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Short Communication

Gas chromatographic method for the determination of chlorobenzophenone isomers*

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ABSTRACT

A simple, rapid and an efficient gas chromatographic method for the determination of chlorobenzophenone isomers is described. This was necessary in order to determine the amounts of *o*- and *m*-chlorobenzophenone isomers in *p*-chlorobenzophenone, which is a starting material in the manufacture of Systral, an anti-Parkinsonism agent. Complete separation of chlorobenzophenone isomers was achieved using Apiezon L as stationary phase. The determination of *o*-chlorobenzophenone in *p*-chlorobenzophenone was carried out by using benzophenone as an internal standard. The minimum detectable amount of *m*-chlorobenzophenone in *p*-chlorobenzophenone was established.

INTRODUCTION

Recently, the existence of a remarkably stable phenyldichlorocarbenium tetrachloroaluminate complex derived from benzotrichloride under Friedel–Crafts acylation conditions has been reported [1]. We have also reported that (trichloromethyl) benzene is a more reactive benzoylating agent for the preparation of substituted benzophenones under milder reaction conditions [2]. As chlorphenoxamine (Systral), which is used as an anti-Parkinsonism agent, can be manufactured from *p*-chlorobenzophenone, we wished to establish a synthetic method in which *p*-chlorobenzophenone is produced in quantitative yields. Therefore, it was necessary to develop a method to determine the amounts of *ortho* and *meta* isomers in *p*-chlorobenzophenone.

The separation of dichlorobenzophenone isomers and of substituted benzils and benzophenones has been reported [3.4]. Bishara and Smith [5] reported the separation of dichloro- and chlorobenzophenone isomers by high-performance liquid chromatography (HPLC). Recently, a collection of analytical data for benzodiazepines and benzophenones has been published which includes GC, HPLC and TLC methods [6,7]. Analyses for chlorophenylphenols, chlorinated products of ketones and alcohols and methyl ethers of chlorinated *o*-phenoxyphenols have been reported [8–10]. However, no reference to the separation of *ortho*, *meta* and *para* isomers of chlorobenzophenone could be found. In this paper, we describe a rapid and an efficient GC method for the determination of *p*-chlorobenzophenone.

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EXPERIMENTAL

Analyses were performed on a Hewlett-Packard Model 5880A gas chromatograph equipped with a level 4 integrator, computing system, and flame ionization detector. A cross-linked methylsilicone gum (25 m × 0.2 mm I.D., 0.33 μm film thickness) fused-silica column from Hewlett-Packard and 10% Carbowax 20M, 3% OV-210 and 5% OV-17 columns were procured from Chromato-Pak Enterprises. In addition, columns from Alltech were used, as follows: 10% OV-351, 3% Dexil 300 and KG-02 on Uniport HP [10 ft. × 2 mm I.D. (1 ft. = 30.48 cm), glass-lined stainless steel (GLT)], 10% Alltech CS-10 [6 ft. × 2 mm I.D., (GLT)], 0.3% Carbowax 20M + 0.1% H_3PO_4 on Graphpac GC and 10% Apiezon L + 2% KOH on Chromosorb W AW (80–100 mesh (GLT) (1.8 m × 1.7 mm I.D.) (column A).

Apiezon L was coated on Chromosorb W AW (80–100 mesh at a concentration of 2% and packed in a 3 m × 2 mm I.D. stainless-steel SS column (column B). SE-30 (5% and 10%) columns and tri[4-(2'-phenylisopropyl)phenyl] phosphate (TPIPP) [11] columns were packed in the laboratory.

Complete separation of all the isomers of chlorobenzophenone was achieved on column B at 160°C. The determination and establishment of the minimum detectable amount of the *meta* isomer in *p*-chlorobenzophenone were achieved on column B at 200°C. The determination of the *ortho* isomer in *p*-chlorobenzophenone was achieved at 200°C on column A by an internal standard method with benzophenone as the internal standard.

The chemicals used were obtained from Aldrich and Merck and their purity was checked by GC. Nitrogen was used as the carrier gas at a flow-rate of 30 ml min^{-1}.

Preparation of the standard and unknown mixtures

Solutions of OCBP (0.1–5.0 mg/ml) were prepared in acetone containing benzophenone [internal standard (ISTD)] (2 mg/ml).

After stabilization of the instrument, 2.0 μl of each standard solution were injected three times. Areas of the individual peaks were obtained from the integrator. The ratios of peak areas of OCBP to ISTD were plotted against concentration (mg ml^{-1}). Separate graphs were plotted for two different concentration ranges, 1–5 and 0.1–0.3 mg ml^{-1}.

