Gas chromatography–mass spectrometry of the stereoisomers of heterocyclic compounds. Part 3.† Perhydro-4-thia-*s*-indacene

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A gas chromatographic–mass spectrometric study of mixtures of the stereoisomers of perhydro-4-thia-*s*-indacene (PHTI) has been carried out. Separation has been accomplished on a column packed with graphitized thermal carbon black (GTCB) and on a capillary column of high efficiency. In addition to the known *cis-syn-cis* isomer, five novel diastereomers have been found. The stereospecificity of their fragmentation under electron impact appeared to be quite distinct and mass spectra (70 eV) of *cis-cis*, *trans-cis* and *trans-trans* conjugated isomers were distinguished. An important part in the structural elucidation of the novel isomers is played by molecular statistical calculations of the thermodynamic parameters of their adsorption on GTCB, which were performed on the basis of hypothetical molecular structures of these compounds optimized by molecular mechanics. Evidence for the existence of *cis-cis* isomers with the middle ring in a boat conformation obtained from these data is discussed.

Introduction

Perhydro-4-thia-*s*-indacene (PHTI) theoretically exists as six diastereomers, as with its homologue perhydrothiaxanthene (PHTX) studied previously.[1] Like other tricyclic congeners, *cis-syn-cis* and *cis-anti-cis* isomers of PHTI can undergo inversion of the middle ring. The inversion proceeds through an intermediate conformation ***C*** with the middle ring as a boat. Conformations ***A*** and ***B*** of *cis-syn-cis* PHTI are different, whereas for the *cis-anti-cis* isomer they are identical (see Scheme 1).

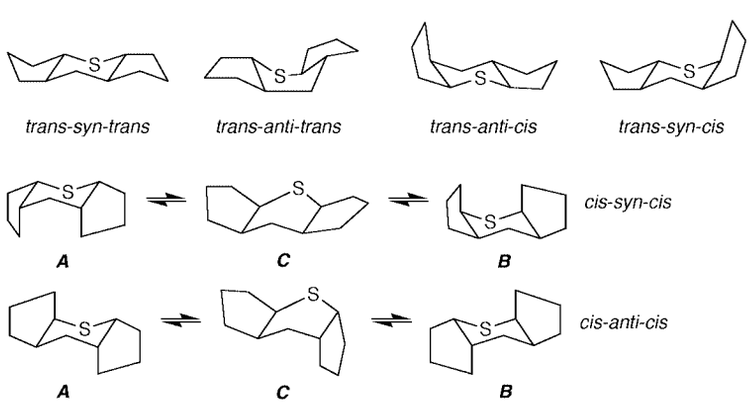
The synthesis of PHTI was developed by Kharchenko *et al*., but the stereochemical composition of the reaction products was not studied.[2] The structural elucidation of *cis-syn-cis* PHTI was performed later by ^{13}C NMR spectroscopy.[3,4] The data obtained by Yudovich[4] provide some evidence for the conformational stability of this isomer that is in contrast to the behavior of *cis-syn-cis* PHTX, which is conformationally mobile. This result was interpreted in terms of the preferred existence of *cis-syn-cis* PHTI as a conformer ***C*** with the middle ring as a boat that is in agreement with the ring distortion effect due to the conjugation of the five- and six-membered rings pointed out by Metzger *et al*.[5]

The existence of the five other stereoisomers of PHTI has not been confirmed in the literature. The separation and structural elucidation of the novel isomers by GC-MS is discussed in this paper. In the same way as for PHTX[1] and perhydroxanthene (PHX)[6,7] attention was paid to the relationships between the structures of isomers, the peculiarities of their GC retention on graphitized thermal carbon black (GTCB) and their molecular-ion fragmentation.

Results and discussion

Two mixtures of PHTI were investigated. The separation of these mixtures on the highly efficient capillary column with a non-polar dimethylpolysiloxane liquid phase (DB-1) is shown in Fig. 1. The chromatogram for the total ion current of mixture 1 shown in Fig. 1(a) exhibits eight peaks, six of which (labelled **X1**–**X6**), in accordance with the mass spectral evidence, correspond to PHTI isomers and two peaks correspond to impurities (labelled *). The chromatogram of mixture 2 obtained under the same conditions exhibits four peaks, which are likewise labelled **X2**, **X3**, **X4** and **X6** [Fig. 1(b)]. The predominant component **X3** in both mixtures is most probably *cis-syn-cis* PHTI.[3,4] This isomer is the third species to appear from the capillary column with the non-polar stationary liquid phase, whereas the *cis-syn-cis* isomer of PHTX is the fifth isomer to elute.[1] This is similar to the retention of the *cis-syn-cis* isomer of PHX[6] and may also be related to the conformational immobility of *cis-syn-cis* PHTI, in keeping with the Yudovich's data.[4] From this GC-data it might be inferred that all six

† For Parts 2a and 2b, see refs. 6 and 7, respectively.



