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Synthesis and conformational analysis of 1,3-azasilinanes

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ABSTRACT

1-Isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** and 1-isopropyl-3,3-dimethyl-1,3-azasilinane **2** were synthesized and a detailed analysis of their NMR spectra, conformational equilibria and ring inversion processes is presented. Low temperature $^{1}H/^{13}C$ NMR spectroscopy, iteration of the ^{1}H NMR spectra and quantum chemical calculations showed slight predominance of the $Ph_{eq}Me_{ax}$ over the $Ph_{ax}Me_{eq}$ conformer of **1** at low temperature. The barrier for the chair to chair interconversion of both compounds was measured to be 8.25 kcal/mol.

1. Introduction

Piperidines are a very important class of compounds generally found in diverse natural products and drugs.[1] The piperidine fragment is a significant structural part of a variety of natural alkaloids and synthetic compounds with interesting biological and pharmacological properties. For example, 3-aryl-3-methylpiperidine derivatives with opioid activity have been described, their stereochemical study reported[2] and the significant role of the Ph-axial or Ph-equatorial conformation in the ligand-receptor interaction was mentioned in the literature.[2]

As analogs of known drugs, bioisosteric 4-silapiperidines were designed by replacement of a carbon atom by silicon.[3–5] Pharmacological activity and the X-ray molecular structure of their aryl derivatives was the subject of numerous investigations performed mainly by Tacke's group.[6–9] On the contrary, limited sets of data are known for 3-aryl-1,3-azasilinanes, which are of special interest from different points of view. As other Si–Ph-substituted compounds, they are useful synthons for the preparation of various Si-functional heterocycles by electrophilic cleavage of the Si–Ph bond.[10,11] Recently, stereocontrolled synthesis of 3-aryl-1,3-azasilinane derivatives as potential Si-containing peptide mimics was reported.[12,13] From the structural point of view these compounds represent an attractive object for investigation of conformational effects caused by two heteroatoms (Si and N in 1,3-position) in the saturated six-membered ring. Recently we have reported the gas phase electron diffraction molecular structure of 1,3,3-trimethyl-1,3-azasilinane[14] and the conformational analysis of 1,3-dimethyl-3-R-1,3-azasilinanes (R=Me, Ph).[14,15] The former compound was shown to adopt a slightly distorted chair conformation with the equatorial *N*-Me group.[14] The latter (1,3-dimethyl-3-phenyl-1,3-azasilinane) exists as an equilibrium mixture of the $Ph_{ax}Me_{eq}$ and $Ph_{eq}Me_{ax}$ chair conformers in the ratio of 1 : 2 with *N*-Me in the equatorial position in both conformers as well.[15]

Our current interest in the stereochemistry of 1,3-silapiperidines prompted us to examine the effect of the *N*-alkyl substituent on the conformational equilibria of 1,3-azasilinanes; up to now only *N*-Me analogs were studied with *N*-Me anancomeric in equatorial position. To begin with, both 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** and 1-isopropyl-3,3-dimethyl-1,3-azasilinane **2** were synthesized and the stereochemistry examined in solution by variable temperature NMR spectroscopy and in the gas phase by theoretical calculations at the DFT and MP2 level of theory.

Although in azasilinanes, as in the parent piperidines, the NR_{eq} conformers are much more stable and the only observable conformers, in other nitrogen-containing diheterocyclohexanes, like 3-alkyl-1-oxa-3-azacyclohexanes, the NR_{ax} conformers can predominate.[16,17]

Finally, an interesting question is also the effect of the second heteroatom in silaheterocyclohexanes on the conformational equilibrium. The so far studied 1-methyl-1-phenyl-1-silacyclohexane and 3-methyl-3-phenyl-3-silathiane were found to be conformationally similar[18] but strongly different from

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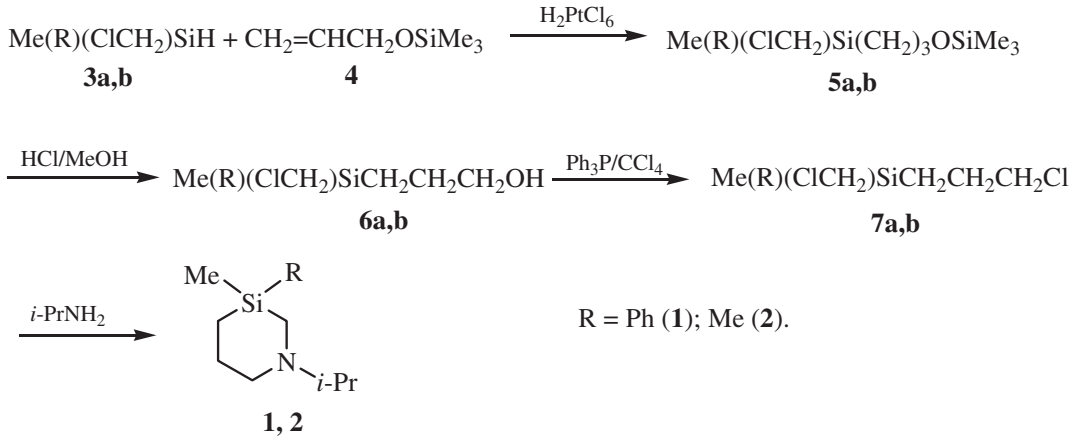
1-methyl-1-phenylcyclohexane.[19,20] How will the relative stability of the conformers be affected by the nitrogen atom having the lone electron pair in the β-position to silicon? All these issues are discussed below.

2. Results and discussion

2.1. Synthesis

Compounds **1** and **2** were prepared by the sequence of reactions including the addition of methyl(chloromethyl)phenylsilane **3a** or dimethyl(chloromethyl)silane **3b** to the silylated allyl alcohol **4** followed by desilylation of adducts **5a**,**b** to the corresponding alcohols **6a**,**b**. Chlorination of the latter and heterocyclization of the formed dichlorides **7a**,**b** with *i*-propylamine, proceed all in good yield (Scheme 1).

