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Synthesis, Molecular Structure, Conformational Analysis, and Chemical Properties of Silicon-Containing Derivatives of Quinolizidine

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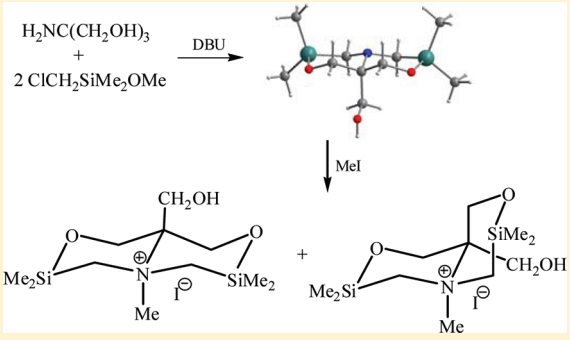
Supporting Information

ABSTRACT: A silicon analog of quinolizidine 3,3,7,7-tetramethylhexahydro-1*H*-[1,4,2]oxazasilino[4,5-*d*][1,4,2]oxazasilin-9a-yl)methanol **3** was synthesized. X-ray diffraction analysis confirmed the *trans* configuration and low temperature NMR spectroscopy both the flexibility (barrier of interconversion 5.8 kcal mol^{-1}) and the conformational equilibrium (chair−chair and chair−twist conformers) of the compound. The relative stability of the different isomers/conformers of **3** was calculated also at the MP2/6-311G(d,p) level of theory. Intra- and intermolecular hydrogen bonding in **3** and the appropriate equilibrium between free and self-associated molecules was studied in solvents of different polarity. Both the N-methyl quaternary ammonium salt and the O-trimethylsilyl derivative of **3** could be obtained and their structure determined.

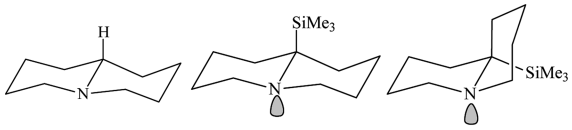


INTRODUCTION

Hundreds of quinolizidine alkaloids of plant origin have been isolated and investigated.[1,2] This wide spreading in nature, the biological activity and the unique structure of quinolizidine derivatives stimulated the elaboration of methods for their synthesis as well as the investigation of their conformational behavior, of their reactivity and potential applications (see, e.g., refs 3−13 and references cited therein).

The bioisosteric replacement of carbon by silicon atoms in organic molecules causes changes in the physiological activity[14,15] such as compounds with the N−C−Si group which display a wide spectrum of biological activity.[16] Actually, in many cases this is directly due to the presence of the silicon atom in α-position to the nitrogen atom which on the other hand strongly affects the stereoelectronic properties of the molecule. For example, the key step of inhibition of the flavin-containing enzyme monoamine oxidase by N-silylmethyl amines is the single electron transfer reaction between the amine and the flavin fragment of the enzyme favored by a low ionization potential (IP) of the nitrogen atom in the silicon-containing amine.[17−20] The same property (low IP) is responsible for the strong inhibitory effect in the Cu(2+)-induced oxidation of human LDL cholesterol by N-silylmethylated aromatic amines[21,22] (comparable with well-known antioxidants as are vitamin E and probucol).

The IP of unsubstituted quinolizidine is 8.3 eV. Introduction of a trimethylsilyl group to the bridge carbon atom (in α-position to nitrogen) results in the appearance of two bands in the photoelectron spectrum of 9a-(trimethylsilyl)octahydro-2*H*-quinolizidine at 7.3 and 7.5 eV, subject to the ionization potential of the nitrogen lone pair in *cis* and *trans* forms.[23]



Endocyclic silicon atoms should also affect the stereoelectronic properties of the molecule and, as a consequence, both reactivity and biological activity of the corresponding quinolizidine derivative.

Therefore, in view of the lack of the corresponding data for the silicon analogs of quinolizidine and due to the potential interest to employ these derivatives as objects for biological and structural investigations, the aim of the present study was to elaborate an expedient approach to the synthesis of compounds possessing the endocyclic N−C−Si moiety and to investigate their structure and reactivity.

RESULTS AND DISCUSSION

Synthesis. In spite of numerous methods for the synthesis of quinolizidine derivatives, none of them can be used for the synthesis of the N−C−Si analogs of quinolizidine because of

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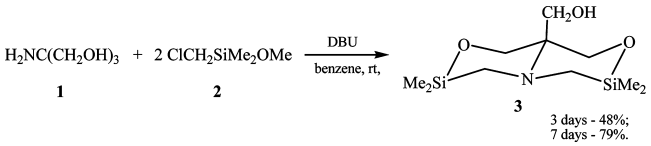
the high lability of the Si−C bond in the N−C−Si fragment. We found out that the reaction of tris(hydroxymethyl)aminomethane **1** with (chloromethyl)(methoxy)dimethylsilane **2** for several days under mild conditions in the presence of DBU resulted in the formation of (3,3,7,7-tetramethylhexahydro-1*H*-[1,4,2]oxazasilino[4,5-*d*][1,4,2]oxazasilin-9a-yl)methanol **3** in up to 80% yield (Scheme 1).

