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GAS CHROMATOGRAPHIC DETERMINATION OF SOLVENT RESIDUES AND OTHER MATERIALS IN CHEMICAL AND FERMENTATION WASTES*

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SUMMARY

The gas chromatographic (GC) determination of solvent residues and other contaminants in a variety of matrices is achieved primarily on columns packed with porous polymers or Carbowax 20M on carbonaceous supports. Certain samples, especially those of spent fermentation broths, may be multi-phase and require "homogenization" prior to GC. Depending on the concentration levels of the residues, one can use external or internal standards for quantitation. A variety of other GC phases are available to allow the resolution of most complex solvent mixtures.

The elution of solvents from porous polymer-packed columns appears to be a function of solvent molecular volume. This differs from columns packed with more conventional, coated supports in which elution is a function of solvent boiling point. A column packed with a carbon support very lightly coated with Carbowax also behaves like one packed with a porous polymer, the elution order being a function of the adsorbate molecular volume.

INTRODUCTION

Most chromatographers would prefer to devote their efforts to the separation and determination of complex molecular systems. Nonetheless, it is often necessary to perform such mundane tasks as the determination of solvent residues. Such determinations, uninteresting as they may appear, often present difficulties with regard to sample preparation, resolution and quantitation, especially when dealing with substances at low concentration levels in a variety of matrices.

In this paper, some gas chromatographic (GC) systems evaluated at Hoffmann-La Roche for separating and determining solvent residues and other similar contaminants in spent fermentation broths, chemical wastes and various plant streams are discussed. Several specific examples are presented, and parameters that affect the

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elution times of solvents on columns packed with porous polymers and on those packed with conventional coated supports are examined.

EXPERIMENTAL

Apparatus

Hewlett-Packard gas chromatographs, Models 5710 and 5830A, equipped with thermal conductivity or flame-ionization detectors, were used. Data were recorded either on strip-chart recorders (1-mV full-scale deflection) or on a Hewlett-Packard 18850A terminal, which provided peak integration. An Auto-Lab System IVB (Spectra Physics) was also used for peak integration.

Chemicals and reagents

Actual production samples were provided by various departments at Roche. Reference chemicals, including solvents, were obtained commercially or from company laboratories, and were of the highest purity available. Gases and column packings were obtained commercially.

GC conditions

The column conditions for the various determinations are given in Table I. Unless specified otherwise, the injector and detector temperatures were 250 and 300°C, respectively. The flow-rate of the carrier gas (helium for thermal conductivity

TABLE I

GC CONDITIONS FOR RESIDUAL SOLVENTS AND OTHER CONTAMINANTS

Analyte	*Matrix*	*Column*		
		Dimensions	*Packing*	*Conditions*
Solvents	Broth	3 m × 4 mm	Chromosorb 101	100°C (2 min) → 240°C at 8°C/min
Solvents	Broth	3 m × 4 mm	Super Q	100°C (2 min) → 240°C at 8°C/min
Solvents	Plant stream	4 m × 4 mm	Porapak P	90°C (2 min) → 200°C at 8°C/min
Solvents	Plant stream	2 m × 4 mm	0.1% SP-1000 on Carbopak C	80°C (8 min) → 200°C at 8°C/min
Solvents	Plant stream	3 m × 2 mm	5% Carbowax 20M on Carbopak B	60°C (10 min) → 200°C at 6°C/min
Solvents	Plant stream	50 m × 0.5 mm	WCOT Carbowax 20M	60°C (8 min) → 150°C at 8°C/min
Phenol	Aqueous waste stream	3 m × 4 mm	10% OV-17 on Gas-Chrom Q	80°C (2 min) → 250°C at 12°C/min
Methyl bromide	Acetone waste stream	3 m × 4 mm	Chromosorb 101	100°C (2 min) → 200°C at 4°C/min
Formic acid	Acetic acid	3 m × 4 mm	Chromosorb 101	140°C, isothermal
Methyl propionate	Ethyl acetate	2 m × 4 mm	7% Bentone-34 + 7% diisodecyl phthalate	50°C, isothermal

and nitrogen for flame-ionization detection) was set at 50 ml/min. For thermal conductivity detection the filament current was set at 125 mA.

RESULTS AND DISCUSSION

Different GC packings have been used in the determination of solvents, the most useful being porous polymers[1–3] and Carbowaxes on various supports. One area in