Scheme 1

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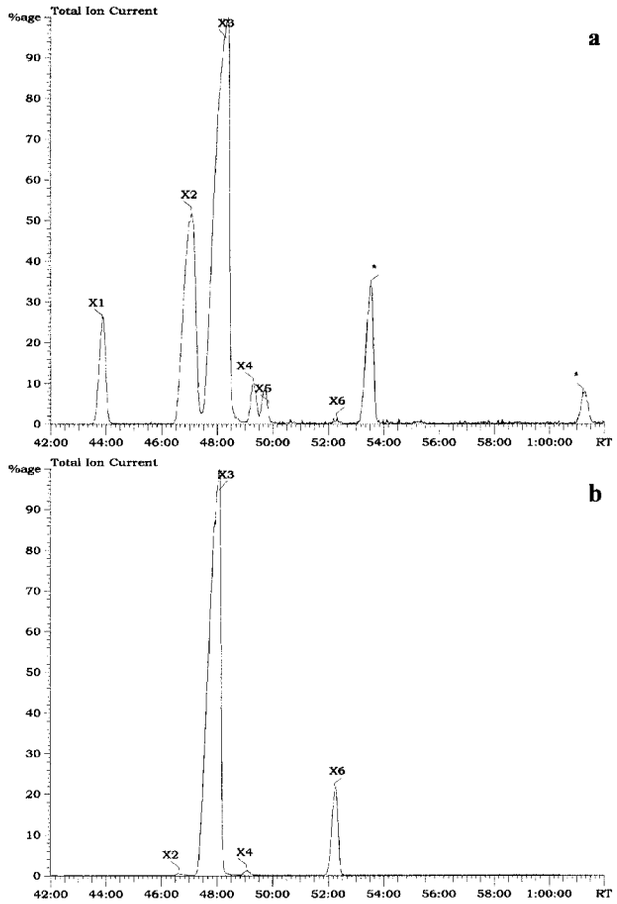


Fig. 1 Total ion current chromatograms of mixture 1 (**a**) and mixture 2 (**b**) of the stereoisomers of perhydro-4-thia-*s*-indacene on DB-1, 60 m × 0.25 mm, 160 °C.

theoretically expected diastereomers of PHTI exist and are available for further investigation.

The complete GC separation of PHTI isomers has enabled the recording of the mass spectra shown in Fig. 2. Three pairs of isomers (**X1**,**X5**; **X2**,**X4** and **X3**,**X6**) could be easily distinguished due to their different fragmentations; the mass spectra of the pairs are similar (Fig. 2). This resembles the mass spectra of *cis-cis*, *trans-cis* and *trans-trans* isomers of PHTX.[1] Comparison of the stereospecific features of the fragmentation of PHTX and PHTI isomers might be useful for the structure elucidation of the latter.

The intensities of the PHTI molecular ions (*m*/*z* 182; electron impact, 70 eV) relative to the total ion current (TIC) are about three times lower relative to PHTX (Table 1). Similarly to PHTX, the fragmentation of PHTI molecular ions is chiefly initiated by two groups of competing processes: either the cleavage of the C–S bond (α-cleavage) or the C(2)–C(7′), C(6)–C(7) bonds (β-cleavage). The main characteristic fragmentation pathways and hypothetical structures of the product ions are shown in Scheme 2. The ions $[C_5H_8S]^{+\bullet}$ (*m*/*z* 100) and $[C_6H_{10}S]^{+\bullet}$ (*m*/*z* 114) form as a result of α-cleavage. However, in contrast to ions with *m*/*z* 114 of PHTX, their homologues with *m*/*z* 100 of PHTI are most probably monocyclic, because an alternative structure with the five- and three-membered *trans*-catacondensed rings would be unstable (Scheme 2). The elimination of H_2S and $HS^{\bullet}$ (*m*/*z* 148, 149) is also analogous to the mass spectra of PHTX (*m*/*z* 176, 177). The ions $[M - C_2H_5]^+$ (*m*/*z* 153), $[M - C_3H_6]^{+\bullet}$ (*m*/*z* 140) and $[M - C_3H_7]^+$ (*m*/*z* 139), which are formed *via* β-cleavage, correspond to the homologue-ions with *m*/*z* 167, 154 and 153 in the mass spectra of PHTX. Thus, in spite of the different size of the side rings of PHTI and PHTX molecules, their fragmentation processes are quite comparable.

