

CHROM. 15,962

## SYNTHESIS AND STATIONARY PHASE PROPERTIES OF BROMOPHENYL ETHERS

SUBHASH C. DHANESAR and COLIN F. POOLE\*

*Department of Chemistry, Wayne State University, Detroit, MI 48202 (U.S.A.)*

(Received May 2nd, 1983)

---

### SUMMARY

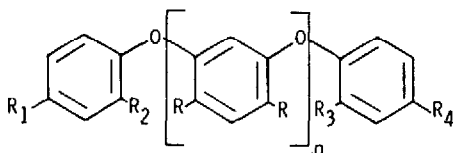
Electrophilic bromination is shown to be a useful reaction for the site-specific bromination of phenyl ethers containing from two to seven benzene rings. Compared to the phenyl ether stationary phases used in gas chromatography, bromination primarily raises the lower and upper operating temperatures, generally leads to a reduction in the efficiency of column packings and changes the selectivity and polarity of the phases only to a small extent. The three-ring bromophenyl ether, 1,3-dibromo-4,6-bis(4-bromophenoxy)benzene is shown to have the most useful stationary phase properties for the separation of organic compounds with a useable temperature range of 80–200°C.

---

### INTRODUCTION

Several years ago work commenced in our laboratory aimed at the preparation of thermally stable polar reference phases for gas chromatography (GC). Such phases would be usable at high temperatures, contain polar/selective functional groups and have a well-defined non-polymeric structure reproducible via synthesis. After several trials, two possible solutions to the above problem have been developed: the substituted phenyl ethers<sup>1-3</sup> and the organic molten salts<sup>4,5</sup>. The phenyl ethers were selected for study because of their simple structure, chemical stability and remarkably low volatility for such low-molecular-weight compounds<sup>6</sup>. Commercial applications of the phenyl ethers take advantage of these properties, and phenyl ethers with different ring numbers are used as stationary phases in GC, lubricants for engines operated in extreme environments and as diffusion pump fluids in vacuum apparatus.

Mathews *et al.*<sup>7</sup> have prepared polysulfones by copolymerizing five or six ring phenyl ethers with diphenyl ether-4,4'-disulfonyl chloride. These polymers are useful high temperature polar phases which are commercially available. The approach we have taken is to explore several reactions for the site-specific introduction of reactive functional groups into the phenyl ether backbone<sup>1</sup>. These reactive centers provide points to which side chain groups containing any desired chromatographic selectivity can be attached. The most versatile reaction for providing site-specific reaction centers is thallium acetate catalyzed electrophilic bromination<sup>2</sup>. Under controlled con-



- PPE-1  $R_1 = R_2 = R_3 = R_4 = R = H$ ,  $n = 3$ ; 1,3-bis(3-phenoxyphenoxy)benzene
- PPE-2  $R_1 = R_4 = R = Br$ ,  $R_2 = R_3 = H$ ,  $n = 3$ ; 1,3-dibromo-4,6-bis[2,4-dibromo-5(4-bromophenoxy)phenoxy]benzene
- PPE-3  $R_1 = R_2 = R_3 = R_4 = R = Br$ ,  $n = 3$ ; 1,3-dibromo-4,6-bis[2,4-dibromo-5(2,4-dibromophenoxy)phenoxy]benzene
- PPE-6  $R_1 = R_2 = R_3 = R_4 = R = H$ ,  $n = 1$ ; 1,3-bis[phenoxy]benzene
- PPE-7  $R_1 = R_4 = R = Br$ ,  $R_2 = R_3 = H$ ,  $n = 1$ ; 1,3-dibromo-4,6-bis[4-bromophenoxy]benzene
- PPE-8  $R_1 = R_2 = R_3 = R_4 = R = H$ ,  $n = 5$ ; 1,3-bis[3-phenoxyphenoxy]benzene
- PPE-9  $R_1 = R_2 = R_3 = R_4 = R = Br$ ,  $n = 5$ ; 1,3-dibromo-4,6-bis[2,4-dibromo-5(2,4-dibromo-5((2,4-dibromophenoxy))phenoxy)phenoxy]benzene

Fig. 1. Structure and nomenclature of the phenyl and bromophenyl ethers used in this study.

ditions bromination occurs at positions *para* to the ether bond. More forcing conditions result in *para* substitution in all rings as well as *ortho* substitution in the terminal phenyl rings. Yields are often quantitative and minimal purification of the reaction products is required. On account of the above properties, and the availability of a wide range of bromophenyl intermediates, it was considered worthwhile to investigate their stationary phase properties. This might also yield useful information concerning the affect of substitution on the physical, chemical and chromatographic properties of the phenyl ethers.