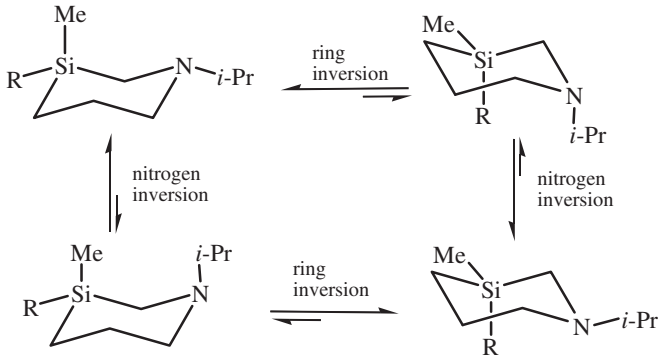
For compound **1**, the conformational equilibrium in Scheme 3 is not degenerate. The aliphatic part of the ^{1}H NMR spectrum of **1** differs from that of **2** by the low-field shifts caused by the ring current effect of the Ph group varying from ~0.1 ppm for remote protons (*i*-Pr, 6-CH_2, 5-CH_2) to ~0.3 ppm for 2-CH_2 and 4-CH_2 protons, which are more close to the silicon atom. Besides, due to the presence of the chiral center at the silicon atom, the protons of the latter two methylene groups are diastereotopic and appear in the ^{1}H NMR spectrum as AB pattern (2-CH_2) or two multiplets of 8 lines (partly overlapped) each (4-CH_2). Upon cooling, the signals decoalesce. The best resolved ^{1}H NMR spectrum of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** is obtained at 143 K and is shown in Fig. 1. Two sets of signals were observed and assigned to the axial or equatorial protons in the two conformers of **1** of slightly diffent population using the well known general principles of ^{1}H/^{13}C NMR stereoanalysis: (i) equatorial protons resonate at



Scheme 1. Synthesis of the studied compounds.

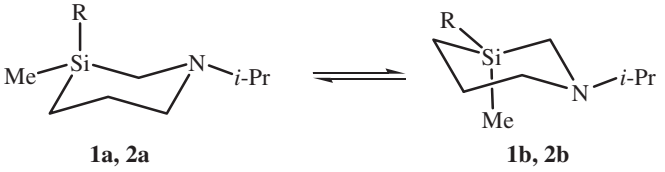
2.2. Variable temperature NMR measurements

The complete intramolecular flexibility of 1,3-azasilinanes **1** and **2** must include both ring inversion and nitrogen inversion (Scheme 2).



Scheme 2. Conformational equilibria of 1,3-azasilinanes **1** and **2**.

However, due to much lower energy of the NR_{eq} versus NR_{ax} conformer (vide infra) and similar to the earlier studied Si, *N*-containing heterocycles,[14,15,21,22] the nitrogen inversion leads to the conformational equilibrium *N*-*i*-$Pr_{ax} \rightleftarrows$ *N*-*i*-Pr_{eq}, which is completely biased to the *N*-*i*-Pr_{eq} conformer, so, Scheme 2 is simplified to Scheme 3.



Scheme 3. Conformational equilibrium of 1,3-azasilinanes **1** and **2**.

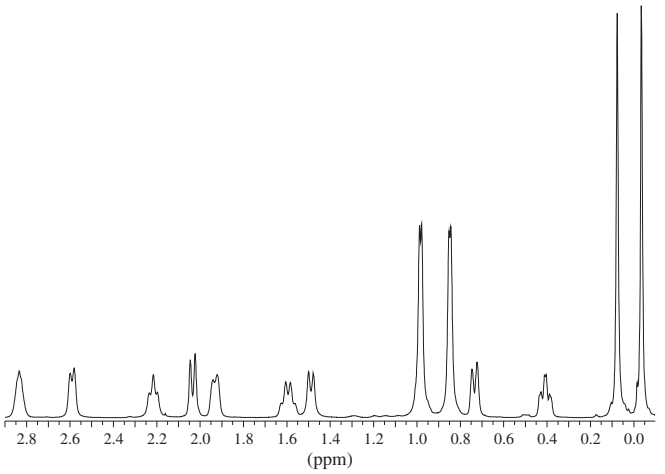


Fig. 1. ^{1}H NMR spectrum of the frozen conformational equilibrium of compound **1** at 143 K in the solvent mixture of CD_2Cl_2, $CHFCl_2$, and CHF_2Cl in a ratio of 1:1:3 at 600 MHz.

lower field as compared to the axial protons at the same carbon atom,[16,23] (ii) axial protons split into triplets or quartets due to large geminal $^{2}J_{HH}$ and vicinal $^{3}J_{HH(ax,ax)}$ coupling constants, whereas the equatorial protons are split only to doublets due to the $^{2}J_{HH}$ coupling constants (the much smaller $^{3}J_{(ax,eq)}$ and $^{3}J_{(eq,eq)}$ are not resolved due to residual low temperature broadening), and (iii) axial Si–Me carbons (protons) are found at higher (lower) field than the corresponding equatorial Si–Me carbons (protons).[24,25] Adequately, ^{1}H NMR spectra of the two conformers were assigned (cf. Table 1).

For the aryl substituted six-membered carbo- and heterocycles another criterion originally asserted by *Eliel* was the upfield shift of the C_{ipso} carbon in the Ph_{ax} relative to the Ph_{eq} conformers,[2,26,27] the difference reaching 5.6 ppm in 1-methyl-1-phenylcyclohexane[19] and ~2.5 ppm in 3-methyl-3-arylpiperidines.[2,27] This criterion is adhered also to 1-methyl-1-phenyl-1-silacyclohexane and 3-methyl-3-phenyl-3-silathiane,[18] although the difference between the C_{ipso} signals in the conformers is reduced to ~1.5 ppm. In contrast, in the 1,3-azasilinanes studied in the present and preceding work,[15] the C_{ipso} carbons of the $Me_{eq}Ph_{ax}$ conformers resonate at a lower field. However, since the difference of the chemical shifts of C_{ipso} in the two conformers is as low as 0.15–0.23 ppm, the relative position of the signals cannot be used as a decisive criterion for the assignment of the conformers.