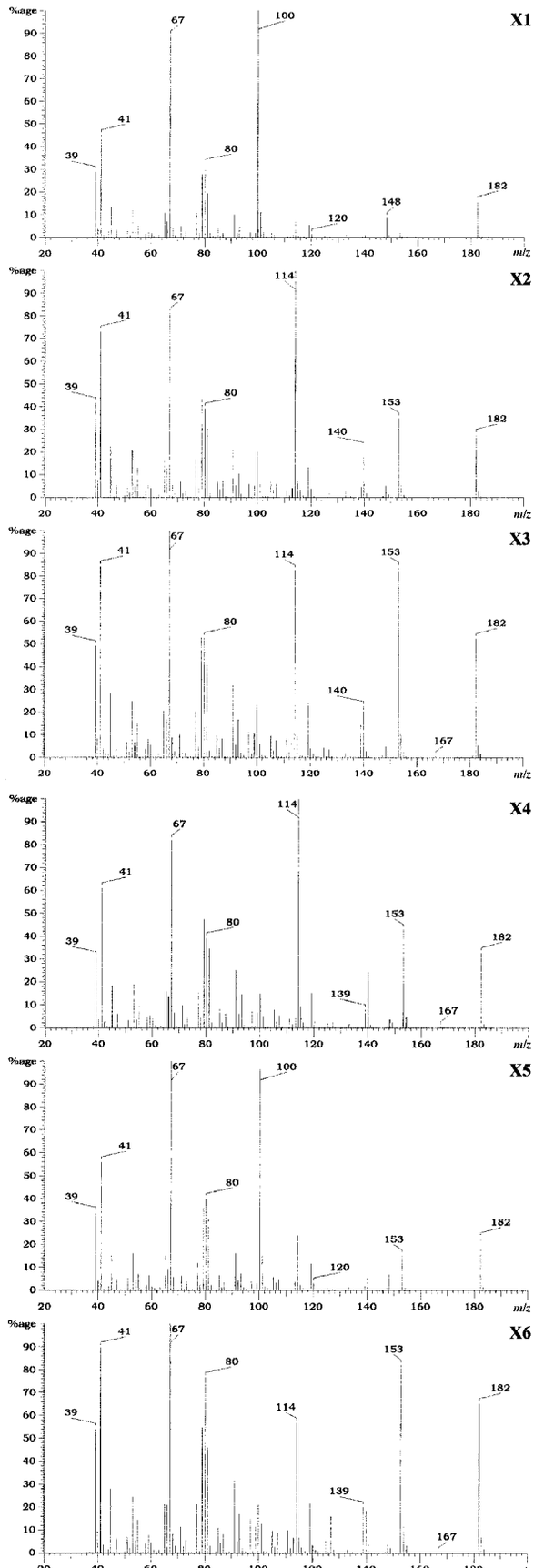
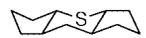
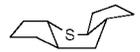
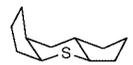
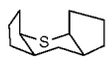
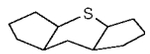
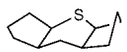
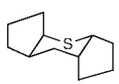
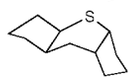
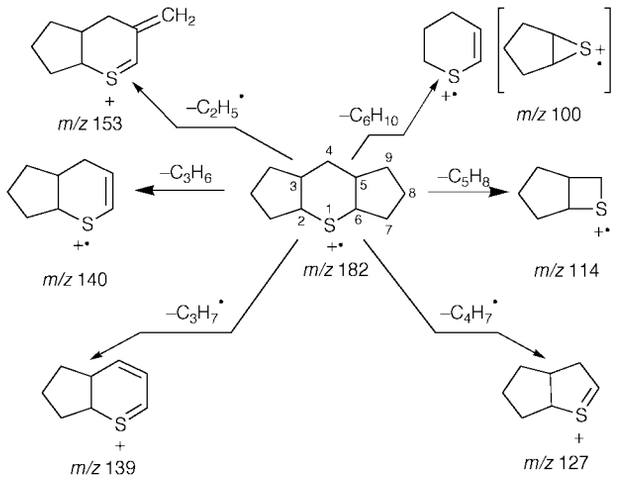