The structures, abbreviations and systematics names for the phenyl and bromophenyl ethers used in this study are given in Fig. 1. The compounds PPE-7 and PPE-9 were prepared for the first time. The synthesis of PPE-6 is an improvement over published procedures<sup>8</sup>.

## EXPERIMENTAL

Thallium(III) acetate sesquihydrate, copper powder, phenol and *m*-dibromobenzene were obtained from Aldrich (Milwaukee, WI, U.S.A.). PPE-1 and PPE-8 were obtained from Monsanto (St. Louis, MO, U.S.A.). The preparation of 4,4'-dibromodiphenyl ether (DPE-2), 2,2',4,4'-tetrabromodiphenyl ether (DPE-3), PPE-2 and PPE-3 has been described previously<sup>2</sup>.

### General methods for preparing bromophenyl ethers

*1,3-Bis(phenoxy)benzene (PPE-6)*. PPE-6 was prepared by a modification of ref. 8. Phenol (0.2 mol), potassium hydroxide 86% (w/w) (0.1 mol) and copper powder (1.0 g) were heated with stirring to 180°C under a nitrogen atmosphere. To the mixture was added dropwise *m*-dibromobenzene (0.03 mol) while maintaining a

temperature of  $180 \pm 5^\circ\text{C}$  during the exothermic reaction. The progress of the reaction was monitored by high-performance liquid chromatography (HPLC). Periodically small aliquots were removed by pipette, added to water and extracted with carbon tetrachloride. Three products were observed in the chromatogram of the organic phase corresponding to *m*-dibromobenzene, *m*-bromophenyl ether and PPE-6. Further quantities of phenol and copper powder were added as required to drive the reaction to completion. After 5-h reflux the reaction was essentially 95% complete. The reaction mixture was cooled to room temperature, poured into water (200 ml) and extracted with carbon tetrachloride. The organic layer was washed several times with water, dried over sodium sulfate and the solvent removed *in vacuo*. The light yellow oil was brominated without further purification. Distillation at reduced pressure ( $210\text{--}212^\circ\text{C}$  at 10 mmHg) gave authentic samples of PPE-6 for stationary phase evaluation.

*1,3-Dibromo-4,6-bis(4-bromophenoxy)benzene (PPE-7)*. To PPE-6 (0.02 mol) in carbon tetrachloride (100 ml) was added thallium acetate sesquihydrate (1.5 g) and the mixture stirred in the dark for 0.5 h. Bromine (0.08 mol) in carbon tetrachloride (25 ml) was added dropwise and the mixture stirred at room temperature for 0.5 h. The mixture was then heated to reflux for approximately 8 h. The reaction was monitored by HPLC and further quantities of catalyst added as required to give an essentially quantitative yield of PPE-7. The reaction mixture was cooled to room temperature, poured into sodium bicarbonate solution, the organic phase collected and washed with sodium bicarbonate solution and water, dried over sodium sulfate and the solvent removed on a Rotovapor. PPE-7 was obtained as a viscous light yellow oil giving a single peak on HPLC. Its structure was confirmed by NMR spectroscopy [7.90 (singlet), 7.50 (doublet), 6.90 (doublet) and 6.70 ppm (singlet)].

