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Prediction of Gas-chromatographic Elution Sequence of Diastereomers and Enantiomers Using the Molecular Dynamics Methods

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Abstract—A possibility was demonstrated of predicting elution sequence in gas chromatography for diastereomers (on standard phases) and enantiomers (on chiral phases, in particular, on cyclodextrins derivatives) in keeping with decreasing intramolecular vibration and rotation energies *E* estimated by computer simulation using the molecular dynamics methods. To characterize enantiomers by this method a hypothetic modification of molecular structure was suggested by introducing additional chiral substituent of R-configuration.

The identification of organic isomers by chromatography and GC-MS method is a sufficiently complicated problem. In many cases isomers have similar mass spectra (oil hydrocarbons, mono- and sesquiterpenes etc.), and thus determination of their structures is impossible without application of chromatographic parameters (retention indices, *RI*). When the mass spectra and *RI* values of such isomers are unknown the present state of art permits a simple listing of these isomers in the order of elution without structure description, e.g., "isomer no. 1", "isomer no. 2" etc. This uncertainty in the most cases corresponds to diastereomers and enantiomers. Just the urgency of the problem in question generated a need in building up of a special Database concerning the chromatographic separation of enantiomers on chiral phases, CHIRBASE; the information contained therein not always involves the data on absolute configuration of molecules [1].

If on a chromatogram are successfully registered the signals from all possible isomers of various groups of compounds then the problem of their identification becomes a task of evaluation of their relative elution order. The latter is equivalent to unambiguous confirmation of presumed molecular structure [2]. The elution sequence may be predicted basing on reference or calculated data on boiling points [3], for within isomer groups the linear dependence between their boiling points and RI is valid with sufficient precision. In other words, the boiling points and retention times vary in parallel.

$$RI \approx aT_x + b \qquad (1)$$

This procedure is sufficiently good for structural isomers, but with diastereomers it is now limited because of a little number of reference data and no methods of calculation. Therewith it is inapplicable in principle to the case of enatiomers elution on chiral phases. A more general method is based on the computer simulation of intramolecular vibration and rotation processes by molecular dynamics method estimating the sum of intramolecular energies [4]. Since for the isomers an approximately equal energy of dispersion interaction "sorbate-stationary phase" is typical, the main distinctions governing both the sequence of chromatographic elution and the variation of the boiling points turn out to be the differences in the intramolecular dynamic parameters *E*.

$$RI \approx aE + b \quad (a < 0) \qquad (2)$$

The negative sign of *E* factors in this relation means that the isomers of smaller intramolecular energy possess larger retention parameters. Just this identification procedure was used for characterizing the products of chlorine and ethanol addition to C=C bonds [4]. Further the method was extended to any addition reaction of molecules with active hydrogens XH to substrates with polarized C=C bonds [5], to determination of the structure of Diels–Alder reaction products [6, 7], of products of reaction between etoxycarbonylcarbene and various substrates [8], of radical chlorination products of arylarenes [9], etc. The physicochemical fundamentals of relation (2) observed in all above cases is discussed in [10]. Besides a correlation was established between the intramolecular dynamic parameters *E* with molecular topologic indices (of Wiener, Josoya, and others) [11].

Thus the opportunities provided by the use of molecular dynamic parameters for prediction of the

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sequence of structural isomers elution in the gas chromatography are now illustrated in sufficient detail and do not cause doubts. In this connection it is possible to consider a more difficult problem: establishing the elution sequence of diastereomers (more exactly, of σ-diastereomers [12]) on universal chromatographic stationary phase, and also of enantiomers which can be separated only on chiral phases (mainly on cyclodextrins derivatives) [13]. Nowadays no methods exist for making such estimations, and the first suggestions that these problems can be solved with the use of molecular dynamics procedures have appeared only in preliminary communications [14, 15].