Fig. 2 Mass spectra of the stereoisomers of perhydro-4-thia-*s*-indacene (70 eV): (**X1**) *trans-syn-trans*, (**X2**) *trans-anti-cis*, (**X3**) *cis-syn-cis*, (**X4**) *trans-syn-cis*, (**X5**) *trans-anti-trans* and (**X6**) *cis-anti-cis*.

The common characteristics of the fragmentation stereospecificity for the molecular ions of PHTI and PHTX isomers might now be considered. The formation of stable onium

Table 1 Structures, thermodynamic adsorption characteristics on GTCB, calculated relative energies and intensities of the characteristic ions in the mass spectra of the stereoisomers of BTMTC

Label	Isomer	Structural formula	K_1^{220C}/cm^3 m^{-2}		$-\overline{\Delta U_1}$/kJ mol^{-1}		ΔE/ kJ mol^{-1}	Intensities of characteristic ions in mass spectra (70 eV), %TIC										
			Calc.	Exp.	Calc.	Exp.		*m/z* 182	*m/z* 153	*m/z* 149	*m/z* 148	*m/z* 140	*m/z* 139	*m/z* 127	*m/z* 119	*m/z* 114	*m/z* 100	*k*
X1	*trans-syn-trans*		51	47	68	66	0	2.9	0.3	0.2	1.6	0.2	0.06	0.06	1.0	1.2	18	0.02
X5	*trans-anti-trans*		40	—	67	—	18.8	3.2	2.1	0.1	0.9	0.9	0.3	0.08	1.7	3.4	14	0.12
X2	*trans-anti-cis*		10.4	10.7	58	61	5.9	3.3	4.1	0.2	0.6	2.6	0.5	0.2	1.6	12	2.4	0.28
X4	*trans-syn-cis*		9.9	—	58	—	5.0	3.9	5.0	0.3	0.4	2.9	0.9	0.3	1.8	12	1.8	0.36
X3	*cis-syn-cis*	***A*** 	3.6		50		22.2	4.6	7.4	0.3	0.4	2.0	1.3	0.3	2.1	7.3	2.1	0.79
		B 	4		51		10.0											
				13		62												
		C 	21		62		3.8											
		C′ 	12		58		7.1											
X6	*cis-anti-cis*	***A,B*** 	7.5		55		10.5	5.5	7.0	0.2	0.3	1.6	1.7	1.4	1.8	4.8	1.9	1.04
				8.1		58												
		C 	7.8		56		7.9											



Scheme 2

cations $[M - C_3H_7]^+$ (*m*/*z* 167) *via* β-cleavage was found to be inherent to *cis*-conjugated isomers of PHTX.[1] The contribution to the total ion current of their congeners $[M - C_2H_5]^+$ (*m*/*z* 153) in the mass spectra of the isomers **X3** (established as *cis-syn-cis* by NMR [3,4]) and **X6** is the most, as compared with the other PHTI isomers (Fig. 2, Table 1). Therefore, isomer **X6** could be assigned as *cis-anti-cis*. As a distinctive feature of the *cis-cis* fused PHTI isomers the onium ions $[M - C_3H_7]^+$ (*m*/*z* 139) also formed *via* β-cleavage could be pointed out (Fig. 2, Table 1).

The isomers **X1** and **X5** were elucidated as *trans-trans* due to the predominating formation of ions $[C_5H_8S]^{+\bullet}$ (*m*/*z* 100) *via* α-cleavage (Fig. 2, Table 1). A similar process is inherent for the *trans-trans* isomers of PHTX[1] and leads to the formation of ions $[C_6H_{10}S]^{+\bullet}$ (*m*/*z* 114), which are the most abundant in their mass spectra.

