SUBSTITUTION OF OH WITH NH$_2$ IN CALIX[4]ARENES:
AN APPROACH TO THE SYNTHESIS OF AMINOCALIXARENES

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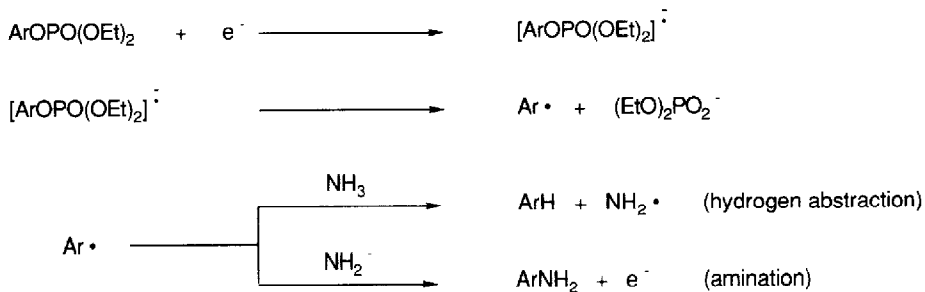University, Fukuoka 812, Japan

Abstract: From p-t-butylcalix[4]arene bis(diethylphosphate) ester(**1**),
monodehydroxymonoamino-p-t-butylcalix[4]arene(**3**) and diamino-p-t-butyl-
calix[4]arene(**4**) were synthesized in liquid ammonia-co-solvent in the
presence of KNH$_2$. This is the first successful example for the
substitution of the OH group with the NH$_2$ group.

Calix[n]arenes are n-meric metacyclophanes bearing OH groups on the lower
rim. These OH groups are conveniently used for introduction of functional
groups: e.g., ionophoric calix[n]arenes are readily derived by the reaction with
ethyl bromoacetate.[1-4] On the other hand, these OH groups act as an obstacle
when one wants to introduce functional groups other than the OR group. Thus, the
calixarene chemistry has been so far limited to that of "cyclic phenols".
Recently, Biali et al.[5,6] and Reinhoudt et al.[7] demonstrated that these OH groups
can be depleted (totally or partially) by the treatment of the diethylphosphate
esters with potassium metal in liquid ammonia. The finding provided a
possibility to introduce novel functional groups onto the lower rim. In fact,
Biali et al. attempted nitration of the OH depleted calix[4]arene but failed.[8]
We here report the first, successful example for the substitution of the OH
group with the NH$_2$ group. This is an important step to "aminocalixarenes" which
possibly serve as new macrocyclic ligands for transition metal cations.

1: R = OPO(OEt)$_2$

2: R$_1$ = R$_2$ = H
3: R$_1$ = H, R$_2$ = NH$_2$
4: R$_1$ = R$_2$ = NH$_2$
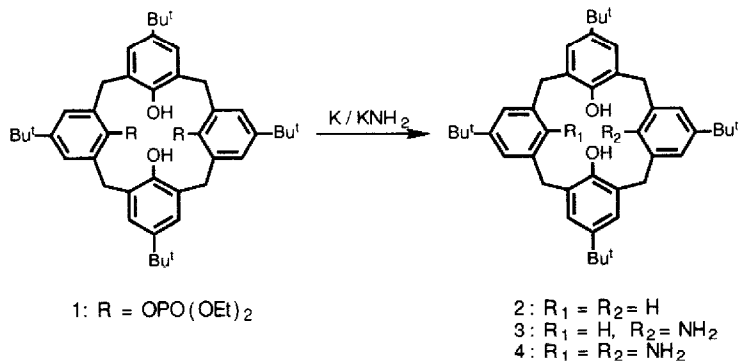
KNH$_2$ was prepared from potassium metal and Fe(NO$_3$)$_3$·9H$_2$O in refluxing ammonia(-33 °C). The solution was cooled to -78 °C. Potassium metal (in three portions) and compound 1[6,7](in co-solvent) were added simultaneously. This operation took about 30 minutes. The reaction was further continued for 1.0-1.2 h at -78 °C. After neutralization with NH$_4$Cl, the mixture was left at room temperature to remove ammonia. The residue was dissolved in ether-water(100 ml each), the ether layer being separated and dried over Na$_2$SO$_4$. The ether solution was evaporated to dryness and the residue was subjected to the column separation(silica gel-chloroform). The results are summarized in Table 1: mp 281-283 °C(lit.[6] 270 °C) for 2, 238.5-240.0 °C for 3, and 277.5-278.5 °C for 4. The products were identified on the basis of IR, mass, and NMR spectral evidence[9] and elemental analysis.

We first attempted the conversion of 2,6-dimethylphenyl diethylphosphate to 2,6-dimethylaniline according to the method described above (ammonia:ether = 50:6 v/v). We isolated 2,6-dimethylaniline in 95% yield. In the reaction with 1, on the other hand, compound 3 was isolated only in 19.0% yield. The main product was didehydroxylated 2(73.2 % yielded). The amination reaction of phenyl diethylphosphate occurs according to the following reaction scheme. Thus, amination to yield ArNH$_2$ basically competes with hydrogen abstraction to yield OH-depleted ArH. In amination of 1, amination becomes disadvantageous because of electrostatic repulsion between NH$_2^-$ and anionic calixarene radical 1$^{-(or 2-)}$ if one or two OH groups are dissociated. This is the main reason for the low yield.

