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Electrospray Mass Spectrometric Evidence of Calixarene *p*-Quinone Methide Formation

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Positive or negative mode electrospray mass spectrometry of various types of tris(*p-tert*-butyl)calix[4]arenes with an active methylene group at the upper rim resulted in most cases in the detection of the highly reactive tris(*p-tert*-butyl)calix[4]arenemono(*p*-quinonemethide). © 1998 John Wiley & Sons Ltd.

KEYWORDS: calix[4]arenes; *p*-quinone methides; electrospray mass spectrometry; elimination reaction

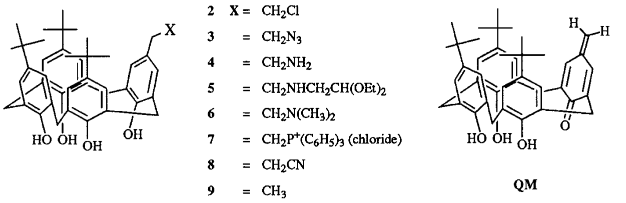
INTRODUCTION

Calixarene tetrol species substituted at the *para* position by an active methylene group have been synthesized in recent years in order to access more elaborate structures. Gutsche and co-workers[1] introduced at the upper rim of the calix[4]arene tetrol, by means of an exhaustive or controlled Mannich reaction, four or one (dimethylamino)methyl substituents which allow, after a preliminary *N*-alkylation, the amino group to be replaced by various substituents. In a different way, Ungaro and co-workers[2] developed a direct soft electrophilic substitution process involving tin(IV)chloride and chloromethyl octyl ether, affording the tetra-*p*-(chloromethyl)calix[4]arene, which was finally transformed into the water-soluble phosphonate. These apparent substitution reactions involve a probable '*p*-quinonemethide route,' i.e. nucleophilic additions on a highly unstable 4-methylenecyclohexa-2,5-dien-1-one calixarene derivative.[3] We demonstrate in the present paper that this intermediate can be generated in its protonated or deprotonated form by electrospray mass spectrometry (ESMS).

We recently described[4] the introduction of various active methylene groups at the upper rim of the *tris*(*p-tert*-butyl)calix[4]arene (**1**) involving, for some of them, procedures adapted from the above-mentioned literature. Species **2**–**8** (Scheme 1) thus synthesized were fully characterized, excepted the amine **4**, which did not give a correct elemental analysis. This observation, corresponding to a loss of nitrogen, was correlated with the possible elimination of NH_3, giving probably some tris(*p-tert*-butyl)calix[4]arenemono(*p*-quinone methide) (**QM**) during the measurement. This quinone methide was not visible by ^1H or ^{13}C NMR analysis of **4**, but was perfectly detected by ESMS which was suspected to generate it under the conditions of analysis (Table 1).

In both the positive (ionizing agent HCO_2H) and negative modes (ionizing agent aqueous NH_3), this technique showed that **QM** was easily generated from **2**–**7**, and that at relatively high cone voltages (60–80 V) the same profile was obtained for most species. It was characterized in the positive mode by a peak at *m*/*z* 605.4 ($[\mathbf{QM} + H]^+$), followed by a succession of deterbutylated fragments at *m*/*z* 549.3, 493.3 and 437.3; the presence of other peaks at *m*/*z* 587.4, 531.4, 475.0 and 419.3 was explained by the loss of H_2O from the above-mentioned species. In the negative mode, it appeared as a single peak at *m*/*z* 603.4 ($[\mathbf{QM} - H]^-$), without fragmentation. The probable mechanisms of these ESMS-induced elimination reactions, given in Fig. 1, show that a pure quinone methide subunit can be expected in the negative mode.

The monomethyl species **9**, obtained by catalytic reduction of the corresponding monoformylcalixarene,[5] was used to calibrate our analyses. It displayed in the negative mode a peak at *m*/*z* 605.5 attributed to the expected monophenate anion. The azide **3** displayed at low and medium cone voltages (−25 and 60 V) a low-intensity peak at *m*/*z* 621.4, which was attributed to the corresponding amine, suggesting that some reductive decomposition occurs during the analysis. Even at high voltage, the nitrile **8** did not give any elimination peak, reflecting as expected the stability of the C—C(N) bond towards further transformations.[1]



1 *tri*-(Bu^t)calix[4]arene
2 X = CH_2Cl
3 = CH_2N_3
4 = CH_2NH_2
5 = $CH_2NHCH_2CH(OEt)_2$
6 = $CH_2N(CH_3)_2$
7 = $CH_2P^+(C_6H_5)_3$ (chloride)
8 = CH_2CN
9 = CH_3

