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N,N-Bis-(dimethylfluorosilylmethyl)amides of *N*-organosulfonylproline and sarcosine: synthesis, structure, stereodynamic behaviour and *in silico* studies†

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(O→Si)-Chelate difluorides R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂F)₂ (**9a–c**, R₁R₂ = (CH₂)₃, R₃ = Ms (a), Ts (b); R₁ = H, R₂ = Me, R₃ = Ms (c)), containing one penta- and one tetracoordinate silicon atoms were synthesized by silylmethylation of amides R₃R₂NCH(R₁)C(O)NH₂, subsequent hydrolysis of unstable intermediates R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂Cl)₂ (**7a–c**) into 4-acyl-2,6-disilamorpholines R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂O)₂ (**8a–c**) and the reaction of the latter compounds with BF₃·Et₂O. The structures of disilamorpholines **8a,c** and difluoride **9a** were confirmed by an X-ray diffraction study. According to the IR and NMR data, the O→Si coordination in solutions of these compounds was weaker than that in the solid state due to effective solvation of the Si–F bond. A permutational isomerisation involving an exchange of equatorial Me groups at the pentacoordinate Si atom in complexes **9a–c** was detected, and its activation parameters were determined by ¹H DNMR. *In silico* estimation of possible pharmacological effects and acute rat toxicity by PASS Online and GUSAR Online services showed a potential for their further pharmacological study.

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Introduction

Hypercoordinate silicon compounds are the focus of intense research due to the diversity of their structures, chemical properties,¹ stereodynamic behaviour² and practical use in stereoselective synthesis³ and medical diagnostics.⁴ In recent years a large number of new types of pentacoordinate silicon compounds have been synthesized, including complexes with five different atoms in the silicon environment, compounds with SiO₅, SiS₂N₂C, SiS₂O₂C, SiN₄X (X = S, Se, Te) skeletons and others.⁵

At the same time, certain classes of organosilanes containing both penta- and tetracoordinate silicon atoms in the same

molecule remain virtually unknown. Among these compounds are *N,N*-bis(dimethylhalogenosilylmethyl)amides, where two silicon centres compete for a single carbonyl group. One of the Si atoms in these amides extends its coordination number to five and forms an (O→Si)-chelate ring while another Si atom remains tetracoordinate. Up to date, very few examples of such compounds have been reported,⁶ with the structures of only four complexes (**1**,^{6b} **2**,^{6b} **3** (ref. 6e) and **4** (ref. 6e)) determined by X-ray method.

Since each of the two silicon atoms in dihalides **1–4** can potentially form a coordination bond with the carbonyl group, these compounds are particularly interesting as models for studying stereodynamic processes in solutions (such as alternating coordination or permutational isomerisation), pathways of S_N2–Si reactions, relative contributions of the silicon centres to O→Si coordination and the effects of such coordination on the reactivity of Si^{IV}Me₂Hal and Si^VMe₂Hal groups within a single molecule.

Earlier we described (O→Si)-monochelate fluorosilanes RSO₂–Pro–N(Me)CH₂SiMe₂F (**5**), containing an electron-withdrawing organosulfonyl group at the nitrogen atom of the amino acid fragment.⁷ In the present work, we report the synthesis, structures and stereodynamic behaviour of dinuclear fluorosilyl derivatives of proline and sarcosine R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂F)₂ (**9**), synthesised by bis-silylmethylation of *N*-organosulfonyl(*S*)-proline

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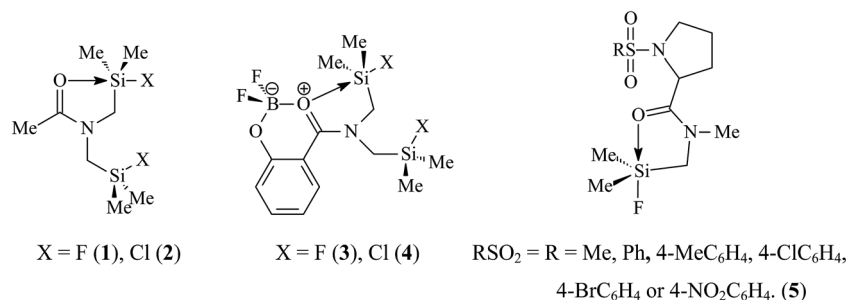
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and *N*-mesylsarcosine amides R₃R₂NCH(R₁)C(O)NH₂ (**6**) via unstable dichlorides R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂Cl)₂ (**7**) and isolable *N*-substituted 2,6-disilamorpholines R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂O)₂ (**8**).

Discussion of the results

Synthesis of disilamorpholines

Disilamorpholines **8** were prepared by the general synthetic approach developed by us for various silacyclanes.^{6d,e,8} The starting compounds, primary amides **6**, were silylmethylated by a mixture of chloro(chloromethyl)dimethylsilane and hexamethyldisilazane with subsequent hydrolysis of unstable dichlorides **7** into target 4-acyl-2,6-disilamorpholines **8** (Scheme 1).

Mesyl and tosyl derivatives of (*S*)-proline, Ms-Pro-N(CH₂-SiMe₂)₂O (**8a**) and Ts-Pro-N(CH₂SiMe₂)₂O (**8b**), and mesyl derivative of sarcosine, MsN(Me)CH₂C(O)N(CH₂SiMe₂)₂O (**8c**), were obtained by one-pot syntheses with yields of 75, 78 and 80%, respectively. The composition and structures of compounds **8** were confirmed by the elemental analysis, IR and multinuclear (¹H, ¹³C, ²⁹Si and CP/MAS ²⁹Si) NMR spectroscopy. The structures of compounds **8a** and **8c** were also determined by X-ray method (see below).

The formation of hydrolytically unstable dichloride **7a** was detected by IR spectroscopy. When a mixture of amide **6a** with three equivalents of ClCH₂SiMe₂Cl and one equivalent of (Me₃Si)₂NH was refluxed in benzene or toluene, the absorption of the NCO fragment in **6a** was gradually replaced by two absorptions (at 1590 and 1505 cm⁻¹) of the same fragment in

7a, which was typical O→Si chelates of pentacoordinate silicon.^{6b,9} IR spectra of all 4-acyl-2,6-disilamorpholines **8a-c** showed a strong absorption of the NCO fragment at 1630 cm⁻¹.

In the ¹H NMR spectra of chiral proline derivatives **8a,b**, the signals of two SiMe₂ groups appear as four singlets.

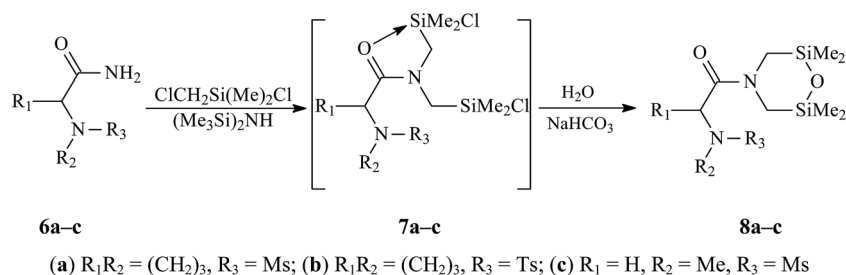
The ²⁹Si NMR spectra of disilamorpholines **8a-c** in solutions contain two signals at approximately 8 and 10 ppm, which are almost independent of the amino acid or *N*-substituent nature. The same chemical shifts of ²⁹Si are observed in the solid-state CP/MAS spectra of these compounds (see Experimental section). Therefore, the solvation of tetracoordinate silicon atoms has no noticeable effect on their chemical shifts.

The above data suggest that both silicon atoms in compounds **8a-c** are tetracoordinate.^{6c} Similar to the double set of signals of SiMe₂ groups in ¹H NMR spectra, the presence of two signals in ²⁹Si NMR spectra of these compounds is probably caused by the hindered amide rotation.

Synthesis of difluorides

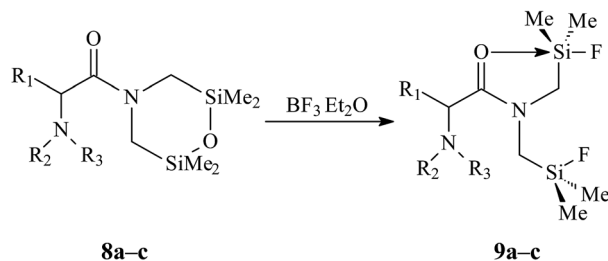
In contrast to hydrolytically labile Si-Cl bonds in pentacoordinate dichlorides **7a-c**, the Si-F bonds in their difluoro analogues **9a-c** were expected to be more stable. (O→Si)-Chelate *N,N'*-bis(dimethylfluorosilylmethyl)-*N*-organosulfonyl-(*S*)-prolinamides (**9a,b**) and *N,N'*-bis(dimethylfluorosilylmethyl)-*N*-mesylsarcosinamide (**9c**) were prepared by the reaction of disilamorpholines **8a-c** with BF₃·Et₂O in acetonitrile (Scheme 2).

