(4 H, C_6H_4, J=9.5 Hz), 7.35 (*dd*, 1 H, 6-H, $J_{6,7}$=9.0 Hz, $J_{6,5}$=7.5 Hz), 7.54 (*dd*, 1 H, 7-H, $J_{7,5}$=1.8 Hz, $J_{7,6}$=9.0 Hz), 7.88 (*dd*, 1 H, 5-H, $J_{5,6}$=7.5 Hz, $J_{5,7}$=1.8 Hz); UV (MeOH) λ_{max} 221 nm (ε 27600), 245 infl (7100), 255 infl (4000), 278, infl (3300), 312 (13500); mass spectrum, *m/e* (%) 415 (3.9, M^+), 383 (23.7, M^+-CH_3OH), 351 (6.1, M^+-2CH_3OH), 324 (3.3), 125 (100, $ClC_6H_{CH_2}^+$).

Anal. Calcdl for $C_{21}H_{18}ClNO_6$ (415.83): C, 60.66; H, 4.36; Cl, 8.52; N, 3.37. Found: C, 60.52; H, 4.26; Cl, 8.34; N, 3.33.

Trimethyl 1-(2-Bromo-5-methoxyphenyl)methyl-1H-indole-2,3,4-tricarboxylate (4f). IR (KBr) 1736, 1718, 1709, 1600, 1571, 1522, 1452, 1443, 1433, 1370, 1346, 1292, 1260, 1220, 1195, 1170, 1128, 1054, 1010, 805, 755, 745 cm^{-1}; NMR (DMSO-d_6) δ 3.51 (*s*, 3 H, OCH_3), 3.79, 3.84, and 3.89 (all *s*, 3 H each, $COOCH_3$), 5.57 (*d*, 1 H, 6'-H, $J_{6',4'}$=3.0 Hz), 5.74 (*s*, 2 H, CH_2), 6.78 (*dd*, 1 H, 4'-H, $J_{4',3'}$=9.0 Hz, $J_{4',6'}$=3.0 Hz), 7.37 (*d*, 1 H, 3'-H, $J_{3',4'}$=9.0 Hz), 7.5-7.7 (*m*, 3 H, 5-, 6-, and 7-H); UV (MeOH) λ_{max} 249 nm (ε 6000), 255 (4000), 261 infl (2600), 310 (15600); mass spectrum, *m/e* (%) 491 (7.4 M^++2), 489 (7.4, M^+), 460 [10.8, (M^++2)-CH_3O], 459 [17.2, (M^++2)-CH_3OH], 458 (11.9, M^+-CH_3O), 457 (15.8, M^+-CH_3O), 379 (25.5), 378 (100, M^+-CH_3OH, Br), 201 (32.5, $^{81}Br(CH_3O)C_6H_3CH_2^+$), 199 (31.2, $^{79}Br(CH_3O)C_6H_3CH_2^+$).

Anal. Calcd for $C_{22}H_{20}BrNO_7$ (490.32): C, 53.89; H, 4.11; N, 2.86. Found: C, 54.26; H, 4.19; N, 2.93.

Reaction of 2g with Bromine. Following procedure 2 a 90% yield of the tribromo compound **5** was isolated, mp 176-179 °C (lit.[4] mp 172-175 °C) and spectral data agreed with the literature.[4]

Trimethyl 1-(2-Methylphenyl)methyl-1H-indole-2,3,4-tricarboxylate (4h). IR (KBr) 1750, 1715, 1686, 1652, 1583, 1433, 1331, 1284, 1245, 1220, 1140, 1006, 822, 791, 762 cm^{-1}; NMR ($CDCl_3$) δ 2.47 (*s*, 3 H, CH_3), 3.87, 3.98 and 4.03 (all *s*, 3 H each, $COOCH_3$), 5.73 (*s*, 2 H, CH_2), 6.22 (*dd*, 1 H, 6'-H, $J_{6'-5'}$=8.0 Hz, $J_{6',4'}$=2.0 Hz), 6.8-8.0 (*m*, 6 H, 5-, 6-, 7-H and 3'-, 4'-, 5'-H); UV (MeOH) λ_{max} 244 nm infl (ε 8100) 255 infl (4800), 310 (16200); mass spectrum, *m/e* (%) 395 (17.9, M^+), 365 (41.7), 364 (100, M^+-CH_3O), 363 (31.2), 348 (11.5), 105 (94.2, $CH_3C_6H_3CH_2^+$).