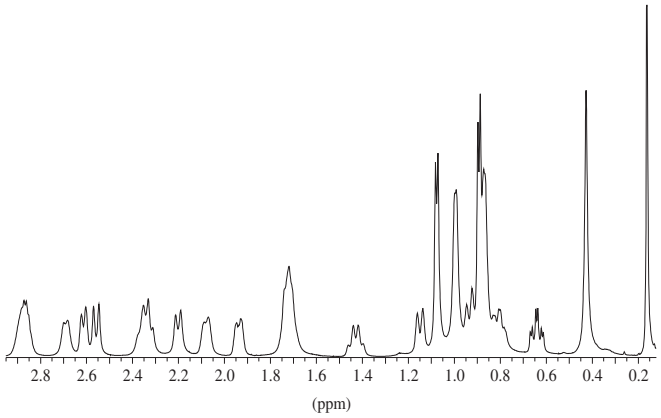


Fig. 2. ^{1}H NMR spectrum of the frozen conformational equilibrium of compound **2** at 143 K in the solvent mixture of CD_2Cl_2, $CHFCl_2$, and CHF_2Cl in a ratio of 1:1:3 at 600 MHz.

shifts at 273 K and for the conformers at low temperature [113 K (**1**) and 103 K (**2**), respectively] are collected; carbon atoms were assigned via HMQC and HMBC 2D correlation spectra (Fig. SI-3 in Supplementary data).

Table 1
^{1}H and ^{13}C NMR spectra of the 1,3-azasilinanes **1** and **2** at various temperatures in $CD_2Cl_2/CHCl_2F/CHClF_2$

T/K, conformer		MeSi	2-CH_2	4-CH_2	5 – CH_2'	6-CH_2	NCH	CCH_3
δ (^{1}H)/ppm								
273, **1**		0.37	2.11	0.86	0.92	2.54	2.87	1.04
			2.24	0.99				1.06
143, **1a**	ax	0.43	2.20	0.81	1.73	2.33	2.86	0.87
$Me_{eq}Ph_{ax}$, *minor*	eq		1.73	0.94	2.08	2.69		0.89
143, **1b**	ax	0.16	2.55	1.15	1.44	2.33	2.86	1.07
$Me_{ax}Ph_{eq}$, *major*	eq		1.73	0.64	1.94	2.61		1.00
δ (^{13}C)/ppm								
273, **1**		−4.6	37.5	17.3	25.9	55.5	58.8	12.1
143, **1a**	eq	−3.8	32.9	20.3	24.2 br	56.4	56.4	10.4
$Me_{eq}Ph_{ax}$, *minor*								
143, **1b**	ax	−7.9	34.2	12.3	24.2	56.4	56.4	10.4
$Me_{ax}Ph_{eq}$, *major*								
δ (^{1}H)/ppm								
273, **2**		0.02	1.79 s	0.55 m	1.74 m	2.32 m	2.87	0.92 d
143, **2a**	eq	0.08	1.49 d	0.41 t	1.59 q	2.22 t	2.83 q	0.85 d
143, **2b**	ax	−0.04	2.03 d	0.73 d	1.93 d	2.59 d	2.83	0.98 d
δ (^{13}C)/ppm								
273, **2**		−3.6	38.7	17.4	25.7	54.5	57.9	12.9
143, **2a**	eq	−3.5	32.3 br	21.2	24.4 br	56.2 br	56.5 br	11.3 br
143, **2b**	ax	−5.3	32.3 br	10.5	24.4 br	56.2 br	56.5 br	11.3 br

It is worth mentioning that, as its *N*-Me analog[15] and unlike 1-methyl-1-phenyl-1-silacyclohexane,[18] or 3-methyl-3-phenyl-3-silathiane,[18] the low temperature ^{13}C NMR spectrum of compound **1** shows two clearly separated sets of all aromatic signals (Figs. SI-1, SI-2 in Supplementary data) with the ratio of intensities practically coinciding with that determined from the low temperature and iterated ^{1}H NMR spectra (vide infra).

For compound **2** the equilibrium in Scheme 3 is degenerate: under the conditions of fast exchange the time-averaged ^{1}H NMR spectrum is represented by 7 signals. Upon cooling down, the equilibrium gets frozen and all methylene and methyl protons give separate signals, the best resolved ^{1}H NMR spectrum of 1-isopropyl-3,3-dimethyl-1,3-azasilinane **2**, again at 143 K, is given in Fig. 2.

Proton chemical shifts at 273 K (when the ring inversion is fast on the NMR time scale) and of the frozen conformational equilibria at 143 K are given in Table 1. In addition, in Table 1 ^{13}C chemical

Both ^{1}H and ^{13}C NMR spectra of the azasilinanes **1** and **2** were studied not only at the certain temperatures mentioned in Table 1 but between 273 K and 103 K in a freon mixture, which is still liquid at the lowest temperatures; in Fig. 3 the variable temperature ^{13}C NMR study of 1-*i*-propyl-3-methyl-3-phenyl-1,3-azasilinane **1** is given. Similar dynamic effects were obtained in the ^{1}H NMR spectrum of **1** and in the temperature variable ^{1}H and ^{13}C NMR spectra of **2** (see Supplement). Both coalescence temperatures T_c and chemical shift differences $\Delta\nu_c$ at T_c ($\Delta\nu_c$ as obtained by extrapolation from frozen spectra to T_c) were determined and employed to calculate $k_c=\pi\Delta\nu_c/\sqrt{2}$ and via the *Eyring* equation $\Delta G_c^{\#}$ at T_c.[27] In case of **1** the population difference of the conformers deviates from 1:1; the $Ph_{eq}Me_{ax}$ conformer is preferred (58.5% beside 41.5% of the $Ph_{ax}Me_{eq}$ conformer) [K=1.41; $\Delta G^{\circ}=-RT\ln K$=0.1 kcal/mol]. Only clearly separated, non overlapping signal pairs were employed for extraction the kinetic information about the ring inversion and are given, together with the dynamic NMR parameters, in Table 2.