The composition and structure of difluorides **9a-c** were determined by the elemental analysis, IR and multinuclear (¹H,



Scheme 1





(a) $R_1R_2 = (\text{CH}_2)_3$, $R_3 = \text{Ms}$; (b) $R_1R_2 = (\text{CH}_2)_3$, $R_3 = \text{Ts}$; (c) $R_1 = \text{H}$, $R_2 = \text{Me}$, $R_3 = \text{Ms}$

Scheme 2

^{13}C and ^{29}Si NMR spectroscopy. The coordination states of both silicon atoms in compound **9a** in the solid state was further confirmed by X-ray single-crystal study (see below) and ^{29}Si CP/MAS NMR.

Multinuclear NMR spectroscopy

^1H NMR spectra of difluorides **9a–c** contain two signals of the SiMe_2 groups in the upfield region. These signals can be attributed to specific SiMe_2 groups using Bruker 2D pulse sequence $\{^1\text{H}-^{29}\text{Si}\}$ HMBS. For example, the cross-peaks in the 2D spectrum of **9b** (Fig. 1) indicate that the upfield signal of SiMe_2 protons corresponds to the signal of pentacoordinate ^{29}Si at -20 ppm while the downfield signal of SiMe_2 protons corresponds to the signal of tetracoordinate ^{29}Si at $+30$ ppm.^{2b,c}

Direct spin–spin coupling constants $^1J_{\text{SiF}}$ in NMR spectra of compounds **9** for tetracoordinate silicon (230–260 Hz) were generally lower than those for pentacoordinate silicon (*ca.* 280 Hz; see Experimental section). Such difference, observed both in solutions and solid state, reflected the weakening of the Si–F bond at Si^{V} in comparison with Si^{IV} (see X-ray data for **9a**).^{2b,c} For the same reason, the spin–spin coupling constant $^3J_{\text{HF}}$ was observed at ambient temperature only for the $\text{Si}^{\text{IV}}\text{Me}_2$ group but not for the $\text{Si}^{\text{V}}\text{Me}_2$ group. Finally, the weakening of the $\text{Si}^{\text{V}}\text{–F}$ bonds affected the $^2J_{\text{CF}}$ constants in ^{13}C NMR spectra: the observed spin–spin coupling frequencies at Si^{V} centres (10–15 Hz) were significantly lower than those at the Si^{IV} centres (*ca.* 30 Hz).

Intramolecular $\text{O} \rightarrow \text{Si}$ coordination in complexes **9** in solutions was further confirmed by the down field shift of the $\text{C}=\text{O}$

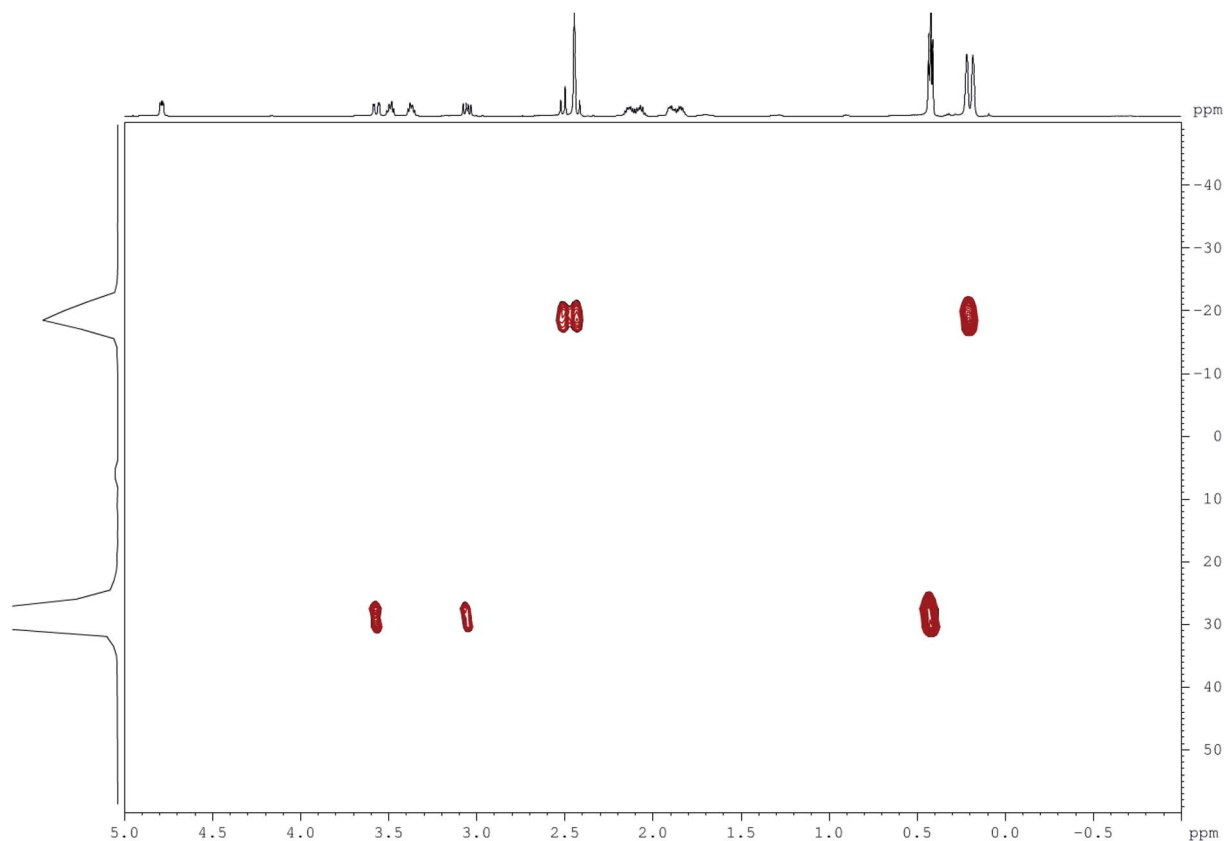


Fig. 1 Two-dimensional NMR spectrum of **9b** (Bruker $\{^1\text{H}-^{29}\text{Si}\}$ HMBS, CDCl_3 , 600 MHz).



signal in their ^{13}C NMR spectra. The characteristic patterns of $\text{Si}^{\text{V}}(\text{CH}_3)_2$ and $\text{NCH}_2\text{Si}^{\text{V}}$ signals in ^1H NMR spectra of difluorides **9a,b** (two singlets of equal intensity and an AB-system quartet, respectively) indicated the presence of a chiral carbon atom in their molecules.

The ^{29}Si signals in solid-state NMR spectra of compounds **9** had greater upfield shifts (*ca.* -40 ppm) than the same signals in solutions (*ca.* -10 ppm). Similar effect was observed for monofluorides **5** and was probably caused by effective solvation of pentacoordinate silicon.^{7a}

Using the difference between the observed chemical shifts of a Si^{V} atom and the typical chemical shift of a Si^{IV} atom (*ca.* 30 ppm), the *coordination contribution* ($-\Delta\delta = \delta\text{Si}^{\text{V}} - \delta\text{Si}^{\text{IV}}$)^{2a} in difluorides **9** can be estimated to be approximately 50 ppm. The comparison of this value to coordination contributions in chlorosilanes $\text{RSO}_2\text{-Pro-N}(\text{Me})\text{CH}_2\text{SiMe}_2\text{Cl}$ (70–75 ppm), silyloxonium halides $[\text{R-Pro-N}(\text{Me})\text{CH}_2\text{SiMe}_2\text{OH}_2]\text{X}$ (R = AlkSO_2 , ArSO_2 , Ac; X = Cl, Br) (70–80 ppm)¹⁰ and theoretical data for monofluorosilanes **5** (ref. 7b) and $\text{MeC}(\text{O})\text{N}(\text{Me})\text{CH}_2\text{SiMe}_2\text{F}^{11}$ (same as above) indicates a relatively weak coordination in difluorides **9**.

All difluorides have two signals in their ^{19}F NMR spectra: one at approximately -159 ppm and another at -119 – -125 ppm. According to literature data, these signals belong to $\text{Si}^{\text{IV}}\text{Me}_2\text{F}$ and $\text{Si}^{\text{V}}\text{Me}_2\text{F}$ groups, respectively.^{2b,c}

Variable-temperature ^1H , ^{19}F and ^{29}Si NMR studies

The strength of intramolecular coordination in monochelates of pentacoordinate silicon strongly depends on the nature of the substituent X (Scheme 3; see^{2c,7a} and references therein).

In the case of compounds with the OSiC_3X coordination set and X = Hal or OTf, structures **A** and **B** are typical for fluorides, **C** for chlorides, **D** for bromides, and **E** for iodides and triflates.

To study the temperature effects on the coordination set structure in difluorides **9a–c**, the temperature-dependent ^1H , ^{19}F and ^{29}Si NMR spectra of these compounds in CDCl_3 were obtained. The decrease in temperature from $+20$ to -60 °C led to reversible downfield shifts of ^1H and ^{19}F signals (by *ca.* 0.03 and 3–4 ppm, respectively) of the $\text{Si}^{\text{V}}\text{Me}_2\text{F}$ group. At the same time, the chemical shift of ^{19}F in the $\text{Si}^{\text{IV}}\text{Me}_2\text{F}$ group was not affected by the temperature. Such behaviour of ^1H and ^{19}F signals suggests an increased contribution of form **B** (Scheme 3) at low temperatures.

