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Bio MSC — Biomedical Mass Spectrometry Center

Stereochemistry studies of some 1,3-dioxane derivatives by differential mass spectrometry and computational chemistry

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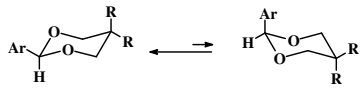
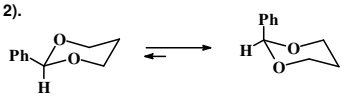
Introduction

Studies[1-4] on the stereochemistry of 2-aryl-1,3-dioxanes revealed the high preference of the aromatic substituent for the equatorial position, the characteristic conformational equilibrium being shifted toward the conformer exhibiting the aryl group in equatorial orientation (Scheme 1).



Scheme 1

The high A-value for aryl groups (e.g. A_{Ph}=3.12 kcal/mol) suggest that these substitutes are efficient "holding groups" [5]. On the other hand, quanto-chemical calculations of the standard forming heats for isolated molecules indicate a higher stability of the structures that have the aromatic substitute axial oriented (Scheme 2).



ΔH^o_f = -68.02 kcal/mol ΔH^o_f = -70.37 kcal/mol

Scheme 2

Taking in consideration that the GC/MS analysis is performed by ionizing the isolated molecule, one should expect that there is a correlation between the intensity of the peaks from the fragmentation spectra and the stability of the dia-stereo isomers 2-Ar-1,3-substituted dioxans. This paperwork presents the way in which correlation degree between the differential mass spectra and calculated heats of formation obtained from quantum chemistry calculations applied to the ions (Diff MS-CQC), can be used in discriminating the dia-stereo isomers possessing this structure.

Experimental

2-phenyl-4-methyl-1,3-dioxane and 2-phenyl-5-methyl-1,3-dioxane obtained by acetalization of benzaldehyde with butane-1,3-diol and respectively iso-butane-1,3-diol were used. The diastereoisomers mixture of obtained compounds (Scheme 3 and 4) were characterized by ^{1}H-NMR, ^{13}C-NMR in other papers[6,7].
The mass spectra were acquired with a HP GC/MSD instrument in the positive ion mode.

Strategy of ΔH^0_f database calculus

The heats of formation (ΔH_f) of molecules and fragment ions database were calculated. The geometries of the molecules and radicals were optimized with the MM+ force field and re-optimized with the semi-empirical method AM1 [8-10], using the RHF operators for molecules or ions and UHF for the radical ions. For each dia-stereo isomer and the corresponding ions a ponderated heat of formation was calculated using the equilibrium constant (K_{eq}) of the two conformers, A and B, from equation (1).

$$\Delta H^0_f = \Delta H^0_{fB}\frac{K_{eq}}{(K_{eq}+1)} + \Delta H^0_{fA}\frac{1}{(K_{eq}+1)} \qquad (1)$$

The calculated ponderated heats of formation were introduced in the data base of Chemical Structure Identification by Differential Mass Spectra - CSI Diff ms program (see table 1 and 2).
The files of the analyses were imported in CSI Differential Mass Spectrometry Data Analysis 2.5.1 software, produced by Bet2 Software Company, prior to which a subtract background correction was performed. For differentiation ms scans having approximately the same TIC on the rising side of each chromatographic peak were considered. The plots of the differential spectra are presented in Figure 1 [11].

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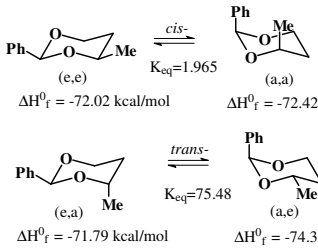
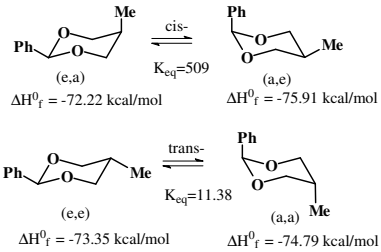
Results and Discussion



Scheme 3. The conformers of 2-phenyl-4-methyl-1,3-dioxane diastereoisomers



Scheme 4. The conformers of 2-phenyl-5-methyl-1,3-dioxane diastereoisomers

Table 1 Heat of formation for 2-phenyl-4-methyl-1,3-dioxane

ΔH^o_f (kcal/mol)		M	M^+	M-H]$^+$	M-Me]$^+$	M-Ph]$^+$	Ph]$^+$
cis- K_{eq}=1.965	(e,e)	-72.02	129.72	100.35	203.78	81.17	
	(a,a)	-72.42	132.06	100.62	182.58	81.45	
$\Delta H^o_{f\ cis\ ponderal}$		-72.28	131.27	100.52	189.72	81.35	283.6
trans- K_{eq}=0.013248	(a,e)	-74.35	131.42	100.35	203.78	81.17	
	(e,a)	-71.79	129.69	100.62	153.57	81.45	
$\Delta H^o_{f\ trans\ ponderal}$		-74.31	131.39	100.35	203.12	81.17	283.6

