 128.83 (CH), 128.53 (C_q), 128.47 (C_q), 128.31 (C_q), 128.16 (C_q), 128.09 (CH), 127.96 (CH), 124.13 (C_q), 122.16 (CH), 82.07 (CH), 40.09 (CH_2), 40.06 (CH_2), 39.18 (CH_2), 31.62 (CH_2); FAB-MS *m/z*: 902 (M^+ + 2).

17 (X = CN): ivory white solid; mp 107-110 °C; ^{1}H-NMR ($CDCl_3$): δ 10.15 (s, 4 H), 7.67-7.59 (m, 8 H), 7.03 (d, 4 H, *J* = 8.1 Hz), 6.96 (s, 4 H), 6.66 (t, 2 H, *J* = 7.4 Hz), 4.97-4.94 (m, 2 H), 4.23 (bs, 4 H), 3.52 (bs, 4 H), 3.32-3.20 (m, 2 H), 2.98-2.90 (m, 4 H), 2.78-2.71 (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 155.15 (C_q), 148.69 (C_q), 147.61 (C_q), 133.81 (C_q), 132.34 (CH), 129.94 (CH), 128.98 (CH), 128.76 (CH), 128.61 (CH), 128.37 (C_q), 128.32 (C_q), 128.16 (C_q), 128.02 (C_q), 126.85 (CH), 122.19 (CH), 118.26 (C_q), 113.08 (C_q), 82.57 (CH), 39.97 (CH_2), 38.70 (CH_2), 31.59 (CH_2); FAB-MS *m/z*: 793 (M^+ + 1). Calcd for $C_{50}H_{40}O_6N_4$-5/2 H_2O: C, 71.68; H, 5.37;

N, 6.69. Found C, 71.53; H, 5.25; N, 6.96.

General procedure for the preparation of 5-allyl-17-[3'-(*para*-X-phenyl)-4',5'-dihydro-Δ^2-isoxazolinomethyl]-25,26,27,28-tetrahydroxy-calix[4]arenes (18-20)

To a well-stirred solution of 0.50 g (1.1 mmol) of 5,17-diallylcalix[4]arene **7**[7b] and 0.46 g (2.96 mmol) of *para*-substituted-benzohydroximoyl chloride **8**-X in CH_3CN (100 mL) was added an excess of Et_3N (1.07 g, 10.5 mmol). The mixture was stirred at reflux for 12 h, washed with water, and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified on a silica gel column by elution with *n*-hexane/chloroform (gradient from 4:1 to 1:1 v/v) to give the desired 5-allyl-17-isoxazolinomethyl-calix[4]arene **18-20**. The isolated yields based on **7** are as follows: **18** (X = H) 55%, **19** (X = OMe) 83%, **20** (X = CN) 68%.

18 (X = H): light yellowish solid; mp 245-246 °C; ^{1}H-NMR ($CDCl_3$): δ 10.24 (s, 4 H), 7.67-7.64 (m, 2 H), 7.39 (t, 3 H, *J* = 2.3 Hz), 7.09 (d, 4 H, *J* = 7.6 Hz), 6.98 (s, 2 H), 6.92 (s, 2 H), 6.76 (t, 2 H, *J* = 7.5 Hz), 5.91-5.78 (m, 1 H), 5.13-5.07 (m, 2 H), 4.96-4.86 (m, 1 H), 4.28 (bs, 4 H) 3.57 (bs, 4 H), 3.32-3.22 (m, 3 H), 3.03-2.97 (m, 2 H), 2.73-2.68 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 157.03 (C_q), 149.34 (C_q), 148.10 (C_q), 147.61 (C_q), 137.93 (CH), 134.08 (C_q), 131.11 (C_q), 130.49 (C_q), 130.24 (CH), 129.57 (C_q), 129.47 (C_q), 129.16 (CH), 128.99 (CH), 128.72 (C_q), 127.16 (CH), 122.78 (CH), 116.32 (CH_2), 82.42 (CH), 40.66 (CH_2), 39.90 (CH_2), 32.29 (CH_2); FAB-MS *m/z*: 624 (M^+ +1). Anal. Calcd for $C_{41}H_{37}O_5N$: C, 78.97; H, 5.93; N, 2.25. Calcd for $C_{41}H_{37}O_5N$-5/4 H_2O: C, 76.22; H, 6.12; N, 2.17. Found: C, 76.11; H, 5.79; N, 2.48.