Similar to monofluorosilanes,^{7a} the increase in temperature to $+60$ °C caused very small reversible broadening of the SiMe_2

and NCH_2 signals in ^1H NMR spectra of difluorides **9a–c**. Such broadening was indicative of a permutational isomerisation at the Si^{V} coordination set of these compounds.

The activation parameters of the permutation were calculated by a ^1H DNMR method using a full line-shape analysis of the signals. For all studied compounds, the stereodynamic processes in CDCl_3 were characterised by a narrow range of activation energies (~ 24 kcal mol $^{-1}$ or greater) and high negative values of the entropy of activation (*ca.* ~ -20 cal mol $^{-1}$ K $^{-1}$). These values were very similar to the activation parameters of *N*-(dimethylfluorosilylmethyl)- and *N*-[fluoro(methyl)(phenyl)silylmethyl]amides and -lactams,^{2a,12–15} as well as $\text{RSO}_2\text{-Pro-N}(\text{Me})\text{CH}_2\text{SiMe}_2\text{F}$ (**5**),^{6a} where R = Me, Ph, 4-MeC $_6$ H $_4$, 4-ClC $_6$ H $_4$, 4-BrC $_6$ H $_4$ or 4-NO $_2$ C $_6$ H $_4$.

XRD studies

Disilamorpholine **8a** (Fig. 2) crystallizes in two polymorph modifications (**8a** and **8a'**).

The orthorhombic ($P2_12_12_1$) crystals **8a** were obtained from a heptane–benzene mixture with a molar ratio of 3 : 1, whereas

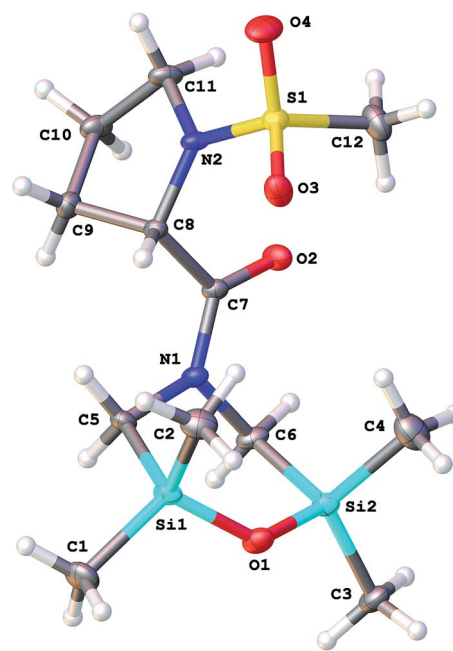
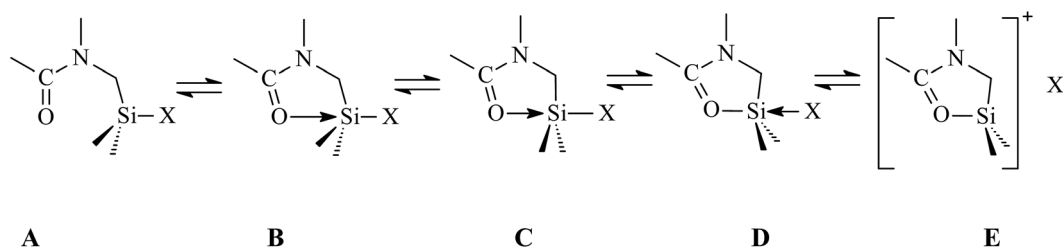


Fig. 2 Molecular structure of **8a** with thermal ellipsoids shown at the 50% probability level.



Scheme 3



monoclinic ($P2_1$) crystals **8a'** were obtained from ethanol. There are two crystallographically independent molecules in the asymmetric unit of **8a**; its volume is 3.84 times larger than that of **8a'**, because the cell **8a'** contains a void of about 40 \AA^3 . The structure of the 2,6-disilamorpholine fragment in compounds **8a**, **8a'** and **8c** (Fig. 3) is analogous to the previously published five structures (CSD refcodes:¹⁶ QOMTAN, QOMTER, XATQIT, XULNAT, XULNEX).

The mesyl group and 2,6-disilamorpholine fragment have *syn*-conformation relative to the proline ring: the corresponding torsion angles C8–N2–S1–C12 and C20–N4–S2–C24 in **8a** are $95.3(2)^\circ$ and $88.8(2)^\circ$ for two crystallographically independent molecules, respectively, and the torsion angle C8–N2–S1–C12 in **8a'** is $94.7(5)^\circ$.

An asymmetric unit of difluoride **9a** contains two crystallographically independent molecules, which differ by mutual orientation of the proline moiety and $\text{Me}_2\text{FSiCH}_2$ group relative to the chelate ring. In the case of *syn*-conformation, the interatomic distance $\text{Si1}\cdots\text{Si2}$ is $5.387(1) \text{ \AA}$, whereas for *anti*-configuration the distance $\text{Si2}\cdots\text{Si4}$ is $6.340(1) \text{ \AA}$. In **9a** (Fig. 4), one of the silicon atoms is pentacoordinated, and its coordination polyhedron is a distorted trigonal bipyramid (axial angles O1–Si1–F1 and O4–Si3–F3 are $172.1(1)^\circ$ and $171.9(1)^\circ$, the deviations of Si1 and Si3 atoms from the planes of equatorial substituents toward fluorine atoms are $0.167(1) \text{ \AA}$ and $0.176(1) \text{ \AA}$ for two crystallographically independent molecules, respectively).

The structures of coordination polyhedra of Si1 and Si2 atoms in **9a** are noticeably different from those in the series of (O→Si)-chelate N' -(dimethylfluorosilylmethyl)- N' -methyl- N -(organosulfonyl)prolinamides,^{7a} complexes **1** (ref. 6d) and **3** (ref. 6e) (selected bond lengths are given in Table 1).

The structure of **3** differs significantly from other difluorides due to the coordination of amide oxygen atom with the difluoro-

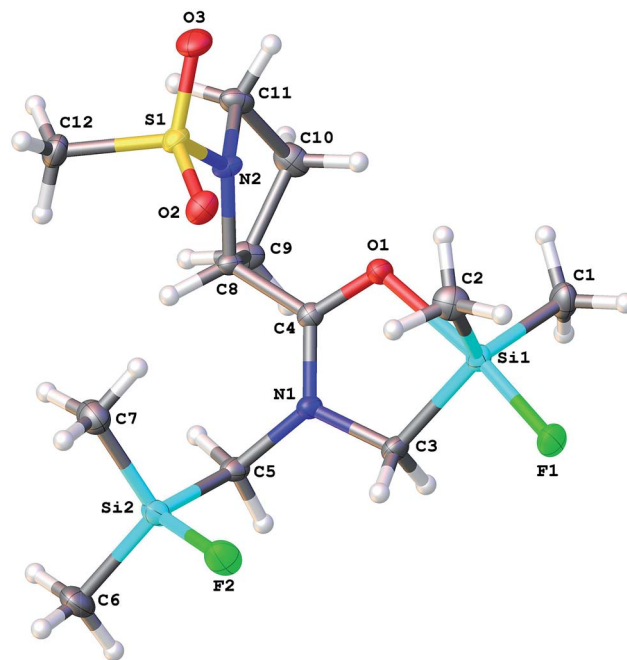


Fig. 4 Molecular structure of **9a** with thermal ellipsoids shown at the 50% probability level.

boron group while the coordination with the silicon atom is very weak. Thus, the axial Si–O bonds are shortened by 0.07 – 0.17 \AA , and $\text{Si}^{\text{V}}\text{–F}$ bonds lengthened by 0.02 – 0.04 \AA compared to similar bonds in prolinamide derivatives and difluoride **1**. The $\text{Si}^{\text{IV}}\text{–F}$ bonds are lengthened by 0.05 – 0.10 \AA in comparison with similar bonds in difluorides **1** and **3**. Atoms Si2 and Si4 are not coordinated by any oxygen atoms, with the shortest intermolecular contact $\text{Si4}\cdots\text{O2}$ of $3.538(1) \text{ \AA}$.

Quantum-chemical studies of the permutational isomerization

To test the applicability of the mechanism (Scheme 4) previously suggested for the permutational isomerisation of N -(dimethylfluorosilylmethyl)amides¹ to N,N -bis-(dimethylfluorosilylmethyl)amides, we carried out quantum chemical studies of molecule **9a**.