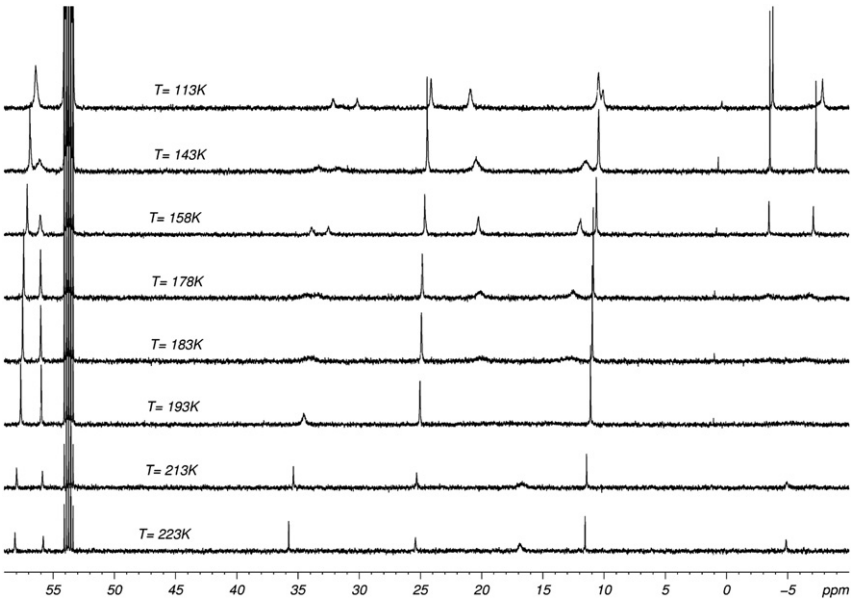


Fig. 3. ^{13}C NMR dynamic NMR study of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** at various temperatures in the solvent mixture of CD_2Cl_2, $CHFCl_2$, and CHF_2Cl in a ratio of 1:1:3 at 150 MHz.

Table 2
Dynamic NMR study of the 1,3-azasilinanes **1** and **2**

No.	Signal studied	T_c/K	$\Delta\nu_c$/Hz	k_c	$\Delta G_c^{\#}$/kcal/mol
1[a]	Si–CH_3 (−4.9 ppm)	188	527.5	1172	8.2
	C-5 (17.3 ppm)	195	1075	2388	8.2
	C-2 (37.5 ppm)	181	162.5	361	8.8
	Si–CH_3 (0.37 ppm)	180	149	331	8.3
	Mean				*8.25*
2	Si–CH_3 (0.02 (ppm)	173	60	133	8.3
	N–CH(CH_3)$_2$ (0.92 ppm)	173	72	160	8.2
	Mean				*8.25*

[a] $\Delta G^\circ = -RT \ln K = 0.1$ kcal/mol; 58.5% $Ph_{eq}Me_{ax}$ and 41.5% $Ph_{ax}Me_{eq}$.

Additionally, the proton NMR spectrum of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** was iterated subject to the present conformational equilibrium at room temperature in CD_2Cl_2 on basis of computed vicinal H,H coupling constants of the frozen conformers, given in Table 3. The $^3J_{H,H}$ values can be successfully employed to calculate the conformational equilibrium at room temperature in CD_2Cl_2 [57.25–64.95 % and 35.05–42.75 % (mean values 61%:39%); K=1.56; ΔG°=−0.3 kcal/mol], which is very similar to the free energy difference at low temperature in the freon mixture [K=1.41; ΔG°=0.08 kcal/mol]. Unfortunately, the vicinal H,H coupling constants in the two conformers are almost identical (cf. Table 3) and, therefore, it cannot be decided, which one is the preferred conformer. It can be suggested, considering our former experiences,[18,28,29] the less stable conformer of compound **1** at low temperature, $Ph_{ax}Me_{eq}$, to be the preferred one at room temperature; different solvents (freon mixture at low temperature and CD_2Cl_2 at room temperature) can be of influence as well but we expect it to contribute only minor. Unequivocally, however, it can be concluded that within $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$ the temperature dependence of the free energy difference of the conformers of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** is only minor and hereby the equilibrium is enthalpically controlled with minor entropy influence.

Table 3
Conformational analysis of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** at room temperature employing PERCH[30–33]

$^3J_{H,H}$	Me(eq)/Ph(ax)[a]	Me(ax)/Ph(eq)[a]	exp. $^3J_{H,H}$	% (**1a**)	% (**1b**)
4ax,5ax	12.25	3.26	8.84	62.07	37.93
4ax,5eq	5.42	3.38	4.74	64.95	35.05
4eq,5ax	3.28	5.69	4.74	39.42	60.58
4eq,5eq	3.44	12.14	8.81	38.28	61.72
5ax,6ax	10.07	4.39	7.69	58.10	41.90
5eq,6eq	4.74	10.12	7.82	42.75	57.25
Mean value				60.2	39.8

[a] Computed at MP2/6-311G(d,p) level of theory.

In order to prove independently the assignment of the conformers of **1** the ring current effect of the Si–Ph substituent in both conformers on the ring protons was computed. For this purpose our spatial NICS approach[34] was employed. These through-space NMR shieldings (TSNMRSs) can be visualized[34] as iso-chemical-shielding surfaces (ICSSs) and employed to quantify the anisotropic effects of functional groups on proton chemical shifts (for determing the stereochemisty of nuclei proximal to the functional group),[35–46] to separate the anisotropic effect of functional groups from the influence of steric hindrance on the same proton chemical shifts,[47,48] and to visualize and quantify planar,[49,50] spherical (anti) aromaticity[51–54] and chelatoaromaticity.[55]

On basis of the optimized geometries of the two conformers $Ph_{ax}Me_{eq}$ and $Ph_{eq}Me_{ax}$ of **1** the TSNMRS values of the phenyl substituent were calculated, visualized by ICCS of various size and direction (cf. Fig. 4) and, finally, the corresponding ring current on the ring protons at C-2 and C-4–C-6 was computed quantitatively. The corresponding ring current effects (σ/ppm, + for shielding and—for deshielding) are given in Table 4 together with experimental chemical shifts δ/ppm.