Characteristics of the elution sequence for diastereomers. The prediction of gas-chromatographic elution sequence of diastereomers possessing different physicochemical characteristics, in particular, boiling points, is based on application of the general relation *RI* – *E*. The efficiency of the corresponding relations for structural isomers is caused by sufficiently large difference in their intramolecular dynamic parameters amounting to 3–8 kcal mol^{-1} and thus exceeding the estimated errors in proper *E* value. It is presumable that the relation *RI*–*E* expressed by (2) would be valid also for diastereomers, but with significantly lesser differences in the E values. Besides, if in characterizing the structural isomers it was possible to compare directly their *RI* and dynamic molecular parameters, the scanty gas-chromatographic information for diastereomers makes such comparisons difficult. In this case instead of *RI* should be used the data on boiling points of the diastereomers at atmospheric pressure that are related to *RI* by expression (1) and that are available for the simplest diastereomers. In Table 1 are given the results of this comparison of boiling points and *E* (300 K) values for some diastereomers. It follows from these data that in all cases the boiling point of *erythro* (*meso*) isomers is lower than that of *threo* (*rac*-) forms, and the corresponding *E* values are always higher. These facts confirm the validity of the general rule (2) stating that isomers possessing larger *E* have lesser gas-chromatographic retention parameters. As should be expected, the difference Δ*E* for diastereomers varies within the range 0.2–1.3 kcal mol^{-1}, a value notably smaller than for structural isomers.

The *RI* values of several 2,3-butandiol derivatives on a standard nonpolar polydimethylsiloxane stationary phase OV-101 are presented in Table 2. Regardless of the type of derivatives and the variation of *E* values the difference in *RI* for diastereomers are approximately constant and equal to 12 ± 1 units. This fact characterizes common for all compounds considered combination of two chiral centers in vicinal position. In the same table are given additionally the estimations of calculated *E* parameters for some other diasteromeric pairs with the corresponding Δ*E* values. The smallest values of Δ*E* (0.2–0.4 kcal mol–1) are characteristic of diastereomers with the simplest substituents at the asymmetric carbon atoms (all 2,3-dihalobutanes, 2,3-butanediol, its monoacetate etc.) in keeping with the minimal effect of the steric factors on the differences in their intramolecular energy. The removal of the hiral centers from each other also results in diminishing Δ*E* (0.2 kcal mol^{-1} for 2,4-dichloropentane). On the other hand, the maximal values of Δ*E* (2.0–4.4 kcal mol^{-1}) correspond to diastereomers with the bulkiest substituents at the chiral centers: 2,3-diphenylbutane, bis-trimethylsilyl and bis(dimethyl-*tert*-butylsilyl) ethers of 2,3-butanediol, etc.

Another fact is also of interest: transformation of the functional groups (in particular, substitution of the active hydrogens in the 2,3-butanediol) does not change the relative order of the diastereomers elution, and in all cases the sequence *eryhro*-(*meso*-) < *threo*-(*rac*) is conserved.

Table 1. Relation between known boiling points of diastereomers and their molecular dynamics parameters *E* (kcal mol^{-1})

Diastereomers	*meso*- (no. 1)		*rac*- (no. 2)	
	bp, °C	*E* (300 K)	bp, °C	*E* (300 K)
2,3-Butandiol	181.7	34.7 × 0.6	182.5	34.3 × 0.6
Diethyl 2,3-dimethylbutanoate	218	64.0 × 1.2	221–222	63.4 × 1.1
2,3-dimethoxtbutane	108	49.3 × 0.8	109–111	48.7 × 0.8
3-Chloro-2-butanol[a]	130.8–132	32.3 × 0.5	135.4–136	31.8 × 0.5
2,3-Dichloropentane[a]	138–139	37.3 × 0.6	143–144	37.0 × 0.7
2,3-Dichlorobutane	112–116.7	30.0 × 0.4	116–117.5	29.8 × 0.4
2,3-Dibromobutane	157.3–159	28.9 × 0.4	160.5–161.5	28.6 × 0.4

[a] Respective erythro and threo-diastereomers of compounds with nonequivalent substituents at two chiral centers.