At higher temperatures, the equilibrium $\text{B} \rightleftharpoons \text{A}$ (Schemes 3 and 4) shifts towards the tetracoordinate topomer **A**. The nucleophilic attack at the Si atom by a fluoride anion (F^{*-}) produces pentacoordinate difluoride **G**, which subsequently loses the F^- anion and forms tetracoordinate intermediate **H**. The rotation around the Si– CH_2 bond produces topomer **A'** and

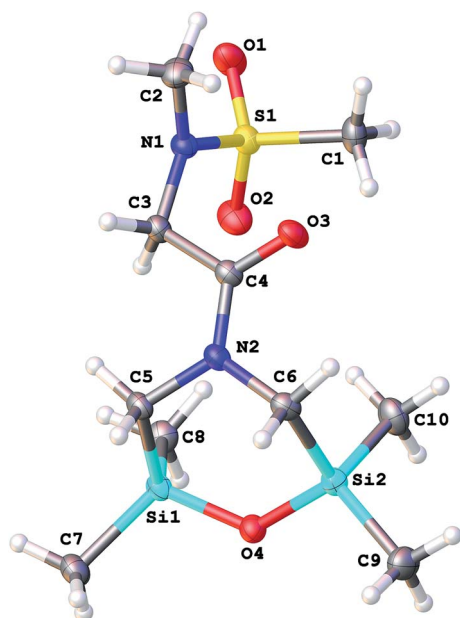
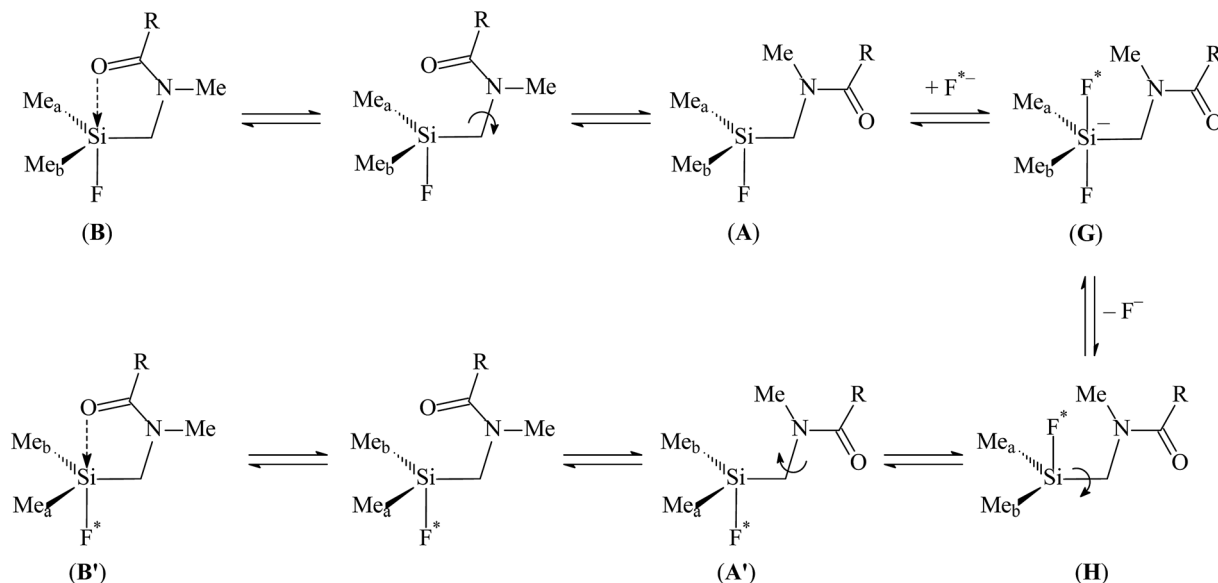


Fig. 3 Molecular structure of **8c** with thermal ellipsoids shown at the 50% probability level.

Table 1 Selected bond lengths for structures **9a**, **1**, **3** and prolinamide derivatives

| | 9a (mean values) | 1 (ref. 6d) | 3 (ref. 6e) | Monofluorides ^{7a} |
|----------------------------------|-------------------------|--------------------|--------------------|-----------------------------|
| $\text{Si}^{\text{IV}}\text{–F}$ | 1.613(1) | 1.603 | 1.608 | — |
| $\text{Si}^{\text{V}}\text{–F}$ | 1.693(1) | 1.668 | 1.620 | 1.651–1.671 |
| $\text{Si}\cdots\text{O}$ | 2.062(1) | 2.187 | 2.918 | 2.131–2.220 |





Scheme 4

finally complex **B'** with inverted orientation of the methyl groups at silicon.

According to our previous study, the external fluoride anion can attack tetracoordinated silicon, and the dissociation energy of resulting Si-F bond in gas phase is equal to ~ 90 kcal mol⁻¹. Solvation of the F⁻ anion leads to significant decrease of the Si-F dissociation energy. It is reasonable to assume that similar processes can occur in solution of **9a** in CDCl₃. Due to the presence of two dimethylfluorosilylmethyl and one bulky tosyl groups, the silicon atoms seem to be less accessible for nucleophilic attack as compared to *N*-(dimethylfluorosilylmethyl) amides, where only one dimethylfluorosilylmethyl group is present. Hence, the stereodynamic processes in solution of **9a** can be more complex as compared to *N*-(dimethylfluorosilylmethyl) amides.^{7a}

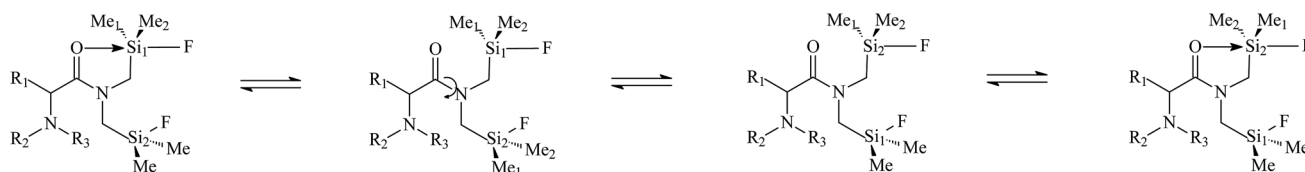
An alternative mechanism can involve the carbonyl group migration from one dimethylfluorosilyl to another (similarly to derivatives urea¹⁷) (Scheme 5).

In any case, the cleavage of the Si-O coordination bond and the certain conformational changes are necessary to the transfer the carbonyl oxygen atom from one dimethylfluorosilylmethyl to another. Thus, the detailed inspection of these processes can be very useful for understanding the nature of permutational isomerisation in the solution of **9a**.

Quantum-chemical calculations of **9a** were carried out using Gaussian 03W program.¹⁸ Hybrid PBE0 functional and 6-

311G(d,p) basis set were utilized for structure optimization, hessian calculations, relaxed potential energy scans and transition state search. To account for the effect of nonspecific solvation, the PCM model was applied (the value of dielectric constant corresponded to chloroform). All calculations were performed with tight optimization criteria (Opt = tight) and precise grid for computation of two-electron integrals (Int(Grid = Ultrafine)). Molecular graphics were drawn with ChemCraft program.¹⁹ General views of calculated structures, atomic coordinates and total energies can be found in ESI.†

Analysis of potential energy surface for **9a** in its isolated molecule and CDCl₃ (PCM calculation) has shown that the presence of two conformational isomers correspond to the cyclic structures (where the Si-O coordination bond is present) and two other conformers belong are acyclic (Si-O coordination bond is absent). According to quantum chemical calculations, the influence of dielectric continuum used in PCM model leads to significant changes in molecular structure of **9a**. The most noticeable change is the decrease of Si1...O1 distance from 2.36–2.37 to 2.25 Å. Cyclic conformers are more favourable as compared to the acyclic conformers. The difference between two isolated most stable cyclic and acyclic structures is 2.51 kcal mol⁻¹. The use of PCM model for the description of solvation increases this difference to 4.37 kcal mol⁻¹, which is in good agreement with our earlier calculations.^{7a} All cyclic conformers can be characterized by the same geometry of coordination



Scheme 5



polyhedra of silicon atoms, so their ^{19}F and ^{29}Si chemical shifts should be very close.

Other differences are related to mutual orientation of *N*-organosulfonyl and dimethylfluorosilyl groups. In isolated cyclic and acyclic forms of **9a**, these fragments are much closer to each other than in the solution. In two conformers (**9a**-cyclic2 and **9a**-acyclic2, Fig. 5S and 6S, see ESI †), the Si2...O2 distances between one of the SiMe₂F groups and the oxygen atom of the sulfonyl group are 3.698 and 3.720 Å, respectively. The optimization of these conformers in terms of PCM model (**9a**-cyclic2-CDCl₃ and **9a**-acyclic2-CDCl₃, Fig. 7S and 8S †) increases the separation of the above fragments (the Si2...O2 distances become 4.533 and 3.962 Å). Conformers **9a**-cyclic and **9a**-acyclic (Fig. 1S and 2S †) are stabilized by weak C-H...O bonds between sulfonyl and methyl groups, so the Si2...O2 distances are 3.724 and 4.450 Å. Again, the application of PCM model increases Si2...O2 distances to 4.292 and 4.376 Å (**9a**-cyclic-CDCl₃ and **9a**-acyclic-CDCl₃, Fig. 3S and 4S †). Thus, the effect of nonspecific solvation prevents the formation of Si2...O2 interactions, so the permutational isomerisation involving the sulfonyl group is unlikely to take place.

