Application of molecular statistical calculations to the prediction of chromatographic separation of isomeric difluorobiphenyls

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Molecular statistical calculations have been used for estimation of the possibility of chromatographic separation of difluorobiphenyl mixtures. GC-MS investigation of the mixture of difluorobiphenyls has been carried out. It is impossible to identify each isomer with only mass spectrometric data due to the similarity of their mass spectra. A chromatographic column that makes adequate chromatographic separation possible has been selected based on the molecular statistical calculations. The identification of each isomer resulted from combination of the mass spectrometric investigation results and molecular statistical calculations.

Key words: molecular statistical calculations, GC-MS, identification of difluorobiphenyl isomers.

Separation and identification of the individual isomers in their mixture is a complex problem. This results from the similarity of the physical and chemical properties of the isomers. It is a special difficulty when the number of isomers represented as peaks on the chromatogram is less than the number of theoretically possible isomers. In this case it is difficult to decide whether it results from insufficient effectiveness and selectivity of the chromatographic separation or the number of isomers in the mixture is just fewer.

The purpose of this work is to investigate the possibility of prediction of chromatographic mixture separation and identification of individual isomers based on semi-empirical molecular statistical calculations. Separation and identification of isomeric difluorobiphenyls was chosen as an example. This mixture was dealt with because other substituents, for instance, chlorine, bromine, methyl, and methoxy groups, result in peaks on the chromatograms of all the theoretically possible isomers, whereas a mixture of the fluorine-substituted derivatives has one peak less, though the synthesis conditions were such that all possible isomers should have been obtained.[1] Thus while the principal possibility of complete chromatographic separation of this mixture was estimated on the basis of the calculations, the chromatographic separation parameters were varied, and identification based on the semi-empirical molecular statistical calculations and the experimental data was accomplished.

Experimental

The procedures for synthesis of dichloro-, dibromo-, dimethyl-, and dimethoxybiphenyls are described in Ref. 1. With these examples, all six possible isomers containing one substituent on each benzene ring were shown to be obtained under certain conditions.

Mass spectra were recorded on a JMS D-300 mass spectrometer under the following conditions: ion source temperature 150 °C, ionizing electrons energy 70 eV, accelerating voltage 3 kV, mass numbers range 40—400 a.m.u. Chromatographic investigation was carried out on a micropacked column filled with graphitized thermal carbon black (GTCB) and on a capillary column 30 m×0.53 mm containing the weakly polar phase DB-5 (5 % phenylmethylsilicon), layer thickness of 1.5 μm. Sterling MT GTCB with a specific surface of 7.6 $m^2\ g^{-1}$ and a grain diameter of 0.14—0.16 mm was used. The carrier gas was helium at the rate of 20 $ml \cdot min^{-1}$ in the case of the micropacked column and of 2 $ml \cdot min^{-1}$ in the case of the capillary one. Chromatographic separation was carried out on a HP 5890 chromatograph connected with a mass spectrometer by means of jet separator, while working with the capillary column the injection was splitted 1:10. In order to optimize the chromatographic separation the different rates of temperature changing (from 0.5 to 10 deg min^{-1}) and the separation at the isothermal conditions with the thermostat temperatures from 210 to 270°C for the micropacked column and from 100 to 150°C for the capillary one were used.

The semi-empirical molecular statistical calculations were described beforehand.[2] Atom-atom potential for interaction of the fluorine atom and graphite carbon atom, found from experimental data obtained for fluorobenzenes, is cited from

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Ref. 3. The geometric structures of the molecules determined electronographically[4] or calculated on the base of the average values of the bonds angles and lengths known for other molecules of the same class[5] were taken into consideration.

The investigated biphenyl derivatives have the capability of internal rotation, but the values of the internal rotation angles are determined only for 2,2′- and 4,4′-difluorobiphenyls.[4,5] By the example of mono- and difluorobiphenyls, it was previously shown[6] that the quantity of atoms in the *ortho* position (relative to the connecting benzene rings bond) is mainly influencing on the internal rotation angles for such molecules. It also appeared that the value of the internal rotation angle determined by the electronographical method exceeds that one found out by adsorption method based on the molecular statistical calculations. The same differences appear in the case of the halobiphenyl isomers which are not substituted at the *ortho* position. The electronographically specified value of the internal rotation angle of these molecules equals 44° and the molecular statistical method gives the value of 38°. Therefore the value of the internal rotation angle for the calculations of the Henry constants was equalled 38° for the *ortho* non-substituted difluorobiphenyls, 49° for the molecules with the only fluorine atom in the *ortho* position, like 2-fluorobiphenyl, and 60° for the *cis* conformation of 2,2′-difluorobiphenyl[5]. Since the different conformers of 2,3′- and 3,3′-difluorobiphenyls, as well as of 2,2′-difluorobiphenyl, are possible (by analogy with *cis* and *trans* isomers they are called "*cis*" and "*trans*") the molecular statistical calculations for these molecules were executed for each conformation keeping the value of the internal rotation angle constant and equal to 49° and 38° correspondingly.