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References

1. Steck, E.A.; Brundage, R. P.; Feltcher, L. T. *J. Am. Chem. Soc.* **75,** 1117 (1953).
2. Eisner, U.; Kuthan, *J. Chem. Rev.* **72,** 1 (1972).
3. Tamura, Y.; Yoshimoto, Y. *Chem. Ind.* 888 (1980).
4. Lee, C. K.; Hahn, C. S.; Noland, *W. E. J. Org. Chem.* **43,** 3727 (1978).
5. Noland, W.E.; Lee, C.K. *J. Org. Chem.* **45,** 4573 (1980).
6. Elming, N.; Clauson-Kass, N. *Acta Chem. Scand.* **6,** 867 (1952).
7. Acheson, R.M.; Vernon, *J. M J. Chem.* Soc., 1148 (1962).
8. Jackman, L.M.; Sternhell, S. "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd Ed., Pergamon Press, New York, 1969, p. 202.

The Synthesis of *p*-Nitrocalix[4]arene

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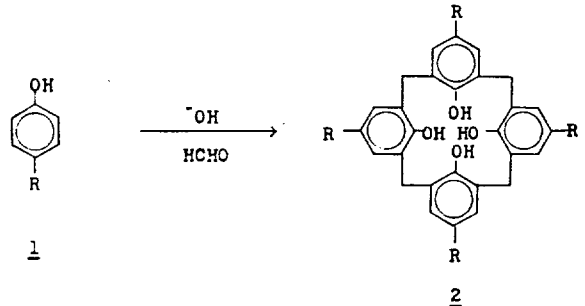
Methods for the preparation of *p*-nitrocalix[4]-arene via the direct substitution reaction of the *p*-*tert*-butylcalix[4]arene which is readily available with high yield from the base-induced direct condensation reaction procedure are described.

Introduction

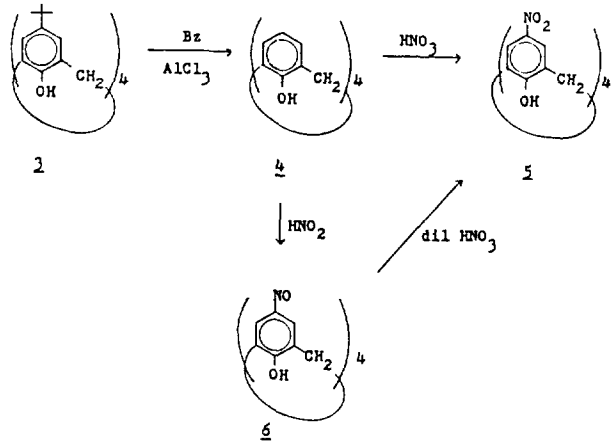
Attempts to construct in vitro systems that mimic the in vivo catalytic activity of enzymes have led chemists to give increase attention to compounds that contain cavities of sufficient diameter and depth to form host-guest complexes. Calixarenes, which are [1$_n$] metacyclophanes comprising cyclic arrays of phenolic residues attached by methylene groups at the positions *"ortho"* to the hydroxyl groups, are members of a small group of organic compounds that are basketlike in shape[1] and possess the potential for forming host-guest complexes in which the guest resides in a cavity completely within a single host molecule.

Since the interesting prospects for enzyme model building



Scheme I

have been proposed by Gutsche[2], various calixarenes have been tried to synthesize by the base-induced condensation reaction between p-substituted phenols with formaldehyde as shown on scheme I[3].



Scheme II

If calixarenes are to serve as enzyme mimics it is necessary that they carry functional groups of various types. The *p*-nitrocalix[4] arene can serve as admirable precursors for functional group introduction, for the *p*-nitro groups can be easily reduced to amino groups and then converted to diazonium ions.

However, the *p*-nitrocalix[4] arene was not able to obtain by the direct base-induced condensation reaction of *p*-nitrophenol with formaldehyde (R: $-NO_2$ on Scheme I). This provides the starting point for the work reported in the present paper where we prepared *p*-nitrocalix[4]arene **5** from *p-tert*-butylcalix[4]arene as described in scheme II.

p-tert-Butylcalix[4] arene **3** has become one of the most accessible of all the known macrocyclic cavity-containing compounds, obtainable in greater than 50 % yield from the direct condensation of *p-tert*-butylphenol and formaldehyde. Gutsche and coworkers[3a] prepared *p-tert*-butylcalix[4]arene using the "modifed Zinke-Cornforth procedure", which is a three step-one flask reaction involving (a) heating a solution of *p-tert*-butylphenol, 37 % formaldehyde, and aqueous NaOH solution for 45h at 50-55°C and 2h at 110-120°C, (b) neutralizing the solid with diluted HCl and then dried it, and (c) adding the solid to diphenyl ether and heating it for 2h at 210-220°C. Not only the yield of cyclic tetramer have varied from 0 % to as high as 35 %[4] but also various workers using the published procedures have frequently encountered difficulties in duplicating the reported results. In this work we slightly modified the published synthetic method in the final step (step c) as follows. The reaction temperature was increased to the boiling point of diphenyl ether (250-260°C) and the evolved water during the reflux was removed from the reaction flask. With these modifications the yield and reproducibility of product are improved substantially.