Table 2. Comparison of gas-chromatographic retention indices of some diastereomers and the respective values of molecular dynamics parameters *E*

Diastereomers	*meso*- (no. 1)		*rac*- (no. 2)	
	RI	*E* (300 K)	RI	*E* (300 K)
2,3-Butanediol monoacetate[a]	920 × 2	42.0 × 0.7	932 × 2	39.8 × 1.1
2,3-Butanediol diacetate	1042 × 2	49.9 × 1.4	1054 × 2	48.6 × 1.4
2,3-Butanediol dibutanoate	1381 × 1	75.0 × 1.4	1394 × 1	74.2 × 1.5
2,3-Trimethylsiloxybutane	1042 × 1	83.1 × 1.4	1053 × 1	79.1 × 1.4
3,4-Dimethylheptane[b]	859 × 3	67.0 × 1.2	859 × 3	66.7 × 1.2
2,4-Dichloropentane	–	36.0 × 0.6	–	35.8 × 0.8
2,3-Butanediol dibenzoate	–	89.1 × 1.7	–	87.7 × 1.7
2,3-(Dimethyl-*tert*-butylsiloxy)butane	–	122.9 × 2.0	–	118.5 × 2.0
2,3-Diphenylbutane	–	80.9 × 1.3	–	78.9 × 1.3
1,2-Dibromo-1,2-diphenylethane	–	64.0 × 1.0	–	63.1 × 1.0
2,3-Diiodobutane	–	28.7 × 0.9	–	28.3 × 0.5

[a] Respective erythro and threo-diastereomers of compound with nonequivalent substituents at two chiral centers.

[b] The difference in *RI* of diastereomers less than 1 index unit.

Table 3. Comparison of differences between molecular dynamic parameters of some pairs of permethylated diastereomers ($\Delta E_{permethyl}$, kcal mol^{-1}) and the corresponding differences of the initial compounds ($\Delta E_{initial}$)

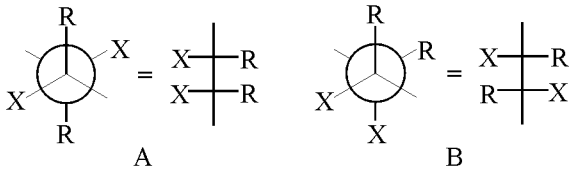
Diastereomers	*E* (400 K) (*meso*-)	*E* (400 K) (*rac*-)	$\Delta E_{permethyl}$	$\Delta E_{initial}$
2,3-Butanediol	148.1 ± 2.1	143.1 ± 1.7	5.0	0.4
3-Chloro-2-butanol[a]	147.0 ± 1.9	144.6 ± 1.9	2.4	0.5
2,3-Dichlorobutane[a]	146.9 ± 1.8	145.0 ± 1.9	1.9	0.2
3-Methyl-2-pentanol[a]	280.9 ± 3.9	277.4 ± 3.3	3.5	0.2
Diethyl 2,3-dimethylbutanedioate[b]	194.8 ± 2.5	192.8 ± 2.3	2.0	0.6

[a] *Erythro*- and *threo*-diastereomers. [b] Without replacement of hydrogens of the ethyl groups by CH_3 fragments.

Small ΔE values impede the unambiguous determination of the gas-chromatographic elution sequence of diastereomers for these values are smaller than the estimated errors in the proper *E* quantities and consequently they are unreliable according to the statistical criteria. Since the principal cause thereof is a weak steric interaction of the substituents attached to the chiral centers the reliability of results can be enhanced by additional structural modification of the diastereomers in question. The simplest way of increasing the steric strain is "permethylation", namely, a replacement of all hydrogen atoms in the molecules of the initial diastereomers by methyl groups (or at least at both chiral centers and in the α-positions with respect to them). The replacement $H \rightarrow CH_3$ falls in the class of structural transformations of one-to-one manner, and benefit thereof is due to two factors: (a) as already mentioned, the elution sequence of diastereomers is independent of the definite type of their derivatives; (b) this replacement essentially should not affect the position of the conformational equilibrium, and that is especially important for cyclic structures.