The dipole moments of the investigated molecules were calculated with the aim of preliminary choosing the stationary liquid phase of the column and the conditions of chromatographic separation.[7] The most important parameter influencing the chromatographic retention is the boiling temperature. Because of the lack of the corresponding data the boiling temperatures of dimethylbiphenyls[8] were used for the preliminary estimation of the chromatographic separation possibility in the gas-liquid variant. The following formula was used to evaluate the number n of theoretical plates:

$$n = 4[(\alpha_r + 1)/(\alpha_r - 1)]^2, \quad (1)$$

where α_r is the ratio of the retention times of the components studied.[9] The number of theoretical plates necessary for the partial separation was calculated by the formula

$$n \geq [(\alpha_r + 1)/(\alpha_r - 1)]^2. \quad (2)$$

The number of theoretical plates in columns was calculated by the formula

$$n = 5.545(t_r/b_h)^2, \quad (3)$$

where t_r is the retention time of the component used for determination of the number of theoretical plates, and b_h is the halfwidth of the chromatographic peak.[9]

Results and Discussion

Graphitized thermal carbon black is an adsorbent with a homogeneous planar surface, adsorption on which is extremely sensitive to the geometric structure of molecules.[2,3,10] That was the reason to choose a column packed with GTCB for the chromatographic separation of the difluorobiphenyl isomers, which are distinguished by their internal rotation angles and by the positions of the substituents relative to the bond connecting the benzene rings. One more advantage of columns packed with GTCB is the possibility of theoretical calculation of the retention values and prediction of the isomer outflow sequence from the column.

Such calculations were executed for the difluorobiphenyls adsorption on GTCB. The calculated dependences of the logarithm of Henry constant ($\ln K_1$) on the inverse temperature are shown in Fig. 1. The K_1 values at 500 K are displayed in Table 1 as well as the internal rotation angles used. It is appeared from Fig. 1 and Table 1 that the isomers could be divided into three groups according to the adsorption values: the first group contains only 2,2′-; the second one includes 2,3′- and 2,4′-; and the third one — 3,3′-, 3,4′-, and 4,4′- difluorobiphenyls. The differences of the K_1 values seem to be sharp among the groups and insignificant within groups. As far as K_1 is equal to the retention volume in the case of the small sample[2] it makes possible the approximate estimation of the theoretical plates number which is necessary for sufficient and partial separation of the isomers investigated. The results of such calculations executed by formulas (1) and (2) are displayed in Table 2. The absolute values of the retention times were used for the calculations in so far as the retention time of the non-sorbing gas is negligible.[2,8] From the table it is seen that the separation of the isomers mixture into three groups could be achieved in any column. But a column with a number of theoretical plates no less than 1300 is necessary to achieve at least partial separation of the isomers within a group.

The estimation of the effectiveness of the micropacked with GTCB column was performed using naphthalene as a standard. The calculated by the formula (3) number of the theoretical plates (TP) equals 1200 that is quite sufficient for the partial separation of the most of the isomers in the mixture investigated (see the chromatogram of the mixture of the investigated isomers obtained in the packed with GTCB column (Fig. 2)). This chromatogram displays the most effectiveness of the separation which was managed to achieve under the isothermal conditions at 270 °C. There is seen one distinct peak, two poorly splitted peaks and a low intensity peak overlapped with a more intensive one. Relying upon the theoretical calculations of the retention values we may claim that the first peak is 2,2′-difluorobiphenyl, the two poorly split peaks are 2,3′- and 2,4′-difluorobiphenyls, and the third group of peaks belongs to 3,3′-, 3,4′-, and 4,4′-difluorobiphenyls. The overlapping of the chromatographic peaks of the last three isomers results from insufficient effectiveness of the chromato-