19 (X = OMe): light yellowish solid; mp 235-237 °C; ^{1}H-NMR ($CDCl_3$): δ 10.14 (s, 4 H), 7.53 (d, 2 H, *J* = 8.9 Hz), 7.00 (d, 4 H, *J* = 7.5 Hz), 6.88-6.82 (m, 6 H), 6.67 (t, 2 H, *J* = 7.6 Hz), 5.86-5.74 (m, 1 H), 5.03-4.97 (m, 2 H), 4.82-4.72 (m, 1 H), 4.21-4.18 (bs, 4 H), 3.79 (s, 3 H), 3.48-3.45 (bs, 4 H) 3.22-3.12 (m, 3 H), 2.94-2.87 (m, 2 H), 2.62-2.57, (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 160.85 (C_q), 156.01 (C_q), 148.70 (C_q), 147.42 (C_q), 146.96 (C_q), 137.31 (CH), 133.45 (C_q), 130.63 (C_q), 129.69 (CH), 128.92 (CH), 128.85 (CH), 128.33 (CH), 128.09 (C_q), 122.15 (CH), 115.69 (CH_2), 113.95 (CH), 81.52 (CH), 55.17 (CH_2), 40.04 (CH_2), 39.57 (CH_2), 39.24 (CH_2), 31.64 (CH_2); FAB-MS *m/z*: 654 (M^++1). Anal. Calcd for $C_{42}H_{39}O_6N$: C, 77.18; H, 5.97; N, 2.14. Calcd for $C_{42}H_{39}O_6N$·1/2 MeOH: C, 76.23; H, 6.13; N, 2.09. Found: C, 76.27; H, 5.90; N, 2.51.

20 (X = CN): ivory-white solid; mp 154-156 °C; ^{1}H-NMR ($CDCl_3$): δ 10.17 (s, 4 H), 7.67-7.58 (m, 4 H), 7.04-7.00 (m, 4 H), 6.92 (s, 2 H), 6.87 (s, 2 H), 6.68 (t, 2 H, *J* =7.5 Hz), 5.90-5.78 (m, 1 H), 5.07-5.01 (m, 2 H), 4.94-4.86 (m, 1 H), 4.21 (bs, 4 H) 3.50 (bs, 4 H), 3.26-3.17 (m, 3 H), 2.99-2.89 (m, 2 H), 2.71-2.65 (m, 1 H); ^{13}C-NMR ($CDCl_3$): δ 155.21 (C_q), 148.70 (C_q), 147.67 (C_q), 147.02 (C_q), 137.29 (CH), 133.91 (C_q), 133.53 (C_q), 132.32 (CH), 129.93 (C_q), 129.01 (CH), 128.90 (CH), 128.77 (CH), 128.49 (C_q), 128.18 (C_q), 128.09 (C_q), 128.03 (C_q), 126.93 (C_q), 122.17 (CH), 118.33 (C_q), 115.76 (CH_2), 113.12 (C_q), 82.72 (CH), 39.87 (CH_2), 39.27 (CH_2), 38.63 (CH_2), 31.67 (CH_2); FAB-MS *m/z*: 649 (M^++1). Satisfactory results of the elementary analysis could not be obtained for this sample.

General procedure for the preparation of 5,17-di-[3'-(*para*-X-phenyl)-4',5'-dihydro-Δ^2-isoxazolino-methyl]-25,26,27,28-tetra-hydroxycalix-[4]arenes (21-23)

To a well-stirred solution of 0.50 g (1.1 mmol) of 1,3-diallylcalix[4]arene **7** and 0.77 g (4.95 mmol) of *para*-substituted-benzohydroximoyl chloride **8**-X in CH_3CN (100 mL) was added an excess of NEt_3 (4.10 g, 40.2 mmol). The mixture was stirred at reflux for 24 h, washed with water, and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified on a silica gel column by elution with *n*-hexane/chloroform (gradient from 4:1 to 1:1 v/v) to give the desired 5,17-diisoxazolinomethylcalix[4]arene **21-23**. The isolated yields based on **7** are as follows: **21** (X = H) 80%, **22** (X = OMe) 87%, **23** (X = CN) 75%.

