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HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY OF HALOGENO DERIVATIVES OF ADAMANTANE AND DIAMANTANE

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SUMMARY

   Chromatographic elution data for monocyclic, aromatic and polycyclic halogeno derivatives of the adamantane type have been measured on silica, using *n*-pentane as mobile phase. The water content in the recycled mobile phase was controlled by an integral moisture control system containing coarse silica with 0.5, 1 and 2% water, respectively.

   Amongst the group of adamantane and diamantane compounds the bromo derivatives have longer retention times than the corresponding chloro derivatives. With monotopic derivatives, the position of the halogen atom has the dominant effect on the chromatographic behaviour. The position of bromine atoms in the molecule also has a dominant effect on the elution order of dibromodiamantanes. Interatomic distance is a secondary effect influencing the retention.

INTRODUCTION

   The many thousand adamantane derivatives prepared up to now are interesting, not only from the point of view of basic reasearch, but also because of their use in many different practical applications, mainly in pharmacy, biochemistry, medicine, chemistry of plastics and in the synthesis of special lubricants, etc.

   Halogeno derivatives of adamantane and diamantane serve mostly as the starting compounds for the syntheses of many diamantoid derivatives. Two isomeric monobromoadamantanes and three monobromodiamantanes can be prepared. By the introduction of an additional bromine atom into the molecule the number of isomers rapidly increases. Thus there are nine possible dibromoadamantanes and twenty-three dibromodiamantanes.

   Only a few methods for separating halogeno diamantoid derivatives have been described. Gund *et al.*[1,2] separated bromodiamantanes by classical column chromatography using alumina or silica as stationary phases and hexane as an eluent. Use of preparative high-performance liquid chromatography (HPLC) using silica gel and *n*-pentane allowed 1,5- and 3,9-dibromodiamantanes to be isolated from their mixture[3]. From a mixture containing 1-bromodiamantane and 1,7-, 1,6- and 1,4-

dibromodiamantanes all the isomers were isolated as pure compounds[3].

This study is part of a project dealing with the chromatographic analysis of diamantoid compounds. Previous reports have dealt with the HPLC characteristic of alcohols[4] and ketones[5], using silica as the stationary phase, or diketones, hydroxy-ketones and dihydroxy derivatives, using a reversed phase[6]. Because the diamantoid compounds differ in some aspects from other organic compounds, the retention data of some other halogeno derivatives, *i.e.* aliphatic, aromatic and cyclic, have also been measured for comparison.

EXPERIMENTAL

Apparatus

A Varian 8500 liquid chromatograph with a syringe pump was used, connected to a refractive index detector and a A 25 dual-channel strip-chart recorder (Varian, Palo Alto, CA, U.S.A.). Sample injection was performed using the stop-flow technique, with a 5-μl syringe (Hamilton, Bonaduz, Switzerland).

A stainless-steel (250 × 8 mm I.D.) column with a tapered inlet (Varian) was filled using the slurry-packing technique with 7.5-μm irregularly shaped silica gel (Silasorb; Lachema, Brno, Czechoslovakia). The column and the lower part of injector were inserted in a water jacket, which was kept at a constant temperature. The water content in the recycling mobile phase was maintained by a moisture control system (MCS) incorporated in the closed circuit. The MCS was filled by 100 g of silica (80–100 μm) containing 0.5, 1 and 2% of water, respectively. Silica was activated by heating for 4 h at 200°C. Deactivation was performed by the addition of such quantities of water so as to make its content 0.5, 1 and 2%, respectively. Both the column and the MCS were kept at 25 ± 0.1°C. The MCS apparatus, designed by Boehme and Engelhardt[7], was modified as described in ref. 8.

Chemicals

Bromo and chloro derivatives of adamantane and diamantane used as standards were prepared in our laboratory. The other halogeno derivatives were commercial products from various manufacturers.

Mobile phase

n-Pentane (analytical-reagent grade) was used as the mobile phase. Before use, it was distilled and dried by percolating over a silica gel column (Mikrosil, 100–150 μm; Lachema) which had been dried for 4 h at 200°C. The flow-rate of the mobile phase was 100 ml/h.