The *E* values of some simplest diastereomers after such exhaustive "methylation" are compiled in Table 3. In all cases for the "derivatives" obtained the relative intramolecular dynamic parameters change in the same order as for the initial unmodified diastereomers, namely *eryhro*-(*meso*) < *threo*- (*rac*-). However this trick makes possible to increase significantly the ΔE values (from 0.2–0.6 to 2–5 kcal mol^{-1}) and thus come to more unambiguous conclusions. Just this version of computer simulation should be recommended for refining the results not only with diastereomers, but also with structural isomers possessing close values of *E* parameters. Besides both calculation patterns may be used simultaneously to increase the reliability of results.

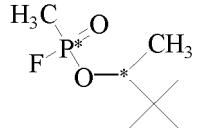
As the simplest explanation (without using the method of molecular dynamics) of the lower boiling points, gas-chromatographic *RI* and accordingly of larger *E* values for the *erythro*- (*meso*-) forms (A) as compared to the threo- (rac-) isomers (B) let us consider the structures of the most stable periplanar conformations of these diastereomers.



A B

The effects of substituents R and X depend mostly on their dispersion interaction E_{disp} and in the first approximation they are proportional to the products of their polarizabilities π (or to molar refractions MR_D). Then for the structure (A) we obtain as a rough estimation $E_{disp(A)} \approx 2\pi(R)\pi(X)$, and for structure (B) $E_{disp(B)} \approx \pi^2(R) + \pi^2(X)$. However since at $X \neq R$ in all cases an inequality $\pi^2(R) + \pi^2(X) > 2\pi(R)\pi(X)$ is valid, then the energy of dispersion interaction of substituents in (B) structure is higher than in (A) structure. Therefore the former structure should be more "rigid" ensuring the smaller values of intramolecular dynamic parameters *E* for meso- (rac-) forms in keeping with all above discussed relations. This simple model obviously is exceeded in opportunities by computer simulation using molecular dynamics methods. The main advantage of the latter is providing weighted average estimations of *E* not for a single but for all possible conformations of each diastereomer.

The general approach under consideration is valid also for diastereomers in whose molecules as chiral centers appear not only carbons but also the other organogenic elements. As an example of application of computer simulation by means of molecular dynamics procedure can serve the establishment of diastereomers structure for pinacolyl methylphosphonofluoridate (soman, **I**). For the compound on the standard nonpolar phases are registered signals from two diastereomers with *RI* 1011±3 (A) and 1014±3 (B) with unknown configurations. Therewith one of the chiral centers of the molecule is a phosphorus atom.



I

Taking into account the above mentioned features of the computer simulation it is presumable that the difference of *E* values for the two diastereomers will be small in this case because the chiral centers are separated by an oxygen atom. This difference really amounts only to 0.2 kcal mol^{-1}. But if the methyl group is preliminary transformed into a *tert*-butyl group and the fluorine atom is replaced by bromine then the forecasted elution order of diastereomers is confirmed but the ΔE_{modif} value grows into 0.6 kcal mol^{-1}.

Diastereomer	*E* (400 K)	E_{modif} (400 K)	Elution order
(*R*)P,(*S*)C or (*S*)P,(*R*)C	99.1±0.9	123.6±1.1	no. 1
(*S*)P,(*S*)C or (*R*)P,(*R*)C	98.9±1.0	123.0±1.1	no. 2

Characteristics of enantiomers elution sequence on chiral phases. Enantiomers having a single chiral center in the molecule are identical in their physicochemical properties and consequently possess identical retention parameters on achiral phases. Their chromatographic separation is possible only on chiral phases. The most often used chiral phases are cyclodextrins and various derivatives thereof [13, 16].

The complicated spatial structure of cyclodextrines results in low efficiency of interaction description between chiral sorbates and these phases, and in numerous limitations for models of chiral recognitions and chromatographic enantioselectivity. Therefore a phenomenological approach still prevails in presentation on the data of enantiomers separation [1]. The computer simulation by means of molecular dynamics discussed in this article is also inapplicable in its simplest form for the *E* values of enantiomers are equal.

