

CHROM. 11,441

Note

Methyl tert.-butyl ether: a new chromatographic eluent

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(Received September 5th, 1978)

The use of diethyl ether (DEE) and diisopropyl ether (DIPE) is well established in liquid and thin-layer chromatography (TLC). However, there is a growing concern about their general use, particularly since the advent of the "Health and Safety at Work Act". Our major concern is the formation of peroxides which are prone to violent detonation during evaporation, a problem which is not too severe in analytical chromatography, but which is rather worrying in preparative-scale liquid chromatography when many litres of solvent have to be removed.

It was with these safety aspects in mind that we investigated the use of methyl tert.-butyl ether (MTBE) as an alternative to both DEE and DIPE. MTBE was obtained through Honeywill and Stein (Wallington, Great Britain) and is now available in an HPLC grade from Rathburn Chemicals (Walkerburn, Great Britain).

PHYSICAL PROPERTIES OF MTBE

A comparison of properties of DEE, MTBE and DIPE is given in Table I, which illustrates several useful properties of MTBE. These are:

(a) The higher boiling point of MTBE (55.2°) is sufficient to prevent the bubble formation which often occurs when using the more volatile DEE (b.p. = 34.5°).

(b) The range of concentrations of the vapour in air which is likely to lead to an explosion is much narrower for MTBE than for DEE and DIPE.

(c) None of the ethers could be termed highly toxic as judged by their LD₅₀ values and although the data quoted for MTBE refer to mouse experiments, the indications are that MTBE could be less toxic than either DEE or DIPE.

(d) Of particular importance is the comparison of *peroxide formation*. DEE and DIPE are very prone to peroxide formation whereas MTBE is relatively stable. So much so, in fact, that no peroxide inhibitor is added to the solvent, a factor of some importance to the chromatographer using UV detection.

TABLE I
COMPARISON OF THE PHYSICAL PROPERTIES OF ETHERS

Property	DEE	MTBE	DIPE
Formula	C ₄ H ₁₀ O	C ₅ H ₁₂ O	C ₆ H ₁₄ O
Structure	[CH ₃ CH ₂] ₂ O	[(CH ₃) ₃ C]OCH ₃	[(CH ₃) ₂ CH] ₂ O
Molecular weight	74.12	88.14	102.18
Specific gravity (at 20°)	0.713–0.717	0.741	0.725
Dipole moment (D)	1.15	1.32	1.21
Melting point (°C)	–116.2	–108.6	–85.9
Flash point (°C)	–45	–28	–28
Boiling point (°C)	34.5	55.2	68
Ignition temperature (°C)	180	224	443
Explosive limits (%)	1.85–48	2.5–15.1	1.4–21
Peroxide formation	Readily	Very slowly	Readily
Peroxide inhibitors present	<i>n</i> -Propyl gallate or copper gauze	None	0.01 % Hydro- quinone
Oral toxicity LD ₅₀ (mg/kg) (approx.)	2200 (rat)	4000 (mouse)	1100 (rat)
Solubility ether in water (% w/w, at 20°)	7.2] A*	4.8] A**	—
Solubility water in ether (% w/w, at 20°)	1.2]	1.5]	—
Miscibility with organic HPLC solvents	Completely	Completely	Completely
Viscosity at 20° (cP)	0.23	0.27	0.37
Refractive index <i>n</i> _D ²⁰	1.353	1.369	1.368
ε° (Al ₂ O ₃)	0.38	0.3–0.4	0.28
UV cut off (nm)	220	235	220

* Forms azeotrope (1.3% water, b.p. = 34.2°).

** Forms azeotrope (4% water, b.p. = 52.6°).

CHROMATOGRAPHIC PROPERTIES OF MTBE

From Table I it can be seen that viscosity, refractive index and UV cut off data for MTBE compare very favourably with those of DEE and DIPE.

The solvent strength, ε°, was estimated by comparison with DEE and DIPE using alumina TLC plates. The estimated figure shows that MTBE behaves very similarly to both DEE and DIPE. To illustrate this, a series of test mixtures have been compared using DEE, MTBE and DIPE in the eluent. The comparative retention data (on silica gel) are shown in Table II. Selected TLC separations are shown in Fig. 1 from which it can be seen that MTBE can be used as a direct replacement for both DEE and DIPE.