TABLE I

EQUILIBRATION TIME OF WATER BETWEEN MOBILE PHASE AND MCS

Amount of water on silica in the MCS (% w/w)	Equilibration time (h)
0.5	140
1.0	40
2.0	25

TABLE II

RETENTION DATA

a = Water content on silica gel in the MCS (see Table I).

Compound	No. of carbon atoms in molecule	a = 0.5		a = 1.0		a = 2.0	
		$t_R(sec)$	k'	$t_R(sec)$	k'	$t_R(sec)$	k'
Diamantane	14	271	0.08	266	0.06	264	0.05
1-Bromodiamantane	14	587	1.33	525	1.09	526	1.09
3-Bromodiamantane	14	529	1.10	496	0.97	481	0.91
4-Bromodiamantane	14	708	1.81	623	1.47	602	1.39
1,7-Dibromodiamantane	14	1064	3.22	1031	3.09	922	2.66
1,6-Dibromodiamantane	14	1196	3.75	1127	3.47	990	2.93
1,4-Dibromodiamantane	14	1800	6.14	1660	5.59	1454	4.77
4,9-Dibromodiamantane	14	–	–	2953	10.72	2700	9.71
1,5-Dibromodiamantane	14	1477	4.86	1325	4.26	1307	4.19
3,9-Dibromodiamantane	14	2273	8.02	1951	6.74	1840	6.30
1-Chlorodiamantane	14	544	1.16	510	1.02	499	0.98
4-Chlorodiamantane	14	679	1.70	608	1.41	596	1.37
Adamantane	10	268	0.06	–	–	263	0.04
1-Bromoadamantane	10	697	1.77	610	1.42	598	1.37
2-Bromoadamantane	10	–	–	–	–	466	0.85
1,3,5-Tribromoadamantane	10	–	–	–	–	1453	4.77
1-(2-Bromoethyl)adamantane	12	491	0.95	425	0.69	424	0.68
1-Bromoethyl-2-methyl-adamantane	12	440	0.74	418	0.66	415	0.65
1,3-Dibromo-5,7-dimethyl-adamantane	12	1027	3.07	948	2.76	841	2.34
1-Chloroadamantane	10	670	1.66	592	1.35	577	1.29
1,3,5-Trichloroadamantane	10	–	–	–	–	1300	4.16
Cyclohexane	6	263	0.04	...	–	257	0.02
Bromocyclohexane	6	539	1.14	496	0.97	490	0.95
Chlorocyclohexane	6	546	1.17	–	–	481	0.91
1-Bromobutane	4	470	0.87	437	0.73	409	0.62
1-Bromopentane	5	466	0.85	–	–	410	0.63
1-Bromohexane	6	444	0.76	413	0.64	403	0.60
Benzene	6	560	1.22	506	1.01	492	0.95
Bromobenzene	6	496	0.97	456	0.81	439	0.74
1,4-Dibromobenzene	6	455	0.81	419	0.66	401	0.59
1,3,5-Tribromobenzene	6	370	0.47	358	0.42	358	0.42
o-Bromotoluene	7	484	0.92	443	0.76	426	0.69
Bromomethylbenzene	7	1321	4.24	–	–	1014	3.02
2-Bromoethylbenzene	8	1549	5.15	1283	4.09	1208	3.80
Chlorobenzene	6	466	0.85	442	0.75	414	0.64
1,2-Dichlorobenzene	6	465	0.85	439	0.74	426	0.69
1,4-Dichlorobenzene	6	414	0.64	385	0.53	378	0.50
Chloromethylbenzene	7	1251	3.96	1039	3.12	962	2.83

Procedure

Three injections (0.5–5 μl) were carried out for each solution of the sample in the mobile phase or in benzene. The equilibration times (Table I) and the column activity during the measurement were checked by periodically injecting a solution of 1,6-dibromodiamantane in benzene. The dead volume of the column was determined by measuring the retention time of isooctane.