Scheme 1. Synthesis of (3,3,7,7-Tetramethylhexahydro-1*H*-[1,4,2]oxazasilino[4,5-*d*][1,4,2]oxazasilin-9a-yl)methanol 3



1 2 3

The reaction proceeds heterogeneously because both educt **1** and DBU hydrochloride are insoluble in benzene. To promote the reaction by heating in order to reduce reaction time and to increase the yield led only to the formation of a number of unidentified products and lower yields of **3** down to ~30%. In the presence of weaker bases like pyridine and triethylamine, tris(hydroxymethyl)aminomethane **1** does not react with silane **2** at all.

We expected that the reaction of **1** with chloro(chloromethyl)dimethylsilane **4** instead of **2** in the presence of DBU to be preferable. However, the side reaction of **4** with DBU in the solution proceeded much faster than the heterogeneous reaction of **2** with the suspended **1** and, apparently, the yield of **3** did not exceed 15%.

Dynamic NMR Study. The room temperature ^{1}H NMR spectrum of the silaquinolizidine derivate **3** in $CDCl_3$ shows two singlets of the SiMe protons at δ 0.17 and 0.26 ppm, two AB doublets of NCH_2Si protons at δ 2.07 and 2.31 ppm (^2J 14.6 Hz), two AB doublets of the endocyclic OCH_2 protons at δ 3.55 and 3.72 ppm (^2J 11.8 Hz), and a singlet of the exocyclic CH_2O protons at 3.91 ppm. The spectrum in DMSO-d_6 shows also the triplet of the intermolecularely bridged OH proton at 4.55 ppm (^3J 4.8 Hz) (Figure S1 in the Supporting Information).

The notably smaller value of the geminal coupling constant for the OCH_2 relative to NCH_2 protons is due to the larger electronegativity of the oxygen atom additionally increased by delocalization of its lone pair electrons to silicon. As result, the value of $^2J_{HH}(OCH_2)$ with negative sign becomes more positive and hereby smaller in absolute value. Although we failed to find such a comparison for OCH_2 and NCH_2 groups, the similar variations were observed for $^2J_{H,H}$ (X−CH_2) with X = O and S.[24]

Heating of the DMSO-d_6 solution of **3** to 100 °C does not change the pattern of NMR signals, so, the observed nonequivalence of the SiMe groups and the methylene protons of the NCH_2Si and the endocyclic CH_2O groups cannot be a result of a frozen dynamic equilibrium. Since in 2,2,4-trimethyl-1,4,2-oxazasilinane, which can be considered as a monocyclic analog of **3**, the $SiMe_2$ and NCH_2Si groups resonate as singlets, the nonequivalence in the fused system **3** ought to be due to cis and trans location of the corresponding protons with respect to the exocyclic CH_2OH group, anisochronous positions which cannot be averaged even if the ring inversion is fast on the NMR time scale.

With lowering the temperature down to 103 K, all proton signals broaden more or less. Also temperature shifts to higher field of different extend were observed. However, only the SiMe signals decoalesce to several overlapping signals (Figure 1).

The ^{13}C NMR spectrum of **3** in DMSO-d_6 contains two signals of the $SiMe_2$ carbon atoms at δ −2.3 and −1.5 ppm, the NCSi signal at δ 46.7 ppm and signals for CH_2OH at δ 52.0 ppm, for the quaternary bridge carbon at 60.0 ppm and for the endocyclic OCH_2 carbon at 64.9 ppm. As in the ^{1}H NMR spectra, also the carbon signals suffer upfield shifts with lowering the temperature, being especially pronounced for the CH_2OH

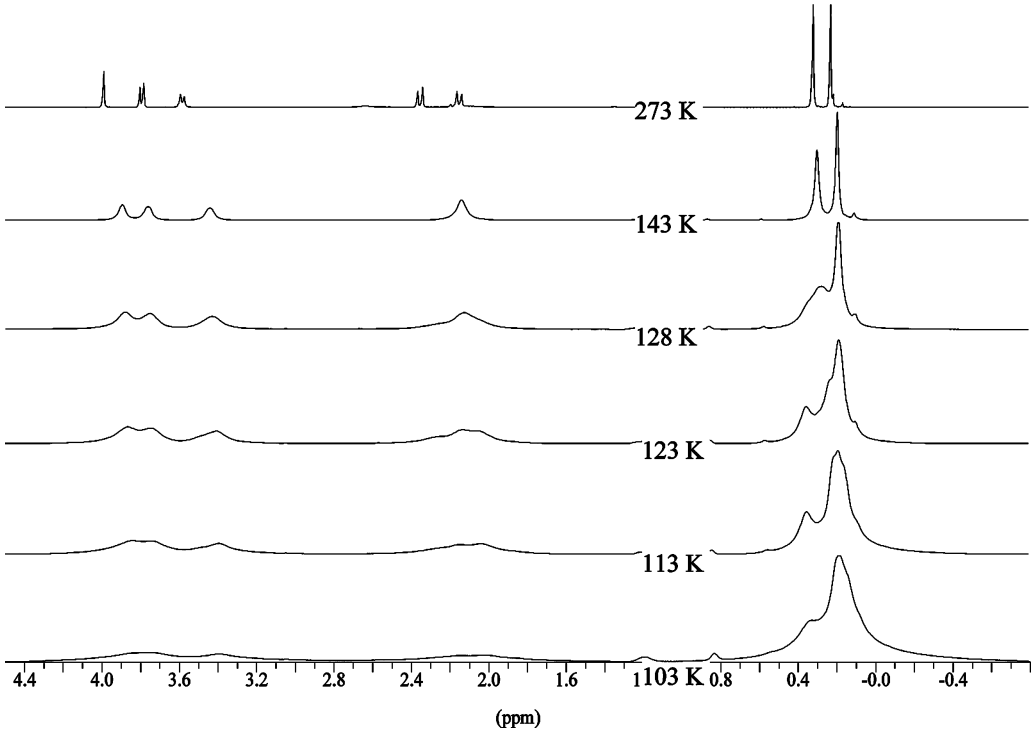


Figure 1. Low-temperature ^{1}H NMR spectra of compound **3**.