The information about the barrier of rotation around Si1-C3 and N1-C4 bonds can be useful to understand the mechanism of permutational isomerisation of **9a**. These barriers were calculated by the relaxed potential energy surface scan of CNCO and F1Si1C3N1 torsion angles (the plots of the energy vs. scan coordinate are placed in ESI (Fig. 9S and 10S †)). The value of the rotation barrier around the Si1-C3 bond in isolated molecule **9a** is approximately 7 kcal mol⁻¹ (Fig. 9S †), so the rotation around the Si-C bond is possible despite the presence of an Si1-O1 coordination bond. In solution, the value of this barrier is even lower than that in isolated molecule (~5.1 kcal mol⁻¹). It is not surprising that the rotation around the N1-C4 bond is less favourable than the rotation around the Si1-C3 bond. Firstly, the N1-C3 bond is intermediate between ordinary and double (Table 2). Secondly, the rotation around the N1-C3 bond is attributed to the formation and cleavage of Si1-O1 and Si2-O1 coordination bonds. Our calculation gave the values of 26.3 kcal mol⁻¹ for isolated molecule **9a** and 24.8 kcal mol⁻¹ for its solution in chloroform (Fig. 10S †). These values are very close to the permutational barriers measured for **9a-c** by ^{19}F DNMR study. Thus, the internal rotation can be responsible for the permutational isomerisation of **9a**. Additional justification for

this assumption was obtained by the localization of transition states (Fig. 11S and 12S †). The modes of negative vibrations (-67.0 and -62.8 cm⁻¹ for isolated molecule and CDCl₃ solution, respectively) correspond to the rotation around the N1-C4 bond and formation/dissociation of Si-O coordination bonds. The difference between energies of the most favourable cyclic conformers and transition state is 28.4 and 29.3 kcal mol⁻¹ for isolated molecules and solution of **9a**, respectively. These values are in agreement with the results of DNMR study. At the same time, the ΔS value calculated as the difference between the transition state and cyclic isomer is ~-2 kcal mol⁻¹ K⁻¹, which is much lower than the experimental value. In our opinion, this difference can be explained by specific solvation (for instance, H-bonds between CDCl₃ and carbonyl or sulfonyl groups, which can be responsible for stabilization of particular conformers).

In silico estimation of possible pharmacological applications

Possible applications of synthesized complexes were evaluated by the search for similar compounds with known activities and computational prediction of biological activity based on "structure-activity" relationships (SAR) models. Such analysis provides a reasonable basis for planning further experimental studies of biological activity.

In this study, we used the PubChem structural search for identification of equivalent and similar structures (<https://pubchem.ncbi.nlm.nih.gov>).²⁰ The similarity was assessed by the Tanimoto equation and the PubChem dictionary-based binary fingerprint analysis (https://pubchem.ncbi.nlm.nih.gov/search/help_search.html). The search results for similar compounds are shown in Table 3.

According to Table 3, the studied complexes have different similar compounds with variable known activities. No two complexes have the same most similar compound, which could indicate their similar biological potentials.

Computational prediction of biological activity for studied complexes was carried out using SAR-based online services. Possible therapeutic effects and mechanisms of action were evaluated by PASS Online²¹ (<http://www.way2drug.com/PASSOnline>) while the LD₅₀ values for acute rat toxicity were estimated by GUSAR Online²² (<http://www.way2drug.com/gusar/acutoxpredict.html>). The results of these predictions are summarized in Table 4.

The prediction results suggest that synthesized compounds may possess cardiovascular and CNS properties. Low levels of predicted acute rat toxicity makes them suitable for all routes of administration.

Table 2 Calculated bond distances and angles in conformers of **9a**

| Conformer | Si1...O1 | Si2...O2 | Si1-F1 | Si2-F2 | O1Si1F1 |
|---------------------------------------|----------|----------|--------|--------|---------|
| 9a -cyclic | 2.368 | 4.450 | 1.665 | 1.632 | 169.20 |
| 9a -acyclic | 3.130 | 3.724 | 1.638 | 1.646 | 79.69 |
| 9a -cyclic-CDCl ₃ | 2.248 | 4.533 | 1.686 | 1.640 | 170.25 |
| 9a -acyclic-CDCl ₃ | 3.222 | 3.962 | 1.652 | 1.644 | 78.82 |
| 9a -cyclic2 | 2.356 | 3.698 | 1.667 | 1.637 | 168.96 |
| 9a -acyclic2 | 2.984 | 3.720 | 1.637 | 1.639 | 76.09 |
| 9a -cyclic2-CDCl ₃ | 2.250 | 4.292 | 1.686 | 1.643 | 169.97 |
| 9a -acyclic2-CDCl ₃ | 3.175 | 4.376 | 1.644 | 1.644 | 77.90 |
| 9a -ts | 4.828 | 3.969 | 1.638 | 1.637 | 112.44 |
| 9a -ts-CDCl ₃ | 4.947 | 3.777 | 1.645 | 1.648 | 115.07 |

Conclusions

New difluorides R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂F)₂ (**9a-c**) with one pentacoordinate and one tetracoordinate silicon atoms were synthesized by silylmethylation of amides R₃R₂NCH(R₁)C(O)NH₂, subsequent hydrolysis of unstable intermediates R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂Cl)₂ (**7a-c**) into 4-acyl-2,6-disilamorpholines R₃R₂NCH(R₁)C(O)N(CH₂SiMe₂O)₂ (**8a-c**) and the reaction of the latter compounds with BF₃·Et₂O.



Table 3 The search results for similar compounds in PubChem^a

| ID | Hits (probability) | The most similar compound with data on patents or activity |
|----|--------------------|--|
| 8a | 0 (90%); 161 (80%) | <i>N</i> -[(3 <i>S</i>)-1-Methyl-2-oxopiperidin-3-yl]- <i>N</i> -(2-oxopropyl)methanesulfonamide (CID 58869395) Patent description: sulfonylaminovalerolactams and derivatives thereof as factor Xa inhibitors |
| 8b | 216 (90%) | 4,4'-Ethylenebis(1-methyl-2,6-piperazinedione) (CID 97592) Patent description: novel drug targets to overcome <i>de novo</i> drug-resistance in multiple myeloma; method of reducing amyloid-beta peptide levels using a bisdioxopiperazine; abatement process for contaminants; bis-dioxopiperazines and their use as protection agents bis-dioxopiperazines and their use as protection agents Known activity: small molecule inhibitors of FGF22-mediated excitatory synaptogenesis & epilepsy measured in biochemical system using RT-PCR – 7012-01_Inhibitor_SinglePoint_HTS_Activity |
| 8c | 0 (90%); 19 (80%) | 2-(4-Acetylpiperazin-1-yl)- <i>N</i> -methylsulfonylacetylacetamide (CID 89504348) Patent description: dual-acting antihypertensive agents having angiotensin II type receptor antagonist activity and neprilysin-inhibition activity |
| 9a | 0 (90%); 74 (80%) | (1) <i>N</i> -(4-Amino-5-oxo-5-pyrrolidin-1-ylpentyl)methanesulfonamide (CID 17960593) Patent description: alpha-amino acid sulphonyl compounds (2) (2 <i>S</i>)-1-[2-[Methyl(methylsulfonyl)amino]ethyl]pyrrolidine-2-carboxamide (CID 57572120) Patent description: quinolinone compounds as 5-HT4 receptor agonists |
| 9b | 59 (90%) | Azepan-1-yl-[1-(4-methylphenyl)sulfonylpyrrolidin-2-yl]methanone (CID 2964486) Known activity: active in HTS assay for activators of cytochrome P450 2A9 |
| 9c | 0 (90%); 10 (80%) | <i>N,N</i> -Dimethyl-2-[methyl(methylsulfonyl)amino]acetamide (CID 57682568) Patent description: HIV integrase inhibitors |

^a Hits – number of similar compounds ($\geq 90\%$ or $\geq 80\%$ Tanimoto index); CID – PubChem Compound ID.

According to IR and NMR data, the O→Si coordination in solutions of these compounds was weaker than in the solid state due to effective solvation of the Si–F bond. The absence of spin-spin coupling constants $^3J_{\text{HF}}$ of the methyl groups at Si^{IV} and their retention at Si^{IV} indicates a significant weakening of the Si–F bond at pentacoordinate silicon, which favours its ionization. Based on *in silico* analysis, the synthesized compounds show a potential for pharmacological studies.

Experimental section

IR-spectra of compounds in solution and in the solid state were recorded on a Bruker Tensor-27 spectrometer using KBr cells and an APR element, respectively. ¹H, ¹³C and ¹⁹F NMR spectra

in CDCl₃ and DMSO-*d*₆ were recorded on a Bruker Avance II 300 (¹H, 300 MHz; ¹³C, 75.6 MHz; ¹⁹F, 282.2 MHz) and Jeol JNM-EX400 (¹H, 400 MHz; ¹³C, 100.6 MHz; ¹⁹F, 376.3 MHz) instruments using standard pulse sequences. ²⁹Si NMR spectra were recorded using the ¹H-²⁹Si HSQC pulse sequence supplied with the Bruker Avance II 600 instrument.²³ The ¹H, ¹³C, ²⁹Si chemical shifts were measured using Me₄Si as internal reference. The ¹⁹F chemical shifts were measured using BF₃ as external reference. Negative values are to high field. ²⁹Si NMR CP/MAS spectra in the solid state were recorded on a Jeol JNM-EX-400 instrument using 5 mm zirconia rotors and a Doty probe.

