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Diazo-Coupling Reactions with Calix[4]arene. pK_a Determination with Chromophoric Azocalix[4]arenes

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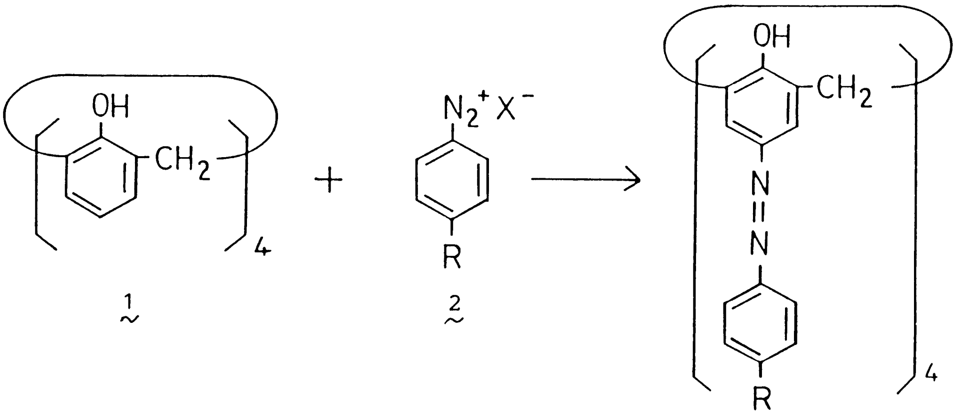
Six azocalix[4]arenes were synthesized for the first time by diazo-coupling reactions with calix[4]arene. The products showed unusual spectral properties including an azophenol - quinine-hydrazone tautomerism. Owing to the chromophoric nature, the four pK_a's for water-soluble p-(4-trimethylammoniopheylazo)calix[4]arene could be determined to be 0.5, 2.0, 10.0, and ca. 13. The marked pK_a split was explained by the strong hydrogen-bonding interactions characteristic of calix[4]arene.

The chemistry of cyclodextrins and crown ethers has been a focus of interest in host-guest chemistry for the last two decades. More recently, Gutsche and co-workers[1,2] have reported on a series of new cyclic oligomers called "calixarenes" which are expected to serve as the third supramolecular host for molecular recognition. Then, what is the principle advantage of calixarenes in comparison to cyclodextrins and crown ethers? We have currently been interested in the functionalization of calixarenes which may lead eventually to totally synthetic enzyme mimics.[3,4] In the course of our study, we recognized that a great number of substitution reactions developed for the modification of aromatic compounds are readily applicable to the functionalization of calixarenes.[4] Undoubtedly, the synthetic convenience is one of the characteristic advantages of calixarenes in comparison to cyclodextrins and crown ethers. Here, we report applications of the diazo-coupling reaction (know as the most typical substitution reaction in phenol derivatives) to calix[4]arene. The products (azocalix[4]arenes) displayed a pH-dependent spectral change. Owing to the chromophoric nature we could easily determine the pK_a of the OH groups. We have found that both the absorption spectra and the pK_a are very unusual because of strong intramolecular hydrogen-bonds among the OH groups.



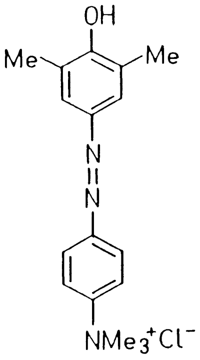
1 **2** **3**

The diazo-coupling reaction with calix[4]arene (**1**) was carried out by three different methods: (A) the reaction of **1** (1.1 mmol) with BF_4 salt of p-substituted benzenediazonium (**2**: 5.5 mmol) in tetrahydrofuran (THF: 20 ml) and pyridine (10 ml), (B) for R = SO_3^- the reaction of **1** with an intramolecular salt ($p\text{-}N_2^+\text{-}C_6H_4\text{-}SO_3^-$) in N,N-dimethylformamide (DMF) and pyridine, and (C) for R = $NMe_3^+Cl^-$ **2** prepared in water was mixed with a DMF solution containing **1** and pyridine. The results are summarized in Table 1. In every case the products (**3**) were identified by IR, NMR, and elemental analysis. Their melting points were higher than 300 °C but the color change was observed from 185 °C for **3**($R=SO_3^-$) and 170 °C for **3**($R=NMe_3^+Cl^-$).