A totally novel approach to prediction of the sequence of enantiomers chromatographic elution is built upon rejection of simulating the complicated interaction "sorbate cyclodextrin" and on applying instead a comparison of parameters of modified enantiomers molecules. In the course of computer simulation an additional substituent with a second chiral center is introduced into the molecule. Therewith the enatiomers get converted into diastereomers, where the difference in dynamic molecular parameters is sufficient for predicting their chromatographic elution sequence (see above). This approach is formally equivalent to a known procedure for enantiomers chromatographic separation (on achiral phases) with preliminary conversion of the enantio-

Table 4. Validity test for prediction of gas-chromatographic elution sequence for enantiomers on chiral cyclodextrin derivatives (βDEX and γDEX) by molecular dynamics method after replacement of CH_3 by (R)-$C^*H(CH_3)C(CH_3)_3$

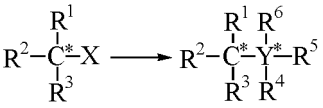
Enantiomers in the order of elution		Retention time, min	*E* (400 K), kcal mol^{-1}	Predicted elution order
2-Butanol	(*R*)(*S*)	no. 1[a]	99.6±1.3	no. 1
		no. 2	96.4±1.2	no. 2
Methyl 3-hydroxybutyrate	(*S*)-(+)	23.7	113.7±1.4	no. 1
	(*R*)-(–)	24.5	110.0±1.3	no. 2
Ethyl 2-methylbutyrate	(*R*)(*S*)	9.6±10.1	148.7±1.6	no. 1
			146.1±1.6	no. 2
Linalool (II)	(*R*)-(–)	13.8	142.2±1.7	no. 1
	(*S*)-(+)	14.2	140.8±2.1	no. 2
β-Citronellol (III)	(*S*)-(–)	51.4	92.4±1.1	no. 1
	(*R*)-(+)	51.8	92.4±1.1	no. 2
γ-Lactonesb (IV)	(*R*)-(+)	no. 1	92.3±1.5	no. 1
	(*S*)-(–)	no. 2	91.3±1.7	no. 2

[a] On different phases. [b] With replacement of any R by (R)–$C^*H(CH_3)C(CH_3)_3$.

mers into diastereomers by treating with chiral reagents [17].

This computer structural modification must fit to certain apriori requirements, among which the most important are the following:

(1) The substituents introduced into the enantiomeric molecules should posses fixed (*R*) or (*S*) configuration in order to unambiguously simulate the sequence of their chromatographic elution on chiral phases.



The structure of "derivatives" obtained should in one-to-one manner correspond to the structure of the initial compounds, namely, after replacing X by $Y^*R^4R^5R^6$ no identical fragments should arise in the molecule.

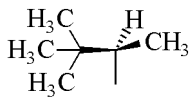
(2) Since the maximum difference in intramolecular energies *E* appears in diastereomers only at vicinal position of the chiral centers in the molecule the asymmetric atoms C^* and Y^* should not be divided with any fragments (for instance, chiral ethers C^*–O–Y should be avoided).

(3) The artificial substituents should not affect the conformational equilibrium in the initial molecules (it is especially important for cyclic structures). This point requires special control at all stages of computer simulation in order to avoid erroneous results.

(4) To get the maximal difference in the *E* parameters of diastereomers the substituents in the $Y^*R^4R^5R^6$ fragment should be sufficiently branched to ensure the maximum steric interaction with the substituents in the fragment $C^*R^1R^2R^3$. On the other hand, an excessive complication also is not feasible for the increased number of atoms in a molecule results in a longer time of simulation.