ArOPO(OEt)$_2$ + e$^-$ ⟶ [ArOPO(OEt)$_2$]$^{\cdot-}$

[ArOPO(OEt)$_2$]$^{\cdot-}$ ⟶ Ar· + (EtO)$_2$PO$_2^-$

Ar· —— NH$_3$ ⟶ ArH + NH$_2$· (hydrogen abstraction)

—— NH$_2^-$ ⟶ ArNH$_2$ + e$^-$ (amination)

After trial-and-error experiments, we eventually found that the yield is significantly improved when the amount of co-solvent is increased. As shown in Table 1, the mixed solvent of ammonia(40ml)-THF(30ml) afforded not only **3**(42.3%) but also **4**(4.3%). The yields were further enhanced by the addition of HMPA. The role of co-solvents is now under investigation from a mechanistic view point.

Table 1. Reductive dehydroxylation and amination of **1**[a]

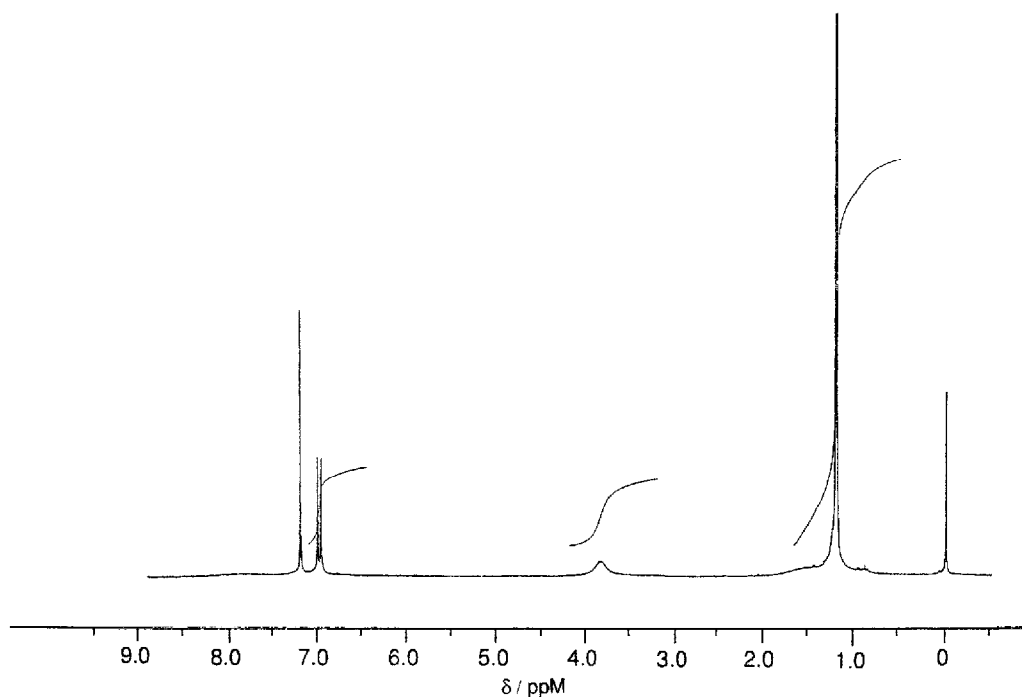| **1** /mmol	NH$_3$ /ml	Co-solvent	K(KNH$_2$) /mmol	K(e⁻) /mmol	Yield /%		
					2	**3**	**4**
3.3	150	ether(6 ml)	0	200	74.6	trace	0
1.1	50	ether(5 ml)	25	25	73.2	19.0	trace
2.2	40	THF(30 ml)	50	50	52.2	42.3	4.3
1.1	40	{THF(25 ml) HMPA(10 ml)}	25	25	46.3	44.5	7.8

[a] -78 °C, 1.0-1.2 h

Figure 1. ^{1}H-NMR spectrum of **4** (CDCl$_3$, 25 °C).

It is known that in ^{1}H-NMR spectroscopy, the ArCH$_2$Ar methylene protons in p-t-butylcalix[4]arene appears as a pair of doublets in CDCl$_3$ at room temperature.[10] This indicates that the rate of ring inversion is slower than the NMR time-scale, because the transition state of ring inversion requires the cleavage or rearrangement of the cyclic, intramolecular hydrogen-bonds among OH groups. The ArCH$_2$Ar methylene protons in **3** and **4** appeared as two singlets and one singlet, respectively, indicating that the rate of ring inversion is much faster(Figure 1).[9] The difference would be attributed to the loss of the cyclic hydrogen-bonding belt among OH groups or to the weak acidity of the NH$_2$ protons (in comparison to that of the OH proton). We are currently devoting our research efforts toward improvement of the amination yield as well as toward further characterization of novel aminated compounds **3** and **4**.

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9. Compound **2** was reported.[6,7] Compound **3**: IR(nujol) V_{OH} and V_{NH2} 3271 and 3354 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 25 °C) δ 1.27, 1.29, and 1.31 (t-Bu, s each, 9H, 18H, 9H), 3.86 and 3.91 (ArCH$_2$Ar, s, 4H each), 6.76 (intra-annular ArH, s, 1H), 7.10 (ArH, m, 8H); MS(EI) m/z 631(M$^+$), 616(M-CH$_3$)$^+$. Compound **4**: IR(nujol) V_{OH} and V_{NH2} 3272 and 3345 cm^{-1}; ^{1}H-NMR (CDCl$_3$, 25 °C) δ 1.19 and 1.22 (t-Bu, s, 18H each), 3.88 (ArCH$_2$Ar, s, 8H), 7.02 and 7.05 (ArH, s, 4H each); MS(EI) m/z 646(M$^+$), 631(M-CH$_3$)$^+$.
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