The temperature calibration of the NMR spectrometers was performed by measuring the differences in chemical shifts between non-equivalent protons in methanol (–90...+30 °C)



Table 4 Prediction of therapeutic effects and mechanisms of action (PASS Online) and LD₅₀ values of acute rat toxicity (GUSAR Online)^a

| ID | Top 5 predicted therapeutic effects with probability > 50% | Top 5 predicted mechanisms of action with probability > 50% | Predicted LD ₅₀ values in mg kg ⁻¹ , type of administration, class of toxicity |
|----|---|---|--|
| 8a | Not predicted | Acetylcholine neuromuscular blocking agent | IP – out of AD, 127, IV, 4 class, 904, PO, 4 class, SC – out of AD |
| 8b | Not predicted | Acetylcholine neuromuscular blocking agent | IP – out of AD, 96, IV, 4 class, 1270, PO, 4 class, SC – out of AD |
| 8c | Spasmolytic | Acetylcholine neuromuscular blocking agent, anaphylatoxin receptor antagonist | IP – out of AD, 156, IV, 4 class, 453, PO, 4 class, 250, SC, 4 class |
| 9a | Antianginal, multiple sclerosis treatment, antiparkinsonian, neurodegenerative diseases treatment | Phosphatidylinositol 3-kinase C2beta inhibitor, RANTES antagonist, insulin growth factor agonist, insulin like growth factor 1 agonist | IP – out of AD, 80, IV, 4 class, PO – out of AD, 487, SC, 4 class |
| 9b | Antianginal, cardiovascular analeptic, multiple sclerosis treatment, cell adhesion molecule inhibitor | Integrin alpha2 antagonist, calmodulin antagonist, nicotinic alpha4beta4 receptor agonist | IP – out of AD, 101, IV, 4 class, PO – out of AD, SC – out of AD |
| 9c | Antianginal | Anaphylatoxin receptor antagonist, phospholipid-translocating ATPase inhibitor, 2-haloacid dehalogenase inhibitor, glycosylphosphatidylinositol phospholipase D inhibitor, NADPH peroxidase inhibitor | IP – out of AD, 130, IV, 4 class, PO – out of AD, 225, SC, 4 class |

^a IP – intraperitoneal route of administration; IV – intravenous route of administration; PO – oral route of administration; SC – subcutaneous route of administration; out of AD – compound is out of applicability domain of QSAR models.

and ethyleneglycol (+30...+85 °C).²⁴ The activation parameters of the permutational isomerisation were calculated using DNMR-SIM software²⁵ and a modified Eyring equation.²⁶ In each case, at least twelve temperature points were obtained to achieve a correlation coefficient of 0.997–0.999.

Chloro(chloromethyl)dimethylsilane, (*S*)-proline hydrochloride, sarcosine and all solvents were purchased from Acros and Sigma-Aldrich. Ethyl esters of *N*-mesyl-(*S*)-proline and *N*-tosyl-(*S*)-proline were synthesised as described earlier.¹⁰

Ethyl-*N*-mesyl-*N*-methylglycinate

Thionyl chloride (83.3 g, 0.27 mol) was added dropwise to a solution of *N*-methylglycine (44.5 g, 0.50 mol) in absolute ethanol (200 mL). The mixture was refluxed for 5 h, then the volatiles were removed in vacuum. The residue was suspended in an ice-cold mixture of water (20 mL) and diethyl ether (100 mL), and a solution of potassium hydroxide (28.0 g, 0.50 mol) in water (20 mL) was added over 5 min at 0 °C, followed by 250 g of anhydrous potassium carbonate. The organic layer was separated, the residue was washed with ether (2 × 50 mL), and the combined organic solutions were dried over magnesium sulfate. The solvent was removed in vacuum, and the residue was distilled to afford 38.0 g (65%) of ethyl *N*-methylglycinate with b.p. 43–45 °C (12 torr) and *n*_D (ref. 20) 1.4105. Literature data:²⁷ b.p. 46 °C (12 torr), *n*_D (ref. 20) 1.4144.

Methanesulfonyl chloride (11.5 g, 0.10 mmol) was added dropwise to a cooled solution of ethyl-*N*-methylglycinate (11.7 g,

0.10 mol) and triethylamine (10.1 g, 0.10 mol) in diethyl ether (80 mL). The mixture was stirred at ambient temperature for 2 h, the precipitate formed was filtered off, washed with ether (15 mL), and the combined organic solutions were evaporated in vacuum. The residue was distilled to afford 13.7 g (70%) of ethyl-*N*-mesyl-*N*-methylglycinate with b.p. 144–145 °C (9 torr) and m.p. 34–35 °C. IR spectrum (KBr, ν , cm⁻¹): 1750 (C=O), 1360 and 1160 (SO₂). ¹H NMR spectrum (CDCl₃, δ , ppm (*J*, Hz)): 1.25 (3H, t, ³*J* 7.3, CH₂CH₃); 2.77 (3H, s, CH₃N); 2.87 (3H, s, CH₃S); 4.05 (2H, s, NCH₂). ¹³C NMR spectrum (CDCl₃, δ , ppm): 8.9 (CH₂CH₃); 35.3 (CH₃N); 38.1 (CH₃S); 51.4 (NCC(O)); 55.5 (CH₂CH₃); 173.9 (C=O). Found, %: C 37.08; H 6.65; N 7.11. C₆H₁₃NO₄S. Calculated, %: C 36.91; H 6.71; N 7.17.

N-Mesyl-(*S*)-prolinamide (6a)

Ethyl ester of *N*'-mesyl-(*S*)-proline (6.6 g, 30 mmol) was stirred with 50 mL of a 25% aqueous ammonia solution for 5 days at ambient temperature. The precipitate formed was isolated by filtration, dried in the open air and used without further purification. Yield 5.5 g (96%), m.p. 156–157 °C (from EtOH), [α]_D²⁵ –101.3° (*c* 1.93, H₂O). IR spectrum (KBr, ν , cm⁻¹): 3449, 3170 (NH₂); 1619 (NCO), 1321 and 1140 (SO₂). ¹H NMR spectrum (DMSO-*d*₆, δ , ppm (*J*, Hz)): 1.75–2.25 (4H, m, 3,4-CH₂); 2.83 (3H, s, CH₃); 3.25–3.47 (2H, m, 5-CH₂); 3.96–4.09 (1H, m, 2-CH); 6.1 and 6.7 (2H, two broad s, NH₂). ¹³C NMR spectrum (DMSO-*d*₆, δ , ppm): 22.0 (Me); 26.0 (C-4); 32.3 (C-3); 50.7 (C-5); 63.5 (C-2); 175.8 (C=O). Found, %: C 37.35; H 6.39; N 14.50. C₆H₁₂N₂O₃S. Calculated, %: C 37.49; H 6.29; N 14.57.



***N*-Tosyl-(*S*)-prolinamide (6b)**

Prepared similar to **6a**. Yield 6.2 g (93%), m.p. 161–162 °C (from EtOH), $[\alpha]_{\text{D}}^{25} -134.6^\circ$ (c 1.06, H₂O). IR spectrum (KBr, ν , cm⁻¹): 1643 (NCO), 1344, 1156 (SO₂). ¹H NMR spectrum (DMSO-d₆, δ , ppm (J , Hz)): 1.31–1.83 (4H, m, 3,4-CH₂); 2.43 (3H, s, CH₃); 3.11–3.22 and 3.35–3.55 (2H, m, 5-CH₂); 3.91–4.01 (1H, m, 2-CH); 5.95 and 6.71 (2H, two broad s, NH₂); 7.36 (2H, d, ³ J = 8.3, H Ar); 7.72 (2H, d, ³ J 8.3, H Ar). ¹³C NMR spectrum (DMSO-d₆, δ , ppm): 22.0 (Me); 25.7 (C-4); 31.8 (C-3); 50.9 (C-5); 63.7 (C-2); 129.2 (C-3,5 Ar); 131.4 (C-2,6 Ar); 135.4 (C-1 Ar); 145.8 (C-4 Ar); 175.5 (C=O). Found, %: C 37.58, H 6.27, N 14.50. C₆H₁₂N₂O₃S. Calculated, %: C 37.49, H 6.29, N 14.57.