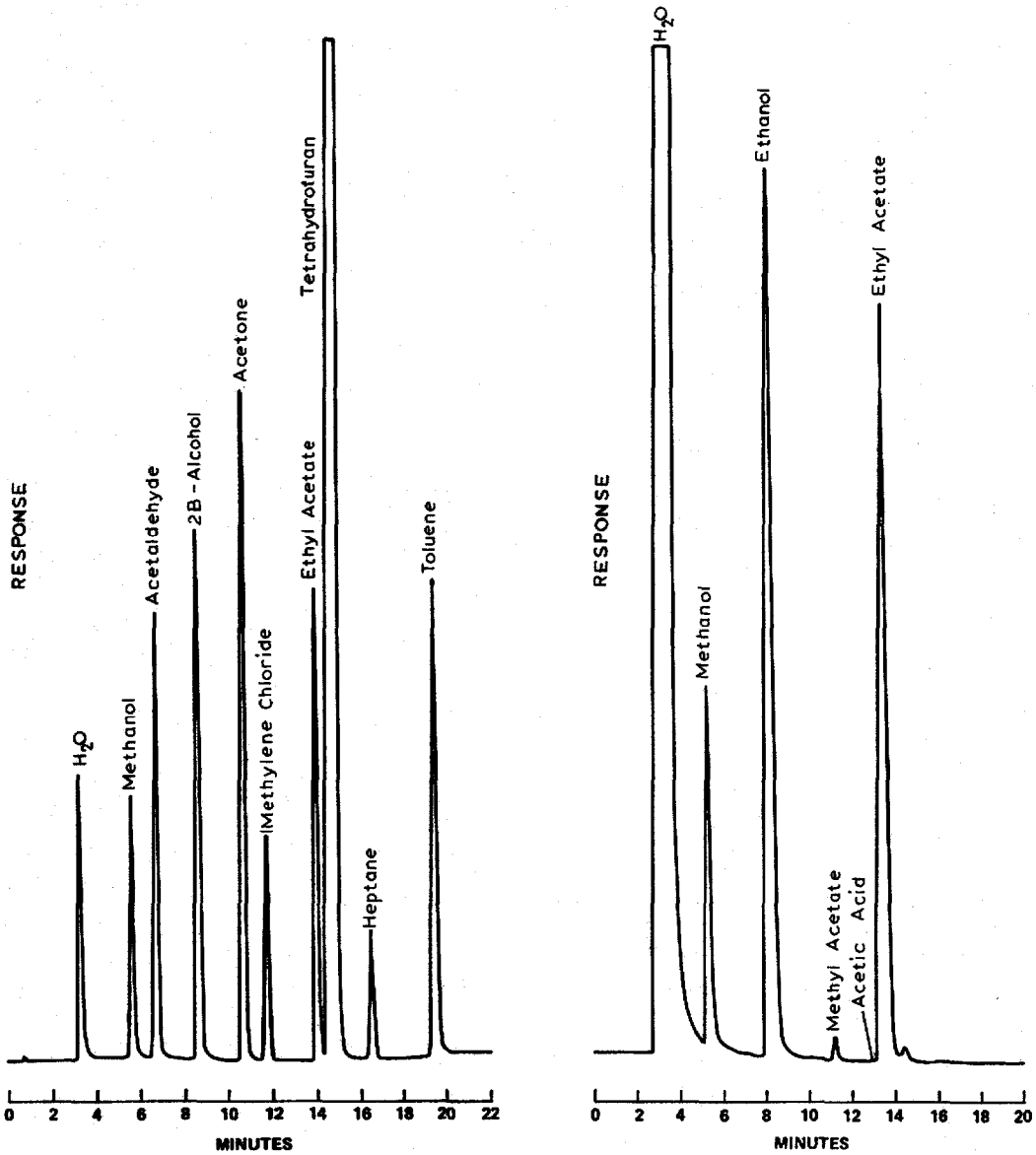


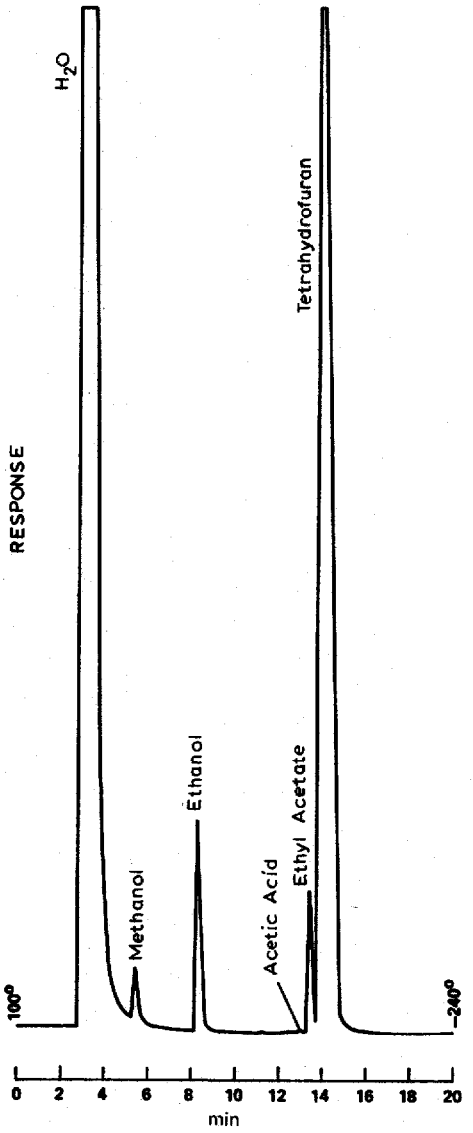
Fig. 1. Resolution of some general solvents on a Chromosorb 101 column. 2B-Alcohol = ethanol.

Fig. 2. Resolution of solvent residues in spent fermentation broth on a Chromosorb 101 column.

which much effort has been devoted is the determination of solvent residues in fermentation broths. Broths have also been examined for other materials, but a discussion of these is beyond the scope of this paper. In addition to the solvent residues in fermentation broths, similar residues in other matrices have also been examined. These are summarized in Table I.