Table 2 Heat of formation for 2-phenyl-5-methyl-1,3-dioxane

ΔH^o_f (kcal/mol)		M	M^+	M-H]$^+$	M-Me]$^+$	M-Ph]$^+$	Ph]$^+$
cis- K_{eq}=509	(e,a)	-72.22	129.78	101.36	158.87	82.65	
	(a,e)	-75.91	130.26	100.41	153.57	81.78	
$\Delta H^o_{f\ cis\ ponderal}$		-75.90	130.25	100.41	153.58	81.78	283.6
trans- K_{eq}=11.38	(e,e)	-73.35	128.55	100.41	158.87	81.78	
	(a,a)	-74.79	131.47	101.36	153.57	82.65	
$\Delta H^o_{f\ trans\ ponderal}$		-74.67	131.23	101.28	153.99	82.57	283.6

There are many similarities between the spectra of the two pairs of dia-stereo isomers, over 98%, which translates in a difficult distinction between them.
After selecting the main fragmentation ions, which correspond to the two dia-stereo isomers *cis*- and *trans*-, and the selection of the computational method, the heats of formation are automatically loaded and the "Calculate Probability" command from the software triggers the calculation of the probability list (Figure 2).

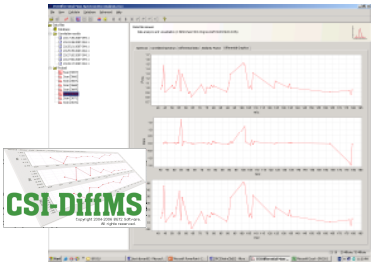


Figure 1 Graphic form of differential mass spectra of *cis*- and *trans*-2-phenyl-5-methyl-1,3-dioxane

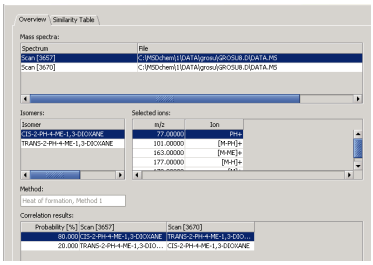


Figure 2 Snapshot of window with compared ms scans, isomers, ions and the list of structures probabilities for *cis*- and *trans*- 2-phenyl-5-methyl-1,3-dioxane isomers

Probability	Isomer X Retention time 24.25 min	Isomer Y Retention time 24.33 min
80 %	*cis*- 2-phenyl-4-methyl-1,3-dioxane	*trans*- 2-phenyl-4-methyl-1,3-dioxane
20 %	*trans*- 2-phenyl-4-methyl-1,3-dioxane	*cis*- 2-phenyl-4-methyl-1,3-dioxane

Table 3
The probability list rezulted by GC/MS and CSI Diff ms - CQC analysis for *cis*- and *trans*- 2-phenyl-4-methyl-1,3-dioxane isomers

Probability	Isomer X Retention time 24.99 min	Isomer Y Retention time 26.26 min
75 %	*trans*- 2-phenyl-5-methyl-1,3-dioxane	*cis*- 2-phenyl-5-methyl-1,3-dioxane
25 %	*cis*- 2-phenyl-5-methyl-1,3-dioxane	*trans*- 2-phenyl-5-methyl-1,3-dioxane

Table 4
The probability list rezulted by GC/MS and CSI Diff ms - CQC analysis for *cis*- and *trans*- 2-phenyl-5-methyl-1,3-dioxane isomers

Conclusions

The results obtained by CSI-Diff-ms on discrimination of these diastereoisomers of 2-phenyl-4-methyl-1,3-dioxane and 2-phenyl-5-methyl-1,3-dioxane presented above are in agreement with the results obtained by conformational analysis [6-7].
The CSI Diff ms - CQC analysis proved that under vacuum the molecules of the studied substances adopt conformations exhibiting the phenyl in axial orientation. Solvation and the energy of the crystalline network, which are involved in NMR and X-Ray analysis, modify this orientation.
The 75-80% agreement between the experimental values P_i from the differential spectrum Pms and the values estimated by calculation, ΔP_i, in the CSI Diff ms program proves the ability of the semiempirical method AM1 to evaluate the heats of formation, to be coupled with Diff MS in order to describe the energy profile of the ionization processes from mass spectrometry.

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