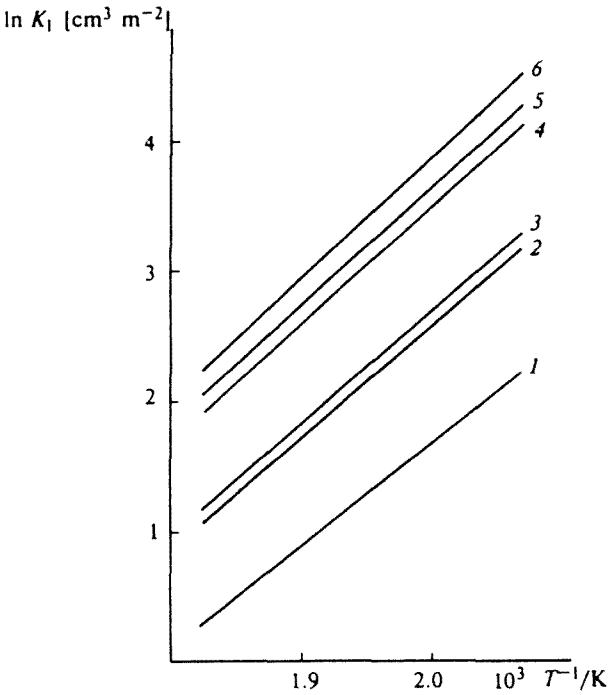

Fig. 1. Dependences of $\ln K_l$ on the inverse temperature for 2,2'- (*1*); 2,3'- (*2*); 2,4'- (*3*); 3,3'- (*4*); 3,4'- (*5*); and 4,4'-isomers (6) of difluorobiphenyl.

Table 1. Calculated values of Henry constant (K_l) at 500 K and values of dipole moments (μ) and internal rotation angles (α) of difluorobiphenyls

Molecule		K_l / cm^3 · m^{-2}	μ/D	α / deg
2,2'-difluorobiphenyl		4.31	2.3	60
2,3'-difluorobiphenyl	"*cis*"	10.7	2.7	49
	"*trans*"	11.0	1.8	49
2,4'-difluorobiphenyl		12.18	2.6	49
3,3'-difluorobiphenyl	"*cis*"	29.67	2.4	38
	"*trans*"	29.37	0.8	38
3,4'-difluorobiphenyl		31.19	1.5	38
4,4'-difluorobiphenyl		33.45	0	38

graphic column and, possibly, from gas-dynamic conditions that are not ideal, because the chromatographic column is connected with the mass spectrometer by the jet separator and functions under reduced pressure at the outlet.

Capillary columns having less selectivity allow one to achieve a high effectiveness of chromatographic separation.[9] Therefore the capillar column with weak-polar phase DB-5 was used in order to achieve higher effectiveness of the separation of the investigated mixture.

Table 2. Number of theoretical plates (*n*) necessary for sufficient (1) and partial (2) separation of the pairs of isomers investigated

Pair of isomers	*n*	
	1	2
2,2'- and 2,3'-difluorobiphenyls	22	5
2,3'- and 2,4'-difluorobiphenyls	1500	380
2,4'- and 3,3'-difluorobiphenyls	22	5
3,3'- and 3,4'-difluorobiphenyls	5100	1300
3,4'- and 4,4'-difluorobiphenyls	3500	900

The choice of this phase was determined by the fact that there is little differences between the dipole moments of the investigated molecules in the case of the most difficultly separated pairs of isomers (see Table 1) and the usage of a column with a high-polar stationary liquid phase could make the separation difficult since the changes of the dipole moments do not coinside with the changes of the boiling temperatures of the isomers.

The effectiveness of the chosen capillar column was adopted equal to that given in the certificate (1400 TP/m) because at the present time there are no any reliable methods of the calculation of the retention times in the case of the gas-liquid chromatography.[9] The best chromatographic separation of the investigated mixture in the chosen column was obtained under the isothermal conditions at 110 °C (Fig. 3). It is seen that the achieved effectiveness of the separation of 3,3'-, 3,4'-, and 4,4'-difluorobiphenyls is much more in comparison with the micropacked with GTCB column and practically complete separation of 3,4'- and 4,4'-difluorobiphenyls is obtained. It could be supposed that the second peak in the chromatogram consists of two not separated peaks of 2,3'- and 2,4'-difluorobiphenyls. Such supposition looks founded well enough while correlating the chromatograms obtained from two different columns (Fig. 2, 3). It is seen that two poorly splitted peaks from the second group in the Fig. 2 correspond to the second peak in the chromatogram from Fig. 3. This confirms that the third group of the peaks in Fig. 2 consists of the peaks of 3,3'-, 3,4'-, and 4,4'-difluorobiphenyls. The chromatogram in Fig. 3 shows practically complete separation of these compounds. Thus six isomeric difluorobiphenyls containing one fluorine atom in each benzene ring occur in the mixture.