Solvent residues in fermentation broths

For determining solvent residues in fermentation broths, a Chromosorb 101



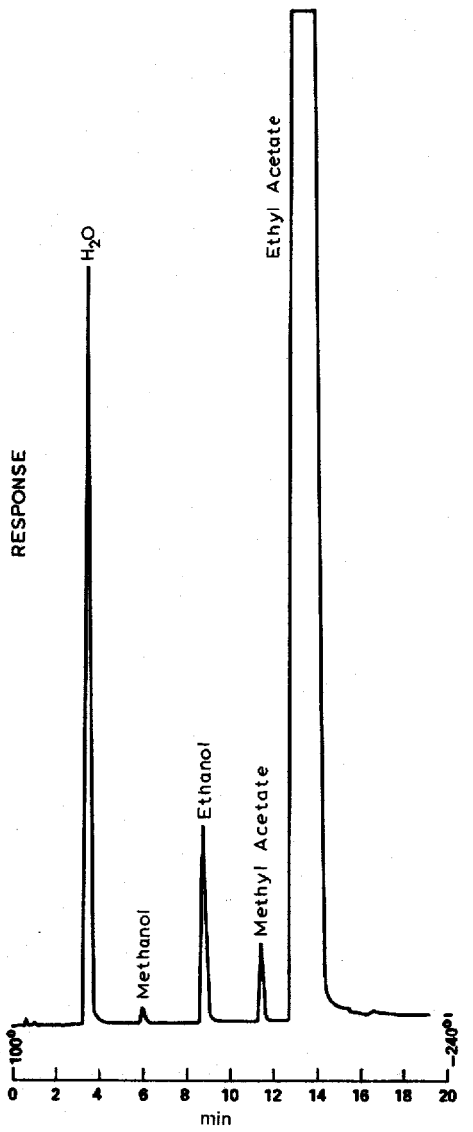


Fig. 3. Solvent residues in a broth "solubilized" with tetrahydrofuran.

Fig. 4. Broth with a large amount of ethyl acetate that obscures a low level of acetic acid.

column was found to be especially useful. This column was also used as a general solvents column (Fig. 1). With Chromosorb 101, it is usually possible to separate and quantitate the solvents of interest in fermentation broths, *viz.*, methanol, ethanol, methyl acetate, ethyl acetate, acetic acid and water. The chromatogram shown in Fig. 2 represents a sample of a spent broth from which much of the ethyl acetate had been stripped. Water is the major constituent, with smaller amounts of ethyl acetate, ethanol, methanol, methyl acetate (about 0.2 %, w/w) and acetic acid (about 0.02 %, w/w). This determination, by external standardization, was straightforward, as the sample was homogeneous and the level of ethyl acetate was not high enough to result in a two-phase system.

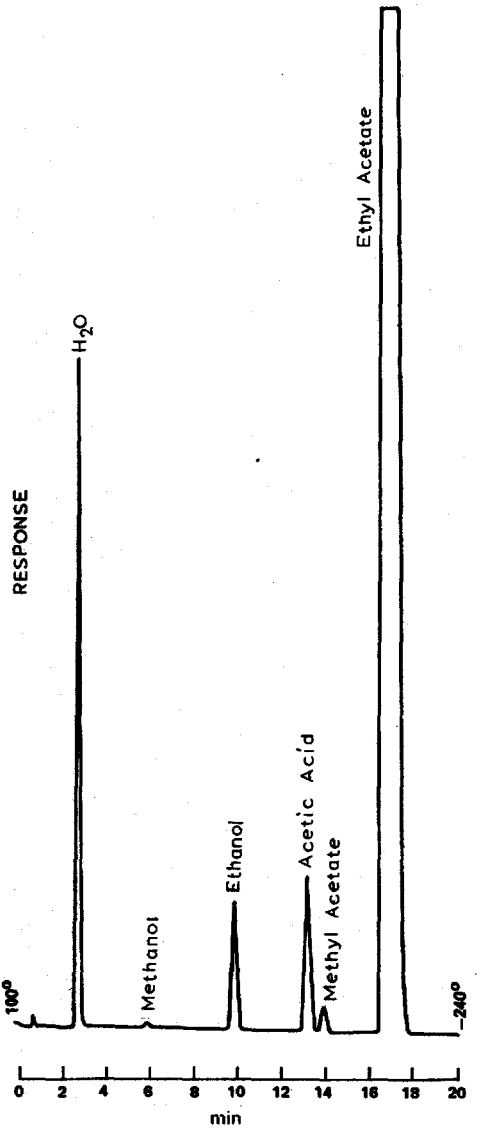


Fig. 5. Resolution of acetic acid and ethyl acetate on Super Q.

TABLE II

ANALYSIS OF SPENT BROTHS FOR SOLVENT RESIDUES: COMPARISON OF COLUMNS

Results in % (w/w).

Sample No.	*Chromosorb 101*			*Super Q*		
	Ethyl acetate	*Ethanol*	*Acetic acid*	*Ethyl acetate*	*Ethanol*	*Acetic acid*
1	94.0	1.6	ND*	92.2	1.2	1.9
2	91.8	1.9	ND*	91.4	1.4	0.2
3	92.0	1.8	ND*	91.2	1.3	0.9

* ND = Not detected, because acetic acid, in low concentrations, merges with the ethyl acetate peak on Chromosorb 101.