According to the analogy with PHTX, the fragmentation of *trans-cis* fused **X2** and **X4** isomers combines the competitive decomposition processes proceeding *via* α- and β-cleavages with the result that corresponding peaks in their mass spectra (*m*/*z* 114 and *m*/*z* 153, 140, respectively) are intense (Fig. 2, Table 1). It should be emphasised that the formation of ions $[C_6H_{10}S]^{+\bullet}$ (*m*/*z* 114), as a diagnostic feature of *trans-cis* conjugation, occurs to a larger extent in the case of PHTI isomers as compared with the similar fragmentation process of PHTX (*m*/*z* 128).[1]

There is a stereospecific fragmentation process, which proceeds through the rupture of C(2)–C(3) or C(5)–C(6) bonds connecting chiral centers of *cis-cis* fused isomers and leads to the formation of ions $[C_7H_{11}S]^+$ (*m*/*z* 127). It is the most inherent for *cis-anti-cis* PHTI and could be considered as a diagnostic feature of this isomer (Table 1). The intensity of the peak with *m*/*z* 127 in the mass spectra of *trans-trans* fused isomers is negligible because in this case the structure of ion $[C_7H_{11}S]^+$ representing two *trans*-fused five-membered rings is unstable (Scheme 2, Table 1).

Similar to PHTX,[1] the stereospecific fragmentation features of PHTI isomers involving the main competing processes of α- and β-cleavages can conveniently be summarized by means of the factor *k* [eqn. (1)] where I_{153}, I_{114} and I_{100} are the peak

$$k = I_{153}/(I_{114} + I_{100}) \quad (1)$$

intensities for the ions *m*/*z* 153, 114 and 100, respectively, expressed as a percentage relative to TIC (Table 1). As discussed above, for the *trans-trans* isomers factor *k* is much smaller than for the *cis-cis* ones, whereas for *trans-cis* isomers it takes intermediate values (Table 1). For *syn*- and *anti*-isomers *k*-values also differ, but to a lesser degree. Assuming the analogy to PHTX fragmentations could be extended it could be proposed

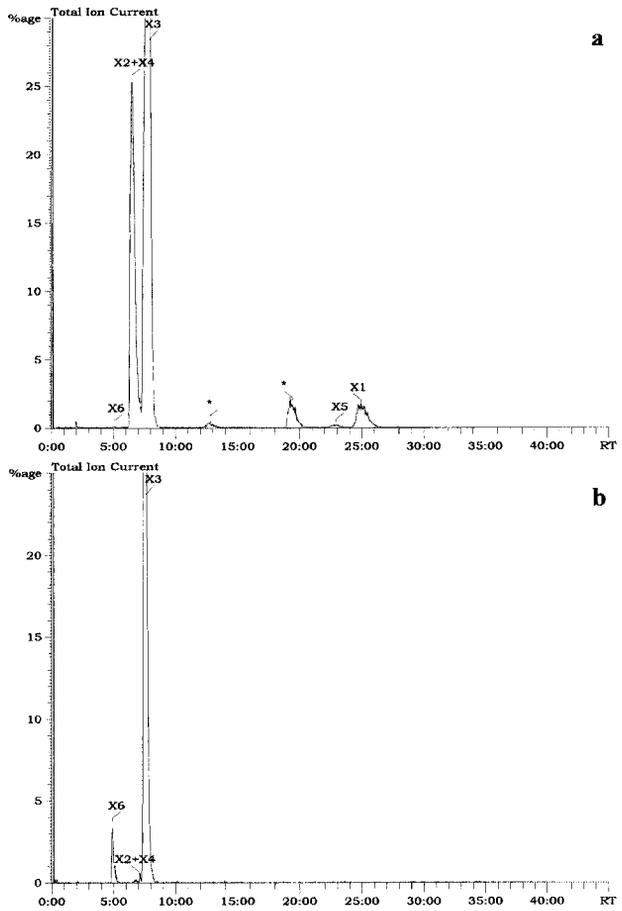


Fig. 3 Total ion current chromatograms of mixture 1 (**a**) and mixture 2 (**b**) of the stereoisomers of perhydro-4-thia-*s*-indacene on GTCB, 2 m × 1 mm, 230 °C.

that the GC-peaks **X1**, **X5**, **X2** and **X4** correspond to *trans-syn-trans*, *trans-anti-trans*, *trans-anti-cis* and *trans-syn-cis* isomers, respectively. It is necessary to note, however, that this assumption requires further confirmation.

