Tetrahedron Letters No. 24, pp 2213 - 2216.
0040-4039/79/0608-2213$02.00/0

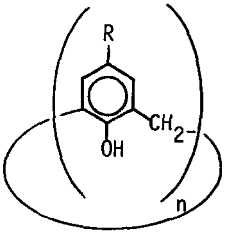
CALIXARENES. II. THE ISOLATION AND CHARACTERIZATION OF THE CALIX[4]ARENE AND THE *BISHOMOOXA*CALIX[4]ARENE FROM A *p-t*-BUTYLPHENOL-FORMALDEHYDE CONDENSATION PRODUCT

C. David Gutsche*, Ramamurthi Muthukrishnan, and Kwang Hyun No

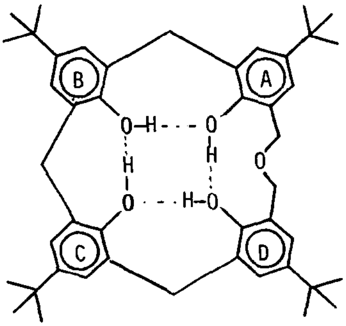
Department of Chemistry, Washington University, St Louis, Mo. 63130

Summary. The base-catalyzed condensation of *p-t*-butylphenol and formaldehyde, which yields a cyclic octamer (I, n=8) as the major product, has been shown to also yield a cyclic tetramer (I, n=4) and a *bishomooxa* cyclic tetramer (II).

The base-catalyzed reaction of *p*-substituted phenols and formaldehyde yields cone-shaped cyclic oligomers (I) to which the name *calixarene* has been assigned[1]. These compounds are of interest because of their ability to form complexes and, when appropriately functionalized, to be enzyme model candidates. The product from *p-t*-butylphenol and formaldehyde, originally assigned a cyclic tetrameric structure (I, n=4)[2], has recently been shown to be a mixture of materials[1] in which the major component is the calix[8]arene (I, n=8) accompanied by a small amount of a second material thought to be the calix[5]arene or calix[6]arene. It has now been discovered that when the reaction conditions are slightly changed two additional materials can also be isolated, and these are shown to be the calix[4]arene (I, n=4) and the *bishomooxa*-calix[4]arene (II).



I



II

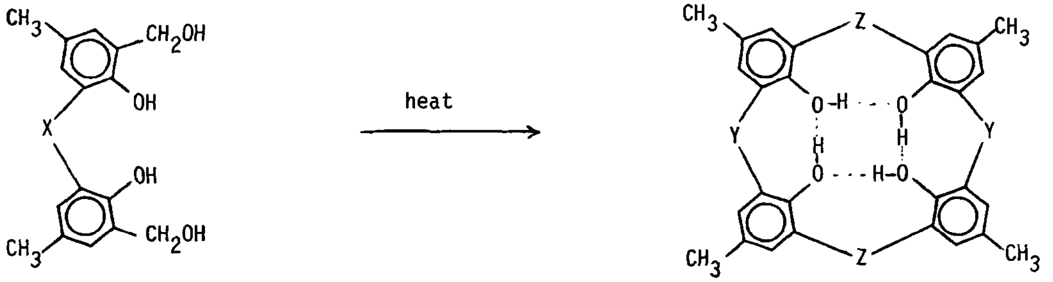
The highest melting component (mp 400-401^{o}C; designated as compound A) from the *p*-*t*-butylphenol/formaldehyde condensation product is obtained when the phenol concentration is 1.6 M in xylene and when the ratio of phenol/formaldehyde/KOH is 40/80/1. The recrystallized product (91% yield) presumably is identical with the major component in the Zinke and Ziegler preparation[2] and the higher-melting component in the Cornforth et al[3] preparation; it is the compound for which a cyclic octameric structure has been established[1]. From the mother liquors of the crystallization it is possible to isolate *ca* 5% of a second compound (mp 367-369^{o}C; designated as compound B) for which a cyclic pentameric or hexameric structure has been suggested[1]. The presence of trace amounts of a third compound is indicated by tlc. When the condensation reaction is carried out under similar conditions but with a 0.8 M concentration of *p*-*t*-butylphenol in xylene and with a phenol/formaldehyde/KOH ratio of 4/8/1 (*i.e.*10 times as much base) the yield of the third component (mp 343-345^{o}; designated as compound C) increases to 14%, the yield of compound A drops to 65%, and little or no compound B is detected. Compound C is isolated as a colorless solid after recrystallization from chloroform-methanol: mp 343-345^{o}C (dec); IR (KBr) 3160 cm^{-1};^{1}H NMR$_{Me_4Si}$ (CDCl$_3$) δ 7.28 (s, 1, ArOH), 7.08 (s, 2, ArH), 4.4-3.0 (br s, 2, CH$_2$), 1.26 (s, 9, C(CH$_3$)$_3$);^{13}C NMR $_{Me_4Si}$(CDCl$_3$) δ 31.2 (84%), 31.6 (100%), 32.8 (27%), 126.4 (45%), 128.3 (40%); mass spec (E.I., 90 eV) m/e 648 (100%), 649 (48%), 650 (13%); Anal. calcd for $C_{44}H_{56}O_4.CHCl_3$ C,70.68; H,7.19 (Found C,71.00; H,7.50).