Problems were encountered when the sample contained, in addition to ethyl acetate and water, cellular particles in suspension. To obtain a uniform aliquot for injection into the gas chromatographic, it was necessary to homogenize the sample with tetrahydrofuran. Although a large tetrahydrofuran peak then occurred in the chromatogram (Fig. 3), it was still possible to see the peaks of interest.

Another problem encountered with this procedure was the inability to determine low levels of acetic acid in the presence of large amounts of ethyl acetate (Fig. 4). The acetic acid peak was apparently masked by the ethyl acetate peak. On examin-

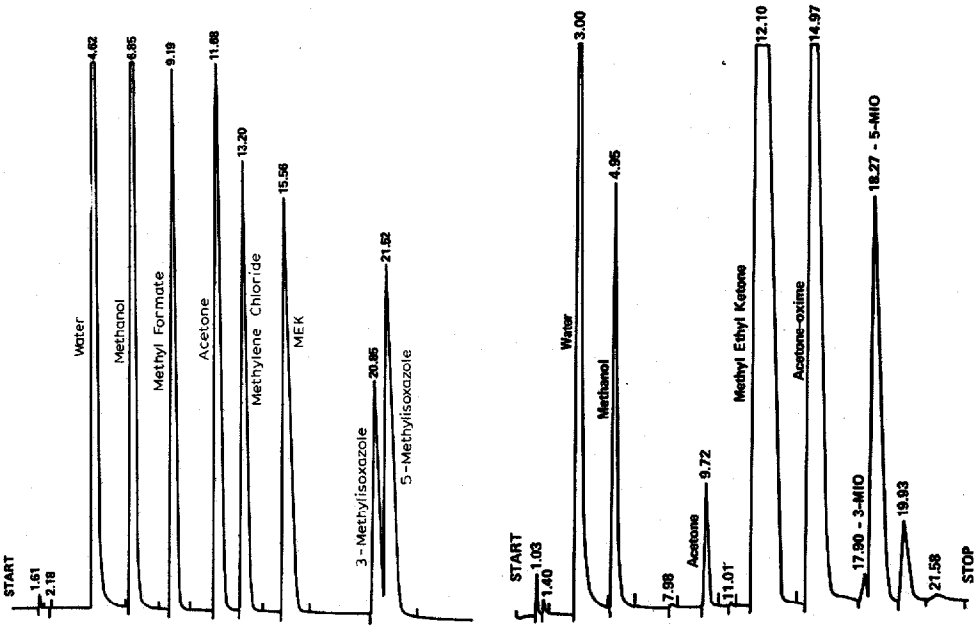


Fig. 6. Reference chromatogram showing components of a plant stream (Porapak P). MEK = methyl ethyl ketone. Retention times in minutes.

Fig. 7. Resolution of components of an actual plant stream. MIO = methylisoxazole. Retention times in minutes.

TABLE III

REPRODUCIBILITY OF RESPONSE FACTORS IN A CALIBRATION MIXTURE

Run No.	*Response factor*						
	Water	*Methanol*	*Methyl formate*	*Acetone*	*Methylene chloride*	*3-Methyl isoxazole*	*5-Methyl isoxazole*
1	1.37	1.22	0.788	1.05	0.748	0.810	0.905
2	1.36	1.22	0.802	1.05	0.759	0.809	0.911
3	1.35	1.22	0.818	1.06	0.768	0.800	0.891
4	1.35	1.22	0.838	1.06	0.785	0.804	0.889
5	1.34	1.23	0.850	1.06	0.789	0.812	0.886
6	1.35	1.29	0.929	1.09	0.773	0.838	0.934
7	1.36	1.28	0.912	1.09	0.765	0.834	0.922
8	1.36	1.32	0.896	1.08	0.737	0.830	0.906
Mean	1.36	1.25	0.854	1.07	0.766	0.817	0.905
Standard deviation	0.009	0.040	0.053	0.017	0.018	0.015	0.017
Coefficient of variation (%)	0.7	3.2	6.2	1.6	2.3	1.8	1.9

ing the chromatogram, it could be concluded that acetic acid was indeed absent. However, on reinjection of the material on to a Super Q column (Fig. 5), a distinct peak was observed. The findings, using both columns for the analysis, are summarized in Table II.