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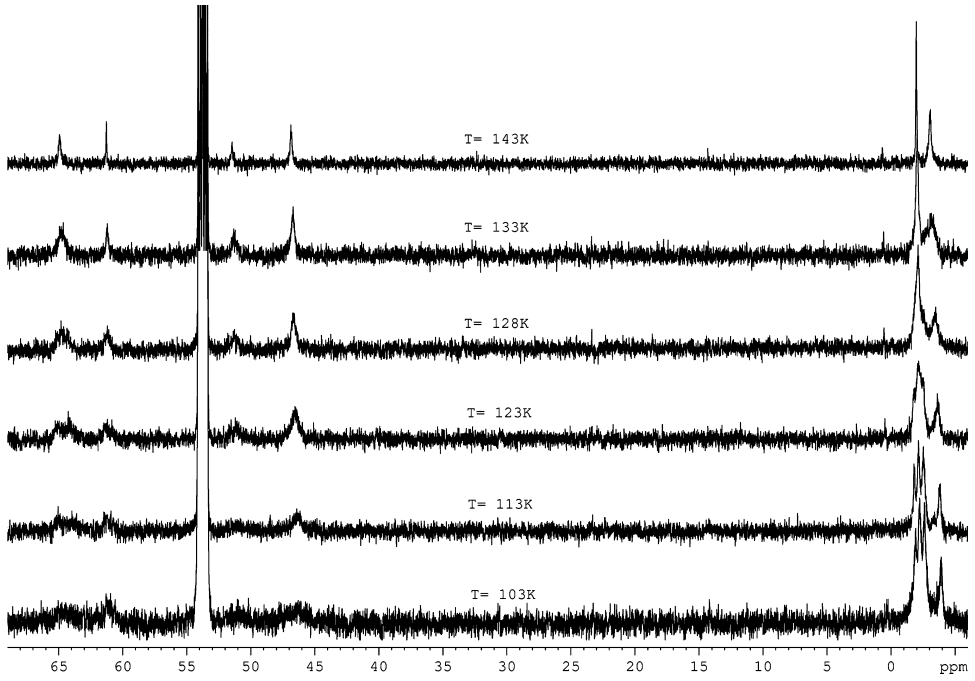


Figure 2. Low-temperature ^{13}C NMR spectra of compound **3**.

signal ($\Delta\delta$ ca. 5.5 ppm). The decoalescence of the $SiMe_2$ carbon signals, as in ^1H NMR spectra just aforementioned, is even more distinct (Figures 2, 3); at 128 K the splitting of the high field SiMe signal can be seen (Figure 3) and at 123 K the splitting of both the OCH_2 and the low field SiMe signals (Figures 2 and 3). From the decoalescence of the SiMe protons and carbon atoms the barrier to interconversion $\Delta G^{\ddagger}$ of **3** was calculated to be 5.8 kcal mol^{-1} (cf. Table 1).

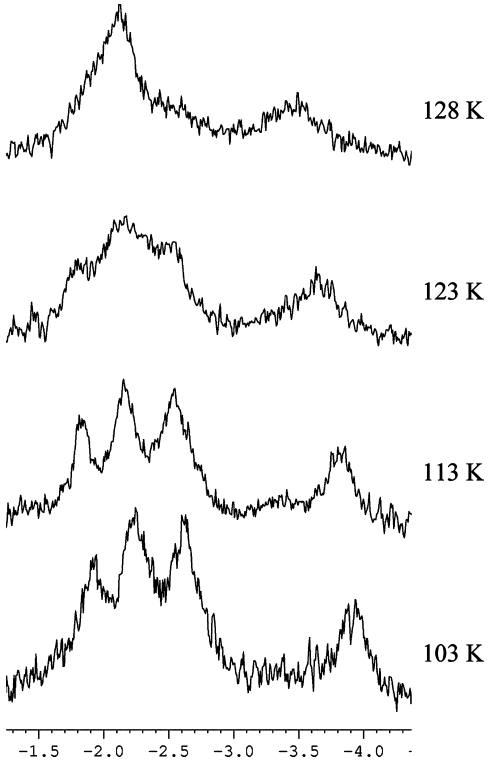


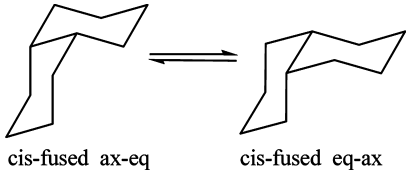
Figure 3. SiMe part of the low-temperature ^{13}C NMR spectra of compound **3**.

Table 1. Dynamic NMR Parameters and Activation Barrier of (3,3,7,7-Tetramethylhexahydro-1*H*-[1,4,2]oxazasilino[4,5-*d*][1,4,2]oxazasilin-9a-yl)methanol 3

signal	T_c, K	$\Delta\nu_c$, Hz	k_c	$\Delta G^{\ddagger}$, kcal mol^{-1}
^1H SiMe (low field)	123	75	167	5.7
^{13}C SiMe (high field)	130	193	429	5.8
^{13}C SiMe (low field)	125	50	111	5.9
Mean				5.8

X-Ray Analysis. The observed dynamic behavior of **3** asks for the configuration/conformation of this silaquinolizidine derivate. The two six-membered rings in the decalin bicyclic system can be fused in *cis* or *trans* mode. In the *cis* isomer, the bonds at the bridgehead atoms are differently oriented (one axial, one equatorial) making ring inversion possible (Scheme 2).