We measured the pH-dependent spectral change in water-soluble **3**($R=NMe_3^+Cl^-$) as well as those in its analogs **4** and **5**. **4**(noncyclic analogue) gave λ_{max} at 358 nm (undissociated species) and 467 nm (dissociated species): the pK_a was estimated to be 8.0. The O-methylated derivative (**5**) (prepared by the reaction of **3**($R=NMe_3^+Cl^-$) with methyl iodide) gave λ_{max} at 343 nm, which is similar to that of undissociated **4**. It is known that 4-hydroxyazobenzene derivatives are subject to an azophenol (A) - quinone-hydrazone(QH) tautomerism and the λ_{max} for QH appears at longer wavelength region.[5,6] The spectral similarity between **4** and **5** supports the view that undissociated **4** exists mostly as an A form. In

Table 1. Syntheses of azocalix[4]arenes (**3**)

2	Method	Yield %
$R=NO_2$	A	39
R=Cl	A	54
R=H	A	60
$R=CH_3$	A	45
$R=SO_3^-$	B	86
$R=NMe_3^+Cl^-$	C	84



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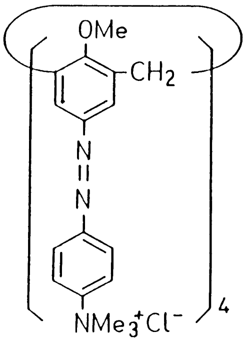

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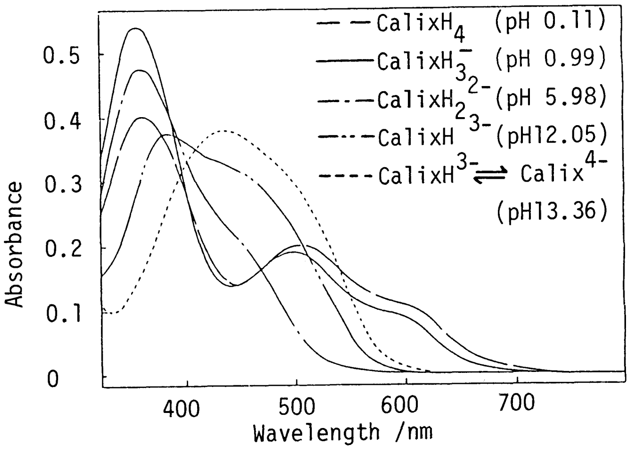


Fig. 1. Absorption spectra of 3(R= $NMe_3{}^+Cl^-$)(1.00×10^{-5} mol dm^{-3}) at 20 °C.

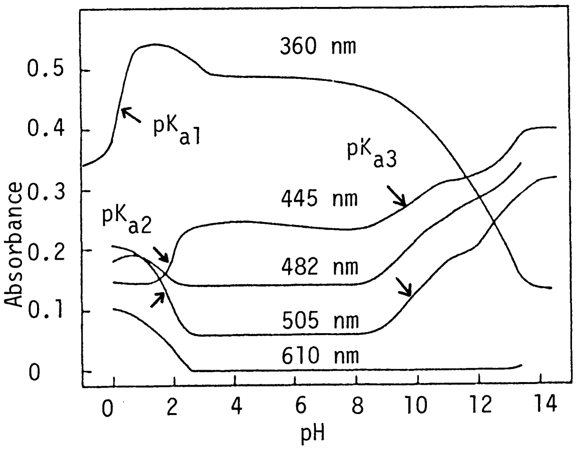
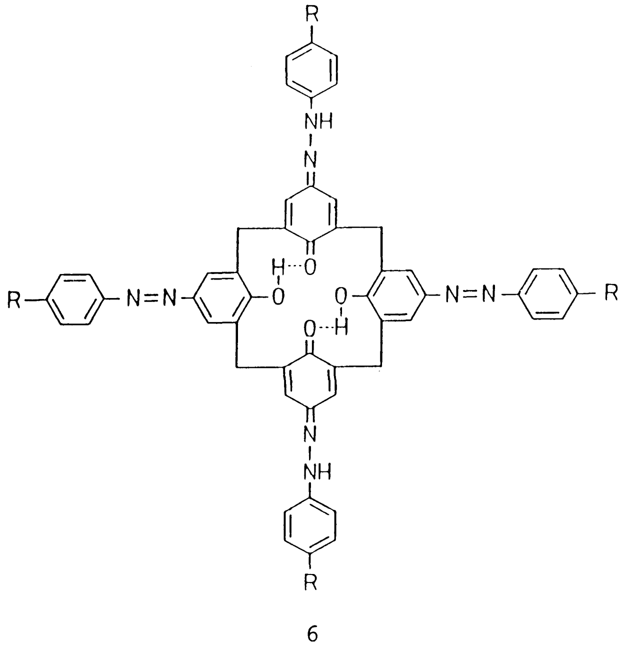


Fig. 2. pH Dependence of the absorption bands. Arrows indicate the absorbance changes used for pK_a determination.