*1,3-Dibromo-4,6-bis{2,4-dibromo-5-[2,4-dibromo-5-(2,4-dibromophenoxy)-phenoxy]phenoxy}benzene (PPE-9)*. To PPE-8 (6.1 g) in carbon tetrachloride (150 ml) was added thallium acetate sesquihydrate (1.5 g) and the mixture stirred in the dark for 0.5 h. A mixture of bromine (19 g) in carbon tetrachloride (50 ml) was added dropwise followed by stirring at room temperature for 0.5 h. The mixture was heated to reflux for a few hours, cooled and the clear supernatant transferred to a second flask leaving behind a muddy precipitate containing catalyst and impurities originally present in PPE-8. Refluxing was continued with a fresh addition of a small amount of catalyst and bromine (5 g). Progress of the reaction was monitored by HPLC and was complete after about 105 h. The reaction mixture was worked-up as described for PPE-7. Preparative HPLC was used for final purification to give PPE-9 as a viscous yellow oil in about 85% yield. The oil crystallized slowly on standing to give a solid, m.p.  $93\text{--}95^\circ\text{C}$ . Its structure was confirmed by NMR spectroscopy [8.06 (doublet), 7.90 (doublet), 7.70 (singlet), 7.05 (singlet) and 6.80 ppm (singlet)].

#### HPLC analysis

Reversed-phase HPLC was used to monitor the progress of the synthesis of the above compounds and to establish the final product purity. A Varian 5000 gradient-elution liquid chromatograph with a variable-wavelength UV-visible detector set to  $\lambda = 245\text{ nm}$  was used. The column was a 30 cm  $\times$  4.0 mm I.D. Micro-Pak CH-10 octadecylsilane type, particle diameter 10  $\mu\text{m}$ , from Varian. For monitoring the syn-

thesis of PPE-6 and PEE-7 a linear gradient of methanol-water (1:1) to methanol over 15 min was used at a flow-rate of  $1.5 \text{ ml min}^{-1}$ . Retention times for *m*-bromophenyl ether, PPE-6 and PPE-7 were 8.25, 9.25 and 11.50 min respectively. To monitor the synthesis of PPE-9 a linear gradient of acetonitrile-water (3:1) to acetonitrile over 15 min with an isocratic hold of 5 min at 100% acetonitrile and a flow-rate of  $2.0 \text{ ml min}^{-1}$  was used. The retention times of PPE-8 and PPE-9 were 10.1 and 17.05 min respectively.

#### Identification by NMR

NMR analysis was performed on a Varian T-60  $^1\text{H}$  NMR spectrometer in carbon tetrachloride or deuteriochloroform solutions using tetramethylsilane as internal standard. Structural assignments were made by analogy to previously studied bromophenyl ethers<sup>2</sup>.

#### GC evaluation

For GC a Varian 3700 gas chromatograph with flame-ionization detectors was used. Column packings were prepared by the rotary evaporator technique using acetone or methylene chloride as solvent for the bromophenyl ethers and Chromosorb P AW (100–120 mesh) as support. Glass columns of various lengths, 0.5–3.0 m, and

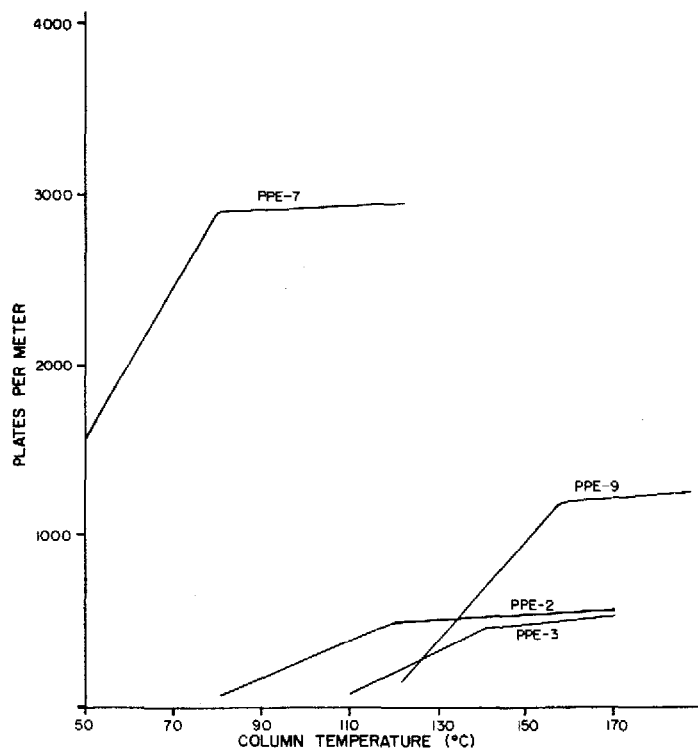


Fig. 2. Relationship between column efficiency and column temperature for the bromophenyl ethers.