Determination of solvents in a plant stream by an internal standard method

In addition to the determination of solvent residues using an external standard, there were occasions on which the use of an internal standard was more appropriate. In such a case, the sample came from an isoxazole stream containing water, methanol, methyl formate, acetone, methylene chloride and others. Of interest were the levels of isoxazoles and solvents present in the stream. Using methyl ethyl ketone as the internal standard, it was possible to determine all the components. The column of choice was another porous polymer, Porapak P. A reference chromatogram is shown in Fig. 6. Such a chromatogram was the basis for determining response factors, which showed good reproducibility (Table III). The chromatogram of an actual sample (Fig. 7) shows that it also contained acetone oxime, as identified by GC–mass spectrometry (MS). In the examples of quantitative results (Table IV), it was possible to

TABLE IV

SAMPLES OF PLANT STREAM SUBMITTED FOR ANALYSIS

Sample No.	*Compounds present (wt.-%)*						
	Water	*Methanol*	*Methyl formate*	*Acetone*	*Methylene chloride*	*3-Methyl-isoxazole*	*5-Methyl-isoxazole*
1	0.4	0.5	ND*	ND*	ND*	1.6	98.2
2	15.6	58.6	ND*	0.9	0.07	1.7	23.8
3	17.7	51.8	0.2	1.2	0.1	1.8	28.1
4	24.7	40.0	0.7	1.4	0.1	2.1	36.0

detect 0.07% of methylene chloride using thermal conductivity detection.

Determination of solvents on Carbowax columns

Carbowaxes, especially those coated on to Carbopak B and C and capillary (wall-coated open tubular, WCOT) columns, are also useful for solvents. Fig. 8 shows the separation of solvents (and other low-boiling compounds) in a plant stream on a column packed with 0.1% SP-1000 on Carbopak C. Note that a mixture of alcohols, hydrocarbons, carbonyls and others was being resolved. Fig. 9a and b shows a separation of similar materials on a column packed with 5% Carbowax 20M on Carbopak B. Fig. 9a represents a reference mixture and Fig. 9b an actual sample. The same mixture (reference) separated on a WCOT Carbowax column is shown in Fig. 10.

Miscellaneous determinations of other contaminants

Other determinations that should be considered in line with the foregoing discussion are (1) phenol in aqueous waste streams, (2) methyl bromide in acetone

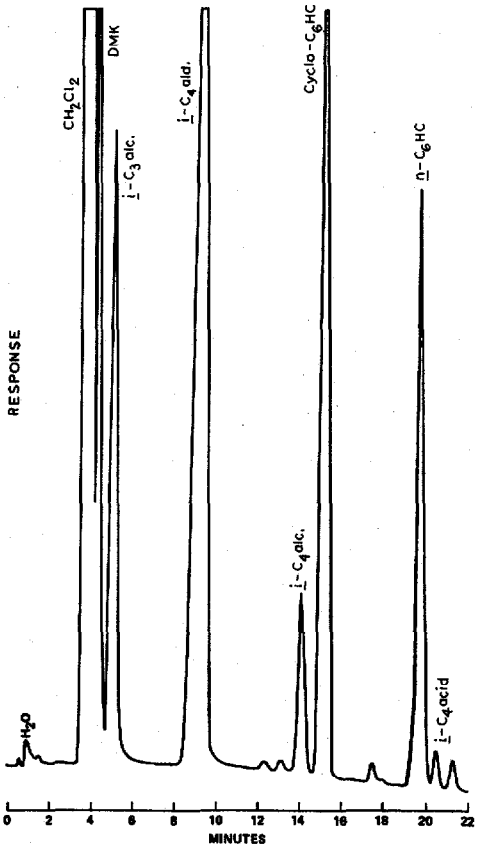


Fig. 8. Components of a stream resolved on a column packed with 0.10% SP-1000 on Carbopak C. HC = Hydrocarbon; alc = alcohol; ald = aldehyde; i = iso.

waste streams and (3) formic acid in acetic acid. The first of these uses *n*-butanol as an internal standard and a column packed with OV-17 on Gas-Chrom Q (Fig. 11). The second and third are external standard methods and are performed on columns packed with Chromosorb 101 (Figs. 12 and 13). All three methods are capable of measuring low levels of residues (see Table I for conditions).

Another interesting problem concerned the purity of ethyl acetate; GC on Chromosorb 101 showed a shoulder on the trailing edge of the major peak that defied separation. After much trial and error, a column was found that achieved this separation, *viz.*, a column containing equal proportions of Bentone-34 and diisodecyl phthalate (Fig. 14). The impurity (*ca.* 2%) turned out to be methyl propionate, an isomer of ethyl acetate, based on GC–MS and other confirmatory studies.

Parameters affecting elution of solvents from porous polymer substrates

Much has been written on the parameters that affect the elution (or retention) of compounds from (or on) GC columns, that is, parameters such as boiling points[4], vapor pressures[4,5], polarities[6] of adsorbates and the nature of the column substrate[6] itself. In inert columns, where adsorbate–adsorbent interactions are at a minimum, the boiling points of compounds eluting from the column may be the primary factor determining the elution order. On the other hand, in more polar columns where adsorbate–adsorbent interactions do come into play, the boiling points of eluting

