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Synthesis of Aminomethylated Calix[4]resorcinarenes

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Abstract: Aminomethylation at the ortho position with respect to hydroxyl groups of calix[4]resorcinarenes, resorcinol-aldehyde cyclotetramers, was achieved by the Mannich reaction with formaldehyde and the appropriate amine in an alcoholic solution.

Calix[4]resorcinarenes **1**, a subclass of calixarenes derived from the acid-catalyzed condensation of resorcinol with aldehyde,[1] have been studied with regard to inclusion of neutral organic guests[2] and selective extraction of sugar molecules.[3,4] A new water-soluble host was recently synthesized by the diazo-coupling reaction of calix[4]resorcinarene with p-sulfonatobenzenediazonium.[5] However methods for functionalization of calix[4]resorcinarenes have been less known in comparison with those of calixarenes. We would like to report herein a new method for preparation of functionalized calix[4]resorcinarenes **2** and **3** bearing substituted aminomethyl groups by the Mannish reaction with formaldehyde and the appropriate amine (Figure 1).

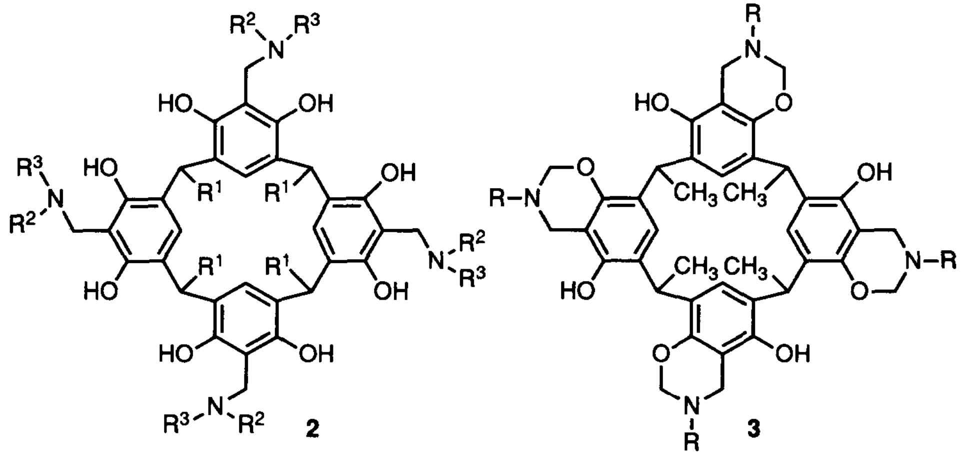
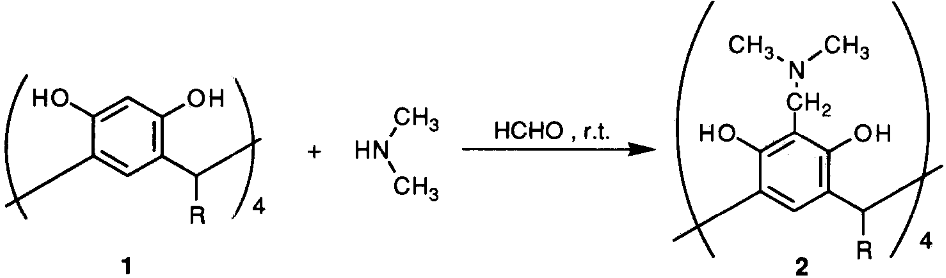


Figure 1. Aminomethylated calix[4]resorcinarenes

Calix[4]resorcinarenes **1a-d** were prepared in good yields according to the previously reported methods.[2,3] Reaction of **1a-d** with 37% aq. formaldehyde (5 eq.) and dimethylamine (5 eq.) in ethanol-benzene or ethanol-dichloromethane solution proceeded smoothly under mild conditions, to give the corresponding N,N-dimethylaminomethylated calix[4]resorcinarenes **2a-d** in good yields (Table 1).