Samples (P-1, P-2, P-1 crude, P-4 and P-5) were

TABLE I

RETENTION TIMES (MIN) OF CHLOROBENZOPHENONE ISOMERS ON VARIOUS STATIONARY PHASES

Stationary phase	Temperature (°C)	Retention times (min)		
		OCBP	MCBP	PCBP
10% Carbowax 20M	210	13.65	13.14	14.29
3% OV 210	150	5.84	6.37	6.74
5% OV 17	160	19.72	19.50	21.00
10% OV 351[a]	170	25.79	–	23.28
3% Dexil 300	150	8.95	11.6	11.95
KG-02	175	23.06	22.62	20.66
10% Alltech CS-10	190	8.0	7.46	8.10
0.3% Carbowax 20M + 0.1% H_3PO_4[b]	220	51.4	42.32	59.33
10% Apiezon L, stainless-steel column	180	14.58	18.83	20.35
2% Apiezon L, 1.8-m column	170	6.39	9.49	9.24
5% SE 30	150	2.17	2.32	2.51
10% SE 30	200	6.87	7.19	7.53
5% TPIPP[a]	180	16.60	17.60	18.90

[a] These columns do not give reproducible retention times.
[b] The peaks are very broad and tailing is observed.

weighed accurately and 2 ml of ISTD stock solution was added to each product before dilution to 10 ml with acetone.

Solutions of MCBP (0.01–0.1%) in PCBP were prepared using acetone as solvent.

After stabilization of the instrument, 1 μl of each standard solution was injected three times on to column B at 200°C. Solutions of the products were also injected at the same temperature.

RESULTS AND DISCUSSION

Separation of chlorobenzophenone isomers was tried on the various liquid stationary phases coated on Chromosorb W AW or HP DMCS (80–100 mesh) at various loadings packed in stainless-steel or glass-lined stainless-steel columns (1.8 m × 1.7 mm I.D.). Table I gives the corresponding retention data. Most of the stationary phases separate either *ortho* and *para* or *meta* and *para* isomers. Dexil 300 shows a good separation between the *ortho* and *para*, but the *meta* and *para* isomers do not separate, whereas KG-02 separates the *para* isomer but the *meta* and *ortho* isomers show overlapping peaks or a single peak. Graphitized carbon modified with Carbowax 20M or SP1000 retains all the isomers for a long time and the peaks are very broad. On TPIPP, all three isomers are partially resolved. Analysis was also tried on cross-linked methylsilicone gum (25 m × 0.2 mm I.D., 0.33 μm film thickness) at 200°C. The carrier gas was nitrogen at a flow-rate of 1.5 ml min^{-1} and the splitting ratio was 1:135. A good separation between the *ortho* and *para* isomers was obtained but the *meta* and *para* isomers were only partially resolved. The separation did not improve further even at lower temperatures. We were able to obtain a very good separation of all three isomers on one of the packed columns which are comparatively cheaper (10% Apiezon L). Additionally, as most users employ packed columns, it was felt unnecessary to try the separations on different capillary columns.

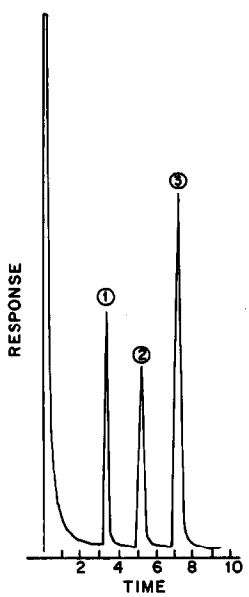

Fig. 1. Separation of benzophenone (ISTD), *o*-chlorobenzophenone and *p*-chlorobenzophenone on column A. Oven temperature, 200°C; carrier gas, nitrogen; flow-rate, 30 ml min^{-1}; injector temperature, 240°C; detector temperature, 300°C. Peaks: 1 = benzophenone; 2 = *o*-chlorobenzophenone; 3 = *p*-chlorobenzophenone.

Apiezon L (10%) coated on 2% KOH-treated Chromosorb W AW in a glass-lined stainless-steel column gave a good separation of all the three benzophenone isomers at 160°C and benzophenone (ISTD), OCBP and PCBP at 200°C (Fig. 1). Hence this column was used for the ISTD method. The calibration graphs for two concentrations ranges, 1–5 and 0.1–0.3 mg ml^{-1}, are linear and the slopes, determined from the equation $y = mx + c$ (here $c = 0$) are 0.48 and 0.7, respectively. Statistical evaluation of the method shows that the reproducibility of quantitative measurements is fairly good, as indicated by the standard deviations, ranging from $4.13 \cdot 10^{-3}$ to $1.27 \cdot 10^{-2}$. Table II gives the

TABLE II

RESULTS OBTAINED FROM CALIBRATION GRAPH FOR TECHNICAL SAMPLES

Sample	Concentration OCBP (mg ml^{-1})	Composition (%)	Standard deviation[b]
P-1[a]	0.08	0.76	$1.27 \cdot 10^{-2}$
P-1 (crude)	0.1	0.95	$2.14 \cdot 10^{-3}$
P-2	0.85	7.94	$8.15 \cdot 10^{-3}$
P-4	1.125	10.96	$1.23 \cdot 10^{-2}$
P-5	0.475	4.75	$4.134 \cdot 10^{-3}$

[a] Recrystallized from hexane.
[b] For area ratio.