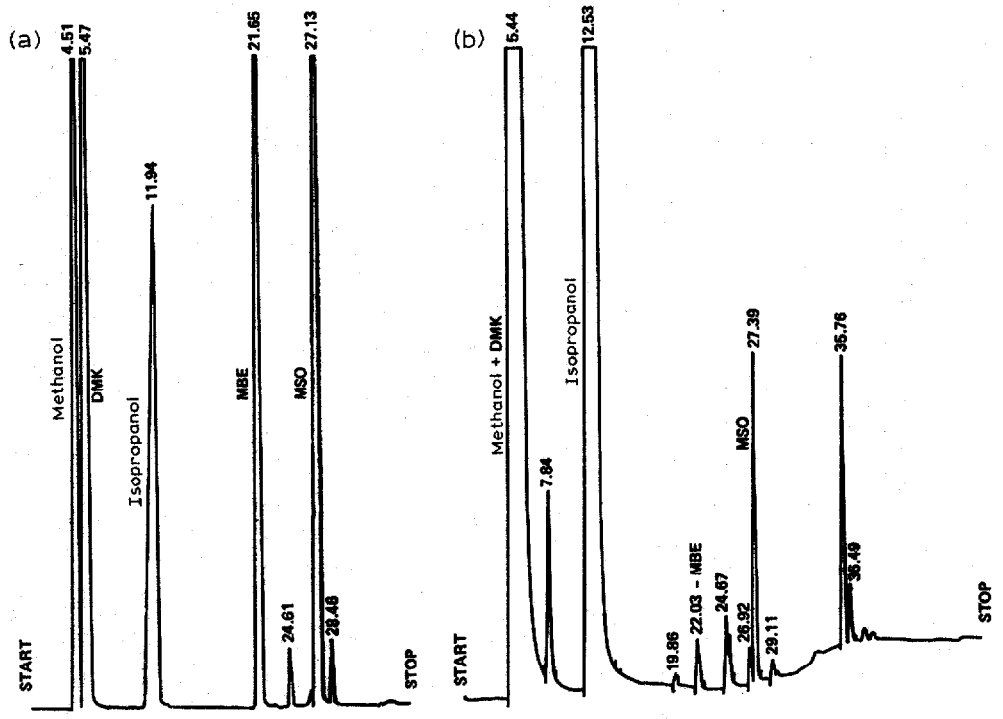
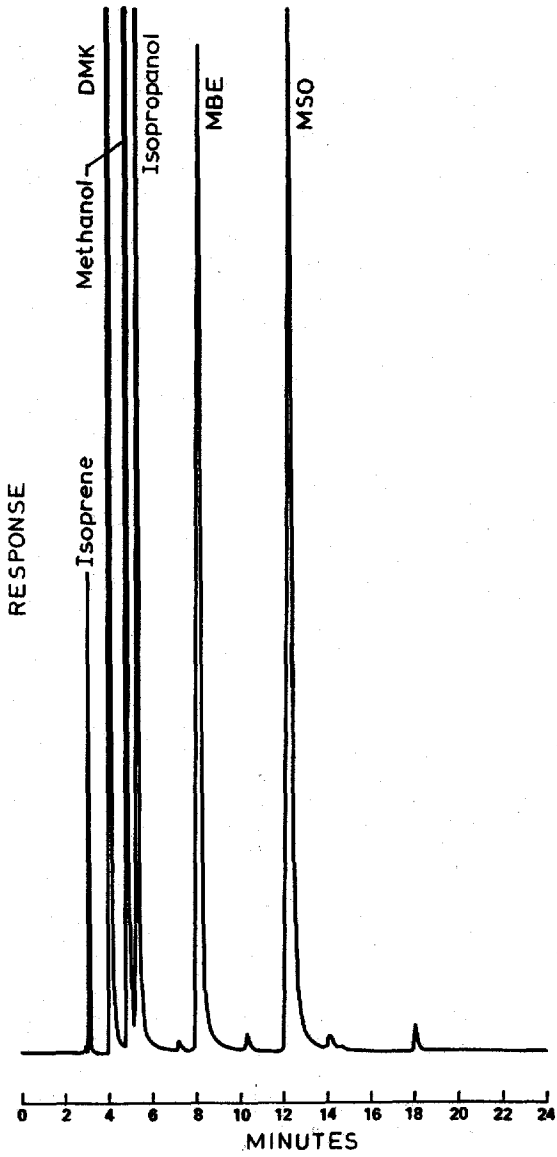


Fig. 9. (a) Reference mixture resolved on a column packed with 5% Carbowax 20M on Carbopak B. (b) Actual plant sample resolved on 5% Carbowax 20M on Carbopak B. DMK = dimethyl ketone (acetone); MBE = methylbutenol; MSO = mesityl oxide. Retention times in minutes.

compounds probably make a less significant contribution to the elution order. Generally, however, a number of factors influence the retention behavior of compounds on GC columns.

In this paper, the two types of columns as they relate to solvents have been discussed —the porous polymer type and the support-coated type exemplified by Carbowax liquid phases. A number of parameters were considered to see how they



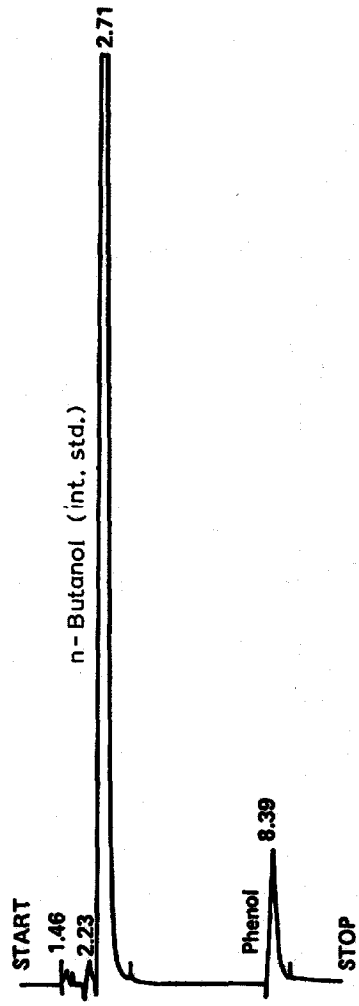


Fig. 10. Reference mixture resolved on a WCOT Carbowax 20M column. Abbreviations as in Fig. 9.