The IR spectrum of **2a** showed $\upsilon_{O\text{-}H}$ at 3250 cm^{-1} and $\upsilon_{N^+\text{-}H}$ at 2500 cm^{-1}.[7] The ^{1}H-NMR spectrum of **2a** in CDCl$_3$ indicates that the protons of benzene rings and bridge positions are equivalent, respectively, while ^{13}C-NMR signals of aromatic carbons attached to hydroxy groups appeared as non-equivarent two peaks. On the other hand, these ^{13}C-NMR signals of the hydrochloride of **2a** are observed as a singlet peak in CD_3OD-D_2O.[8] These observations suggest that **2a** has the zwitter form of phenolates and ammonium ions. Although the conformation of **2a** is unclear, its hydrochloride is assumed at least to exist in a cone conformation on the basis of its equivalency in ^{1}H- and ^{13}C-NMR spectra and the previous results; calix[4]resorcinarenes have been reported to favour the cone conformation both in solid state[2] and in the solution.[4, 9]

Table 1. Synthesis of N,N-Dimethylaminomethylated Calix[4]resorcinarenes.[a]



a : R = CH_3
b : R = $(CH_2)_8CH_3$
c : R = CH_2CH_2Ph
d : R = Ph

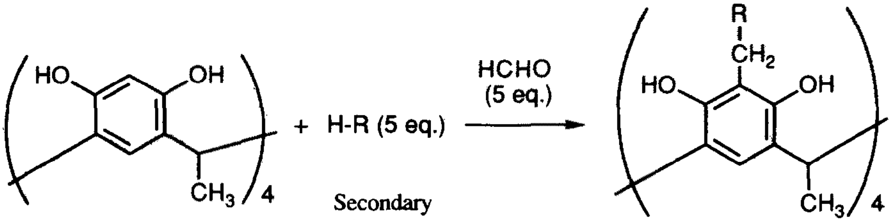
Calix[4]resorcinarene	Solvent (cm^3)	Time/h	Yield/%
1a	EtOH-benzene (20/40)	12	68
1b	EtOH-benzene (20/20)	24	88
1c	EtOH-benzene (20/20)	24	70
1d	EtOH-CH_2Cl_2 (60/60)	48	82

a) Reaction conditions : **1** (1.0 mmol), dimethylamine (5.0 mmol), 37% aq. HCHO (5.0 mmol), under N_2.

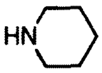
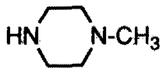
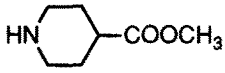
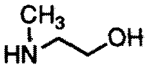
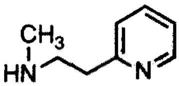
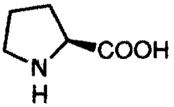
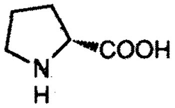
Next, the present aminomethylation was applied to various secondary amines having functional group (Table 2). The reaction mixture was needed to heat for several hours in order to complete the reaction in the cases of Entries 3 and 5. The reaction with L- and D-proline was started in the mixture of 15 cm^3 of ethanol and 5 cm^3 of water, and the additional water (35 cm^3) was added after 12h in order to prevent the precipitation of incomplete products (Entries 7 and 8). The aminomethylated products were obtained in good yields in all cases. The products shown in Entries 3, 5, and 6 were soluble in weak acidic buffer below pH 5.0 and those obtained from L- and D-proline (Entries 7 and 8) soluble even in a neutral water.

General procedure for the preparation of the aminomethylated calix[4]resorcinarene **2**: To a solution of calix[4]resorcinarene **1** (1.0 mmol) and the secondary amine (5.0 mmol) in ethanol and the co-solvent was added 37% aqueous solution of formaldehyde (5.0 mmol) at room temperature under a nitrogen atmosphere, and the mixture was stirred for 4-48 h; the completion of the reaction was checked by thin layer chromatography on silica-gel (TLC). After evaporation of the solvent followed by the addition of methanol, the precipitate was collected by filtration, washed with methanol, and dried *in vacuo* at 100°C over P_2O_5, to give the aminomethylated calix[4]resorcinarene **2**. Thus obtained product was sufficiently pure by TLC, IR, ^{1}H- and ^{13}C-NMR, FAB mass, and/or the elemental analysis. The melting point was generally unclear except for that shown in table notes, because the colorless solid turned black gradually over 200°C.

Table 2. Aminomethylation of **1a** with Various Secondary Amines.[a]