Scheme 2. Conformationally Flexible *cis*-Fused Bicyclic System



The framework of the *trans* isomer is locked. It can invert into chair−boat or even boat−boat conformers, which are of considerably higher energy, but not into the alternative chair−chair system which is geometrically impossible (two axial positions on opposite sides of the chair conformer with four connecting methylene groups (Scheme 3).

However, the situation changes in N-fused azabicyclic analogs like quinolizidine; N-inversion as another dynamic process

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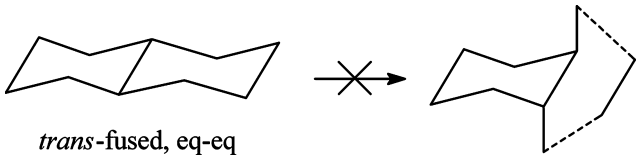
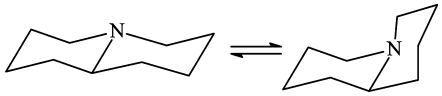
Scheme 3. Conformationally Rigid *trans*-Fused Bicyclic System



gets possible and, hereby also *cis/trans* isomers can interconvert (Scheme 4).[4]

Scheme 4. *Cis*−*trans* Isomerization of Quinolizidine



Therefore, the occurrence of dynamic behavior of compound **3** does not necessarily imply the *cis*-structure and, actually, the refined crystal structure of a single crystal of **3** revealed the *trans*-fused configuration of **3** with C_s symmetry and the N−C−C−O−H fragment lying in the plane of symmetry (Figure 4).

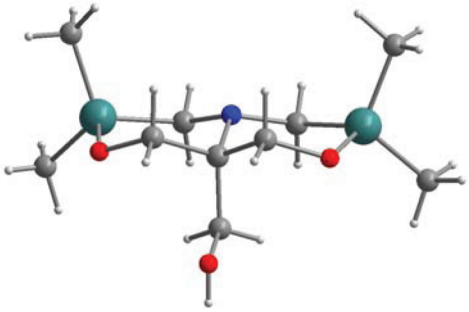
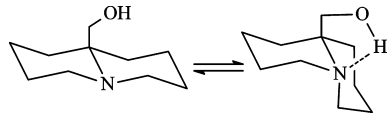


Figure 4. Single crystal X-ray structure of compound **3**.

The two rings adopt a slightly distorted *chair* conformation. The nitrogen pyramid is only slightly flattened with the sum of the CNC bond angles being 336.6°. The crystal packing is stabilized by intermolecular O−H···N bonds of 2.056 Å length (for details see Supporting Information). No reduced intramolecular contacts O−H···N or O−H···O were found, although the formation of the five- or six-membered ring closed by an intramolecular hydrogen bond O−H···N or O−H···O seem to stabilize the molecule. This result is consistent with the generally accepted higher stability of the *trans*-fused bicyclic systems[25] but it refers to the solid state only. And because, as aforementioned, extremely strong chemical shift changes of both endo- and exocyclic CH_2 groups in proton NMR spectra were observed, a solution IR study of the hydroxy groups in **3** was performed in order to check the possibility of formation of intra/intermolecular hydrogen bonding in the quinolizidine derivative **3**.

IR Spectroscopy. The IR spectrum of 9a-hydroxymethylquinolizidine, which is the carbon analog of compound **3**, in carbon tetrachloride, contains a wide ν(OH) absorption band at 3400 cm^{-1} belonging to the O−H···N hydrogen-bonded form, and a narrow band of the free hydroxy group at 3600 cm^{-1}.[26] This was interpreted as an indication of the existence of the conformational equilibrium between the *trans* and *cis*-conformers, the latter being stabilized by the intramolecular hydrogen bond.



Lupinine, another quinolizidine alkaloid [octahydro-1H-quinolizin-1-yl)methanol], containing the CH_2OH group in 5-position of the ring exists (in CCl_4 solution and concentrations up to 2.5×10^{-3} mol L^{-1}) also as an equilibrium mixture of two conformers,[27] one of them with a free OH group, in the other one with an intramolecular hydrogen bond O−H···N.

The IR spectroscopy study of **3** revealed principal differences to its carbon analogs. Even in dilute solutions of nonpolar carbon tetrachloride ($c = 10^{-3}$−10^{-6} mol L^{-1}), **3** exists as self-associate formed by intermolecular O−H···N hydrogen bonding characterized by a wide ν(OH) absorption band at 3300 cm^{-1}. Both shape and position are close to those in the spectrum of the solid sample (3260 cm^{-1}) and allow to rule out the formation of an intramolecular hydrogen bond. The absence of intramolecular H-bonds is also confirmed by the ^{15}N spectroscopy data of the O-silylated derivative of **3** (vide infra). Generally, no absorption band of free OH groups is observed suggesting very strong intermolecular hydrogen bonding between the molecules.