In order to confirm the identification made the chromatograms were recorded at full ion current and the mass spectra obtained were studied in details. The observed mass spectra of difluorobiphenyls are typical for aromatic compounds[11] and are characterized by the intensive molecular ion peak and by the presence of the two-charge ions and such ions as $[M-H]^+$ and $[M-2H]^+$ (Fig. 4). There were no differences detected in the mass spectra of the compounds studied that could

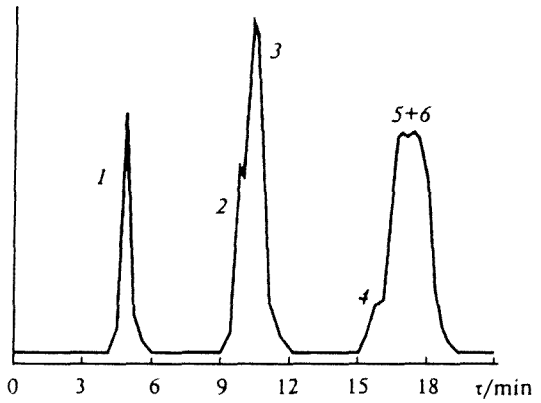

Fig. 2. Chromatogram of the mixture of isomers obtained in a column packed with GTCB for 2,2′- (*1*); 2,3′- (*2*); 2,4′- (*3*); 3,3′- (*4*); 3,4′- (*5*); and 4,4′-isomers (6) of difluorobiphenyl.

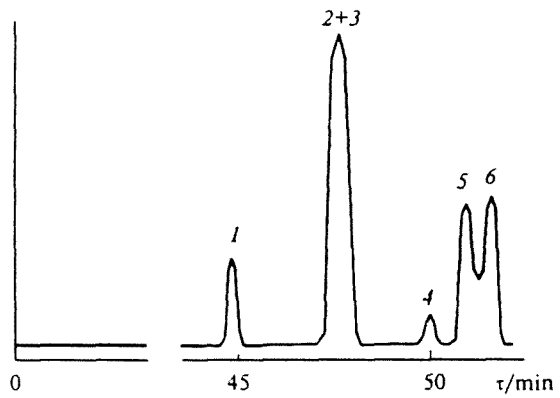

Fig. 3. Chromatogram of difluorobiphenyl mixture obtained in a capillary column for 2,2′- (*1*); 2,3′- (*2*); 2,4′- (*3*); 3,3′- (*4*); 3,4′- (*5*); and 4,4′-isomers (6) of difluorobiphenyl.

be explained by the higher energy of C—F bond in comparison with C—Cl bond and by the low intensity of the $[M-F]^+$, $[M-HF]^+$, and $[M-2F]^+$ fragments peaks similar to the fragments occurred in the case of the difluorobiphenyls.[12] The ion with m/z = 85 could be either the two-charge ion $[M]^{++}$ or the fragment yielded while breaking of the connecting benzene rings bond. The ion with m/z = 164 yields probably when the molecular ion loses the C_2H_2 fragment. All the listed above ions are characteristic of the each difluorobiphenyl isomer and no specific path of the fragmentation of any isomer could be supposed as it is confirmed experimentally by the lack of significant differences among the isomers mass spectra. In this case the application of a mass spectrometer allowed to confirm the presence in the mixture of the difluorobiphenyls only, but as far as the isomers mass spectra do not differ from each other the identification of the individual isomers appeared to

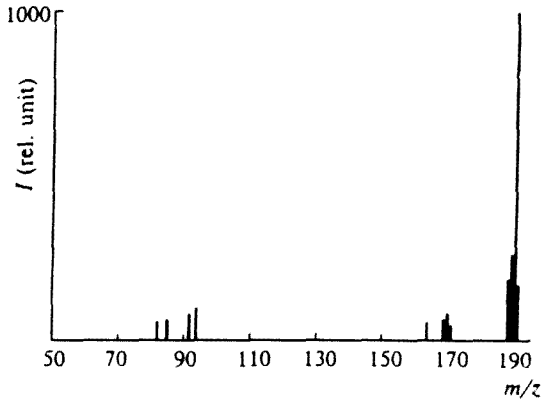

Fig. 4. Mass spectrum typical for all the isomeric difluorobiphenyls.

be impossible. In this case even the usage of literature mass spectra should not allow one to identify the individual isomers without using the retention values data.

The investigation carried out allowed us to theoretically predict and to experimentally confirm the possibility of chromatographic separation of the difluorobiphenyl mixture on the basis of semi-empirical statistical molecular calculations. All the isomers present in the mixture studied were identified with the help of a correlation of the GC-MS data and statistical molecular calculations.

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