Critical comparison of the computed and experimental chemical shift differences prove the correct assignment of the two conformers of **1**: while proton chemical shifts of H-2 and H-4 are dominated by other/additional effects and ring current effects on the H-6 protons are too small, only (as expected) the protons H-5 can be employed. Both ring current effect as computed ($\Delta\sigma$) and chemical shift differences $\Delta\delta$ of the protons are completely congruent, and prove independently the correct assignment of the NMR spectra of compound **2** (Table 4).

The barriers to ring inversion in the *N*-*i*-Pr-substituted 1,3-azasilinanes **1**, **2** (Table 2) are ~0.8 kcal/mol lower than those in their *N*-Me-substituted analogs, which were measured to be 9.0 kcal/mol[15] and 9.1 kcal/mol,[14] respectively. Probably, this is due to slight

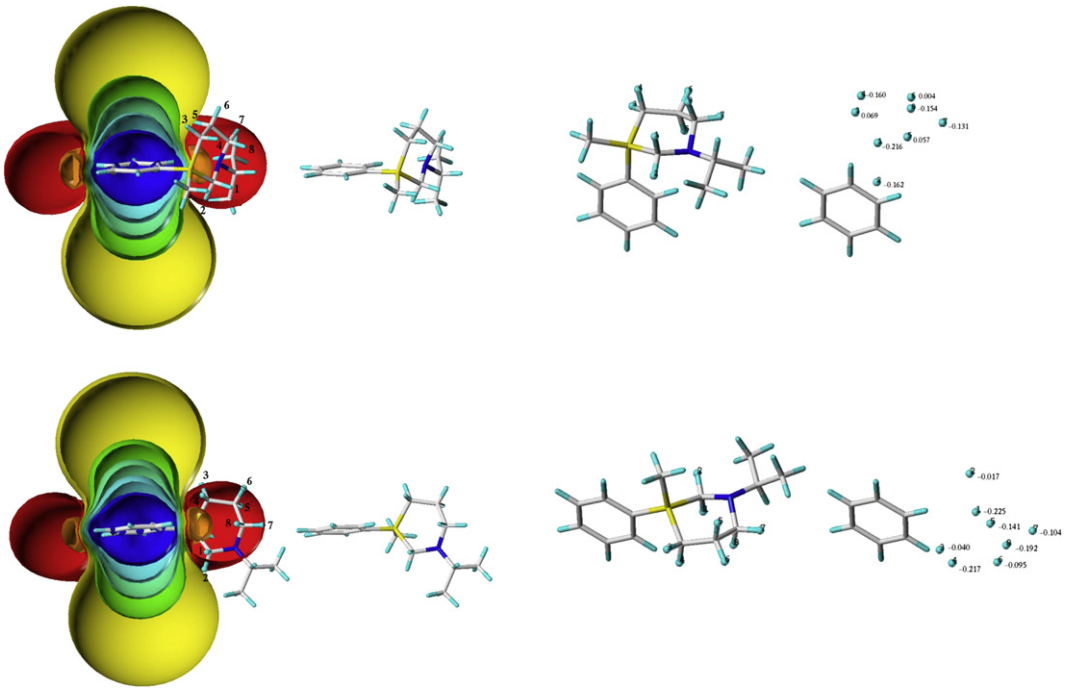


Fig. 4. Ring-current effect of the phenyl ring in the two conformers of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** on the ring protons (cf. Table 4) as ICSS of different direction and size (blue represents 5 ppm shielding, cyan 2 ppm shielding, greenblue 1 ppm shielding, green 0.5 ppm shielding, yellow 0.1 ppm shielding, and orange −0.5 ppm and red −0.1 ppm deshielding).

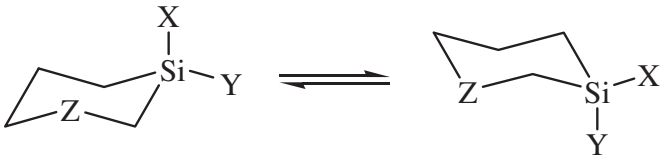
Table 4
Ring current effect of Si-Phenyl on the ring protons in the two conformers of 1-isopropylisopropyl-3-methyl-3-phenyl-1,3-azasilinane **1**

Proton	Conformer/δ(exp.)/ppm			Ring current effect/$\Delta\sigma$/ppm		
	Ph(eq), Me(ax)	Ph(ax), Me(eq)	$\Delta\delta$/ppm	Ph(eq), Me(ax)	Ph(ax), Me(eq)	$\Delta\sigma$/ppm
H(2ax)	2.20	2.55	+0.35	−0.225	−0.216	+0.01
H(2eq)	1.73	1.73	—	−0.017	−0.162	−0.14
H(4ax)	0.81	1.15	+0.34	−0.21	−0.16	+0.06
H(4eq)	0.94	0.64	−0.3	−0.040	0.069	+0.02
H(5ax)	1.73	1.44	−0.29	−0.141	0.057	+0.2
H(5eq)	2.08	1.94	−0.12	−0.095	0.004	+0.1
H(6ax)	2.33	2.33	—	−0.192	−0.154	+0.04
H(6eq)	2.69	2.61	−0.08	−0.104	−0.131	−0.03

planarization of the nitrogen atom for a branched alkyl group. The MP2 calculated sum of the bond angles around nitrogen increases from 330.7° in the *N*-Me-substituted 1,3-azasilinanes to 332.8° in molecules **1**, **2**, irrespective of the substituents at silicon (vide infra).

The question that we put in the Introduction on how the relative stability of the conformers of various silacyclohexanes is affected by the second heteroatom in β-position to silicon suggests the analysis of the following conformational equilibria.