In keeping with above requirement we tested a number of chiral functional groups, in particular, $C^*H(CH_3)C_6H_5$, C^*H $[C(CH_3)_3]$ C_6H_5, and even $P^*(O)(CH_3)C(CH_3)_3$ [15]. The best version of the structural transformation is the replacement of the junior alkyl substituent at the asymmetric carbon, for the substitution of a hydrogen may be structurally ambiguous and may significantly affect the conformations of the initial enantiomers. Therewith we established that the introduction into enantiomeric molecules of any among the above substituents in the R-configuration made possible the prediction of their elution sequence on any cyclodextin type phases. In the other words, the condition (2) for diastereomers with one chiral center in a fixed R-configuration simulates the sequence of enantiomers elution.

Among all the tested substituents the best results provided the simplest one, 1,2.2-trimethylpropyl (C, pinacolyl) in the R-configuration.



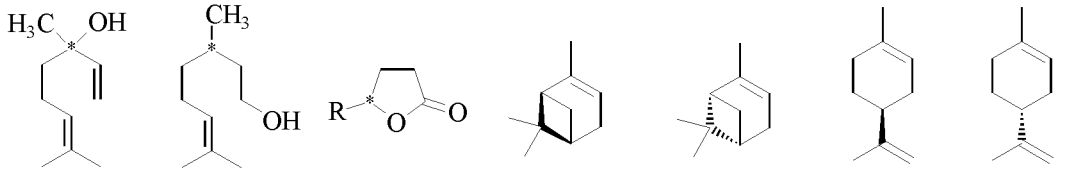
B

Some prediction results of the elution sequence for enantiomers belonging to different classes, among them compounds **II** **IV**, on cyclodextrin type chiral

Table 5. Prediction of gas-chromatographic elution sequence for enantiomers after preliminary replacement of hydrogen atoms by methyl groups followed by substitution of CH3 by (*R*)-C*H(CH$_3$)C(CH$_3$)$_3$

Enantiomers in the order of elution		*E* (400 K), kcal mol^{-1}	Predicted elution order
2-Butanol	(*R*)	243.7 ± 3.2	no. 1
	(*S*)	237.6 ± 2.8	no. 2
α-Pinene (V) [18]	(1R),(5R)-(–)	525.6 ± 9.7	no. 1
	(1S),(5S)-(+)	517.0 ± 9.3	no. 2
β-Pinene [18]	(1R),(5R)-(+)	558.8 ± 7.3	no. 1
	(1S),(5S)-(–)	546.8 ± 7.3	no. 2
Limonene (VI) [18]	(*S*)-(–)	458.6 ± 7.2	no. 1
	(*R*)-(+)	454.1 ± 8.1	no. 2
1-(2-Furyl)ethanol [19]	(*S*)	177.0 ± 2.9	no. 1
	(*R*)	175.0 ± 2.9	no. 2

phases are compiled in Table 4. The replacement of alkyl groups by (*R*)-pinacolyl ensures considerable difference in the *E* parameters of diastereomers obtained (0.5–3.7) and in all cases provided a correct elution order of the initial enantiomers in keeping with the decrease in intramolecular vibration and rotational energies according to condition (2). In case the pinacolyl fragment is taken in the reversed S-configuration all the below discussed relations concerning the rules of diastereomers retention as regards enantiomers are changed to the opposite. Thus the suggested approach turned out to be general as concerns computer simulation, but it is not free from certain "chemical" limitations related to structural features of enantiomers with no alkyl substituents at the chiral centers.