Scheme 1

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Table 1. ESMS data for calixarenes 2–9 at different cone voltages

Formula	Molecular mass	Mass profile (*m*/*z* relative intensity (%), ion)
$C_{41}H_{49}O_4Cl$ (**2**)	641.2	−20 V: 639.4–641.5 (100) [**2** − H]$^-$
		−60 V: 603.5 (100) [**QM** − H]$^-$
$C_{41}H_{49}N_3O_4$ (**3**)	647.9	−25 V: 646.6 (100) [**3** − H]$^-$; 621.4 (10) [**4** − H]$^-$
		−60 V: 603.4 (100) [**QM** − H]$^-$; 646.5 (10) [**3** − H]$^-$; 621.4 (10) [**4** − H]$^-$
$C_{42}H_{49}NO_4$ (**8**)	631.9	−40 V: 630.4 (100) [**8** − H]$^-$
		−120 V: degradation
$C_{41}H_{50}O_4$ (**9**)	606.8	−60 V: 605.5 (100) [**9** − H]$^-$; 591.5 (10) [**9** − CH_3]$^-$; 549.4 (10) [**9** − (Bu^t)]
$C_{41}H_{51}NO_4$ (**4**)	621.9	+20 V: 622.5 (100) [**4** + H]$^+$; 605.4 (80) [**QM** + H]$^+$
		+60 V: 605.4 (100) [**QM** + H]$^+$; 549.4 (85); 493.4 (45)
		+80 V: 605.4 (10) [**QM** + H]$^+$; 587.4 (10); 549.4 (10); 531.4 (10); 493.4 (40); 475.0 (10); 437.2 (100)
$C_{47}H_{63}NO_6$ (**5**)	738.0	+40 V: 738.8 (100) [**5** + H]$^+$
		+80 V: 738.6 (45); 605.4 (100) [**QM** + H]$^+$; 549.4 (75); 493.4 (45)
$C_{43}H_{55}NO_4$ (**6**)	649.9	+25 V: 651.2 (100) [**6** + H]$^+$
		+60 V: 651.2 (50); 605.4 (100) [**QM** + H]$^+$; 549.4 (30)
		+110 V: 651.2 (10); 605.4 (30) [**QM** + H]$^+$; 587.4 (15); 549.4 (10); 531.4 (30); 493.4 (15); 475.0 (30); 437.2 (70); 419.3 (100)
$C_{59}H_{64}O_4PCl$ (**7**, Cl)	868.0	+50 V: 867.6 (100) [**7**]$^+$
		+80 V: 867.6 (100); 605.4 (5) [**QM** + H]$^+$; 587.4 (5); 549.4 (25); 531.4 (5); 493.4 (40); 437.2 (30); 263.3 ($P(C_6H_5)_3$ + H]$^+$

According to Neureiter,[3c] addition of NEt_3 to **2** should lead to the quantitative formation of **QM**. This reaction was followed by ^{1}H-NMR in $CDCl_3$. The CH_2Cl resonance signal disappeared after addition of 1 equiv. of base, while the aromatic pattern was strongly modified, confirming the formation of a new species. Nevertheless, unambiguous specific methide proton signal did not clearly appear in the 5.50–6.20 ppm region.[6] Attempts to generate a stabilized variant of this quinone methide entity for a specific mass analysis[7] and the development of a crystallographic approach, failed until now.

EXPERIMENTAL

To prepare 5,11,17-tris(*p*-*tert*-butyl)-23-methylcalix[4]arene (**9**), a mixture of (*p*-formyl)tris(*p*-*tert*-butyl)calix[4]arene (0.25 g, 0.4 mmol), 5% Pd/C (0.03 g) and Na_2SO_4 (0.5 g) in 15 ml of EtOH was stirred at room temperature under H_2 overnight. The solid was filtered over Celite and rinsed with warm EtOH and CH_2Cl_2. The filtrates were evaporated to dryness and the residue was recrystallized from CH_2Cl_2–MeOH to give **9** (0.2 g;