Unfortunately, the available data are very limited and, for the same substituents at silicon (X=Ph, Y=Me) are confined to Z=CH_2,[18] Z=S,[18] Z=NMe,[15] and Z=*N*-*i*-Pr (this work), in all cases the $Me_{ax}Ph_{eq}$ conformer being predominant. The content of the conformer with the equatorial phenyl group is 63% (Z=CH_2),[18] 68% (Z=S),[18] 67% (Z=NHMe),[15] and 58.5% (Z=*N*-*i*-Pr, this work), which corresponds to free energy differences close to 0.1 kcal/mol. For other pairs of the substituents at silicon (Z=CH_2, X=Me, Y=F;[56,57] Z=CH_2, X=Me, Y=CF_3;[56] Z=S, X=Me, Y=F)[57] the free energy difference is substantially larger. Therefore, the only conclusion to be made is that the conformational equilibrium in silaheterocyclohexanes is determined, first of all, by the nature of the substituents at silicon and that the effect of the presence and the nature of the second heteroatom is negligible in spite of notable variations of the C–Z bond length and the degree of the ring folding for Z=N, C or S in Scheme 4. Moreover, the effect of the substituent at the second heteroatom (cf. Z=NMe and *N*-*i*-Pr) may be even larger than that of this heteroatom itself.



Scheme 4.

In view of the aforementioned role of the Ph-axial conformation in the ligand-receptor interaction[2] the latter effect might play a pivotal role in determining the biological activity of Si, *N*-heterocycles. Since the experimental value of the equilibrium constant in Scheme 4 decreases from 2 to 1.4 on going from Z=*N*-Me to *N*-*i*-Pr, the fraction of the Ph_{ax} conformer may increase upon further planarization of the nitrogen atom, thus providing the synthetic chemists with a guide for the design of new drugs.

2.3. Theoretical calculations

Theoretical calculations proved that compounds **1** and **2** exist as chair conformers with the equatorial NR group. For compound **1**, the NR_{ax} conformers are 3.06 (for **1a**) or 3.36 kcal/mol (for **1b**) higher in energy than the corresponding NR_{eq} conformers, and for compound **2** it is 3.62 kcal/mol at the MP2/6-311G(d,p) level of theory. Therefore, as suggested above, for both compounds the conformational equilibrium $NR_{ax} \rightleftarrows NR_{eq}$ is completely biased to the NR_{eq} conformers. With this, conformers **2a** and **2b** in Scheme 2 are

identical whereas conformers **1a** and **1b** are different in energy. All calculations give the total energy of conformer **1a** to be lower than of **1b**, ΔE being 1.81 (MP2), 0.84 (DFT) and 0.24 kcal/mol (HF). Apparently, this is due to the intramolecular H-bond of one of the *ortho*-protons with the nitrogen atom lying in the plane of the phenyl ring (Fig. 5). Note, that practically the same structure was obtained for the *N*-Me analog of **1a**.[15]

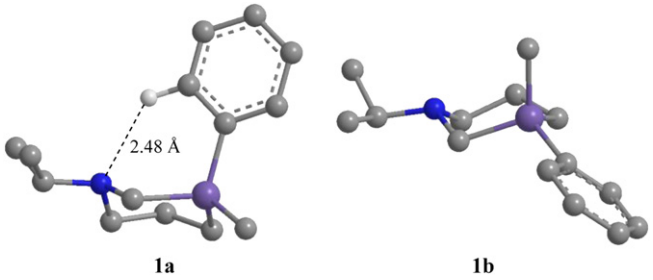


Fig. 5. Orientation of the phenyl ring in the two conformers of 1-isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1**.

However, the ratio of the conformers is determined by the free energy difference ΔG°, which is expected to be different for the two conformers since the H-bonding lowers the entropy and, thus, disfavors conformer **1a**. As a result, the value of ΔG^{o} calculated at the B3LYP/6-311(d,p) level (the corresponding MP2 frequency calculations are computationally too time-consuming) is 0.07 kcal/mol in favor of conformer **1a**, which is in excellent agreement with the experimental value of 0.08 kcal/mol (vide supra). Taking into account solvent effects using the PCM, as was shown on the example of the *N*-Me analog of compound **1**, cannot reverse the ratio of the conformer in favor of the $Me_{ax}Ph_{eq}$ conformer.[15] Neither does taking into account specific solvation by calculation of the solvate complexes of **1a** and **1b** with chloroform. Whereas with conformer **1b** chloroform forms the H-bond of 2.66 Å length with the nitrogen atom, with conformer **1a** it forms the H-bond with the π-system of the axial phenyl ring, the H_{ortho}–N hydrogen bond remains intact being only somewhat elongated to 2.70 Å.

3. Conclusion

1-Isopropyl-3-methyl-3-phenyl-1,3-azasilinane **1** and 1-isopropyl-3,3-dimethyl-1,3-azasilinane **2** were synthesized and studied experimentally by low temperature ^{1}H and ^{13}C NMR spectroscopy down to 103 K, and theoretically at the DFT and MP2 levels of theory. The ratio of the two conformers of **1**, $Ph_{eq}Me_{ax}$/$Ph_{ax}Me_{eq}$ at low temperature of ~60:40 confirms the difference between silaheterocyclohexanes and their carbon analogs, for which the $Ph_{ax}Me_{eq}$ conformers are more stable. The barrier for the ring inversion of compounds **1** and **2** is 8.25 kcal/mol, that is, ~0.8 kcal/mol lower as compared to their *N*-Me-substituted analogs. Such a decrease can be assigned to some planarization of the nitrogen atom surrounding for a branched alkyl group, as proved by theoretical calculations.