Fig. 11. GC determination of phenol in aqueous waste streams on an OV-17 column. Retention times in minutes.

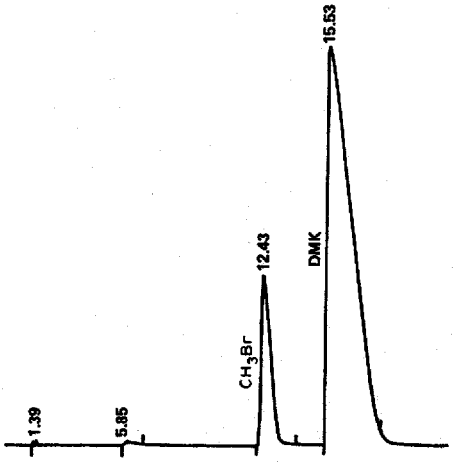


Fig. 12. GC determination of methyl bromide in acetone waste streams on a Chromosorb 101 column. DMK = dimethyl ketone (acetone). Retention times in minutes.

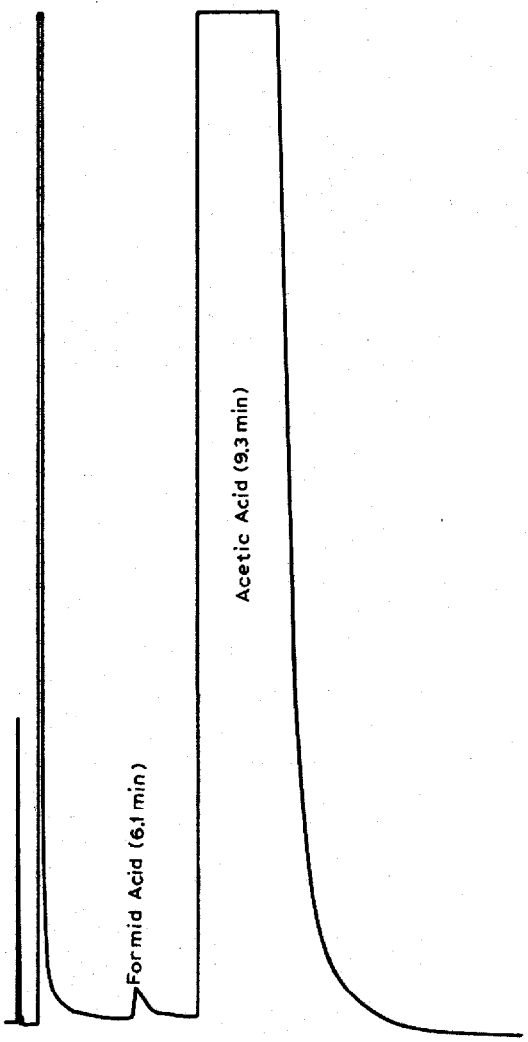


Fig. 13. GC determination of trace formic acid in acetic acid.

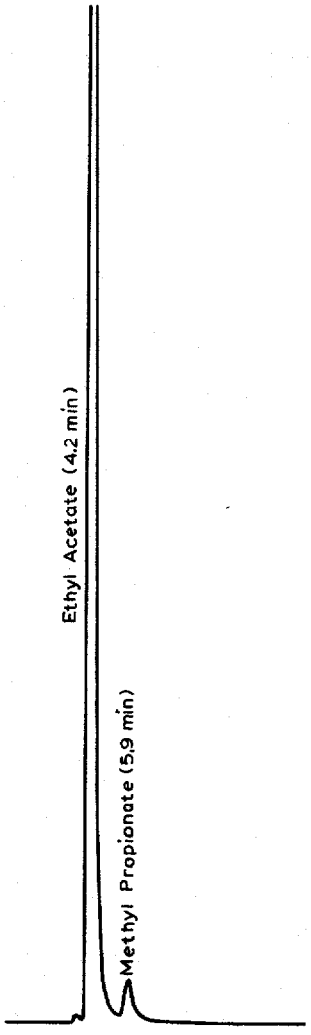


Fig. 14. Separation of ethyl acetate and methyl propionate on Bentone–diisodecyl phthalate.