The gas adsorption chromatography with graphitized thermal carbon black (GTCB) successfully applied previously[1,6,7] has been used for the structural elucidation of PHTI stereoisomers. The chromatograms from the separation of mixtures 1 and 2 of these compounds on a GTCB column are shown in Fig. 3. The GC peaks in Figs. 1 and 3 are in agreement with the mass spectra and on the abundance of isomers in the mixtures. Only five isomers of mixture 1 were completely separated; the peak of *trans-syn-cis* PHTI appeared to be overlapped by either the *trans-anti-cis* or *cis-syn-cis* isomers (Fig. 3).

Similar to the *trans-syn-trans* and *trans-anti-trans* isomers of tricyclic compounds with six-membered side rings[1,6,7] the *trans-trans* conjugated isomers **X1** and **X5** have planar structures that allow a large contact area with the flat surface of GTCB and have the longest retention times (Fig. 3). The adsorption on GTCB of the *cis-cis* conjugated isomers of PHTI and the tricyclic compounds with six-membered side rings[1,6–8] differs greatly. The GC-peak of *cis-syn-cis* PHTI is the third on the chromatogram, whereas the GC-peak of *cis-anti-cis* PHTI is the first (Fig. 3). *Cis-syn-cis* isomers of perhydroanthracene (PHA),[8] PHX (conformer **A**)[6,7] and PHTX[1] are the first to elute from the column due to the lowest number of contacts of their molecules with the flat surface of GTCB, as compared with other isomers, in particular, *cis-anti-cis*. The most likely interpretation of this unusual behavior of *cis-syn-cis* PHTI on GTCB is that the nearly flat conformation ***C*** of this isomer predominates over the bent conformations ***A*** and ***B***.

The retention order of PHTI isomers on the column packed with GTCB was calculated on the basis of their hypothetical

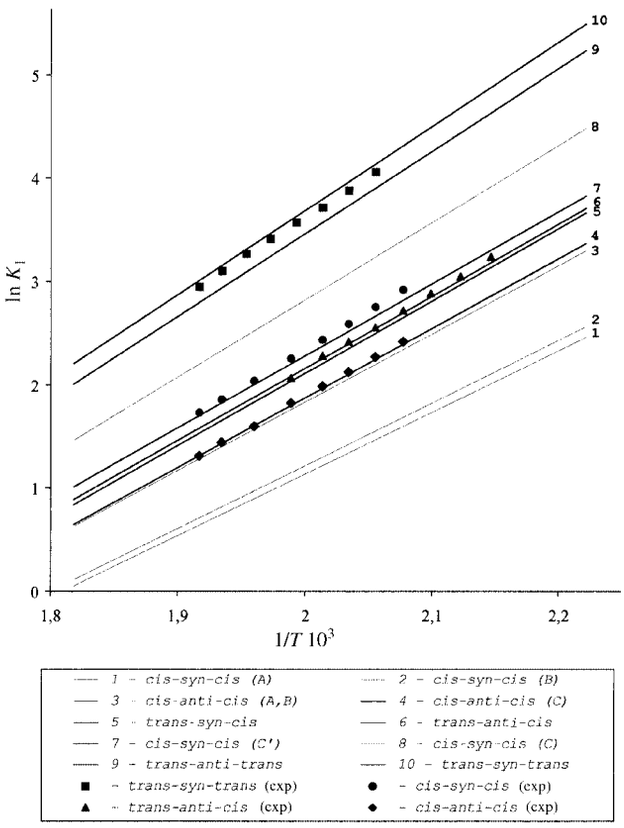


Fig. 4 Calculated (lines) and experimental (points) dependence of ln K_1 on $1/T$ for the adsorption of the stereoisomers of perhydro-4-thia-*s*-indacene on GTCB.

molecular structures to confirm the structural assignment. As previously[6,7] it was determined by molecular-statistical calculations of the adsorption equilibrium constants (Henry constants, K_1) of isomers using Kiselev's method.[10–12] The atomic coordinates of adsorbate molecules, required by this method, were obtained after energy minimization of their hypothetical structures by molecular mechanics according to the approach successfully tried out earlier.[6,7,12] This results in plots of the dependence of ln K_1 on the reciprocal temperature $1/T$ which are shown in Fig. 4. The upper plot corresponds to the longest retention time, the lowest plot to the shortest one. To verify the theoretical predictions the similar dependencies for isomers **X1**, **X2**, **X3** and **X6** were obtained experimentally according to the procedure described earlier.[9] These experimental data are shown in Fig. 4 as a series of points. In Table 1, together with intensities of the characteristic ions in the mass spectra of the stereoisomers of PHTI, their calculated and experimental adsorption characteristics on GTCB and calculated relative energies are shown.