The ^{1}H NMR, ^{13}C NMR, IR, and mass spectra of compound C are in agreement with a cyclic tetrameric structure, and this assignment has been conclusively established by comparison with material obtained by a "stepwise" synthesis according to the method of Hayes and Hunter[4]. The product of the stepwise synthesis, mp 341-343^{o}C, has spectral characteristics identical with those of compound C, and a mixed mp determination shows no depression in mp. Kämmerer and Happel[5] have also reported the stepwise synthesis of the cyclic tetramer from *p*-*t*-butylphenol.

Thin layer chromatography of the preparation described above indicates the presence of still another compound, designated as compound D, whose isolation in pure form is difficult. Compound D proved to be more accessible from a reaction in which the concentration of *p*-*t*-butylphenol is 0.8 M in xylene and the ratio of phenol/formaldehyde/KOH is 80/160/1 (*i.e.*half as much base as in the original experiment in which compound A is the major product). In this case 2.4 g. (37%) of xylene-insoluble product (compound A) can be separated by filtration and the xylene then removed from the filtrate by evaporation under vacuum at *ca* 50°C to leave a residue which, upon trituration with 15 mL of hexane, affords 3.6 g. (54%) of a colorless solid; shrink at 340°C and dec at 350°C. A tlc of this material shows one major component but also indicates the presence of compounds A, B, and C in small amounts. Two recrystallizations from methylene chloride-methanol produces 1.8 g. (22%) of compound D as colorless, fine needles: dec at 350°C; IR (KBr) 3300 (OH), 1076 cm^{-1}(aliphatic C-O stretch); ^1H NMR $_{Me_4Si}$ ($CDCl_3$) δ 9.60 (s, 2, OH on rings B and C), 8.92 (s, 2, OH on rings A and D), 7.3-6.8 (m, 8, ArH), 4.60 (s, 4, $ArC\underline{H}_2OC\underline{H}_2Ar$ between rings A and D), 3.85 (s, 6, $ArC\underline{H}_2Ar$), 1.26 (s, 36, $C(CH_3)_3$); ^{13}C NMR_{Me_4Si} ($CDCl_3$) δ 31.3 (100%, $C(\underline{C}H_3)_3$), 31.4 (21%, $Ar\underline{C}H_2Ar$), 32.8 (8%, $\underline{C}(CH_3)_3$), 34.0 (12%, $Ar\underline{C}H_2O\underline{C}H_2Ar$), 122.4 (15%, Ar), 125.3 (21%, Ar), 126.0 (24%, Ar), 126.4 (23%, Ar), 127.5 (17%, Ar), 128.2 (21%, Ar), 139.2 (3%, Ar), 142.2 (4%, Ar), 143.7 (9%, Ar), 144.9 (8%, Ar), 147.5 (15%, Ar), 151.3 (12%, Ar); osmometric molec. wt. ($CHCl_3$, 37°C) 681 (calcd 678); mass spec (E.I., 90 eV) m/e 678 (100%), 679 (54%), 680 (16%); Anal. calcd. for $C_{45}H_{58}O_5$ C,79.64; H,8.55 (Found C,79.47; H,8.70). The compound initially isolated from the recrystallization described above proved to be a CH_2Cl_2 complex of compound D, as indicated by a ^{13}C NMR resonance at δ 71.3 (CH_2Cl_2) and an elemental analysis in reasonably good agreement with a 1:1 complex; Anal. calcd. for $C_{45}H_{58}O_5 \cdot CH_2Cl_2$ C,72.34; H,7.80, Cl,9.30 (Found C,73.06; H,8.06; Cl,10.17). Treatment of compound D with acetyl chloride in pyridine yields the tetraacetate of compound D as colorless crystals after three recrystallizations from 95% ethanol: mp 282-287°C; IR (KBr) 1762 (C=O), 1100 ($ArCH_2$-O stretch), 1020 cm^{-1} ($OCOCH_3$); osmometric molec. wt. ($CHCl_3$, 37°C) 868 (calcd 846); Anal. calcd. for $C_{53}H_{66}O_9 \cdot H_2O$ C,73.60; H,7.87 (Found C,73.59; H,7.70).