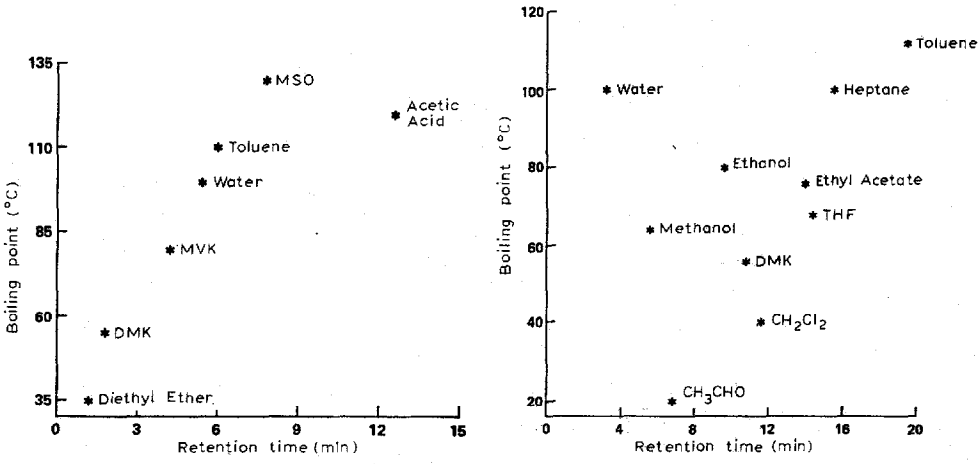


Fig. 15. Solvents eluted on Carbowax 20M: relationship between boiling points and elution order. MVK = methyl vinyl ketone; other abbreviations as in Fig. 9.

Fig. 16. Solvents eluted on Chromosorb 101: effect of boiling points. DMK = dimethyl ketone (acetone); THF = tetrahydrofuran.

related to the retention times of solvents. For example, on columns packed with Carbowax 20M coated on to Chromosorb T, the elution order of solvents related extremely well with their boiling points (Fig. 15), even though Carbowax 20M is a polar stationary phase, and perhaps one would have expected more effects of adsorbate–adsorbent interactions. In contrast, on a column packed with Chromosorb 101 (a porous polymer), the boiling points of solvents had less effect on their elution order (Fig. 16). What did relate well to the order of elution was molecular volume (Fig. 17). It might be added, of course, that molecular volume had no relation to elution order on the Carbowax 20M (on Chromosorb T) column (Fig. 18).

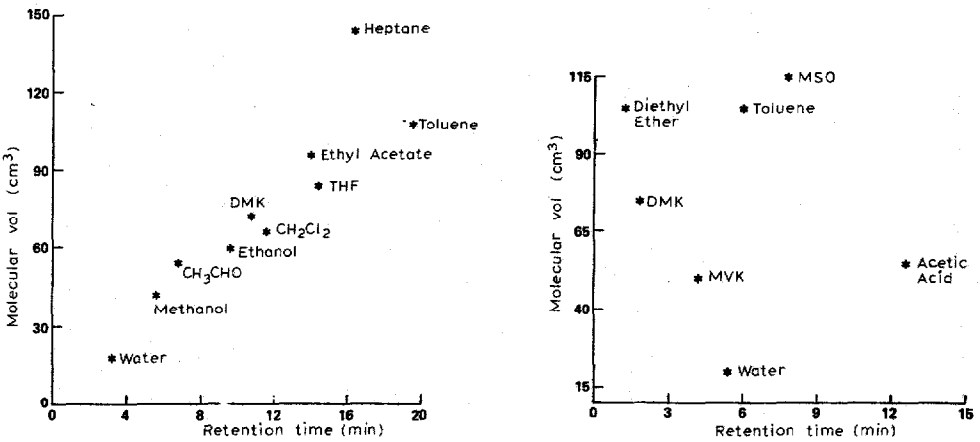


Fig. 17. Solvents eluted on Chromosorb 101: effect of molecular volume (molecular volume = molecular weight/density). Abbreviations as in Fig. 16.

Fig. 18. Solvents eluted on Carbowax 20M: effect of molecular volume. Abbreviations as in Fig. 15.

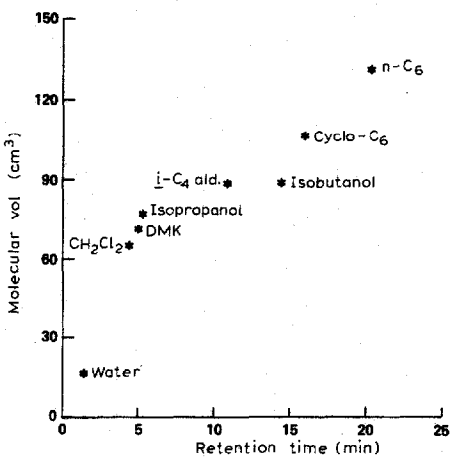


Fig. 19. Solvents eluted on Carbopak C coated with 0.1 % SP-1000: effect of molecular volume. DMK = dimethyl ketone (acetone); ald = aldehyde.

Of additional interest was the observation that, on a column containing Carbopak C coated with 0.1 % SP-1000 (a Carbowax-type stationary phase), the elution order of solvents was also related to molecular volume (Fig. 19). In this instance, it is apparent that the stationary phase itself had little effect on the elution order of adsorbates; rather, the interaction between the carbonaceous support and the solvents apparently determined the elution order, the support acting like a porous polymer. Perhaps, the major function of the liquid phase in this case is to "hold" the support together.

Other parameters, such as dipole moment and dielectric constant, were also examined. However, apart from the effects of boiling points and molecular volumes mentioned previously, no other parameters seemed to have any measurable relation to the retention order of the compounds examined.

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