Brief Communications

Determination of the configuration of piperidin-4-ol silyl ethers by mass spectrometry with chemical ionization

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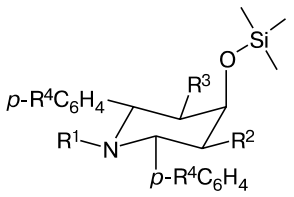
Mass spectrometry with chemical ionization (isobutane as reactant gas) can be used for the determination of the configuration of the chiral center at the C(4) atom in molecules of silyl ethers of 2,6-diaryl-substituted piperidin-4-ols.

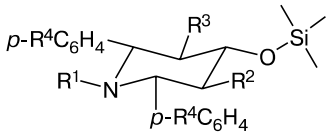
Key words: piperidin-4-ols, mass spectrometry, stereochemistry, chemical ionization.

Mass spectrometry with chemical ionization (CI) is an efficient method for the solution of stereochemical problems, especially in the series of di- and polyfunctional compounds.[1] In particular, noticeable differences in the degree of dehydration of protonated molecules were found for conformationally flexible cyclic amino alcohols[2—4] and conformationally rigid *trans*-decahydroquinolin-4-ols.[5,6]

In the present work, we studied a possibility to use CI (isobutane as reactant gas) for the determination of the configuration of the chiral center C(4) in molecules of diastereomeric silyl ethers of secondary alcohols of the series of 2,6-diaryl-substituted piperidin-4-ols (**1—10**) with the conformationally rigid system.



1a—10a



1b—10b

Experimental

Silyl ethers of piperidinols (**1—10**) were synthesized from individual alcohols, whose structures and spatial arrangement have been determined earlier.[6] Alcohol (0.05 g) was placed in a quartz ampule, and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide

Compound	R^1	R^2	R^3	R^4	Compound	R^1	R^2	R^3	R^4
1	Me	H	H	H	**6**	H	Me	Pr^n	H
2	H	Me	H	H	**7**	H	Pr^n	Et	H
3	H	Me	Me	H	**8**	H	n-C_5H_{11}	H	H
4	Me	Me	Me	H	**9**	H	Me	H	Me
5	H	Et	Et	H	**10**	H	Me	H	MeO

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1625—1627, September, 2006.

1066-5285/06/5509-1684

(3 μL) containing 1% trimethylchlorosilane (Aldrich) was added. The ampule was stored at 90 °C until the alcohol dissolved completely. Then the solution was cooled down and diluted with 30 μL of chloroform, and a sample (1 μL) was taken for analysis by mass spectrometry.

Spectra were recorded on a Finnigan MAT 95XL instrument. Solutions of individual stereoisomers in chloroform were introduced into the ion source through a gas-liquid chromatograph using a quartz capillary column with the polymethylsiloxane phase (30 m×0.19 mm, partition 1 : 30, helium as carrier gas). Experiments were carried out at a temperature of the ion source of 200 °C. The pressure of the reactant gas (isobutane) in the chamber for CI was selected by the characteristic plasma spectrum. Five measurements were conducted for each sample, and the error of measurement of intensities of the characteristic peaks did not exceed 5 rel.%.