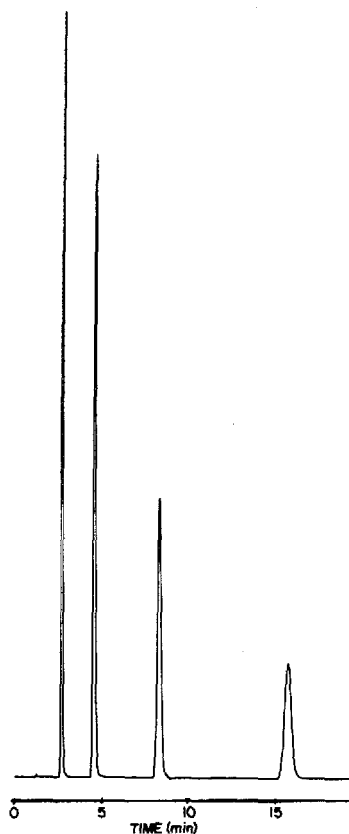


Fig. 3. Separation of  $C_8$ - $C_{11}$  alkanes at  $100^\circ\text{C}$  on a  $3\text{ m} \times 2\text{ mm}$  I.D. column of 10% (w/w) PPE-7 on Chromosorb P (100-120 mesh) and nitrogen flow-rate  $30\text{ ml min}^{-1}$ .

2.0 mm I.D. were vacuum packed with packings containing from 3 to 20% (w/w) of stationary phase. Separation conditions are given in the figure and table legends.

## RESULTS AND DISCUSSION

The primary properties which characterize a stationary phase are its minimum and maximum operating temperature, the efficiency of the columns prepared using the phase compared to values normally obtained for other phases or predicted by theory and the polarity or selectivity of the phases determined by measuring McReynolds' constants. Minimum column operating temperatures were established from a plot of the column efficiency (measured as theoretical plates) against column temperature, Fig. 2. In all cases a sharp plateau exists in these plots which serves to define the minimum operating temperature. The maximum column operating temperature is established by evaporation or thermal degradation of the phase. This was measured by establishing the highest column temperature to which the column could be heated for 12 h without any change in the capacity factor, column efficiency or peak asymmetry values for the components of a test chromatogram measured at a

TABLE I  
STATIONARY PHASE CHARACTERISTICS OF THE PHENYL ETHERS

Phenyl ether	Melting point (°C)	Operating temperature range (°C)		Average plate count, $N$ ( $m^{-1}$ )
		Minimum	Maximum	
DPE-2	52-53	—	180	< 50
DPE-3	78-80	—	—	< 50
PPE-1	Liquid	< 20	200	3200
PPE-2	80-81	120	325	500
PPE-3	95-96	145	325	500
PPE-6	Liquid	< 20	185	3500
PPE-7	Liquid	80	200	3000
PPE-8	Liquid	< 20	290	3500
PPE-9	93-95	155	325	1200

\* Calculated for a stationary phase loading of 10% (w/w) on Chromosorb P (100-120 mesh).

lower temperature before and after the conditioning period. A typical test chromatogram for PPE-7 is shown in Fig. 3. The data for minimum and maximum operating temperature and average column efficiencies for all phases studied are summarized in Table I. For the phases which are solid at room temperature the minimum operating temperature is well-above the melting point and presumably corresponds to the clearing point temperature. The principal effect of introducing bromine into the phenyl ethers is to increase the temperature for minimum and maximum allowable column operation. An upper temperature limit of 325°C was found for PPE-2, PPE-3 and PPE-9. Above this temperature the bromophenyl ethers are thermally unstable. Thus

TABLE II  
McREYNOLDS' CONSTANTS FOR PPE-6 AND PPE-7 MEASURED AT 100°C

$I$  = Retention index value;  $\Delta I$  = McReynolds' constants;  $\Sigma_1^5$  = sum of first five McReynolds' constants;  $\Delta I_6^7$  = retention index difference between PPE-7 and PPE-6.