Free molecules of compound **3** (in equilibrium with their self-associates) exist in more polar dichloromethane at concentrations of 10^{-2}−10^{-3} mol L^{-1}. The IR spectra are characterized by two bands − a narrow one at 3610 cm^{-1} belonging to ν(OH) vibrations of the free OH groups, and a wide band at 3450 cm^{-1} with the shoulder at 3300 cm^{-1} due to vibrations of the associated OH groups forming the intermolecular hydrogen bonds O−H···O(Si) and O−H···N, respectively. Upon dilution, the intensity of the latter band with the shoulder drastically decreases supporting hereby its intermolecular nature. The difference between the ν(OH) frequencies of the free and associated hydroxy groups $\Delta\nu$(OH), which characterizes the strength of the formed hydrogen bonds amounts to 160 and 310 cm^{-1}, respectively. We have measured $\Delta\nu$(OH) upon the formation of the H-bond between methanol and trimethylmethoxysilane in the CH_2Cl_2 solution to be 165 cm^{-1}. From the vibration frequency of the free hydroxyl group in the IR spectrum of simple alcohols in CCl_4, which is equal to ∼3640 cm^{-1},[27,28] we calculated the value of $\Delta\nu$(OH) for the self-associate of compound **3** in this solvent to be ∼340 cm^{-1}.

The decrease of the strength of the intermolecular hydrogen bond in dichloromethylene solution of **3** is consistent with the behavior of a large series of intermolecularly hydrogen-bonded complexes of nitrogen bases with alcohols and is due to the increase of the polarity/polarizability of these solvents.[29]

The N-methyl iodide salt of **3** (salt **5**, vide infra), in the solid state, exists predominantly in the conformation with the intramolecular hydrogen bond O−H···OSi; the IR spectrum gives a narrow intense band ν(OH) at 3323 cm^{-1}.

In CH_2Cl_2 solution an equilibrium between intra- and intermolecular associates with the O−H···O(Si) hydrogen bonds is observed. The ν(OH) band in the spectrum of this solution is a doublet with a narrow high-frequency component at 3317 cm^{-1} and a wider low-frequency component at 3271 cm^{-1} corresponding to the intra- and intermolecularly H-bonded forms. The intensity of the low-frequency band decreases with dilution. The shift of the two maxima of this doublet band with respect to the free OH group of compound **3** in the same

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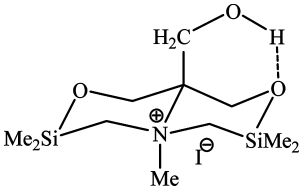
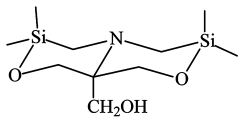


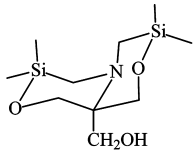
solvent is 293 and 339 cm^{-1}, respectively, which is much larger than the value of $\Delta\nu$(OH) in self-associates of **3** suggesting a substantial strengthening of the O–H···O(Si) bonds in the N-methyl iodide salt **5**.

This widespread intermolecular hydrogen bonding in **3** explains the large temperature coefficients of CH_2 proton chemical shifts in the variable temperature ^1H NMR spectra.

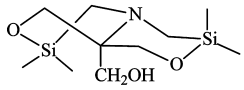
Theoretical Calculations. To gain a better understanding of the conformational behavior of compound **3**, in particular to answer the question if the solid-state *trans*-fused conformation could have been transformed into the *cis*-fused conformation by N-inversion, we calculated the *trans* (**3a**) and the *cis* isomer **3b**, the chair–twist **3c** and the twist–twist conformer **3d** of the *trans* isomer at the MP2/6-311G(d,p) level of theory.



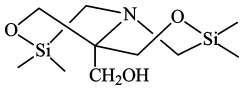
3a, 0 kcal/mol



3b, 2.46 kcal/mol



3c, 0.44 kcal/mol



3d

Conformer **3d** does not correspond to a minimum on the potential energy surface and upon optimization is transformed into the chair–twist conformer **3c**. Interestingly, the latter, in spite of the general rule of a higher stability of the chair vs twist conformation, is 2.02 kcal mol^{-1} more stable than **3b**. Therefore, **3c** proves to be the second stable conformer lying only 0.44 kcal mol^{-1} higher in energy than the most stable *trans*-isomer/conformer **3a**.

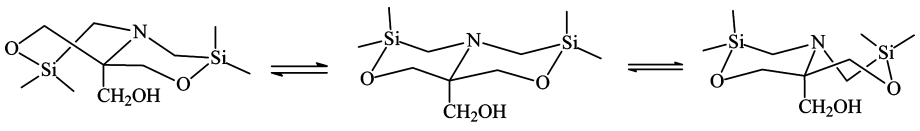
For quinolizidine itself, the MP2/6-31G(d) calculations give 4.1 kcal mol^{-1} energy difference between the *trans*- and *cis*-fused isomers/conformers[25] which is in good compliance with previous results.[4] For the 9a-R-substituted quinolizidines, the equilibrium constant for the *trans* ⇆ *cis* equilibrium sharply decreases with the decrease of the conformational energy of the substituent, being equal to 1.5, <0.05, 0.0 kcal mol^{-1} for R = Me_3Si, Me_3Ge, Me_3Sn, respectively.[23] Since the conformational energy of the CH_2OH group is in between those for Me_3Ge and Me_3Sn,[23,30] the equilibrium for compound **3** must be fully shifted to the *trans* conformer. Indeed, the calculated energy difference between the *cis* and *trans* isomers of ca. 2.5 kcal mol^{-1} suggests the presence of only one conformer in the mixture and is consistent with the presence of only one set of signals in the NMR spectra down to 143 K. The existence of one set of signals cannot be due to fast nitrogen inversion since the corresponding barriers in quinolizidine conformers are rather high[25] (vide infra).