RESULTS AND DISCUSSION

Retention times, t_R, and capacity factors, k', are given in Table II. Halogeno derivatives of monocyclic or polycyclic hydrocarbons have longer retention times than the parent hydrocarbons. Amongst the group of adamantane and diamantane derivatives, the bromo derivatives have longer retention times than the respective chloroderivatives.

When we compare halogeno derivatives with the same formal substitution but with a different basic skeleton size, the larger compounds have the higher t_R values, *e.g.* 4-bromodiamantane has a longer t_R than 1-bromoadamantane and 4-chlorodiamantane a higher t_R than 1-chloroadamantane. These results are contrary to the matographic behaviour of diamantoid compounds having a more polar group in the molecule, *e.g.* ketones[5] or alcohols[4]. In this case, compounds with the same functional group, but differing in the size of the basic skeleton, have shorter retention times when the molecule is larger.

Effect of halogen position

In the group of monotopic derivatives, the position of the halogen atom has a dominant effect on the chromatographic behaviour. Compounds with a halogen atom at a tertiary position have the longest retention time, while the retention time of 1-bromodiamantane in comparison to that of 4-bromodiamantane is diminished by steric effects. Such a shortening of retention times is not as notable as with the hydroxy derivatives, where the corresponding 1-hydroxydiamantane has the shortest retention time of all hydroxy derivatives[4]. Shorter elution times are observed for compounds in which the halogen is bonded to a secondary carbon atom, *i.e.* 2-bromoadamantane or 3-bromodiamantane.

For the bromo derivatives, the retention times increase in the following order:
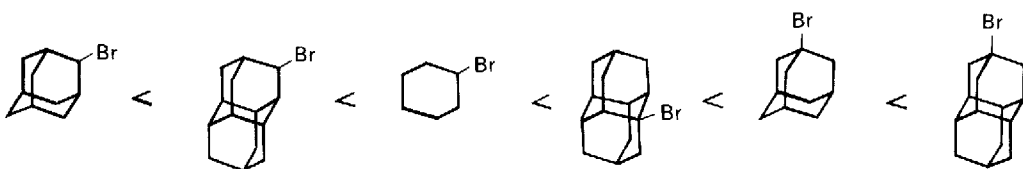
The position of bromine atoms in the diamantane molecule also has a dominant effect on the elution order of dibromodiamantanes, which is as follows: 1,7 < 1,6 < 1,5 < 1,4 < 3,9 < 4,9. Fig. 1 shows the base-line separation of all bromo- and dibromodiamantanes with the exception of the 1,6 and 1,7 isomers. It is evident that the elution order of the dibromo derivatives is related to that of the monosubstituted compounds. The 1,4-, 1,6-, 1,7- and 4,9-dibromodiamantanes represent four out of the six possible dibromo derivatives with both bromine substituents located on tertiary carbon atoms. Amongst these compounds, the 4,9-isomer, with both substituents on apical carbon atoms, has the longest retention time.

The 1,6- and 1,7-derivatives, with both substituents located on medial carbon atoms, have the shortest t_R. A medium retention time has been found for 1,4-dibro-
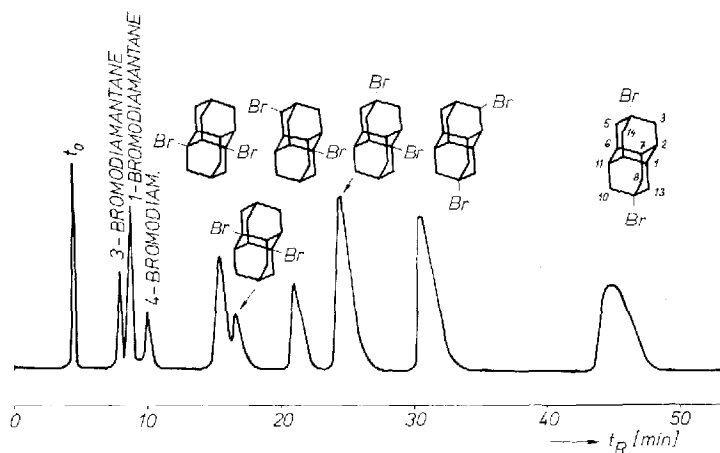
Fig. 1. Chromatogram of bromo- and dibromodiamantanes. Column: 250 × 8 mm I.D., packed by 7.5-μm silica gel. Mobile phase: moisture controlled *n*-pentane; 2% water in the MCS. Flow-rate: 100 ml/h.

modiamantane, with one substituent on the medial and a second one on the apical carbon atoms.