Test probe	Squalane	PPE-6		PPE-7		$\Delta I_6^7$
		$I$	$\Delta I$	$I$	$\Delta I$	
Benzene	653	860	207	815	162	-45
Butanol	590	900	310	842	252	-58
2-Pentanone	627	819	192	830	203	11
1-Nitropropane	652	922	270	925	273	3
Pyridine	699	1012	3313	1006	307	-6
1,4-Dioxane	654	1021	367	913	259	-108
2-Methyl-2-pentanol	690	803	113	858	168	55
2-Octyne	841	958	117	950	109	-8
1-Iodobutane	818	935	117	975	157	40
cis-Hydrindane	1006	1051	45	1090	84	39
$\Sigma_1^5$			1292		1197	

TABLE III

COMPARISON OF THE RETENTION OF McREYNOLDS TEST PROBES ON PPE-1, PPE-2, PPE-3 AND PPE-8 AT 150°C.

$$\Delta I_A^B = I_B - I_A.$$

Test probe	PPE-1	PPE-2		PPE-3		PPE-8
	<i>I</i>	<i>I</i>	$\Delta I_1^2$	<i>I</i>	$\Delta I_1^3$	<i>I</i>
Benzene	822	848	26	854	32	822
Butanol	804	817	13	804	0	841
2-Pentanone	841	852	11	854	13	878
1-Nitropropane	961	952	-9	946	-15	916
Pyridine	981	1041	60	1041	60	1004
2-Methyl-2-pentanol	904	948	44	954	50	900
1,4-Dioxane	845	844	-1	850	5	984
1-Iodobutane	981	948	-33	946	-35	996
2-Octyne	988	1032	44	1036	48	965
<i>cis</i> -Hydrindane	1104	1152	48	1127	23	1120

thermal degradation and not phase volatility established the maximum operating temperature in these cases. The three ring bromophenyl ether, PPE-7, may be used up to 200°C before volatility losses become significant.

The phenyl ethers provide column packings with an average of 3200–3500 theoretical plates per meter. The bromophenyl ethers produce column packings of lower efficiency ranging from an acceptable value of 3000 plates per meter for PPE-7, through a usable value of 1200 plates per meter for PPE-9, to inadequate values of 500 plates per meter or less for DPE-2, DPE-3, PPE-2 and PPE-3. For the bromophenyl ethers there is no obvious correlation between melting point or structure and column efficiency. It must, therefore, depend on other properties such as viscosity or coating efficiency, although, visual inspection of the different packings did not provide evidence for uneven coating.

The McReynolds' constants for the phenyl ether PPE-6 and the bromophenyl ether PPE-7 are given in Table II. Surprisingly, bromine substitution causes fairly small changes in selectivity of the phase and actually leads to a reduction in its polarity, measuring the latter as  $\Sigma_1^5$  value for the first five McReynolds' probes. The decrease in polarity is accounted for primarily by the reduced retention of benzene and butanol. The most marked change in selectivity is observed with dioxane. Thus the results in Table II would suggest that bromination of the phenyl ether primarily caused a reduction in the charge transfer and proton donor/acceptor properties of PPE-7 compared to PPE-6.

Squalane was not sufficiently stable at 150°C to permit direct measurement of the McReynolds' constants of PPE-2, PPE-3 and PPE-9. For the purpose of comparison the retention index values of the McReynolds test probes were determined on PPE-1, PPE-2 and PPE-3. The results are summarized in Table III. Although differences in selectivity can be seen between PPE-1 and PPE-2 or PPE-3, these differences are really quite small compared to the extensive structural changes made by the introduction of bromine. A comparison between PPE-8 and PPE-9 could not be made due to the low capacity factor values for the test probes on PPE-9.

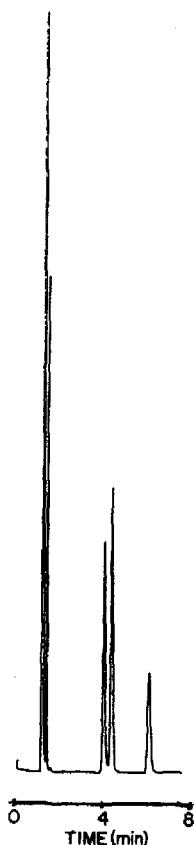


Fig. 4. Separation of decane, decene and decyne at 135°C. The conditions are the same as for Fig. 3.