We have also optimized the structure of conformation **3d** at the HF/6-311G(d,p) level, searching not for a minimum but for a transition state. Indeed, the transition state stationary point was found, for which the frequency analysis showed it to be a true first-order saddle point with the imaginary frequency of 183*i* cm^{-1}. One six-membered ring in the transition state has a 3,9a-twist conformation, whereas the other one has a slightly distorted sofa conformation with the C-9 atom deviating from the least-squares plane defined by the other five atoms (the C–N–C–Si–O fragment is close to planar). The single point energy calculations performed at MP2/6-311G(d,p)//HF/6-311G(d,p) level of theory predict the transition state to lie 10.6 kcal mol^{-1} higher in energy relative to the chair–twist-conformer **3c** (cf. with the barriers to ring inversion/nitrogen inversion in quinolizidine of 15 − 18 kcal mol^{-1}).[25] The vibration mode analysis has shown that this transition state connects the conformer having the 2,5-boat and 6,9-boat conformations of the two rings and the conformer with one ring adopting the 3,9a-boat conformation and the other one being close to chair.

Unfortunately, we failed to localize a first order saddle point corresponding to a transition state connecting the **3a** and **3c** conformers. However, the barriers connecting the chair and twist conformers of silathiacyclohexanes or silathiacyclohexanes were found to be ∼5.5 kcal mol^{-1},[31,32] which is very close to the measured value of 5.8 kcal/mol for compound **3**, and only slightly depending on the presence and position of the second heteroatom in heterosilacyclohexanes. Small energy difference of 0.44 kcal/mol between the conformers **3a** and **3c** (especially taking into account the presence of two equivalent conformations **3c** relative to one conformation **3a**) is in agreement with a comparable ratio of the interconverting species (Figures 1–3). All this suggests that the observed low-temperature dynamic behavior of compound **3** refers to the following equilibrium (Scheme 5) with about the same population of *trans*-chair–chair **3a** and *trans*-chair–twist conformers **3c,c′**.

N-Alkylation and O-Silylation of 3. Quaternization of the nitrogen stops the N-inversion, the isomeric quaternary ammonium salts do not undergo interconversion.[33] The 9a-R-substituted quinolizidines react with methyl iodide to give a mixture of the *trans* and *cis* isomers of the corresponding salts with the ratio depending on the steric effect of substituent R. For the free base, the 1,3-diaxial interactions between R and the ring hydrogen atoms destabilize the *trans* conformer and its content decreases in the order: H > CN > CH_3 > CH_2OH > CH_2NO_2.[33] As a result, the content of the *cis* isomer of the salt increases in the same order.

Scheme 5. Conformational Equilibrium of (3,3,7,7-Tetramethylhexahydro-1*H*-[1,4,2]oxazasilino[4,5-*d*][1,4,2]oxazasilin-9a-yl)methanol 3



3c **3a** **3c'**

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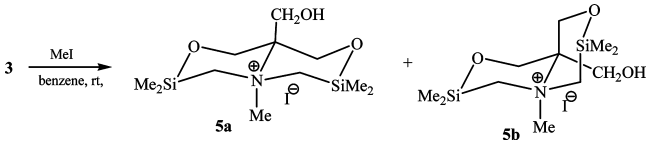
We have found that compound **3** reacts with methyl iodide to give the corresponding ammonium salt **5** under mild conditions in close to quantitative yield (Scheme 6).

Scheme 6. Quaternization of Compound 3 in Benzene at Room Temperature



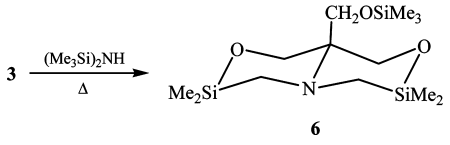
According to the multinuclear NMR spectroscopy data, the quaternization gives rise to the formation of almost equimolar mixture of the *trans* (**5a**) and *cis*-fused (**5b**) salts (**5a**:**5b** = 1:1.2). This ratio is substantially different from the ratio of 1:5 for 9a-hydroxymethylquinolizidine iodomethylate (carbon analog of compound **3**).[33] For the latter salt, the 1,3-diaxial interactions between the NMe and two SiMe groups in the *trans*-fused isomer cause its destabilization with respect to the *cis*-fused isomer, in which there is only one such interaction.[33] For compound **3**, 1,3-diaxial interactions are much less important due to the longer Si−C bonds compared to C−C bonds. As a result, the ratio **5a**:**5b** is much closer to unity than that of its carbon analog.

The proton signals of the isomers **5a** and **5b** were assigned based on the fact that the NMe protons of the *trans*-isomer carbon analog of **5a** resonate at a lower field[33] and taking into account the intensity of the signals. The carbon signals lying in a narrow range of 51−62 ppm were assigned using the 2D $^{1}H-^{13}C$ HMBC spectrum (see Supporting Information).

The resonances of the equatorial methylene protons are slightly broadened due to long-range coupling as compared to the axial protons. Quaternization of the nitrogen atom results in deshielding of the NCH_2 and OCH_2 protons (0.8−1.0 ppm), NCH_2 and C-9a carbons (10−12 ppm) and the nitrogen atom (28 ppm), and shielding of the SiMe (1−2.6 ppm) and OCH_2 carbons (4−6 ppm).