II **III** **IV** (1*S*),(5*S*)-**V** (1*R*),(5*S*)-**V** (*S*)-**VI** (*R*)-**VI**

This case can be illustrated by an example of α-pinene (**V**) and limonene (**VI**). The replacement of isopropenyl group by pinacolyl one in structure **VI** is in principal possible but the resulting diastereomers possess equal *E* values since the fragment controlling their structural difference (the double bond in the ring) is separated from the asymmetric carbon atom in position *4* by a methylene group, whereas the substitution of the axial hydrogen in position *4* by a fragment (*R*)-C*H(CH$_3$)C(CH$_3$)$_3$ changes the ring conformation, and that is inadmissible. However with all similar structures it is possible to reliably estimate *E* and consequently to make right conclusions on the elution sequence with the use of the same trick that has been recommended for diastereomers, namely, preliminary substitution of all hydrogen atoms in the molecule by methyl groups followed by replacement of one of them by (*R*)-pinacolyl one. The data compiled in Table 5 [18, 19] show that the differences Δ*E* reach here 2 - 12 kcal mol^{-1}. The example with 2-butanol demonstrated that both the direct substitution CH3 → (R)-C*H(CH$_3$)C(CH$_3$)$_3$ and the analogous operation after "permethylation" predict the same order of elution of (R)- and (S)-2-butanols on chiral phases (cf. data in Tables 4 and 5). Therefore, just this mode of computer simulation may be recommended with cyclic enantiomers with no alkyl groups at the chiral centers of molecules.

Thus the use of molecular dynamics method turned out to be an efficient way of predicting chromatographic retention parameters and therefore of identification for both σ-diastereomers and enantiomers on chiral phases. The latter problem nowadays has no other means of solution. Besides the comparison of gas-chromatographic elution sequence for enantiomers and diastereomers provides a possibility of formulation of important common laws relating the chromatographic characteristics of these groups of isomers, for instance:

On chiral cyclodextrin phases	Enantiomers $(R,S)X^*$ on standard phases
$(R)X < (S)X$	$(R)X–(R)Y < (S)X–(R)Y$ or $(R)X–(S)Y > (S)X-(S)Y$
$(R)X > (S)X$	$(R)X-(R)Y > (S)X-(R)Y$ or $(R)X-(S)Y < (S)X-(S)Y$

Consequently when the sequence of gas-chromatographic elution of enantiomers is known it is possible to forecast the elution sequencies of diastereomers derived therefrom, and vice versa. For instance, when the *meso*-2,4-dichloropentane (*R*,*S*) has smaller retention parameters compared to the *rac*-isomer (*R*,*R*) (see Table 2), replacing the common fragment of these two structures (*R*)-C H(Cl)CH_3 by a methyl group we can conclude that on chiral phases the (*R*)-2-chlorobutane should have smaller retention parameters than the (*S*)-enantiomer.

It is possible to presume existence of chiral phases opposite in qualities to those existing now, e.g., hypothetical cyclodextrines with reversed molecular configuration, or synthetic phases with other chiral structural fragments. With them all the above laws should be reversed, or, in the other words, both the inequalities referred to should change the signs to the opposite.

EXPERIMENTAL

Simulation of intramolecular vibration and rotational processes by molecular dynamics methods was carried out with the use of HyperChem (version 5.1) software applying the following parameters after preliminary molecular geometry optimization by MM+ procedure:

Simulation temperature 300 and 400 K.
Simulation period 20–30 ps.
Simulation discreteness 0.0005 ps.
Relaxation time 0.1 ps.
Number of cycles for energy averaging 10.

To increase the precision of *E* estimation the initial simulation period equivalent to "heating" of molecules till the desired temperature (about 1.0 ps) was rejected, and the calculations were commenced again by RESTART command. Overall calculation time was varied depending on the moment when the *E* values of the required precision were obtained (no more than 1–2 rel%). The increasing of simulation temperature from 300 K (in the previous publications) to 400 K was necessary for optimization of averaging the dynamic parameters for various molecular conformations. All standard errors of *E* parameters listed in Tables 1–5 may be diminished N-fold by increasing the simulation period N_2 times.

As the source of physicochemical constants of diastereomers we used Beilstein database. The conditions of gas-chromatographic separation of enantiomers on chiral phases were published elsewhere [18, 19].

Gas-chromatographic analysis of 2,3-butanediol derivatives was carried out on a chromatograph Biokhrom-1 equipped with a flame-ionization detector and a capillary column 25000×0.25 mm with a stationary phase OV-101, oven temperature programmed from 60 to 150–200°C at a rate 6 deg min^{-1}. The retention indices were evaluated applying added mixture of reference *n*-alkanes C_6–C_{16}; retention times were registered with an integrator TR 2213.

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