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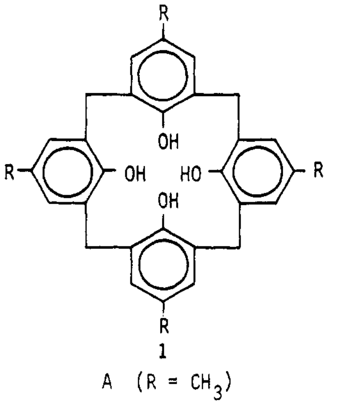
Calixarenes. 1. Analysis of the Product Mixtures Produced by the Base-Catalyzed Condensation of Formaldehyde with Para-Substituted Phenols

Summary: The products obtained from the base-catalyzed condensation of formaldehyde with several para-substituted phenols have been shown to be mixtures of two or more components which appear to be cyclic oligomers with five or more aromatic units in the cyclic array.

Sir: The recent publication[1] of a method for the preparation of compounds thought to have structure **1A–E** and the subsequent appearance of these compounds on the commercial market[2] prompts us to publish a preliminary account of our experiments with these materials to which we have given the name *calixarenes.*[3]



1

A (R = CH_3)
B (R = $C(CH_3)_3$)
C (R = C_6H_5)
D (R = OCH_3)
E (R = CO_2CH_3)

In 1944 Zinke and Ziegler[4] obtained high melting solids from the reaction of para-substituted phenols and formaldehyde, and they assigned a cyclic tetrameric structure (i.e., **1**) to these compounds. This assignment has gained acceptance as the result of X-ray crystallographic data by Cornforth et al.[5] (who obtained crystal lattice constants that are not incommensurate with a cyclic tetramer) and the stepwise synthesis of Hayes and Hunter,[6] repeated and extended by Kämmerer and co-workers.[7] Data recently obtained in our laboratory, however, are difficult to reconcile with some of these earlier observations, and the structures of these compounds appear to be less well established than had been supposed.

The synthesis of calixarenes by the "direct" method by Zinke and Ziegler[4] involves treating para-substituted phenols in aqueous base with formaldehyde for 45 h at 50–55 °C, acidifying the reaction mixture with dilute acid, separating an oil which solidified on heating at 110–120 °C, and heating this solid in linseed oil at 200–220 °C. Cornforth and coworkers[5] used a similar procedure but substituted Dowtherm for linseed oil. A shorter method was worked out several years ago by J. H. Munch[8] in which the phenol and paraformaldehyde are dissolved in xylene and treated with a small amount of concentrated aqueous potassium hydroxide, and the mixture is refluxed for several hours to yield the product as an easily separable precipitate. The recently published method[1] represents only a slight modification of the Munch method, substituting tetralin for xylene and potassium *tert*-butoxide for potassium hydroxide.[9] However, a comparison of the products from these two methods has revealed some differences in yield, melting points, and IR spectra, and solvent extraction–partition procedures and TLC separations of trimethylsilyl derivatives have shown that the products from paraformaldehyde and *p*-cresol, *p*-*tert*-butylphenol, *p*-phenylphenol, or *p*-carbomethoxyphenol are mixtures of two or more compounds produced in somewhat different ratios by the two methods.