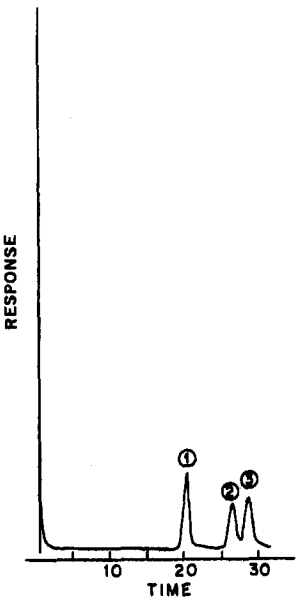

Fig. 2. Separation of chlorobenzophenone isomers on column B. Oven temperature 160°C; carrier gas, nitrogen; flow-rate, 30 ml min^{-1}; injector temperature, 200°C; detector temperature, 250°C. Peaks: 1 = OCBP; 2 = MCBP; 3 = PCBP.

results obtained for our products. In order to find the minimum detectable amount of MCBP in PCBP, a standard solution of 0.1% MCBP in PCBP was injected on to column A. As MCBP was not detected on this column, a longer column with a lower loading was prepared (column B). This gave a complete separation of all the three isomers (Fig. 2) and can detect MCBP at levels up to 0.04% in PCBP even at 200°C. When 1 μl of 0.1 and 0.05% solutions of MCBP in BCPB was injected, the MCBP peak could be detected whereas detection of the MCBP peak was not possible for 1 μl of 0.02% solution. Therefore, 0.03 and 0.04% solutions were prepared and it was confirmed that the minimum detectable amount of MCBP in PCBP is 0.04%. The minimum detectable amount (MDA) of the *meta* isomer was found because the peaks of the *meta* and *para* isomers are very close and injecting a larger volume decreases the resolution. Our products contain the *meta* isomer in trace amounts whereas the *ortho* isomer is present in a significant amount. Preparing more concentrated solutions is difficult because of solubility problems. Determination of the MDA of the *ortho* isomer was not carried out as the *ortho* isomer is separated very well from the *meta* and *para* isomers. Therefore, the separation is not affected by the injection of larger volumes or more concentrated solutions.

Table III gives the retention times of the chlorobenzophenone isomers and ISTD on columns A and B. When our products were injected onto column B, the presence of MCBP in the range 0.04–0.16% was determined. An important point to be noted is that PCBP synthesized by our method contains 0.04% of the *meta* isomer at the crude stage. It disappears completely after recrystallization of PCBP from hexane. The recrystallized PCBP does not show presence of the *meta* isomer as an impurity. This suggests that, if present, it must be at a negligible concentration (less than the detection limit, *i.e.*, <0.04%).

CONCLUSION

We have described an efficient and rapid GC method for the determination of *o*-chlorobenzophenone in *p*-chlorobenzophenone using Apiezon L as stationary phase and benzophenone as an internal standard. The total analysis time is only 8 min and

TABLE III

RETENTION TIMES (MIN) OF CHLOROBENZOPHENONE ISOMERS AND BENZOPHENONE (ISTD)

Column	Temperature (°C)	Retention time (min)			
		Benzophenone	OCBP	MCBP	PCBP
A	200	3.46	5.29	6.34	7.34
B	160	12.43	20.61	26.75	28.95
B	200	5.39	8.00	9.94	10.92

the standard deviation ranges from $4.13 \cdot 10^{-3}$ to $1.27 \cdot 10^{-2}$. Complete separation of the *ortho, meta* and *para* isomers of chlorobenzophenone was achieved using 2% Apiezon L coated on Chromosorb W AW DMCS (80–100 mesh) packed in a 3 m × 2 mm I.D. stainless-steel column. The minimum detectable amount of the *meta* isomer in the *para* isomer is 0.04%.

REFERENCES

1 U. S. Racherla, T. Daniel, P. R. Rajmohanan and N. R. Ayyangar, *J. Am. Chem. Soc.*, 111 (1989) 7659.
2 N. R. Ayyangar, R. J. Lahoti, K. V. Srinivasan and T. Daniel, *Synthesis*, (1991) 322.
3 M. H. Abraham, D. Huq, R. U. Koenigsberger and J. B. Rose, *J. Chromatogr.*, 206 (1981) 147.
4 W. F. Brubakar and M. A. Ogliaruso, *J. Chromatogr.*, 324 (1985) 450.
5 R. H. Bishara and S. L. Smith, *J. Chromatogr.*, 234 (1982) 261.
6 M. Japp, K. Garthwaite, A. V. Geeson and M. D. Osselton, *J. Chromatogr.*, 439 (1988) 317.
7 S. I. Weston, M. Japp, J. Partridge and M. D. Osselton, *J. Chromatogr.*, 538 (1991) 277.
8 B. J. Gudzinowicz, *Anal. Chem.*, 34 (1962) 1032.
9 C. Walling and A. Padwa, *J. Am. Chem. Soc.*, 85 (1963) 1593.
10 C. A. Nilsson and K. Andersson, *Chemosphere*, 6 (1977) 263.
11 N. R. Ayyangar, A. S. Tambe, and S. S. Biswas, *J. Chromatogr.*, 483 (1989) 33.