***N*-Mesyl-*N*-methylglycinamide (6c)**

Prepared similar to **6a**. Yield 4.1 g (82%), m. p. 170–171 °C (EtOH). IR spectrum (KBr, ν , cm⁻¹): 3315, 3170 (NH₂); 1657 (NCO), 1320 and 1150 (SO₂). ¹H NMR spectrum (DMSO-d₆, δ , ppm (J , Hz)): 2.79 (3H, s, CH₃); 2.87 (3H, s, CH₃S); 3.58 and 3.71 (2H, two s, NCH₂); 5.5 and 6.1 (2H, two broad s, NH₂). ¹³C NMR spectrum (DMSO-d₆, δ , ppm): 34.3 (CH₃N); 37.1 (CH₃S); 50.9 (NCC(O)); 174.9 (C=O). Found, %: C 29.18, H 5.92, N 16.81. C₄H₁₀N₂O₃S. Calculated, %: C 28.91, H 6.06, N 16.86.

2,2,6,6-Tetramethyl-4-[*N*-mesyl-(*S*)-prolinyl]-2,6-disilamorpholine (8a)

A mixture of **6a** (0.96 g, 5 mmol), hexamethyldisilazane (0.81 g, 5 mmol), chloro(chloromethyl)dimethylsilane (2.15 g, 15 mmol) and toluene (10 mL) was refluxed for 4 h, then allowed to cool down, and the precipitate formed was filtered out. The

remaining solution was evaporated in vacuum, the residue was dissolved in chloroform (30 mL) and stirred with a solution of NaHCO₃ (0.84 g, 10 mmol) in water (10 mL) for 2 h. The organic layer was separated, the aqueous layer was extracted with chloroform (20 mL), and the combined organic solutions were evaporated in vacuum. Recrystallisation of the residue from heptane/benzene (3 : 1) mixture afforded 1.32 g (75%) of compound **8a** with m.p. 121–124 °C and $[\alpha]_{\text{D}}^{25} -55.0^\circ$ (c 1.31, CHCl₃). Found, %: C 41.25, H 7.56, N 7.80, S 9.03. C₁₂H₂₆N₂O₄SSi₂. Calculated, %: C 41.11, H 7.48, N 7.99, S 9.15. IR spectrum (KBr, ν , cm⁻¹): 1631 s (C=O), 1325 s, 1148 s (SO₂). ¹H NMR spectrum (CDCl₃, δ , ppm): 0.18, 0.19, 0.21 and 0.31 (four s, 12H, 2Si(CH₃)₂); 1.88–2.34 (m, 4H, C³H₂ and C⁴H₂ Pro); 2.7 and 3.42 (dd, 2H, NCH₂Si, ³ J_{HH} 15.34 Hz); 2.83 (dd, 2H, NCH₂Si, ³ J_{HH} 15.34 Hz); 3.01 (s, 3H, SCH₃); 3.45–3.52 and 3.56–3.63 (two m, 2H, C⁵H₂ Pro); 4.80–4.87 (m, 1H, C²H Pro). ¹³C NMR spectrum (CDCl₃, δ , ppm): -0.76 ÷ 0.00 (m, 2SiMe₂); 24.65 (¹³C Pro); 30.79 (³C Pro); 39.9 (SC); 38.1 and 40.29 (two s, NCH₂Si); 47.54 (⁵C Pro); 58.92 (C² Pro); 169.64 (C=O). ²⁹Si NMR spectrum (CDCl₃, δ , ppm): 8.0, 10.5.

2,2,6,6-Tetramethyl-4-[*N*-tosyl-(*S*)-prolinyl]-2,6-disilamorpholine (8b)

Prepared similar to **8a** from 1.34 g of **6b**. Yield 1.66 g (78%) with m. p. 110–112 °C (from heptane–benzene, 10 : 1) and $[\alpha]_{\text{D}}^{25} -2.92^\circ$ (c 1.85, CHCl₃). Found, %: C 50.51, H 7.24, N 6.62, S 7.45. C₁₈H₃₀N₂O₄SSi₂. Calculated, %: C 50.67, H 7.09, N 6.57, S 7.52. IR spectrum (KBr, ν , cm⁻¹): 1629 s (C=O), 1580 m (Ar), 1325 s, 1148 s (SO₂). ¹H NMR spectrum (CDCl₃, δ , ppm): 0.17, 0.21, 0.23 and 0.34 (four s, 12H, 2Si(CH₃)₂); 1.88–2.05 (m, 4H,

Table 5 Crystallographic data and refinement parameters for the structures **8a**, **8a'**, **8c** and **9a**

| | 8a | 8a' | 8c | 9a |
|--|--|--|--|---|
| Molecular formula | C ₁₂ H ₂₆ N ₂ O ₄ SSi ₂ | C ₁₂ H ₂₆ N ₂ O ₄ SSi ₂ | C ₁₀ H ₂₄ N ₂ O ₄ SSi ₂ | C ₁₂ H ₂₆ F ₂ N ₂ O ₃ SSi ₂ |
| Formula weight | 350.59 | 350.59 | 324.55 | 372.59 |
| Crystal system | Orthorhombic | Monoclinic | Monoclinic | Orthorhombic |
| Space group | <i>P</i> 2 ₁ 2 ₁ | <i>P</i> 2 ₁ | <i>P</i> 2 ₁ / <i>n</i> | <i>P</i> 2 ₁ 2 ₁ |
| Flack parameter | 0.027(18) | 0.03(9) | — | 0.016(13) |
| <i>Z</i> | 8 | 2 | 4 | 8 |
| <i>a</i> , Å | 9.6000(5) | 7.436(4) | 15.1089(9) | 13.0441(9) |
| <i>b</i> , Å | 14.2422(7) | 9.474(6) | 6.6275(4) | 15.9282(11) |
| <i>c</i> , Å | 27.0844(14) | 14.125(9) | 16.4442(10) | 18.2980(13) |
| α , ° | 90 | 90 | 90 | 90 |
| β , ° | 90 | 104.082(9) | 98.7620(10) | 90 |
| γ , ° | 90 | 90 | 90 | 90 |
| <i>V</i> , Å ³ | 3703.1(3) | 965.2(10) | 1627.41(17) | 3801.8(5) |
| ρ_{calc} (g cm ⁻³) | 1.258 | 1.206 | 1.325 | 1.302 |
| μ , cm ⁻¹ | 3.19 | 3.06 | 3.57 | 3.25 |
| <i>F</i> (000) | 1504 | 376 | 696 | 1584 |
| $2\theta_{\text{max}}$, ° | 61.03 | 60.22 | 60.06 | 61.06 |
| Reflections collected | 50 072 | 10 584 | 30 094 | 65 941 |
| Independent reflections (<i>R</i> _{int}) | 11 308 (0.0355) | 5331 (0.00) | 4740 (0.0311) | 11 597 (0.0327) |
| Number of reflections with <i>I</i> > 2σ(<i>I</i>) | 10 588 | 3228 | 3981 | 10 557 |
| Parameters | 389 | 195 | 178 | 411 |
| <i>R</i> ₁ [<i>I</i> > 2σ(<i>I</i>)] | 0.0344 | 0.0579 | 0.0484 | 0.0266 |
| w <i>R</i> ₂ (all independent reflections) | 0.0793 | 0.1168 | 0.1022 | 0.0698 |
| GO F | 1.071 | 1.000 | 1.034 | 1.084 |
| $\rho_{\text{min}}/\rho_{\text{max}}$ (e Å ⁻³) | 0.556/−0.323 | 0.873/−0.494 | 0.565/−0.358 | 0.381/−0.197 |



C^3H_2 and C^4H_2 Pro); 2.42 (s, 3H, ArCH₃); 2.95 and 3.14 (dd, 2H, NCH₂Si, $^3J_{HH}$ 15.0 Hz); 2.99 and 3.04 (dd, 2H, NCH₂Si, $^3J_{HH}$ 15.95 Hz); 3.39–3.46 and 3.50–3.57 (two m, 2H, C⁵H₂ Pro); 4.87–4.92 (m, 1H, C²H Pro); 7.28 and 7.79 (two d, 4H, Ar, $^3J_{HH}$ 8 Hz). ¹³C NMR spectrum (CDCl₃, δ, ppm): –0.57 ÷ 0.00 (m, 2SiMe₂); 21.47 (Me); 24.75 (⁴C Pro); 30.89 (³C Pro); 37.96 and 40.41 (two s, NCH₂Si); 48.09 (⁵C Pro); 57.60 (C² Pro); 127.48 (C² and C⁶ Ar), 129.30 (C³ and C⁵ Ar), 136.50 (C¹ Ar), 143.04 (C⁴ Ar), 169.52 (C=O). ²⁹Si NMR spectrum (CDCl₃, δ, ppm): 7.9, 10.4.