The lines 4,5,6,8,9 and 10 in Fig. 4 correspond to the calculated values of ln K_1 for the *cis-anti-cis*, *trans-syn-cis*, *trans-anti-cis, cis-syn-cis*, *trans-anti-trans* and *trans-syn-trans* PHTI, respectively, in the global minimum of potential energy. The comparison of these data with Fig. 3 demonstrates that the calculated retention order confirms the preliminary assignment of isomers **X6**, **X4**, **X2**, **X3** (known), **X5** and **X1**. The lines 4, 5, 6 and 10 appeared close to the experimental values (Fig. 4, Table 1). The lines 5 and 6, which correspond to *trans-syn-cis* and *trans-anti-cis* PHTI, appeared very close to each other, in agreement with the supposed coelution of these isomers from the column packed with GTCB (Figs. 3, 4; Table 1). The calculated dependence of ln K_1 on $1/T$ for conformer ***C*** of *cis-syn-cis* PHTI (line 8) does not match the experimental points for this isomer (Fig. 4, Table 1).

In order to explain the origin of this disagreement some other conformations of the *cis-syn-cis* isomer were considered. As expected, the calculated Henry constants for conformers ***A*** and ***B*** of *cis-syn-cis* PHTI, which have a middle ring as a chair, were far from the experimental values (lines 1,2 of Fig. 4, Table 1). Intermediate conformations corresponding to local minima of the potential energy for conformer ***C***, which are distinguished by the torsion angles of five-membered rings, were also considered. The calculated values of ln K_1 for one of these conformations ***C′***, which is the nearest to the global minimum, appeared close to the experimental ones (line 7 of Fig. 4, Table 1). However, it should be emphasized that the comparison of calculated and experimental values of Henry constants for isomers with the middle ring as a boat is not entirely reliable. The boat conformation is characterized by pseudorotation, whereas the molecular-statistical method used was developed for quasi-rigid molecules.[10,11] In this case the influence of the force field of adsorbent on the molecular geometry of the stereoisomer with the boat in skeleton could not be excluded. However, this remark does not relate to the chair–boat interconversion, because the barrier to this process is higher than pseudorotation. The results obtained show that *cis-syn-cis* PHTI in the gas phase most probably exists in a conformation with the middle ring as a boat, which is in agreement with ^{13}C NMR data obtained earlier for solutions.[3,4]

In case of the *cis-anti-cis* PHTI, along with the conformer ***C*** (corresponding to the global minimum of potential energy) the conformer ***A***(***B***) was considered. The calculated thermodynamic adsorption parameters of these conformers, in spite of their different molecular geometries, appeared close to each other (lines 3 and 4 of Fig. 4, Table 1). The experimental values of ln K_1 agree closely with line 4 corresponding to calculated values for conformer ***C*** with the middle ring as a boat, which is somewhat more stable than conformer ***A***(***B***) with the middle ring as a chair (Fig. 4, Table 1). However, the differences between the calculated values are small and do not exceed the errors of the calculational method and the experiment. Therefore, the results are insufficient for the assignment of conformer ***C*** as the predominant for *cis-anti-cis* PHTI isomer in the gas phase.

Thus, it may be concluded that all six theoretically expected diastereomers of PHTI exist. On the basis of stereospecific features of their fragmentation and adsorption on GTCB five novel diastereomers—*trans-syn-trans*, *trans-anti-trans*, *trans-syn-cis trans-anti-cis* and *cis-anti-cis*—have been found and structurally elucidated. The validity of the quantitative concept applied to the determination of the retention order of novel isomers from a column packed with GTCB was confirmed within the limits of the method. The data obtained have confirmed the assumption about the preferred existence of *cis-syn-cis* PHTI in a conformation with the middle ring as a boat. The prevalence of the conformation with the middle ring as a boat for the *cis-anti-cis* isomer is less certain.

Calculations

Molecular mechanics was used to optimize the hypothetical molecular structures of PHTI stereoisomers. For this purpose the Amber force field of HYPERCHEM 5.0 was used. The final atomic coordinates obtained after energy minimization have been used for further molecular-statistical calculations.