Among the bromophenyl ethers investigated, PPE-7 is the most promising in terms of its chromatographic properties. It provides efficient column packings with a usable temperature range of 80–200°C. Fig. 3, discussed previously, shows a good separation of a mixture of alkanes. The phase has useful selectivity for the separation of alkanes, alkenes and alkynes. This is illustrated in Fig. 4 for the separation of decane (b.p. 174°C), decene (b.p. 181°C) and decyne (b.p. 174°C). Fig. 5 is an example of a separation of compounds covering a wide polarity range. The substituted benzenes are separated without obvious signs of peak tailing further indicating the useful properties of PPE-7 for the separation of different compound types. Its McReynolds' constants are similar, if not identical, to the five ring phenyl ether (PPE-1), which is commercially available.

The bromophenyl ethers are easily prepared by thallium acetate catalysed electrophilic bromination of the two to seven ring phenyl ethers. Bromination does not always impart useful chromatographic properties to the phenyl ethers. It lowers their volatility leading to higher available operating temperatures but generally results in packings having lower chromatographic efficiency. The presence of bromine in the phenyl ethers does not produce large changes in the selectivity of the phases. It is unlikely that the bromophenyl ethers will replace common phases already in use,



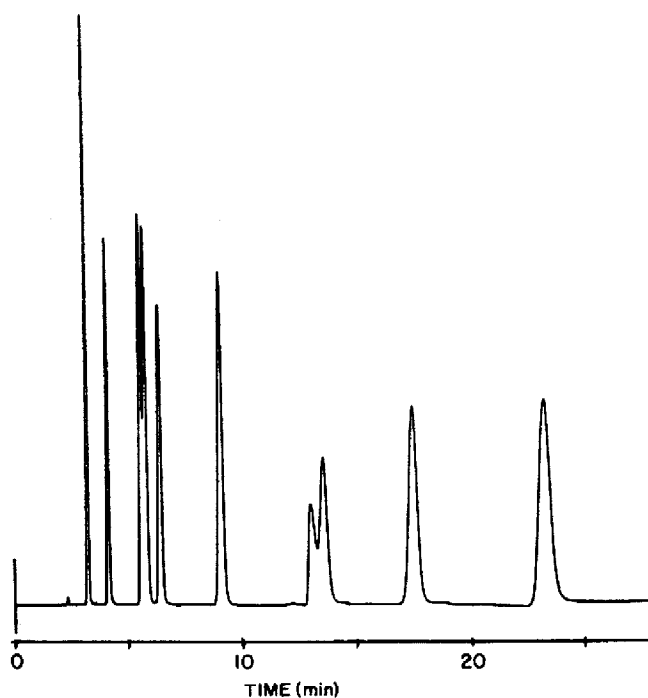


Fig. 5. Separation of substituted benzenes at 170°C. Other conditions the same as for Fig. 3. Order of elution: benzene, toluene, *m*-xylene, chlorobenzene, *o*-xylene, *p*-dichlorobenzene, benzaldehyde, *o*-dichlorobenzene, iodobenzene and nitrobenzene.

particularly as their properties are somewhat similar to the parent phenyl ethers. Their main use remains that of intermediates from which other reference stationary phases can be prepared by substitution reactions.

#### REFERENCES

- 1 C. F. Poole, H. T. Butler, S. A. Agnello, W.-F. Sye, A. Zlatkis and G. Holzer, *J. Chromatogr.*, 217 (1981) 39.
- 2 S. C. Dhaneasar and C. F. Poole, *J. Chromatogr.*, 252 (1982) 91.
- 3 S. C. Dhaneasar and C. F. Poole, *J. Chromatogr.*, 253 (1982) 255.
- 4 F. Pacholec, H. T. Butler and C. F. Poole, *Anal. Chem.*, 54 (1982) 1938.
- 5 F. Pacholec and C. F. Poole, *Chromatographia*, (1983) in press.
- 6 C. L. Mahoney and E. R. Barnum, in R. C. Gunderson and A. W. Hart (Editors), *Synthetic Lubricants*, Rheinhold, New York, 1962, p. 402.
- 7 R. G. Mathews, R. D. Schwartz, C. D. Pfaffenberger, S.-N. Lin and E. C. Horning, *J. Chromatogr.*, 99 (1974) 51.
- 8 G. P. Brown, *U.S. Pat.*, 3,567,783 (1971).