Aluminum chloride catalyzed de-*tert*-butylation has been shown to proceed in excellent yield[4,5], making calix[4]arene **4** an extremely attractive starting material for the preparation of various *p*-functionalized calix[4]arenes including title compound.

The ease of nitration of phenols is well known, and because they are liable to oxidation it is necessary to use nitric acid in some suitable solvent such as glacial acetic acid or chloroform. However, direct nitration of calixarenes was repeatedly attempted in the past without favorable results. Recently, Shinkai and coworkers[6] reported the preparation of *p*-nitrocalix[6]arene using an indirect substitution reaction of calix[6]arenehexasulfonate. We prepared *p*-nitrocalix [4]arene for the first time using a direct electrophilic substitution reaction. The dispersed solution of calix[4]arene **4** in benzene and glacial acetic acid was treated with conc.nitric acid to give the yellow colored product in 87 % yield. The structure of product was confirmed by spectral data. The ^{1}H-nmr resonance peak of the phenyl protons was down-field shifted by 1.35 ppm from 6.95 ppm of starting material to 8.30 ppm of the product due to the substitution of the strong electron withdrawing nitro groups on the phenyl rings. IR spectrum also showed two strong NO_2 stretching bands at 1530 and 1360 cm^{-1}.

The title compound can be prepared from calix[4]arene **4** by two-steps procedure as shown on scheme II. It was reported[7] that the *p*-nitrosophenol was prepared by treatment phenol in aqueous alkaline solution with $NaNO_2$ and then concentrated sulfuric acid. Following the Bridge's procedure, the calix[4]arene **4** was suspended in aqueous alkaline solution, treated with $NaNO_2$, acidified with 25 % sulfuric acid. Light brown colored *p*-nitrosocalix[4]arene was collected, washed with water. Without further purification, the *p*-nitrosocalix[4]arene was suspended into a diluted nitric acid solution and then oxidized to give *p*-nitrocalix[4]arene in 53 % yield. The physical and chemical properties of product was identical to the product obtained by the direct nitration method.

The preparations of various functionalized calix[4]arenes which can not be prepared by the direct base-induced condensation reaction of *p*-substituted phenol with formaldehyde are under investigation using the *p*-nitrocalix[4]arene as starting material.

Experimental

IR spectra were obtained by using a Perkin-Elmer 170B spectrophotometer and ^{1}H-nmr spectra were recorded on Varian EM 360A instrument, with TMS as internal standard. Analytical sample was dried for at least 24h at 150°C and 1-2 mmHg of pressure.

***p-tert*-Butylcalix[4]arene (3)** was prepared in 52% yield from *p-tert*-butylphenol and formaldehyde by following literature procedure[3a] with modification. To a 250m*l* round bottom flask were added 20.0g (0.133 mole) of *p-tert*-butylphenol, 20.0m*l* of 3N NaOH and 19.0m*l* of 35 % formaldehyde. The contents of the reaction flask were heated (oil bath) at 50-55°C for 45h, and then at 110-120°C for 2h to give a yellow solid. After cooling to room temperature the thick yellow mass was crushed into powder and then stirred with 10m*l* of 1N HCl for 1h to neutralized the base, and the pale yellow solid was removed by filtration, washed with water, and dried in an oven at 110-120°C for 30 min. To a 1*l* three-neck flask were added this yellow solid and 140g of diphenyl ether. The reaction mixture was refluxed at 250-260°C for 2h. During the reflux the evolved water was removed from the reaction flask using a Dean-Stark water trap. The reaction mixture was cooled, treated with 300m*l*

of ethyl acetate, and filtered to yield 10.98g of white solid, which was indicated by TLC to contain calix[4]arene as major product with or without a trace amount of cyclic octamer (calix[8]arene). This material was treated with 150m*l* of toluene, heated at relfux for 30 min, and filtered hot to remove insoluble mass. Upon cooling 8.74g of pure tetramer was deposited. Additional 1.25g of pure product was obtained from the concentration of toluene solution. Concentration of diphenyl ether solution deposited 1.30g of white crystals which were the pure cyclic tetramer. The total yield was 52 %: mp 344–346°C (literature 344–346°C)[3]; IR(KBr) 3160cm^{-1} (OH stretching); ^{1}H-nmr ($CDCl_3$) δ9.6 (s, 4, ArOH), 7.08 (s, 8, ArH), 3.90 (br, 8, CH_2), 1.26 (s, 36, *tert*-Butyl).