In addition to the atom–atom potential functions used previously[7] one more potential function (expressed in kJ mol^{-1}) given in eqn. (2) has been used, where r is the distance between

$$\varphi_{S\cdots C(GTCB)} = -3.472 \times 10^{-3}\, r^{-6} - 6.667 \times 10^{-5}\, r^{-8} + 5.953 \times 10^{5} \exp(-35.7r) \quad (2)$$

the interacting atoms of the adsorbed molecule and the adsorbent (expressed in nm).[13]

For each isomer a series of calculations with different initial dispositions of the heterocycle on a flat GTCB surface was performed. The result with the highest value for the potential energy of the molecule–adsorbent interaction was selected.

The results are shown as a widely used graphical dependence of ln K_1 on the reciprocal column temperature $1/T$, which can be approximated by eqn. (3), where $V_{A,1}$ is retention volume at

$$\ln K_1 = \ln V_{A,1} = A + B/T \quad (3)$$

zero sample size per unit surface area. The coefficients A and B are related to the molar differential changes in entropy ($\overline{\Delta S}_1$) and internal energy ($\overline{\Delta U}_1$) (the differential heat of adsorption q_1) by the relationships given in eqns. (4) and (5).[9] The effect of

$$A = \overline{\Delta S}_1/R + 1 \quad (4)$$

$$B = -\overline{\Delta U}_1/R \quad (5)$$

the temperature on these values is neglected. Subscript 1 indicates small (zero) surface coverage.

Experimental

GC separation was carried out in a glass column 2 m in length with 1 mm internal diameter, packed with HT GTCB Sterling MT (7.6 $m^2\ g^{-1}$) of particle diameter 0.22–0.25 mm and on a DB-1 capillary column (J&W Scientific) 60 m in length and 0.25 mm internal diameter using a Varian 3740 gas chromatograph. The flow rates of carrier gas (Helium) were 10 ml min^{-1} and 25 cm s^{-1}, respectively. Mass spectra were obtained using a Finnigan MAT 112S, at ionizing energy 70 eV and ionizing chamber temperature 220 °C.

The measurements of Henry constants were carried out according to the procedure previously described in detail[9] using a Varian 3740 gas chromatograph equipped with a flame ionization detector, the measurement error was 3%. A glass column 40 cm in length with 2 mm internal diameter, packed with HT GTCB Sterling MT (7.6 $m^2\ g^{-1}$) of particle diameter 0.25–0.50 mm was used. The flow rate of carrier gas (Helium) was 25 ml min^{-1}.

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References

1 V. G. Adeeva, M. S. Bobyleva, N. S. Kulikov, V. G. Kharchenko and L. M. Yudovich, *J. Chem. Soc.*, *Perkin Trans. 2*, 1992, 965.
2 V. G. Kharchenko, N. I. Martemyanova, N. D. Zaytzeva and M. I. Kuramshin, *Zh. Org. Khim.*, 1976, **12**, 1802.
3 V. G. Kharchenko, L. M. Yudovich, O. A. Bozhenova and A. D. Shebaldova, *Khim. Geterotsikl. Soedin.*, 1987, N9, 1187.
4 L. M. Yudovich, PhD Thesis, Saratov, 1988.
5 P. Metzger, C. Cabestaing, E. Casadevall and A. Casadevall, *Org. Magn. Reson.*, 1982, **19**, 144.
6 M. S. Bobyleva and N. S. Kulikov, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 951.
7 N. S. Kulikov and M. S. Bobyleva, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 955.
8 A. V. Kiselev, N. S. Kulikov and G. Curthoys, *Chromatographia*, 1984, **18**, 297.
9 M. S. Bobyleva, A. V. Kiselev, N. S. Kulikov, E. B. Polotnyuk and K. D. Shcherbakova, *Adsorption Sci. Technol.*, 1985, **2**, 165.
10 A. V. Kiselev and D. P. Poshkus, *Faraday Symp. Chem. Soc.*, 1980, **15**, 13.
11 A. V. Kiselev, *Physical Chemistry*, *Modern Problems*, Khimiya, Moscow (in Russian), 1982.
12 N. S. Kulikov, *Adsorption Sci. Technol.*, 1997, **15**, 115.
13 A. K. Buryak, P. B. Dallakyan and A. V. Kiselev, *Dokl. Acad. Nauk*, 1985, **282**, 349.

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