The greatest advantages of MTBE occur in its use for high-performance liquid chromatography (HPLC). Fig. 2 shows the separation of a mixture of chloroanilines on a Hypersil column using an eluent composition of 10% (v/v) ether in hexane. Essentially there is little to choose between the three ethers under comparison. However, apart from those already mentioned, MTBE does exhibit some slight chromatographic advantages as shown in Fig. 2b. The chromatographic efficiency is at least as good as for DEE and DIPE. Its selectivity is favourable as indicated by the partial resolution of peak 4 and the analysis time is shorter, illustrating the slightly higher dipole moment of MTBE. It can also be seen that DIPE, apart from being one of the most dangerous ethers to use, is also the least selective ether for the separation of chloroanilines.

TABLE II
COMPARISON OF R_F DATA USING DEE, MTBE and DIPE
TLC plates used: pre-coated silica gel 60 F₂₅₄ (Merck).

Compound	R_F			% ether in hexane
	DEE	MTBE	DIPE	
Acetophenone	0.24	0.36	0.27	10
Propiophenone	0.38	0.49	0.45	10
Valerophenone	0.44	0.58	0.51	10
Decanophenone	0.51	0.68	0.62	10
3-Aminophenol	0.02	0.01	0	20
4-Aminophenol	0	0	0	20
2-Nitrophenol	0.53	0.59	0.57	20
3-Nitrophenol	0.07	0.14	0.14	20
4-Nitrophenol	0.04	0.09	0.08	20
Salicylaldehyde	0.59	0.58	0.57	20
Salicylic acid	0.01	0.03	0.02	20
3-Hydroxybenzaldehyde	0.09	0.17	0.12	20
Phenol	0.26	0.34	0.29	20
2-Ethylphenol	0.39	0.49	0.43	20
Catechol	0.07	0.12	0.08	20
Resorcinol	0.04	0.04	0.03	20
<i>o</i> -Cresol	0.29	0.33	0.31	20
<i>m</i> -Cresol	0.23	0.29	0.26	20
<i>p</i> -Cresol	0.23	0.31	0.26	20
<i>p</i> -Chloro- <i>m</i> -cresol	0.22	0.30	0.25	20
4-Chlorophenol	0.08	0.22	0.20	20
4-Bromophenol	0.06	0.18	0.18	20
4-Iodophenol	0.08	0.21	0.20	20
4-Methoxyphenol	0.07	0.15	0.13	20
3-Chloroaniline	0.16	0.18	0.16	20
2,3-Dichloroaniline	0.30	0.32	0.32	20
2,4,6-Trichloroaniline	0.66	0.66	0.68	20
Anthraquinone	0.70	0.86	0.70	50
Anthrone	0.67	0.81	0.68	50
Benzoquinone	0.56	0.71	0.45	50
Acetanilide	0.53	0.60	0.66	100
Benzanilide	0.92	0.93	0.22	100
<i>p</i> -Bromoacetanilide	0.42	0.57	0.24	100
Sulphanilamide	0.40	0.42	0.12	100
Sulphadimethoxine	0.51	0.48	0.18	100
Mefruside	0.63	0.73	0.24	100
5-Oxo-mefruside	0.21	0.34	0.05	100

More pronounced differences between the solvents can be seen in the separation of sulphonamides¹ on a Zorbax-Sil column using an eluent composition of 100% ether (Fig. 3). The differences between these two applications brings into question the relevance of ϵ^c values, often quoted to two decimal places, and suggests that they should only be used as a guideline for making an initial choice of solvent. It should be noted that the MTBE eluent has been diluted with hexane (10%, v/v) in order to achieve baseline resolution of the sulphonamides. This is advantageous and results in the most efficient separation in the minimum time.

