

Notes

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Gas chromatographic separation of diastereoisomeric haloalkanes and *o*-, *m*- and *p*-isomers of monosubstituted halobenzenes with Igepal CO-880

For a study of the stereochemical course of hot substitution reactions on asymmetric carbon atoms¹, it was necessary to separate diastereoisomeric haloalkanes, labelled with short-lived radiohalogens, such as ¹⁸F (half-life, $T = 110$ min), ³⁸Cl ($T = 37$ min) and ¹²⁸I ($T = 25$ min). The separation therefore had to be relatively fast in order to achieve a quantitative radioactivity measurement with a reasonable statistical error. A good resolution was also desirable, since small activities of one diastereoisomeric form had to be determined in the presence of large activities of the opposite diastereoisomeric haloalkane. For the same reason, large sample volumes (up to 100 μ l) of the reaction mixture had to be injected, and hence capillary columns were not applicable. A similar problem, though less pronounced, arose with respect to the separation of *o*-, *m*- and *p*-isomers of monosubstituted halobenzenes, the radioactivity of which had to be quantitatively determined by a discontinuous radio gas chromatographic technique² after recoil halogenation.

Very little information is available on the gas-liquid chromatographic (GLC) separation of diastereoisomeric haloalkanes. The liquid phases which have been used so far, such as Carbowax 20 M (ref. 3) and Carbowax 300 (ref. 4) or tritolyl phosphate⁵, were unsatisfactory for our purpose with respect to retention times and/or resolution.

The GLC separation of *o*-, *m*- and *p*-isomers of substituted halobenzenes is a simpler problem and a number of useful columns have been described⁶⁻¹². For multi-component systems in the presence of an excess of a monosubstituted substrate or solvent, it seemed desirable to have a more versatile column, which could even be used on a semi-preparative scale.

In the present note, we report on the application of Igepal CO-880 (Nonylphenoxy polyoxyethylene ethanol), a versatile and effective liquid phase for both the separation of diastereoisomeric haloalkanes and monosubstituted isomers of halobenzenes.

Experimental

All GLC analyses have been carried out with a Hewlett-Packard Research Chromatograph 5750, using a thermal conductivity detector. Glass columns of 3.5–5 mm I.D. with lengths of 4, 8, 12 and 20 m were filled with either 30 % Igepal CO-880 on Chromosorb P-NAW, 60–80 mesh (column I) or 20 % Igepal CO-880 on Chromosorb W-AW-DMCS, 60–80 mesh (column II). Igepal CO-880 was obtained from Serva International, and the solid support was coated with it by the rotating evaporator method, using dichloromethane as solvent. The data given in Tables I and II were obtained by injecting about 0.06 μ l of solution containing 0.02 μ l of each

isomer. For the actual analyses during our kinetic studies, reaction mixtures of 20–100 μ l were used, containing 5–10 μ l of each isomer in a solvent such as *n*-pentane, cyclohexane or carbon tetrachloride. The samples were injected directly into the column in order to avoid thermal decomposition on hot metal inlet ports, particularly in the case of the bromo and iodo compounds. Helium was used as carrier gas at a flow-rate of 100 ml/min. All other parameters are given in the tables.

Results and discussion

The results obtained for the separation of diastereomeric haloalkanes are given in Table I. The most difficult case is the separation of meso and racemic 1,2-dichloro-1,2-difluoroethane (b.p. 59.4° and 59.9°, respectively). PALINO AND ROWLAND¹ have separated these diastereoisomers by using a 15-m column with Carbowax 300 as liquid phase. At 65°, retention times of 400 and 375 min, respectively, were necessary to obtain resolution (tailing factor 20%). It can be seen from Table I that Igepal CO-880 on Chromosorb P-NAW under our experimental conditions leads to a considerably faster separation (68 and 72 min, respectively) with a resolution of about 92%, corresponding to an impurity level of about 0.6%. Chromosorb P has been used as solid support because of its large surface area and high capacity for the liquid phase. As expected, it exhibits considerably better resolution than Chromosorb W, but a longer retention time. The height equivalent to a theoretical plate (HETP) was higher for the Chromosorb W (0.9 mm) than the Chromosorb P column (0.5 mm). The relatively small inertness of Chromosorb P did not cause any problems, mainly due to the heavy loading with Igepal (30%). Also, the tailing factor was reasonably good (80%) and decomposition of the haloalkanes could not be observed.

A fast and 100% separation of diastereoisomeric 2,3-dihalobutanes could also

TABLE I

DATA FOR GLC SEPARATION OF DIASTEREOISOMERIC 1,2-DICHLORO- 1,2-DIFLUOROETHANES AND 2,3-DIHALOBUTANES WITH IGEPAL CO-880

Column I: glass, 5 mm I.D., 30% Igepal CO-880 on Chromosorb P-NAW, 60–80 mesh (0.5 mm HETP). Column II: glass, 5 mm I.D., 20% Igepal CO-880 on Chromosorb W-AW-DMCS, 60–80 mesh (0.9 mm HETP).