21 (X = H): colorless solid; mp 248-250 °C; ^{1}H-NMR ($CDCl_3$): δ 10.09 (s, 4 H), 7.53-7.50 (m, 4 H), 7.25 (d, 6 H, *J* = 2.4 Hz), 6.94 (d, 4 H, *J* = 7.6 Hz), 6.85 (s, 4 H), 6.66 (t, 2 H, *J* = 7.5 Hz), 4.79-4.73 (m, 2 H), 4.15 (bs, 4 H), 3.43 (bs, 4 H), 3.18-3.09 (m, 2 H), 2.89-2.81 (m, 4 H), 2.60-2.52, (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 156.40 (C_q), 148.63 (C_q), 147.50 (C_q), 130.50 (C_q), 129.86 (CH), 129.70 (C_q), 129.52 (CH), 128.87 (CH), 128.52 (C_q), 128.30 (C_q), 128.00 (C_q), 126.48 (CH), 122.18 (CH), 81.71 (CH), 40.03 (CH_2), 39.30 (CH_2), 31.56 (CH_2); FAB-MS *m/z*: 743 (M^++1). Anal. Calcd for $C_{48}H_{42}O_6N_2$.: C, 77.63; H, 5.66; N, 3.77. Calcd for $C_{48}H_{42}O_6N_2$·5/12 $CHCl_3$: C, 73.38; H, 5.36; N, 3.54. Found: C, 73.26; H, 5.47; N, 3.87.

22 (X = OMe): pinkish solid; mp 237-239 °C; ^{1}H-NMR ($CDCl_3$): δ 10.13 (s, 4 H), 7.52 (d, 4 H, *J* = 8.7 Hz), 7.00 (d, 4 H, *J* = 7.5 Hz), 6.90 (s, 4 H), 6.85 (d, 4 H, *J* = 8.7 Hz), 6.66 (t, 2 H, *J* = 7.5 Hz), 4.82-4.76 (m, 2 H), 4.22-4.17 (bs, 4 H), 3.78 (s, 6 H), 3.49-3.44 (bs, 4 H), 3.25-3.15 (m, 2 H), 2.93-2.85 (m, 4 H), 2.61-2.57 (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 160.91 (C_q), 156.06 (C_q), 148.71 (C_q), 147.54 (C_q), 130.70 (C_q), 129.76 (CH), 128.93 (CH), 128.36 (CH), 128.09 (C_q), 122.16 (CH), 114.00 (CH), 81.50 (CH), 55.27 (CH_3), 40.12 (CH_2), 39.67 (CH_2), 31.64 (CH_2); FAB-MS *m/z*: 803 (M^++1). Anal. Calcd for $C_{50}H_{46}O_8N_2$: C, 74.81; H, 5.74; N, 3.49. Calcd for $C_{50}H_{46}O_8N_2$·1/2 CH_3OH: C, 74.08; H, 5.87; N, 3.42. Found: C, 74.12; H, 5.87; N, 3.71.

23 (X = CN): white solid; mp 147-148 °C; ^{1}H-NMR

($CDCl_3$): δ 10.11 (s, 4 H), 7.62-7.48 (m, 8 H), 6.98-6.84 (m, 8 H), 6.61 (t, 2 H, J = 7.0 Hz), 4.96-4.84 (m, 2 H), 4.20-4.17 (bs, 4 H), 3.48 (bs, 4 H), 3.36-3.17 (m, 2 H), 2.92-2.78 (m, 4 H), 2.71-2.65, (m, 2 H); ^{13}C-NMR ($CDCl_3$): δ 155.21 (C_q), 148.64 (C_q), 147.79 (C_q), 133.90 (C_q), 133.08 (CH), 132.36 (CH), 130.05 (CH), 128.93 (CH), 128.45 (C_q), 128.06 (C_q), 126.95 (CH), 122.24 (CH), 119.00 (CH), 118.34 (C_q), 113.18 (C_q), 82.67 (CH), 40.00 (CH_2), 38.74 (CH_2), 31.67 (CH_2); FAB-MS *m/z*: 793 (M^++1). Anal. Calcd for $C_{50}H_{40}O_6N_4 \cdot 1/2\ CHCl_3$: C, 71.15; H, 4.75; N, 6.57. Found: C, 71.07, H, 5.07; N, 7.03.

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Key Words

1,3-Dipolar; Calix[4]arene; Isoxazoline; Nitrile oxides; Claisen rearrangement.

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21. In the reaction of **21** with Raney-Ni/H_2 a water soluble product was isolated whose ^{1}H NMR signals were very broad which indicates the existence of ferromagnetic nickel species. FAB-Mass of the deuterium exchanged (M-d_4) sample at *m*/*z* 753 (M-d_4^+ + 1) and 810 (M-d_4^+ + Ni^{58}) supports the four-deuterium exchanged ring-opened products of *p*-5,17-dihydroxy-ketone derivative of calix[4]arene and its complex with Ni^{+2}, respectively. IR spectra of the reduction products reveal the characteristic stretching frequencies of hydroxyl and carbonyl groups.