Heating of compound **3** with hexamethyldisilazane gives 3,3,7,7-tetramethyl-9a-((trimethylsilyloxy)methyl)-hexahydro-1*H*-[1,4,2]oxazasilino[4,5-d][1,4,2]oxazasiline **6** (Scheme 7).

Scheme 7. O-Silylation of Compound 3 with Hexamethyldisilazane



The ^{15}N chemical shift of ether **6** (−343.8 ppm) is very close to that of its precursor **3** (−344.6 ppm). This is an independent evidence for the absence of an intramolecular hydrogen bond in molecule **3** (vide supra) since the hydrogen bond formation as well as the protonation of amines results in a downfield shift of the ^{15}N signal.[34,35]

CONCLUSIONS

(3,3,7,7-Tetramethylhexahydro-1*H*-[1,4,2]oxazasilino[4,5-*d*]-[1,4,2]oxazasilin-9a-yl)methanol **3**, its N-methyl iodide **5** and O-trimethylsilyl ether **6**, which are quinolizidine derivatives with an endocyclic silicon atom, have been synthesized. Both the structural and dynamic properties have been studied. Compound **3** exists as *trans* isomer both in solution (NMR) and in the solid state (X-ray). As distinct from its carbon analog, compound **3** does not form an intramolecular hydrogen bond between the CH_2OH group and the nitrogen atom, but only self-associates with very strong intermolecular hydrogen bonding. At very low temperatures (<130 K) the compound displays dynamic behavior with the barrier of interconversion of 5.8 kcal/mol. Quantum chemical calculations at the MP2/6-311G(d,p) level allow to assign the observed dynamic behavior to the equilibrium between the chair−chair- and chair−twist-conformers of the *trans*-isomer of **3**. Alkylation of **3** with methyl iodide gives two isomers of salt **5** at the ratio close to unity. Silylation of **3** with hexamethyldisilazane gives the O-trimethylsilyl derivative **6**, for which the ^{15}N chemical shift almost coincides with that of **3**, thus corroborating the absence of intramolecular hydrogen bonding in the latter.

EXPERIMENTAL SECTION

General. The FT-IR spectra were taken in KBr pellets and CCl_4 or CH_2Cl_2 solution. The ^{1}H, ^{13}C, ^{15}N and ^{29}Si NMR spectra were registered for 10−20% solutions on a 400 MHz instrument at 400.1, 100.6, 40.5, and 79.5 MHz, respectively. Chemical shifts are given relative to TMS (^{1}H, ^{13}C, ^{29}Si) or $MeNO_2$ (^{15}N). ^{15}N NMR chemical shifts were obtained from HMBC spectra recorded by the use of a gradient probe working in the *hmbcgp* mode optimized to the long-range coupling constant J_{NH} of 9 Hz. All solvents were purified and dried according to standard procedures.[36]

Synthesis of (3,3,7,7-Tetramethylhexahydro-1*H*-[1,4,2]-axazasilino[4,5-d][1,4,2]oxazasilin-9a-yl)-methanol 3. To the suspension of 1.21 g (0.01 mol) of tris(oxymethyl)aminomethane **1** in 150 mL of dry benzene 3.04 g (0.04 mol) of DBU was added and then slowly upon stirring the solution of 2.72 g (0.02 mol) of chloromethyldimethyl(methoxy)silane **2** was added dropwise. The reaction mixture was stirred at room temperature for a week, then the solution was decanted from DBU hydrochloride, the residue washed with benzene (2 × 25 mL), the extract combined with the main solution, benzene removed on a rotary evaporator, the solid residue crystallized from heptane to give 2.05 g (79%) of compound **3**, m.p. 168−170 °C. IR, ν(KBr), cm^{-1}: 3260 br, m, 2965 m, 2896 m, 2866 m, 1255 s, 1108 m, 1053 s, 981 m, 881 s, 843 s, 779 m, 758 m. ^{1}H NMR ($CDCl_3$), δ, ppm: 0.17 s (6H, SiMe), 0.26 s (6H, SiMe), 2.07 d (2H, $SiCH^{A}N$, J 14.6 Hz), 2.08 s (1H, OH), 2.31 d (2H, $SiCH^{B}N$, J 14.6 Hz), 3.55 d (2H, $OCH^{A}C$, J 11.8 Hz), 3.72 d (2H, $OCH^{B}C$, J 11.8 Hz), 3.91 s (2H, CH_2OH). ^{13}C NMR ($CDCl_3$), δ_C, ppm: −1.9, −1.6 (SiMe), 46.8 (SiCN), 57.5 (CH_2OH), 60.3 (NCC), 66.1 (OCC). The signals were assigned based on the HMQC experiment. ^{15}N NMR (CD_3CN), δ_N, ppm: −344.6. ^{29}Si NMR ($CDCl_3$), δ_{Si}, ppm: 12.53. Found: H 8.43; C 45.59; N 5.41. $C_{10}H_{23}NO_3Si_2$. Calcd: H 8.87; C 45.94; N 5.36.