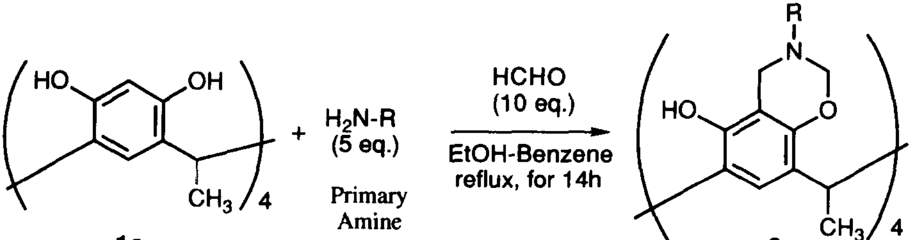
1a **2**

Entry	Amine H-R	Solvent (cm^3)	Time / h (Temp / °C)	Yield /%[b]
1		EtOH-Benzene (10/10)	4 (rt)	79
2		EtOH-Benzene (10/10)	48 (rt)	83
3		EtOH-Benzene (10/10)	12 (rt) then 2 (70)	68
4		EtOH-Benzene (10/10)	12 (rt)	71
5		EtOH-Benzene (10/10)	14 (rt) then 2 (70)	59 [b]
6		EtOH-Benzene (15/15)	48 (rt)	64 [c]
7		EtOH-H_2O (15/5+35)	48 (rt)	69 [d]
8		EtOH-H_2O (15/5+35)	48 (rt)	65 [e]

a) Reaction conditions: **1a** (1.0 mmol), the secondary amine (5.0 mmol), 37% aq. HCHO (5.0 mmol), under N_2.
b) Mp 225-230°C (dec.). c) Mp 130-133°C. d) $[\alpha]_D^{20}$ -33.7° (c=0.999, H_2O). e) $[\alpha]_D^{20}$ +33.8° (c=0.987, H_2O).

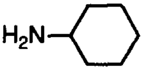
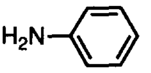
Finally, the reaction with the primary amines was examined. The use of 5 eq. of both the primary amine and formaldehyde to **1a** under the same conditions as described above resulted in yielding the complex reaction mixture. However, when using 5 eq. of the amine and 10 eq. of formaldehyde to **1a** in the refluxing solution, the desired aminomethylated product **3**, having 2,3-dihydro-1,3-oxazine structure, was obtained in good yield (Table 3). The reaction with aromatic amine such as aniline gave the corresponding product as well as that with the aliphatic amines.

Table 3. Aminomethylation of **1a** with Primary Amines.[a]



1a

3

Entry	Amine H_2N-R	Yield /%
1		72
2	H_2NCH_2COOEt	75 [b]
3		84

a) Reaction conditions: **1a** (1.0 mmol), the primary amine (5.0 mmol), 37% aq. HCHO (10.0 mmol), EtOH (10 cm^3)- benzene (10 cm^3) under N_2 at reflux for 14h. b) Mp 196.5-198.5°C.

It is noted that functionalized calix[4]resorcinarenes were synthesized by the aminomethylation with formaldehyde and the secondary or primary amines in good yields and some of them became water-soluble. Their ability for inclusion of the organic guests or complexation of metal ions is now studied.

References and Notes

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6 The Mannich reaction of calixarenes have been reported: see C. D. Gutsche, M. Iqbal, K. S. Nam, K. See, and I. Alam, *Pure and Appl. Chem.*, **1988**, 60, 483-488.

7 Spectral data of **2a**: FAB mass *m/e* 773 (M+H)$^+$; IR (CHCl$_3$) υ 3250, 2500, 1650, 1470, 1450 cm^{-1}; ^{1}H-NMR (250MHz, CDCl$_3$) δ_{ppm} 1.73 (12H, d, J=7.3 Hz, ^{9}H), 2.23 (24H, s, ^{10}H), 3.68 (8H, s, ^{7}H), 4.55(4H, q, J=7.3 Hz, ^{8}H), 7.26 (4H, s, ^{5}H), 10.99 (8H, brs, OH); ^{13}C-NMR (62MHz, CDCl$_3$) δ_{ppm} 19.56 (9), 27.52 (8), 44.16 (10), 56.71 (7), 107.80 (2), 121.42 (5), 124.76 (4 and 6), 149.98 (1 or 3), 152.05 (1 or 3).

8 NMR spectra of the hydrochloride of **2a** in CD_3OD-D_2O (6:1): ^{1}H-NMR δ_{ppm} 1.66 (12H, d, J=6.6 Hz), 2.81 (24H, s), 4.63 (4H, q, J=6.6 Hz), 7.24 (4H, s); ^{13}C-NMR δ_{ppm} 20.39 (9), 31.15 (8), 43.44 (10), 52.93 (7), 109.41(2), 127.22 (5), 128.22 (4 and6), 153.13 (1 and 3).

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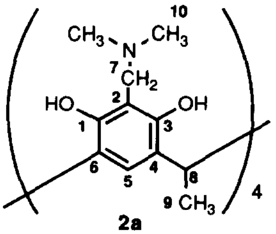

2a

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