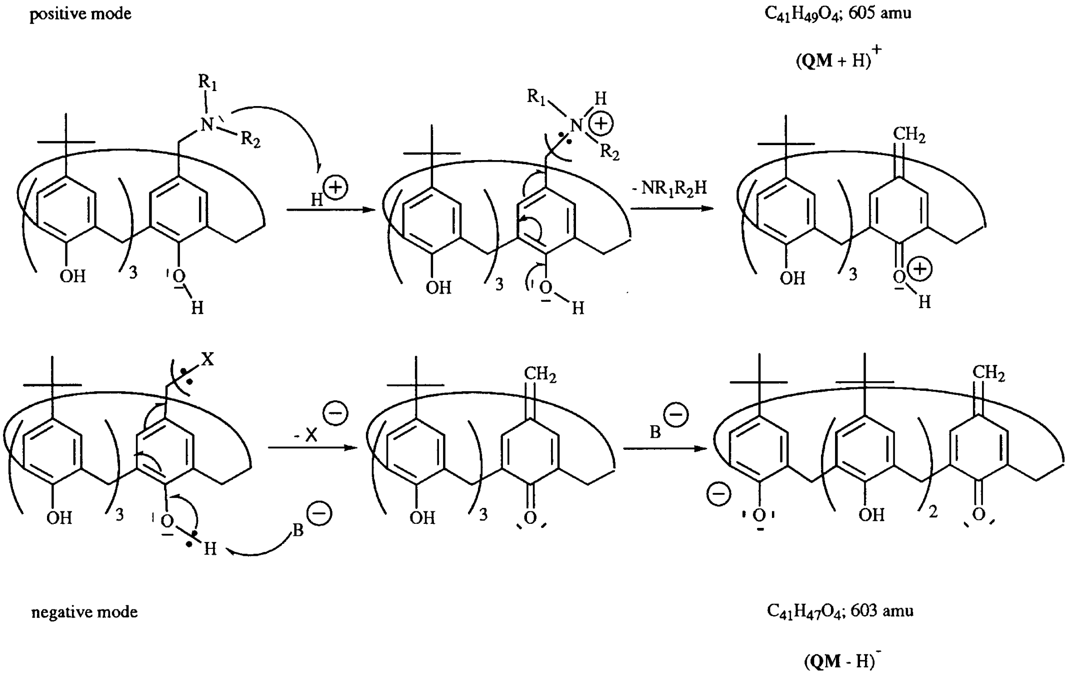

Figure 1. Schematic representation of the formation of calixarene quinone methide analytes in ESMS experiments.

80%). M.p. 349 °C; λ_{max} (CH_2Cl_2)/nm 279.5 (ε/dm^3 mol^{-1} cm^{-1} 10 600), 286.0 (sh, 8500). IR (KBr): 3140 (OH), 2970 (CH), 1200 cm^{-1} (C—OH). ^{1}H NMR, δ ($CDCl_3$ + TMS, 300.133 MHz, J values in Hz): 1.24 (s, 9H, Bu^t); 1.28 (s, 18H, Bu^t); 2.18 (s, 3H, Me); 3.54–4.29 (AB, $J_{AB} = 12.8$, 8H, bridge CH_2); 6.89 (s, 2H, Ar); 7.07 (s, 4H, Ar); 7.12 (s, 2H, Ar); 10.32 (s, 4H, OH). ^{13}C NMR, δ ($CDCl_3$ + TMS): 20.70 (Me); 31.46, 31.54 (Me, Bu^t); 32.34, 32.58 (bridged CH_2); 34.07, 34.12 (C, Bu^t); 125.71, 125.94, 126.12, 129.61 (3,5-Ar); 127.48, 127.79, 128.03, 128.38, 131.22, 144.50, 144.57, 146.35, 146.68, 146.83 (2,6-Ar, 4-Ar, 1-Ar). Found: C, 79.53; H, 7.85; O, 10.44. Calculated for $C_{41}H_{50}O_4$, 0.2 CH_2Cl_2 (623.83): C, 79.32; H, 8.14; O, 10.26%.

Mass spectra were obtained with a Platform Micromass apparatus (Service Central d'Analyse, CNRS, Solaize, France). Positive mode ionization profile of quinone methide (QM): m/z 605.4 $[QM + H]^+$; 549.4 $[QM - Bu^t + H]^+$; 493.4 $[QM - 2Bu^t + H]^+$; 437.2 $[QM - 3Bu^t + H]^+$; 587.4 $[QM - H_2O + H]^+$; 531.4 $[QM - H_2O - Bu^t + H]^+$; 475.0 $[QM - H_2O - 2Bu^t + H]^+$; 419.3 $[QM - H_2O - 3Bu^t + H]^+$.

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