Synthesis of 9a-(Hydroxymethyl)-3,3,5,7,7-pentamethylhexahydro-1*H*-[1,4,2]oxazasilino[3,4-*c*][1,4,2]oxazasilin-5-ium iodide 5. To the solution of 0.52 g (2 mmol) of compound **3** in 25 mL of dry benzene 0.28 g (2 mmol) of methyl iodide was added, the solution kept for a day at room temperature, the precipitate formed filtered off, washed with ether and dried in vacuum. Yield 0.78 g (97%), mp 124−127 °C. Found: H 6.39; C 32.41; N 3.29. $C_{11}H_{26}INO_3Si_2$. Calcd: H 6.50; C 32.75; N 3.47.

trans-Isomer ***5a***. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.28 s (3H, MeSi), 0.42 s (3H, MeSi), 3.28 d (2H, NCH_{ax}, ^{2}J 15.4 Hz), 3.34 d (2H, NCH_{eq}, ^{2}J 15.4 Hz), 3.45 s (3H, NMe), 4.04 d (2H, CH_2OH, ^{3}J 4.1 Hz), 3.83 d (2H, OCH_{eq}, ^{2}J 13.9 Hz), 4.01 d (2H, OCH_{ax}, ^{2}J 13.9 Hz), 5.77 br. t (1H, OH, ^{3}J 4.1 Hz). ^{13}C NMR (DMSO-d_6), δ_C, ppm: −0.7 (SiMe), 0.6 (SiMe), 50.8 (NMe), 58.8 ($C_{4(6)}$); 55.1 (CH_2OH); 58.5($C_{1(9)}$); 72.5(C_{9a}). ^{15}N NMR (DMSO-d_6), δ_N, ppm: −318.1. ^{29}Si NMR (DMSO-d_6), δ_{Si}, ppm: 10.78 ppm.

cis-Isomer ***5b***. ^{1}H NMR (DMSO-d_6), δ, ppm: 0.37 s (3H, MeSi), 0.40 s (3H, MeSi), 3.20 d (2H, NCH_{eq}, ^{2}J 15.4 Hz), 3.42 d (2H,

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NCH_{ax}, ^2J 15.4 Hz), 3.36 s (3H, NMe), 3.93 d (2H, CH_2OH, ^3J 4.1 Hz), 4.19 d (2H, OCH_{eq}, ^2J 14.2 Hz), 4.35 d (2H, OCH_{ax}, ^2J 14.2 Hz), 5.58 br. t (1H, OH, ^3J 4.1 Hz). ^{13}C NMR (DMSO-d_6), δ_C, ppm: −0.2 (SiMe), −0.1 (SiMe), 54.9 (NMe), 56.6 ($C_{4(6)}$); 58.7 (CH_2OH); 61.9 ($C_{1(9)}$); 72.3 (C_{9a}). ^{15}N NMR (DMSO-d_6), δ_N, ppm: −317.2. ^{29}Si NMR (DMSO-d_6), δ_{Si}, ppm: 11.49 ppm.

Synthesis of 3,3,7,7-Tetramethyl-9a-((trimethylsilyloxy)-methyl)-hexahydro-1H-[1,4,2]oxazasilino-[4,5-d][1,4,2]-oxazasiline 6. Compound **3** (0.52 g (2 mmol)) in 1 mL of hexamethyldisilazane was refluxed under argon for 10 h (until evolution of ammonia ceased). The mixture was cooled, excess of hexamethyldisilazane evacuated to obtain viscous oil, which was slowly crystallized. Compound **6** was purified by sublimation, 190−200 °C/8 mmHg, yield 0.53 g (80%), mp 51−53 °C. ^1H NMR (CD_3CN), δ, ppm: 0.09 s (9H, $SiMe_3$), 0.11 s (6H, MeSi), 0.18 s (6H, MeSi), 1.94 d (2H, $SiCH^AN$, J 14.7 Hz), 2.23 d (2H, $SiCH^BN$, J 14.7 Hz), 3.30 d (2H, OCH^AC, J 11.7 Hz), 3.63 d (2H, OCH^BC, J 11.7 Hz), 3.86 s (2H, CH_2OSiMe_3). ^{13}C NMR (CD_3CN), δ_C, ppm: −2.5 (SiMe), −1.6 (SiMe), −0.4($SiMe_3$), 47.9 (SiCN), 54.7 (CH_2OH), 61.4 (NCC), 66.1 (OCC). ^{15}N NMR (CD_3CN), δ_N, ppm: −343.8. ^{29}Si NMR (CD_3CN), δ_{Si}, ppm: 12.10 (Me_2Si), 18.19 (Me_3Si). Found: H 9.52; C 47.09; N 4.11. $C_{13}H_{31}NO_3Si_3$. Calcd: H 9.37; C 46.80; N 4.20.

Low-temperature NMR Measurements. The low temperature ^1H and ^{13}C NMR spectra were recorded at 600 and 150 MHz. Chemical shifts were determined relative to residual $CHCl_3$ (^1H, δ 7.3), internal $CDCl_3$ (^{13}C, δ 77.0), internal CD_2Cl_2 (^{13}C, δ 53.7) and are given in ppm downfield to TMS (for ^1H, ^{13}C). 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 ±2 K. The chemical shifts difference $\Delta\nu_c$, Hz, at T_c was determined by extrapolation of the chemical shift differences from the lowest temperature available to T_c and used to calculate $k_c = \pi\ \Delta\nu_c/\sqrt{2}$ and the ring inversion barriers by the Eyring equation at T_c.

■ ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C, HMQC and HMBC NMR spectra of **3** in DMSO-d_6, ^1H, ^{13}C, COSY and HMBC 2D NMR spectra of salts **5a**, **5b**, ^1H and ^{13}C NMR spectra of **6**, IR spectra of **3** and **5**, X-ray data files and the results of the MP2 calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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