For the 1,5- and 3,9-derivatives the situation is similar. Both compounds have one substituent located on secondary carbon atoms. Their separation depends mainly on the position of the second bromine atom. When it is located on a medial carbon atom (*i.e.* the 1,5-position), this isomer is eluted first. When it is in an apical position (the 3,9-isomer), the elution time is longer.

Interatomic distance effect

Interatomic distance (ID) is a secondary effect influencing the retention of dibromo derivatives: the elution time increases with increasing ID value. As an example, 1,7-dibromodiamantane (ID, 564 pm) is eluted before the 1,6-isomer (ID, 655

TABLE III

INTERATOMIC DISTANCES OF BROMINE ATOMS IN DIBROMODIAMANTANES

Isomer	ID [pm]	Type of substitution*	k'**
1,7	564	M,M	2.66
1,6	655	M,M	2.93
1,5	617	M,S	4.19
1,4	503	M,A	4.77
3,9	723	S,A	6.30
4,9	844	A,A	9.71

* Type of carbon atom substituted by bromine: A = apical; M = medial; S = secondary.
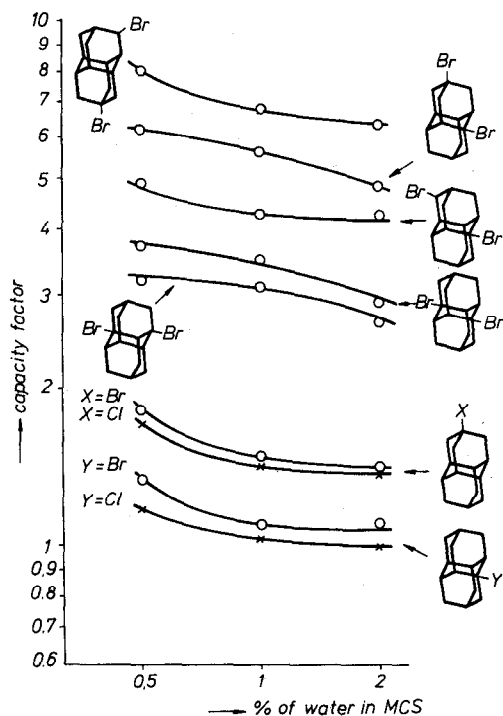** k' = Capacity factor at a water content on silica in the MCS of 2%.

Fig. 2. Dependence of capacity factor on water content in the MCS.

pm). Table III lists values of interatomic distances computed on the basis of covalent . diameter[9] and on the premise that there is no distortion in the dibromodiamantane molecules.

Of the 23 theoretically possible dibromodiamantanes, only six isomers (substituted on different types of carbon atoms) have had their elution data measured. A more detailed correlation of retention data with molecular structure could be done by investigating additional compounds.

Effect of water content in the mobile phase

The elution times of the investigated halogeno derivatives decrease with increasing water content in the mobile phase. The application of a moisture-control system facilitates good reproducibility of retention data. The quantity of water in the mobile phase itself is too small and it is therefore not easy to measure its absolute value. Therefore the dependence of k' on the water content in the mobile phase in the MCS was studied (Fig. 2). From the curves it is evident that a change in water concentration influences the selectivity to only a small extent. The selectivity, α, for two partly separated 1,6- and 1,7-dibromodiamantanes increases only slightly with diminishing water content in the MCS.

The experience gained from the analytical separation of halogeno derivatives was utilized for the isolation of individual bromo- and dibromodiamantanes from their mixtures by preparative HPLC[3].

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