The elemental analysis of compound D is in agreement with a $C_{45}H_{58}O_5$ formula, the osmometric and mass spectral determinations indicate a molecular weight of 678, the IR shows an aliphatic C-O stretching mode, the ^1H NMR possesses two different types of CH_2 groups in a ratio of 3:2, and the ^{13}C NMR indicates the presence of twelve sets of non-equivalent aromatic carbons. This constitutes a set of data that is in complete accord with structure II for compound D, *viz.* a cyclic tetramer having three $ArCH_2Ar$ bridges and one $ArCH_2OCH_2Ar$ bridge which can be designated as a *bishomo (i.e.* two additional atoms in the cyclic array) *oxa (i.e.* oxygen in place of a carbon) calix[4]arene.

Compounds similar to II but having two oxygens (compound IV)[6] and four oxygens (compound V)[7] in the ring have been prepared, although in extremely low yield, by heating *o,o'-bis*hydroxymethyl compounds of structure III, suggesting that II is formed in a thermal process from a *o,o'-bis*hydroxymethyl linear tetramer. Why seemingly small changes in phenol and base concentration change the ratio in which compounds A, B, C, and D are formed in the *p-t*-butylphenol/formaldehyde condensation, however, remains puzzling, and work is continuing in an effort to understand this reaction in more detail.



III (X = CH_2 or CH_2OCH_2)

IV (Y = CH_2, Z = CH_2OCH_2)
V (Y = Z = CH_2OCH_2)

Acknowledgment. This research was supported by grant GM-23534 from the National Institutes of Health. We are indebted to Mr. Ralph Fuhrhop of the Monsanto Co for the mass spectral data.

REFERENCES

(1) C. D. Gutsche and R. Muthukrishnan, J. Org. Chem., *43*, 4905 (1978).

(2) A. Zinke and E. Ziegler, Chem. Ber., *77*, 264 (1944); A. Zinke, G. Zigeuner, K. Hossinger, and G. Hoffman, Monatsh., *79*, 438 (1948); A. Zinke, R. Kretz, E. Leggewie, and K. Hossinger, ibid., *83*, 1213 (1952).

(3) J. W. Cornforth, P. D'A Hart, G. A. Nichols, R. J. W. Rees, and J. A. Stock, Brit. J. Pharmacol., *10*, 73 (1955).

(4) B. T. Hayes and R. F. Hunter, J. Appl. Chem., *8*, 743 (1958).

(5) H. Kämmerer and G. Happel, Makromolec. Chem.,*179*, 1199 (1978), report a mp of 329°C.

(6) H. von Euler, E. Adler, and B. Bergstrom, Ark. Kemi Mineral Geol., *14B*, Nr. 30 (1941).

(7) H. Kämmerer and M. Dahm, KunstspPlast (Solothurn, Switz), *6*, 20 (1959).

(Received in USA 27 December 1978)