2,2,6,6-Tetramethyl-4-(*N*-mesylsarcosinyl)-2,6-disilamorpholine (8c)

Prepared similar to **8a** from 0.83 g of **6c**. Yield 1.3 g (80%) with m.p. 151–153 °C (from heptane–benzene, 7 : 1). Found, %: C 37.28, H 7.24, N 8.64, S 9.51. C₁₀H₂₄N₂O₄SSi₂. Calculated, %: C 37.01, H 7.45, N 8.63, S 9.88. IR spectrum (KBr, ν, cm^{–1}): 1628 s (C=O), 1323 s, 1153 s (SO₂). ¹H NMR spectrum (CDCl₃, δ, ppm): 0.18 and 0.23 (two s, 12H, 2Si(CH₃)₂); 2.79 and 3.06 (two s, 4H, NCH₂Si); 2.98 (s, 3H, NCH₃); 2.99 (s, 3H, SCH₃); 4.13 (s, 2H, NCH₂). ¹³C NMR spectrum (CDCl₃, δ, ppm): –0.37 and –0.19 (two s, 2Si(CH₃)₂); 35.44 (NMe); 37.95 and 39.70 (two s, NCH₂Si); 38.15 (SMe); 51.56 (NCC=O); 165.58 (C=O). ²⁹Si NMR spectrum (CDCl₃, δ, ppm): 8.3, 10.4.

N,N'-Bis(dimethylfluorosilylmethyl)-*N*-mesyl-(*S*)-prolinamide (9a)

Boron trifluoride (0.36 g, 2.5 mmol) was added dropwise to a solution of **8a** (0.88 g, 2.5 mmol) in acetonitrile (5 mL). The reaction mixture was refluxed for 2 h, then evaporated in vacuum. The remaining oil was refluxed with benzene (15 mL), the precipitate was filtered out, and the solution was evaporated in vacuum. The residue was recrystallised from heptane to afford 0.76 g (82%) of **9a** with m.p. 100–101 °C. Found, %: C 34.61, H 6.88, N 7.86, S 8.92. C₁₀H₂₄F₂N₂O₃SSi₂. Calculated, %: C 34.66, H 6.98, N 8.08, S 9.25. IR spectrum (KBr, ν, cm^{–1}): 1610 s, 1505 w (C=O), 1319 s, 1134 s (SO₂). ¹H NMR spectrum (CDCl₃, δ, ppm): 0.22 and 0.31 (two s, 6H, Si^{IV}(CH₃)₂); 0.41 and 0.46 (dd, 6H, Si^{IV}(CH₃)₂, $^3J_{HF}$ 7.67 Hz); 1.86–1.93, 2.03–2.18 and 2.28–2.36 (m, 4H, C³H₂ and C⁴H₂ Pro); 2.44 and 2.59 (dd, 2H, NCH₂Si^V, $^3J_{HH}$ 15.74 Hz); 2.98 (s, 3H, SCH₃); 3.00–3.05 and 3.25–3.30 (two m, 2H, NCH₂Si^{IV}); 3.44–3.5 and 3.58–3.63 (two m, 2H, C⁵H₂ Pro); 4.75–4.77 (m, 1H, C²H Pro). ¹³C NMR spectrum (CDCl₃, δ, ppm): –1.9 ÷ –1.7 (m, Si^{IV}CH₃); 1.1–1.7 (m, Si^VCH₃); 24.95 (C⁴ Pro); 30.93 (C³ Pro); 39.23 (SC); 41.1 ÷ 41.5 (m, CH₂Si^V and CH₂Si^{IV}); 47.72 (C⁵ Pro); 56.59 (C² Pro); 172.51 (C=O). ¹⁹F NMR spectrum (CDCl₃, δ, ppm): –159.15; –121.88. ²⁹Si NMR spectrum (CDCl₃, δ, ppm): –15.5 (d, $^1J_{SiF}$ 252 Hz), 28.9 (d, $^1J_{SiF}$ 284 Hz). ²⁹Si NMR CP/MAS spectrum (δ, ppm): –37.2 (d, $^1J_{SiF}$ 880 Hz), 32.7 (d, $^1J_{SiF}$ 1024 Hz).

N,N'-Bis(dimethylfluorosilylmethyl)-*N*-tosyl-(*S*)-prolinamide (9b)

Prepared similar to **9a** from 1.1 g of **8b**. Yield 0.9 g (80%) with m.p. 87–88 °C (from heptane). Found, %: C 48.23, H 6.80, N 6.15, S 7.20. C₁₈H₃₀F₂N₂O₃SSi₂. Calculated, %: C 48.18, H 6.74, N 6.24, S 7.15. IR spectrum (KBr, ν, cm^{–1}): 1602 s, 1515 w (C=O), 1336

s, 1151 s (SO₂). ¹H NMR spectrum (CDCl₃, δ, ppm): 0.18 and 0.22 (two s, 6H, Si^V(CH₃)₂); 0.41–0.44 (m, 6H, Si^{IV}(CH₃)₂); 1.83–1.93 and 2.05–2.16 (two m, 4H, C³H₂ and C⁴H₂ Pro); 2.43 and 2.51 (dd, 2H, NCH₂Si^V, $^3J_{HH}$ 15.74 Hz); 2.45 (s, 3H, ArCH₃); 3.04–3.08 and 3.52–3.59 (two m, 2H, NCH₂Si^{IV}); 3.35–3.4 and 3.46–3.52 (two m, 2H, C⁵H₂ Pro); 4.78–4.81 (m, 1H, C²H Pro), 7.32 (d, 2H, Ar, $^3J_{HH}$ 8.07 Hz), 7.75 (d, 2H, Ar, $^3J_{HH}$ 8.07 Hz). ¹³C NMR spectrum (CDCl₃, δ, ppm): –1.92 ÷ –1.78 (m, Si^{IV}CH₃); 1.20–1.37 (m, Si^VCH₃); 21.46 (ArMe); 24.89 (C⁴ Pro); 30.63 (C³ Pro); 41.27 (d, CH₂Si^{IV}, $^3J_{CF}$ 16.69 Hz); 41.36–41.47 (m, CH₂Si^V); 48.24 (C⁵ Pro); 55.45 (C² Pro); 127.31 (C² and C⁶ Ar), 129.64 (C³ and C⁵ Ar), 135.89 (C¹ Ar), 143.74 (C⁴ Ar); 172.39 (C=O). ¹⁹F NMR spectrum (CDCl₃, δ, ppm): –159.47; –119.31. ²⁹Si NMR spectrum (CDCl₃, δ, ppm): –19.1 (d, $^1J_{SiF}$ 236 Hz), 28.1 (d, $^1J_{SiF}$ 276 Hz). ²⁹Si NMR CP/MAS spectrum (δ, ppm): –32.0 (d, $^1J_{SiF}$ 251 Hz), 30.7 (d, $^1J_{SiF}$ 292 Hz).

N,N'-Bis(dimethylfluorosilylmethyl)-*N*-mesylsarcosinamide (9c)

Prepared similar to **9a** from 0.80 g of **8c**. Yield 0.73 g (85%) with m.p. 135–136 °C (from heptane). Found, %: C 34.61, H 6.88, N 7.86, S 8.92. C₁₀H₂₄F₂N₂O₃SSi₂. Calculated, %: C 34.66, H 6.98, N 8.08, S 9.25. IR spectrum (KBr, ν, cm^{–1}): 1610 s, 1505 w (C=O), 1319 s, 1134 s (SO₂). ¹H NMR spectrum (CDCl₃, δ, ppm): 0.30 (two s, 6H, Si(CH₃)₂); 0.39–0.43 (m, 6H, Si^{IV}(CH₃)₂); 2.56 and 3.05 (two s, 4H, NCH₂Si); 2.96 (s, 3H, NCH₃); 2.98 (s, 3H, SCH₃); 4.17 (s, 2H, NCH₂). ¹³C NMR spectrum (CDCl₃, δ, ppm): –1.8 (d, SiMe₂, $^2J_{CF}$ 14.5 Hz), 1.2 (s, SiMe₂); 35.3 (NMe); 37.9 and 40.8 (two s, NCH₂Si); 41.4 (SMe); 49.7 (NCC=O); 168.6 (C=O). NMR ¹⁹F spectrum (CDCl₃, δ, ppm): –159.15; –125.46. ²⁹Si NMR spectrum (CDCl₃, δ, ppm): –10.5 (d, $^1J_{SiF}$ 248 Hz), 29.2 (d, $^1J_{SiF}$ 287 Hz).

Single crystals suitable for X-ray diffraction analysis were obtained by recrystallisation from: orthorhombic **8a**—heptane/benzene 3 : 1; monoclinic **8a'**—ethanol; **8c**—heptane/benzene 7 : 1; **9a**—heptane. X-ray diffraction measurements were carried out using Bruker Smart 1000 CCD and Bruker Smart Apex II CCD diffractometers at 100 K. The frames were integrated using SMART and APEX2 program packages.²⁸ The correction for absorption was made using SADABS program.²⁹ The details of crystallographic data and experimental conditions are given in Table 5.

The structures were solved by the direct method by XS program³⁰ and refined by full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation using XL program.³⁰ Atom H20 in **s** was located from the difference Fourier maps and refined freely. All remaining hydrogen atoms were placed in geometrically calculated positions and refined in rigid body model ($U_{iso}(H) = 1.2U_{eq}(CH, CH_2)$, $U_{iso}(H) = 1.5U_{eq}(CH_3)$). The Flack parameter confirms (*S*)-configuration of the proline fragment. Preparation of graphic materials was performed using OLEX2 software package.³¹ Crystallographic data for the structural analysis of **8a**, **8a'**, **8c** and **9a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC nos 1059570–1059573).



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