4. Experimental section

4.1. Synthesis and NMR study

Reagents were purchased from commercial sources and used without further purification. Solvents were freshly distilled from the appropriate drying agents immediately before use (diethyl ether, sodium benzophenone ketyl; benzene, methylene chloride, methanol, CaH_2). Thin layer chromatography (TLC) was performed on SiO_2-60 F254 aluminum plates (visualization with iodine vapors). Column chromatography was performed using Silica Gel SiO_2-60, 230–400 mesh from ICN. Room-temperature ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded on a Brucker DPX 400 spectrometer (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{29}Si, 79.5 MHz). Chemical shifts (ppm) were determined relative to residual $CHCl_3$ (^{1}H, δ 7.27, $CDCl_3$), internal $CDCl_3$ (^{13}C, δ 77.0, $CDCl_3$), and external TMS (^{29}Si, δ 0.00, $CDCl_3$). The assignment of the ^{1}H and ^{13}C signals was made from the *j*-mod and 2D{^{1}H–^{13}C} NMR spectra at 298 K and 143 K.

Low-temperature ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-600 (at 600 and 150 MHz, respectively). Chemical shifts were determined relative to residual internal CD_2Cl_2 (^{13}C, δ 53.73) and are given in parts per million downfield to TMS. Analysis and assignment of the ^{1}H NMR data were supported by homonuclear (COSY) and heteronuclear (HSQC ^{13}C–^{1}H, HMBC ^{13}C–^{1}H) 2D correlation experiments. A solvent mixture of CD_2Cl_2, $CHFCl_2$, and CHF_2Cl in a ratio of 1:1:3 was used for the low temperature measurements. The probe temperature was calibrated by means of a thermocouple PT 100 inserted into a dummy tube. The low temperature measurements were estimated to be accurate to $\pm$2 K. The chemical shifts difference $\Delta\nu_c$, Hz was determined by extrapolation to the lowest temperature available and used to calculate k_c and the ring inversion barriers by the Eyring equation at T_c.

Methylphenyl(chloromethyl)silane (**3a**) and dimethyl(-chloromethyl)silane (**3b**) were synthesized as described in the literature.[15,58,59]

*4.1.1. (Allyloxy)trimethylsilane (**4**).* (Allyloxy)trimethylsilane (**4**) was prepared by silylation of allyl alcohol with 1,1,3,3-hexamethyldisilazane in 89% yield by the known procedure.[59] δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.15 (9H, s, CH_3Si), 4.15 (2H, d t, ^{3}J=4.9 Hz, ^{4}J=1.6 Hz, OCH_2), 5.11 (1H, d q, ^{3}J=10.3 Hz, ^{4}J=1.5 Hz, H^{cis}), 5.26 (1H, d q ^{3}J=17.1 Hz, ^{4}J=1.8 Hz, H^{tr}), 5.94 (d d t, ^{3}J=17.1 Hz, ^{3}J=10.3 Hz, ^{3}J=5.1 Hz, $1H^{gem}$). δ_C (100 MHz; $CDCl_3$; Me_4Si): −0.47 (CH_3Si), 63.65 (OCH_2), 114.49 (=CH_2), 137.28 (CH=). δ_{Si} (79 MHz; $CDCl_3$; Me_4Si): 18.80.

*4.1.2. Methylphenyl(chloromethyl)(3-trimethylsiloxypropyl)silane (**5a**).* A 0.1 M solution of $H_2PtCl_6{\cdot}6H_2O$ in isopropyl alcohol (0.05 mL) was added to a small portion of the mixture of (allyloxy) trimethylsilane (6.51 g, 0.05 mol) and $MePh(ClCH_2)SiH$ (8.52 g, 0.05 mol) that resulted in an exothermic reaction, the temperature increased to 65 °C. The remaining portion of (allyloxy)trimethylsilane was added at 75 °C, the reaction mixture heated at stirring to 110 °C, allowed to cool and the volatiles removed in vacuo. The crude product (13.07 g, 87%) was used in next stage without purification. δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.11 (9H, s, Me_3SiO), 0.43 (3H, s, $MeSiC$), 0.93 (2H, m, $SiCH_2C$), 1.62 (2H, m, CCH_2C), 2.99 (1H, d, ^{2}J=13.7 Hz, $SiCH^{A}Cl$), 3.04 (1H, d, ^{2}J=13.7 Hz, $SiCH^{B}Cl$), 3.56 (2H, t, ^{3}J=6.9 Hz CH_2O), 7.39 (3H, m, $H_{m,p}$), 7.54 (2H, m, H_o). δ_C (100 MHz; $CDCl_3$; Me_4Si): −6.35 ($SiCH_3$), 8.31 ($MeSiO$), 15.23 ($SiCH_2C$), 26.70 ($SiCH_2Cl$), 29.13 (CCH_2C), 65.35 (CH_2O), 128.04 (C_m), 129.77 (C_p), 133.90 (C_o), 135.01 (C_i). δ_{Si} (79 MHz; $CDCl_3$; Me_4Si): −2.51.

*4.1.3. Dimethyl(chloromethyl)(3-trimethylsiloxypropyl)silane (**5b**).* Dimethyl(chloromethyl)(3-trimethylsiloxypropyl)silane (**5b**) was prepared similar to **5a**. δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.11 (6H, s, Me_2Si), 0.12 (9H, s, Me_3SiO), 0.62 (m, 2H, $SiCH_2C$), 1.56 (2H, m, CCH_2C), 2.79 (2H, s, $SiCH_2Cl$), 3.54 (2H, t, ^{3}J=6.9 Hz, CH_2O).