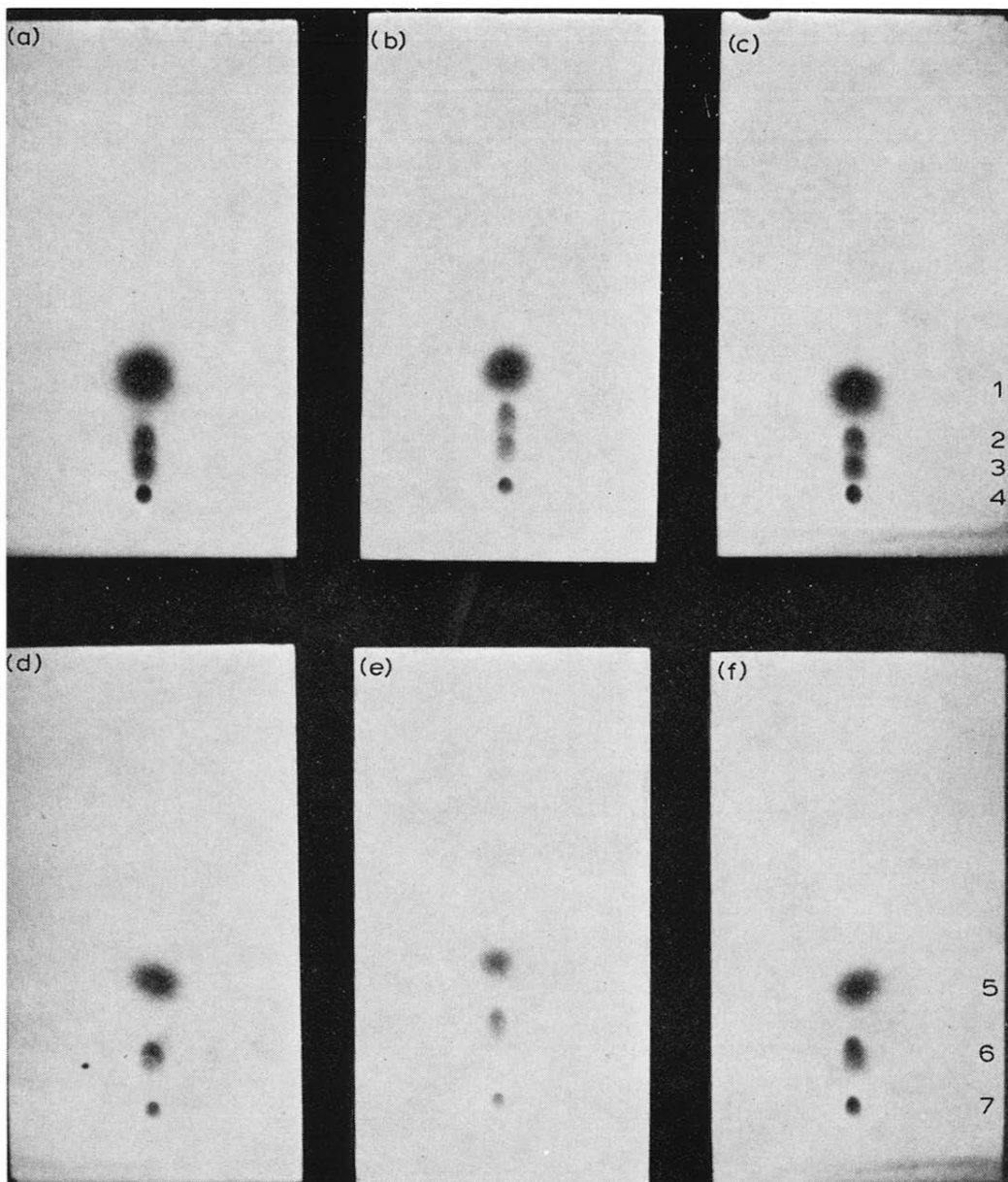


Fig. 1. Thin-layer chromatography of phenols and ketones. Eluent: Phenols (a-c), 20% ether in hexane; ketones (d-f), 10% ether in hexane, where a,d = DEE; b,e = MTBE; c,f = DIPE. Solutes: 1 = 2-chlorophenol; 2 = 4-iodophenol; 3 = 4-methoxyphenol; 4 = salicylic acid; 5 = decanophenone; 6 = valerophenone; 7 = propiophenone.