The product from *p*-*tert*-butylphenol and formaldehyde prepared by the "direct" method proved to be amenable to purification by simple recrystallization and, therefore, was selected for the initial experiments aimed at gaining further insight into the calixarene structures. The crude product, mp 361–372 °C, was twice recrystallized from chloroform to give colorless, fine needles: mp 400–401 °C; IR (KBr) 3230 cm^{-1}; IR ($CHCl_3$) 3200 cm^{-1}; ^1H NMR (Me_4Si, pyridine-d_5) δ 7.33 (br, 2, ArH), 4.18 (br, 2, CH_2), 1.28 (s, 9, $C(CH_3)_3$); ^{13}C NMR (Me_4Si, $CDCl_3$) δ 21 (89%, $C(\mathbf{CH_3})_3$), 24 (17.5%, $\mathbf{C}(CH_3)_3$), 26.5 (30%, $Ar\mathbf{CH_2}Ar$), 131.5 (92%, Ar), 141 (100%, Ar), 156 (25%, Ar), 162 (30%, Ar); osmometric molecular weight 1330 ($CHCl_3$ at 37 °C), 1400 (pyridine at 37 °C), 1225 (pyridine at 65 °C) (calcd for octamer, 1296). The trimethylsilyl derivative was obtained as colorless needles from hexane–acetone: mp 356–358 °C; IR (KBr) 1251 and 841 cm^{-1} (CSi); ^1H NMR (Me_4Si, CCl_4) δ 6.86 (m, 2, ArH), 3.83 (br s, 2, CH_2), 1.20 (s, 9, $C(CH_3)_3$), −0.02 (s, 3, $Si(CH_3)_3$); ^{13}C NMR (Me_4Si, $CDCl_3$) δ 0.8 (53%, $Si(CH_3)_3$), 30.3 (100%, $C(\mathbf{CH_3})_3$), ~31 (very weak, $\mathbf{C}(CH_3)_3$), 32.8 (15%, CH_2), 124.4 (28%, Ar), 128.8 (43%, Ar), 141.7 (19%, Ar), 148.2 (10%, Ar); mass spectrum (EI, 90 eV) *m/e* 1872 (100%, octamer), 936 (13%, tetramer).

From the mother liquors of the crystallization of the higher melting calixarene from *tert*-butylphenol a lower melting fraction was obtained. A sample of this material was converted to the trimethylsilyl derivative, purified by TLC, and hydrolyzed to yield a compound with mp 367–369 °C: IR (KBr)

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3400 (shoulder), 3150 cm^{-1}; ^{1}H NMR (Me_4Si, CD_2Cl_2) δ 10.2 (s, 1, Ar**OH**), 7.10 (s, 2, ArH), 3.88 (s, 2, CH_2), 1.25 (s, 9, $C(CH_3)_3$); ^{13}C NMR (Me_4Si, $CDCl_3$) δ 31.4 (100%, $C(\mathbf{CH}_3)_3$), 33.1 (25%, $\mathbf{C}(CH_3)_3$), 34.0 (17%, $Ar\mathbf{C}H_2Ar$), 126.1 (64%, Ar), 126.9 (40%, Ar), 144.2 (15%, Ar), 147.2 (15%, Ar); mass spectrum (FD) *m/e* 972 (hexamer). The trimethylsilyl derivative was obtained as colorless crystals from methylene chloride–methanol: mp 235–240 °C; IR (KBr) 1251 and 841 cm^{-1} (CSi); ^{1}H NMR (Me_4Si, CD_2Cl_2) δ 7.2–6.7 (m, 10, ArH), 4.7–3.3 (m, 10, CH_2), 1.40 (s, 9, 20% of $C(CH_3)_3$), 1.25 (s, 36, 80% of $C(CH_3)_3$), 0.35 (s, 36, 80% of $Si(CH_3)_3$), −0.80 (s, 9, 20% of $Si(CH_3)_3$; osmometric molecular weight ($CHCl_3$ at 37 °C) 1187 (calcd for pentamer, 1170).

The data for both the higher and lower melting compounds are entirely compatible with cyclic oligomeric structures. Linear oligomers from *p-tert*-butylphenol and formaldehyde have been prepared,[11] and all have considerably lower melting points (generally below 250 °C) and considerably more complex ^{13}C NMR spectra than the compounds described above. The appearance of only four resonances for the aromatic carbon atoms in the ^{13}C NMR spectrum of these compounds provides strong support for a symmetrical structure, for which cyclic oligomers are the most obvious candidates. That neither of these compounds is the cyclic tetramer, however, is indicated by the melting points of 400 and 367 °C, both of which are much higher than the 329 °C reported for the cyclic tetramer prepared by Kämmerer and Happel[12] using the stepwise synthesis of Hayes and Hunter.[6]

In similar fashion the crude product from the condensation of *p*-cresol and paraformaldehyde was shown to contain 60% of a compound with mp 383–386 °C and 30% of a compound that decomposes at ~430 °C, which are indicated by mass spectral and osmometric molecular weight determinations to be the cyclic heptamer and cyclic octamer, respectively. That neither is the cyclic tetramer is indicated, as in the previous case, by their melting points, which are much higher than the 320 °C reported for the cyclic tetramer prepared by a stepwise synthesis.[6,7,12]

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