*4.1.4. Methylphenyl(chloromethyl)(3-hydroxypropyl)silane (**6a**).* A mixture of crude **5a** (13.00 g, 43 mmol), MeOH (15 mL), H_2O (2.5 mL) and 2 drops of conc. HCl was heated at reflux for 0.5 h. Then reaction mixture was taken in H_2O (40 mL) and extracted with diethyl ether (2×15 mL). The organic extract was dried over $MgSO_4$ and concetrated in vacuo. The product was purified by

column chromatography using eluents with increasing polarity from hexane to Et_2O to give the title compound as a colorless oil (6.70 g, 59% yield calculated on the initial hydrosilane). δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.44 (3H, s, *Me*Si), 0.98 (2H, m, SiCH_2C), 1.65 (3H, m, CCH_2C+O*H*), 3.00 (1H, d, ^2J=13.7 Hz, SiCH^ACl), 3.05 (1H, d, ^2J=13.7 Hz, SiCH^BCl), 3.63 (2H, t, ^3J=6.6 Hz, CH_2O), 7.41 (3H, m, $H_{m,p}$), 7.55 (2H, m, H_o). δ_C (100 MHz; $CDCl_3$; Me_4Si): −6.35 (SiCH_3), 8.29 (SiCH_2C), 26.70 (SiCH_2Cl), 29.14 (CCH_2C), 65.37 (CH_2O), 128.04 (C_m), 129.78 (C_p), 133.90 (C_o), 134.99 (C_i). δ_{Si} (79 MHz; $CDCl_3$; Me_4Si): 2.51. Found: C, 57.44; H, 7.67; Si, 12.36; Cl, 15.31%. $C_{11}H_{17}SiOCl$ requires C, 57.74; H, 7.49; Si, 12.28; Cl, 15.50.

*4.1.5. Dimethyl(chloromethyl)(3-hydroxypropyl)silane (**6b**).* Dimethyl(chloromethyl)(3-hydroxypropyl)silane (**6b**) was prepared similar to **6a** in 54% yield. A crude product was chromatographed on silica gel using eluents with increasing polarity from hexane to Et_2O to afford (**6b**) as a colorless oil (2.00 g, 54%) δ_H (400 MHz; $CDCl_3$; Me_4Si): 0.14 (6H, s, Me_2Si), 0.67 (2H, m, SiCH_2C), 1.61 (2H, m, CCH_2C), 1.78 (1H, br s, O*H*), 2.80 (2H, s, SiCH_2Cl), 3.62 (2H, t, ^3J=6.7 Hz, CH_2O). δ_C (100 MHz; $CDCl_3$; Me_4Si): −4.72 (SiCH_3), 9.36 (SiCH_2C), 26.66 (SiCH_2Cl), 30.12 (CCH_2C), 65.36 (CH_2O). δ_{Si} (79 MHz; $CDCl_3$; Me_4Si): 4.23. ^{1}H NMR data are consistent with reported those reported earlier.[59]

*4.1.6. Methylphenyl(chloromethyl)(3-chloropropyl)silane (**7a**).* Methylphenyl(chloromethyl)(3-chloropropyl)silane (**7a**) was prepared by chlorination of the above product **6a** using the described procedure.[60,61] A mixture of **6a** (2.4 g, 10.5 mmol), triphenylphosphine (2.59 g, 11.6 mmol) and CCl_4 (15 mL) was refluxed for 8 h, then cooled to room temperature and *n*-pentane (30 mL) was added. The precipitate formed was filtered off, the filterate concentrated in vacuo, the residue purified by column chromatography on silica gel (63–230 mesh, Gerudan) with *n*-hexane as an eluent. The relevant fractions were combined and the solvent removed under reduced pressure to give the product (1.221 g, 47%) as a colorless oil. ^{1}H and ^{13}C NMR spectra coincide with those reported by us earlier.[15]

*4.1.7. Dimethylphenyl(chloromethyl)(3-chloropropyl)silane (**7b**).* Dimethylphenyl(chloromethyl)(3-chloropropyl)silane (**7b**) was obtained by the above procedure in 32% yield. ^{1}H and ^{13}C NMR spectra coincide with those reported by us earlier.[14]

*4.1.8. 1-I-Propyl-3-methyl-3-phenyl-1,3-azasilinane (**1**).* A mixture of **7a** (1.2 g, 4.9 mmol), *i*-propylamine (1.437 g, 24.3 mmol) and benzene (10 mL) was heated in a sealed tube at 100 °C for 13 h, then the tube was cooled, opened, the precipitate removed by filtration and washed with *n*-pentane. The volatile components of the combined organic phase were removed under reduced pressure. Judged from the ^{1}H NMR spectrum, the residue (1.166 g) was a ~1:1 mixture of the nonreacted starting silane and the target product **1**. The latter was isolated by column chromatography on silica gel using CH_2Cl_2/MeOH (4:1, *v*/*v*) as the eluent. The solvent was removed from combined relevant fractions under reduced pressure to give **1** (0.424 g, 37%) as a colorless oil. ^{1}H and ^{13}C NMR data for **1** are given in Table 1. δ_{Si} (79 MHz; $CDCl_3$; Me_4Si): −11.30. Found: C, 72.44; H, 10.03; N, 5.57; Si, 11.94%. $C_{14}H_{23}NSi$ requires C, 72.04; H, 9.93; N, 6.00; Si, 12.03.

*4.1.9. 1-I-Propyl-3,3-dimethyl-1,3-azasilinane (**2**).* 1-I-propyl-3,3-dimethyl-1,3-azasilinane (**2**) was prepared in a similar manner. The filtrate and wash solutions were combined, the solvents were removed under usual pressure, and the residue was purified by distillation to give **2** in 84% yield as a colorless liquid (2.22 g), bp 105 °C/24 mmHg. ^{1}H and ^{13}C NMR data for **2** are given in Table 1. δ_{Si} (79.5 MHz; $CDCl_3$; Me_4Si): −6.75. Found: C 63.12; H 12.44; Si 16.42; N 7.97%. $C_9H_{21}SiN$ requires C 63.08; H 12.36; Si 16.39; N 8.17%.

4.2. Theoretical calculations

The geometry of the conformers was optimized at the MP2 and DFT (B3LYP) level of theory with the 6-311G(d,p) basis set. No restrictions on the variation of geometric parameters were imposed during the optimization procedure. Vibrational calculations were performed at the B3LYP/6-311G(d,p) level, unscaled ZPE corrections were used. All calculations were performed with the Gaussian 09 computational program.[62]

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Supplementary data

Supplementary data containing additional NMR spectra of compound **1** and **2**, and the results of calculation of various conformers of **1** and **2** may be found in the online version of this article. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.106.

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