Results and Discussion

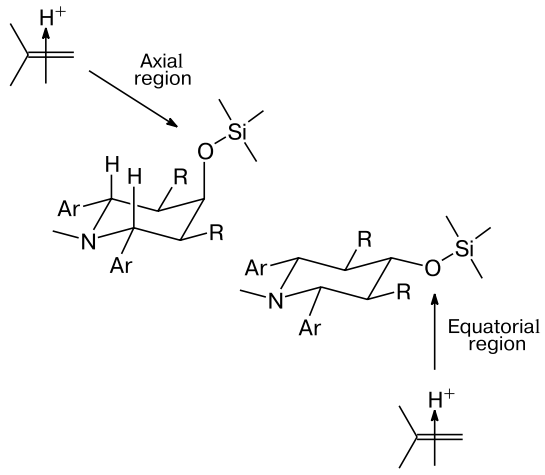
The CI mass spectra contain virtually only intense peaks of protonated molecules $[MH]^+$ and products of elimination of the trimethylsilanol molecule $[MH - SiMe_3OH]^+$. The total intensity of the peaks caused by the decomposition of the $[MH]^+$ ions ($[MH - H]^+$, $[MH - alkyl]^+$) did not exceed 5% of the total ion current. It is known[1] that protonated molecules of carbocyclic alcohols are quantitatively dehydrated, and a trimethylsilanol molecule is also eliminated very easily. Thus, the $[MH]^+$ and $[MH - SiMe_3OH]^+$ ions correspond to the molecules protonated at the N and O atoms, respectively, and their intensities are proportional to the content of these protonated molecules ($[M_NH]^+$ and $[M_OH]^+$) in the ion current (Table 1).

A comparison of the relative intensities of the peaks of the $[MH]^+$ and $[MH - SiMe_3OH]^+$ ions shows that the protonated ether molecules with the equatorial trimethylsilyloxy group, regardless of the character of substituents at the C(2), C(3), C(5), C(6), and N atoms, eliminate trimethylsilanol much more easily than their axial epimers for which this process sometimes is not observed at all (see Table 1). Perhaps, this difference in the degree of dehydration depends on different abilities of the stereoisomers to coordinate the proton between the O and N atom. Although the aryl substituents in positions 2 and 6 stabilize the chain conformation, which decreases its ability to inversion into the boat conformation, ions with the bridging hydrogen bond can be formed. It has earlier[3,4] been shown that the formation of such ions can easily be found by studying the products of decomposition of the $[MH]^+$ ions activated by collisions with neutral atoms of noble gases in the field-free region. In the case of silyl ethers **1—10**, activation by collision results in the formation of the $[MH - SiMe_3OH]^+$ ions for the epimers with both the equatorial and axial hydroxyl groups, although in a much smaller amount in the latter case. This indicates that the formation of a chelate complex is more probable in the case of the equatorial epimer, which contradicts the observed stereospecificity of the decomposition.

Table 1. Relative intensity (%) of characteristic peaks in the CI mass spectra (isobutane) and the ratio of molecules protonated at the N and O atoms

Compound	$[MH]^+$	$[MH - SiMe_3OH]^+$	$[M_NH]^+/[M_OH]^+$
1a	100	0	100/0
1b	100	22.0	82/18
2a	100	0	100/0
2b	100	33.6	75/25
3a	100	0	100/0
3b	100	55.6	64/36
4a	100	0	100/0
4b	100	90.0	53/47
5a	100	0.4	100/0
5b	100	55.1	64/36
6a	100	0.7	99/1
6b	100	70.7	58/42
7a	100	0.6	99/1
7b	100	27.6	78/22
8a	100	0	100/0
8b	100	57.6	63/37
9a	100	0.6	99/1
9b	100	22.3	82/18
10a	100	0	100/0
10b	100	37.1	73/27

The stereoisomeric effects observed in the CI mass spectra can be explained by steric factors determining the probability of protonation. In fact, it is more difficult for the bulky protonating cation to approach to the 4-Me_3SiO axial group from the axial region than from the equatorial region because of steric hindrance caused by the axial H atoms in positions 2 and 6.



Thus, the observed regularity can be used for the determination of the configuration of the chiral center at the C(4) atom in molecules of the piperidin-4-ol derivatives

by comparison of the CI mass spectra of the diastereomers. They are well separated in gas chromatographic columns with nonpolar liquid phases. The quantitative composition of mixtures of diastereomers and the configuration of the C(4) center in each diastereomer can be determined by gas chromatography coupled with mass spectrometry using chemical ionization.

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Received February 1, 2006;
in revised form June 15, 2006