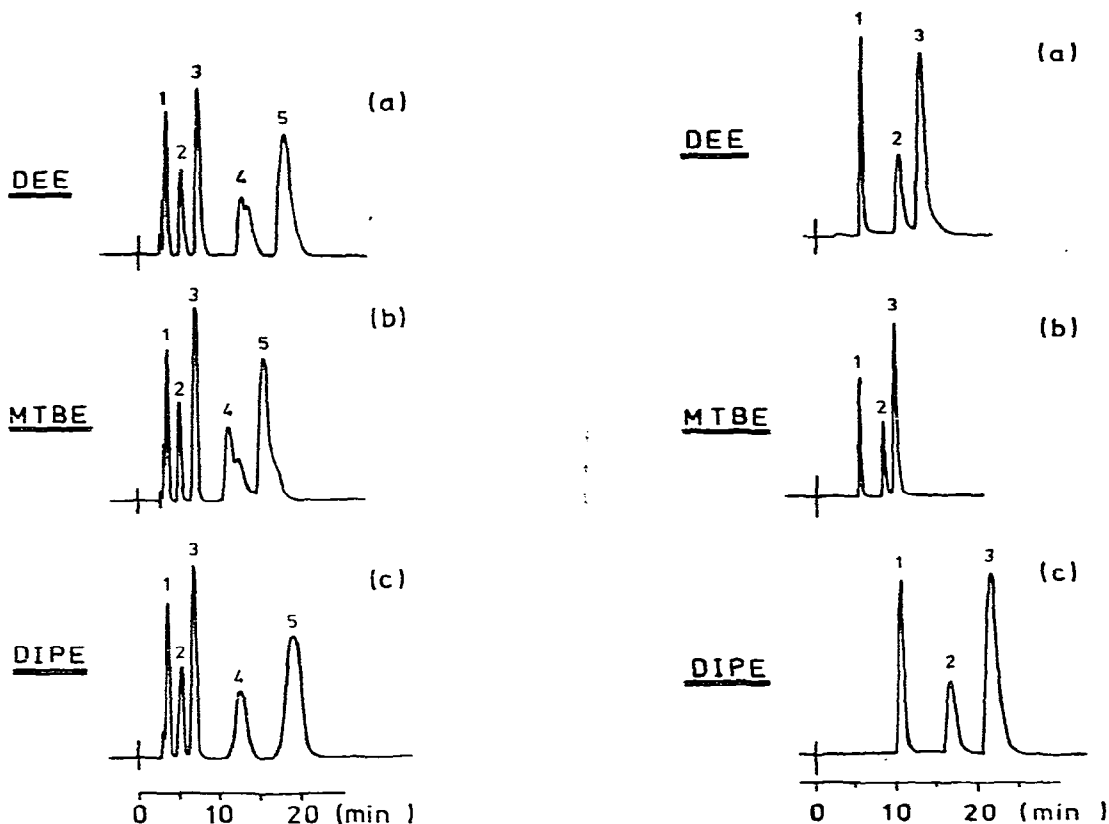


Fig. 2. Separation of chloroanilines. Mobile phase: (a) hexane-DEE (9:1); (b) hexane-MTBE (9:1); and (c) hexane-DIPE (9:1). Flow-rate, 1.0 ml/min; detector UV at 254 nm; column, 25 cm \times 0.42 cm I.D. packed with Hypersil ($5\mu\text{m}$). Peaks: 1 = 2,4,6-trichloroaniline with traces of 2,6-dichloroaniline and benzene; 2 = 2-chloroaniline; 3 = 2,3-dichloroaniline; 4 = 3-chloro- and 3,5-dichloroaniline; 5 = 4-chloroaniline with a trace of unknown impurity. Equipment used: modular, comprising a constametric I pump, a Cecil CE 212 UV detector and a Rheodyne 7120 syringe loading valve.

Fig. 3. Separation of sulphonamides. Mobile phase: (a) DEE; (b) MTBE-hexane (9:1); (c) DIPE. Flow-rate, 1.0 ml/min; detector, UV at 260 nm; column, 25 cm \times 0.4 cm I.D. packed with Zorbax Sil ($5\mu\text{m}$). Peaks: 1 = Mefruside; 2 = sulphadimethoxine; 3 = sulphanilamide. Equipment as in Fig. 2.

In conclusion we would like to summarise by saying that MTBE has been shown to be a suitable replacement for both DEE and DIPE both from the safety and chromatographic aspects. Indeed, not only is MTBE a satisfactory replacement for these well established solvents, but in many cases it should be considered as the solvent of choice.

REFERENCE

- 1 C. J. Little, A. D. Dale, D. A. Ord and T. R. Marten, *Anal. Chem.*, 49 (1977) 1311.