contrast, undissociated 3($R=NMe_3{}^+Cl^-$) (abbreviated to $CalixH_4$) gave two absorption maxima at 360 and 505 nm (Fig. 1), which are assigned to A and QH, respectively. Since the absorbance at 360 nm is about two times that of undissociated 4, $CalixH_4$ should involve two A-form units in the ring. The situation substantiates the structure 6 which consists of two pairs of quinhydrone-like components.$^{7)}$ It is interesting to consider why 3($R=NMe_3{}^+Cl^-$) partly exists as a QH form whereas 4 exists as an A-form. According to the solvent effect on the A-QH tautomerism the QH form is more stabilized in protic (particularly, acidic) solvents.$^{5)}$ Conceivably, the QH-form units in $CalixH_4$ are stabilized by intramolecular hydrogen-bonds with the neighboring A-form units.



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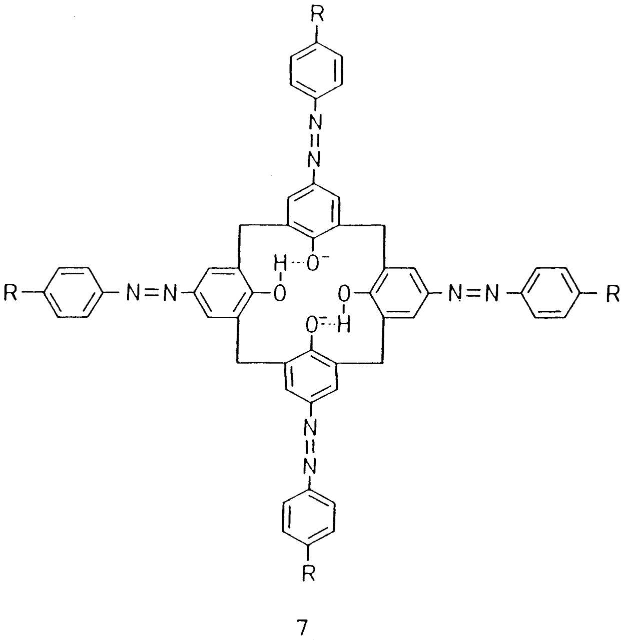

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The absorption spectrum for $CalixH_2^{2-}$ (at pH 5.98) is also peculiar because of two reasons: (i) the absorption band ascribable to the QH form disappears and (ii) the λ_{max} ascribable to the dissociated O^- units appears as a week shoulder. These findings are rationalized in terms of strong hydrogen-bonding interactions in calix[4]arene[1,2,8,9]: that is, the A form in the undissociated units is efficiently stabilized by the hydrogen-bonds with O^- while the intramolecular charge-transfer from O^- to NMe_3^+ is suppressed by the same hydrogen-bonds (structure 7). As a result the strong absorption band, characteristic of the intramolecular charge-transfer is scarcely observed for $CalixH_2^{2-}$ (and also for $CalixH^{3-}$). In Fig. 2, five absorption bands are plotted as a function of medium pH. From the spectral changes we estimated four pK_a's for $CalixH_4 \rightleftharpoons CalixH_3^- \rightleftharpoons CalixH_2^{2-} \rightleftharpoons CalixH^{3-} \rightleftharpoons Calix^{4-}$ to be 0.5, 2.0, 10.0, and ca. 13. Comparison with the pK_a of 4 (8.0) indicates that two pK_a's shift to acidic region by 7.5 and 6.0 whereas remaining two pK_a's shift to basic region by 2.0 and ca. 5. The remarkably large pK_a split is related to the strong hydrogen-bonding interactions in calix[4]arene.[1,2,8-10]

In conclusion, the present paper demonstrated that azocalixarenes, having chromophoric azo groups as well as pK_a-split OH groups, would behave as a new class of host molecules. Of particular interest are (i) solvent effects on the A-QH isomerism, (ii) metal selectivities, and (iii) metal-induced spectral changes. The studies are currently continued in these laboratories.

References

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7) The additional λ_{max} at 610 nm in $CalixH_4$ is possibly assigned to a charge-transfer transition between A and QH forms. The ^1H-NMR of $CalixH_4$ suggests that protons are not fixed, as illustrated in 6, but delocalized in the ring through a rapid exchange.
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10) The pK_a's for p-nitrocalix[4]arene were determined in 85.4 wt% $EtOH/H_2O$ at 25 °C by a potentiometric titration using tetrabutylammonium hydroxide to be pK_{a1} 2.9, pK_{a2} 10.9, pK_{a3} 12.3, $pK_{a4} > 13$, where the pK_a of p-nitrophenol is 8.67 in this solvent: p. Grootenhuis and D. N. Reinhoudt, private communication. These values show a good agreement with the present and previous data,[9] indicating that the strong hydrogen-bonding interactions cause the unusually large pK_a split.

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