Compound	Meso or erythro		Racemic or threo		Conditions				
	t_{ret} (min)	r	t_{ret} (min)	r	Reso- lution (%)	Temp. (°C)	Inlet pressure (kp/cm ²)	Length (m)	Column
1,2-Dichloro-1,2- difluoroethane	68.38	1.000	72.06	1.054	91.9	110	ca. 5	12	I
	42.15	1.000	44.24	1.050	86.3	110	ca. 6	20	II
2-Chloro-3-fluorobutane	11.09	0.497	15.75	0.705	100	90	2.20	8	II
2-Bromo-3-fluorobutane	22.34	1.000	30.88	1.383	100	90	2.20	8	II
	9.11	1.000	11.95	1.312	100	125	2.45	8	II
2,3-Dichlorobutane	37.38	1.074	44.21	1.979	100	90	2.20	8	II
	14.43	1.584	16.53	1.814	100	125	2.45	8	II
2-Chloro-3-bromobutane	25.93	2.845	28.90	3.171	100	125	2.45	8	II
2,3-Dibromobutane	45.27	4.968	49.58	5.441	100	125	2.45	8	II

be achieved with an 8-m column of Igepal CO-880 on Chromosorb W-AW-DMCS (cf. Table I). Compared with Carbowax 20 M (ref. 3) and tritolyl phosphate⁵, which have been used previously for the separation of 2,3-dichlorobutanes, the present separation is considerably faster.

Igepal CO-880 on Chromosorb W-AW-DMCS is also an efficient liquid phase for the separation of a variety of monosubstituted halobenzenes. The results obtained for the *o*-, *m*- and *p*-isomers of fourteen different monosubstituted halobenzenes are listed in Table II. The first two columns show the two variable substituent groups (Y the halogen introduced and X the substituent group of the substrate C_6H_5X to be halogenated).

It can be seen from Table II that 100% (or almost 100%) resolution can be achieved for most of the fourteen isomer triplets with retention times ranging from about 6 to 50 min, at temperatures between 75 and 195°. The Igepal column, however, fails to resolve *o*-, *m*- and *p*-isomers of monohalogenated toluenes. For the separation of monochloro- and monobromotoluene we used liquid crystals as stationary phase, as described by KELKER⁶ and DEWAR AND SCHROEDER⁷ for the separation of dihalobenzenes. A 100% resolution was obtained when using a 4-m column of 20% 4,4'-azoxydianisole on Chromosorb W-AW-DMCS, 60-80 mesh, at 100° within about 12 min. But for most of our purposes, columns with liquid crystals could not be used because they often drastically restricted sample capacities, their limited temperature range caused too long retention times for high-boiling compounds, and because occasionally they made the separation of the *o*-isomer from the other isomers difficult.

TABLE II

DATA FOR GLC SEPARATION OF *o*-, *m*- AND *p*-ISOMERS OF SUBSTITUTED HALOBENZENES WITH IGEPAL CO-880

Column: glass, 3.5 mm I.D., 20% Igepal CO-880 on Chromosorb W-AW-DMCS, 60-80 mesh (0.7 mm HETP).

Y	X	Ortho		Meta		Para		Resolution <i>m-p</i> (%)	Conditions		
		<i>t_{ret}</i> (min)	<i>r</i>	<i>t_{ret}</i> (min)	<i>r</i>	<i>t_{ret}</i> (min)	<i>r</i>		Temp. (°C)	Inlet pressure (kp/cm ²)	Length (m)
F	F	17.64	1.426	12.91	1.000	16.83	1.353	80	75	3.25	8
	Cl	37.89	1.508	25.13	1.000	32.08	1.277	100	75	2.75	4
	Br	16.24	1.415	11.48	1.000	13.48	1.174	100	120	3.25	4
	I	22.96	1.396	16.64	1.000	18.32	1.125	100	120	3.25	4
Cl	NO ₂	32.06	1.368	23.44	1.000	26.37	1.125	100	180	3.70	4
	CF ₃	11.24	1.945	5.78	1.000	6.49	1.122	100	110	2.95	4
	CCl ₃	31.56	1.630	10.25	1.000	21.30	1.107	100	195	3.70	4
	Cl	16.63	1.368	12.15	1.000	13.47	1.109	99	130	3.37	4
	Br	24.14	1.350	17.88	1.000	19.30	1.085	98	140	3.45	4
	I	47.21	1.288	37.04	1.000	38.52	1.042	82	170	3.4	8
Br	NO ₂	30.24	1.307	23.14	1.000	25.78	1.114	100	195	3.70	4
	CN	28.13	1.415	19.87	1.000	22.17	1.115	100	195	3.70	4
	Br	32.90	1.331	24.72	1.000	26.40	1.068	92	150	3.50	4
	I	24.26	—	—	—	19.38	—	—	195	3.70	4

It should be pointed out that a comparable separation of the monosubstituted halobenzenes listed in Table II has been obtained² with a 2-m column of 5 % polyethylene glycol on Chromosorb G-AW-DMCS, 80-100 mesh, at temperatures between 60 and 135°, but the retention times were generally considerably longer.

Depending on the individual application and problem, Igepal CO-880 is probably not always the best choice for the separation of disubstituted benzenes, but it seems to be one of the most versatile and fast phases.

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