Calix[4]arene(4). A slurry of 4.39g (6.77 mmole) of *p-tert*-butylcalix[4]arene in 100m*l* of benzene was heated to 65–70°C and then treated with 5.42g (1.5 mole equivalent per *tert*-butyl group of **3**) of aluminum chloride. After stirring for 1h at 65–70°C, the reaction mixture was poured into 250m*l* of ice-cold diluted HCl solution. Benzene layer was collected, washed with water 5 times, dried over anhyd. $MgSO_4$. The orange-brown colored residue obtained from the evaporation of benzene was treated with methanol to collect 2.43g of slightly waxy solid, which was recrystallized from $CHCl_3$–methanol two times to yield compound **4** (2.13g, 74 %) as fine colorless powder: mp 315–317°C (literature 315–318°C)[4]; IR(KBr) 3120cm^{-1} (OH stretching), 730 (1,2,3-trisubstituted benzene); ^{1}H-nmr ($CDCl_3$) δ 10.37 (*s*, 4, ArOH), 7.19–6.72 (*m*, 12, ArH), 3.88 (br.*s*, 8, CH_2).

***p*-Nitrocalix[4]arene (5).** (a). Direct Nitration Method. A slurry of 4.51g (0.011 mole) of calix[4]arene **4** in 45m*l* of benzene and 36m*l* of glacial acetic acid was treated with 8.2m*l* of concentrated nitric acid in an ice bath. Stirring was continued for overnight. The yellow colored solid product was filtered, washed, in succession, with 50m*l* portions of benzene, water, ethanol and finally ether and then gently boiled with 50m*l* of chloroform to remove any remaining unreacted starting material to afford 5.63g (88 %) of the *p*-nitrocalix[4]arene as pale yellow colored powder: mp 348°C (decompose); IR(KBr) 3200cm^{-1} (OH stretching), 1530 and 1360 (NO_2 stretching); ^{1}H-nmr (DMSO-d_6) δ11.18 (*s*, 4, ArOH), 8.30 (*s*, 8, ArH), 4.08 (br.*s*, 8, CH_2).

Anal. Calcd. for $C_{28}H_{20}N_4O_{12}$; C, 55.74; H, 3.35: Found C, 55.68; H, 3.36. (b). Nitrosoation Method. A suspension of 3.62g (8.54 mmole) of calix[4]arene **4** in 70m*l* of water was treated with 1.78g NaOH in 17m*l* of water and 3.11g of $NaNO_2$, and cooled in an ice bath. To this suspension total 28m*l* of 25 % sulfuric acid was added dropwise. After the reaction mixture was stirred for 1h in an ice bath, brown colored solid was collected by filtration, washed with water several times. Without further purification this solid was added into 70m*l* of diluted nitric acid in small portions. Stirring was continued for 2h at 40°C. The yellow-brown colored solid was collected, washed, in succession, with 30m*l* portions of water, ethanol and ether and then dried, which was treated as the same way as above to yield a 2.73g (53 %) of *p*-nitrocalix[4]arene.

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References

1. C.D. Gutsche, *Acc. Chem. Res.*, **16,** 161 (1983).
2. C.D. Gutsche, T.C. Kung, M.L. Hsu, Abstracts of the 11th Midwest Regional Meeting of the ACS, Carbondale Ill, 1975, no. 517.
3. (a) C.D. Gutsche, B. Dhawan, K.H. No, R. Muthukrishnan, *J. Am. Chem. Soc.*, **103,** 3782 (1981). (b) A. Ninagawa, H. Matsuda, *Makromol. Chem. Rapid Commun.*, **3,** 65 (1982). (c) Y. Nakamoto, S. Ishida, *ibid.*, **3,** 705 (1982). (d) R. Buriks, A.R. Fauke, J.H. Munch, US patent 4,259,464 (1981).
4. C.D. Gutsche, J.A. Levine, *J. Am. Chem. Soc.*, **104,** 2652 (1982).
5. (a) M. Tashiro, *Synthesis,* 921 (1979). (b) D. Böhmer, H. Rathay, H. Kämmerrer, *Org. Prep. Proc. Int.*, **10,** 13 (1978).
6. S. Shinkai, T. Tsubaki, T. Sone, O. Manabe, *Tetrahedron Lett.*, **26,** 3343 (1985).
7. J.L. Bridge, *Ann. Chem.*, **277,** 85 (1983).