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STUDIES ON BIOACTIVE ORGANO-SILICON COMPOUNDS

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Abstract

The activity of the research group for biologically active organosilicon compounds is described in the paper. The group is concerned with the investigation of silatranes and their derivatives, N,N′–diarylcyclodisilazanes, silaarylalkylamines. The compounds were synthesized and studied by X-ray diffraction and different spectroscopic techniques.

Keywords: bioactive organosilicon compounds, silatranes, cyclodisilazanes, silaarylalkylamines.

Introduction

The group for bioactive silicon compounds was organized within the research group for silicon chemistry at the Institute for Inorganic Chemistry of the Technical University, Budapest, in 1973. The group deals with the synthesis of organosilicon compounds which are expected to have biological activity, with the investigation of their structure and properties and in some cases of their biological effect. The compounds studied can be divided into three groups:

— Silatranes and their derivatives
— N,N′–diarylcyclodisilazanes
— Silaarylalkylamines

In the present paper some important results of our earlier work are summarized and some recent studies are presented.

Silatranes and Derivatives

Silatranes are cyclic silicon esters of triethanolamines and their derivatives (see *Fig. 1*). These compounds belong to the group of bioactive organosilicon compounds which have no carbon analogs. They have varied biological effects and a characteristic bond structure. Their structure is characterized

by an Si ⇐ N dative bond, pentacovalent silicon and tetrahedral nitrogen atom. The following compounds were synthesized:

— unsubstituted silatranes $RSi(OCH_2CH_2)_3N$
— trimethylsilatranes $RSi(OCH(CH_3)CH_2)_3N$
— silatranones $RSi(OCOCH_2)(OCH_2CH_2)_2N$
— carbasilatranes $RSi(CH_2CH_2CH_2)(OCH_2CH_2)_2N$
— pseudosilatranes $R_2Si(OCH_2CH_2)_2NR'$

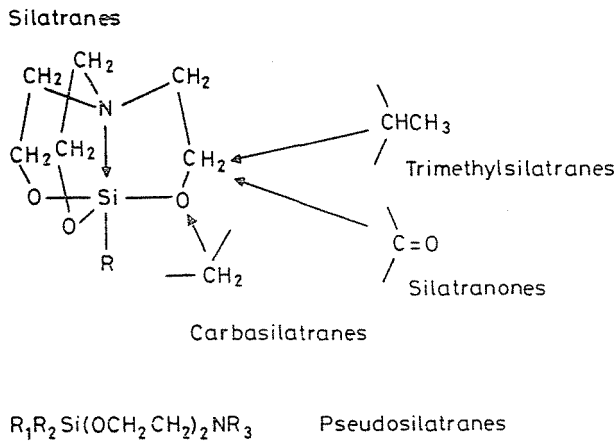


Fig. 1. The structural formula of silatranes and its derivatives

The structure of 17 of the compounds synthesized was determined in cooperation with researchers of the Central Research Institute for Chemistry by X-ray diffraction method. Based on the data it was stated that the Si ⇐ N bond length which is the most characteristic feature of the silatrane molecule depends on the following factors:

— nature of the substituent R bond to Si
— number of equatorial O atoms
— basicity of the N atom
— structure of the five-membered rings
— nature of the substituents on the ring
— steric effects.

Of the six factors the group R has the greatest role in determining the Si ⇐ N distance.

The electron withdrawing or releasing effect of the group was characterized by the Sanderson group electronegativity ($\overline{X}_R$) and an exponential correlation was established between the distance d(Si ⇐ N) and the value of $\overline{X}_R$ [1]. Applying structural data taken from the literature further relationships were deduced by calculation to characterize the structure of the

compounds. These correlations are summarized in *Table 1.* In the table ΔSi is the distance of the silicon atom from the plane of the three equatorial oxygen atoms, while ΔN is the distance of the nitrogen atom from the plane of the three adjacent carbon atoms, i(Si $\Leftarrow$ N) is the modified Wiberg index calculated by the CNDO/2 method.

Table 1
Correlation relationships for study of silatrane structures

d(Si $\Leftarrow$ N)	$= 302.1 \cdot X_R \cdot \exp(-0.257)$	(pm)	$r = 0.804$ [1]
ΔSi	$= 0.488\mathrm{d} - 86.3$	(pm)	$r = 0.990$ [1]
ΔN	$= -0.391\mathrm{d} + 121.4$	(pm)	$r = 0.965$ [1]
α(NSiO)	$= -0.200\mathrm{d} + 126.5$	(°)	$r = 0,964$ [1]
δ_{15_N}	$= -0.678\mathrm{d} - 211.46$	(ppm)	$r = 0.993$ [2]
i(Si $\Leftarrow$ N)	$= -6.16 \cdot 10^{-3}\mathrm{d} + 1.705$		$r = 0.969$ [3]
ΔSi[a]	$= 0.345\mathrm{d} - 58.4$	(pm)	$r = 0.985$ [1]
α(NSiO)[a]	$= -0.158\mathrm{d} + 118.1$	(°)	$r = 0.995$

[a]: for pseudosilatranes

Of the results obtained by other methods the following are worth mentioning. Dipole moments were calculated by the bond momentum method. The bond momentum of the Si $\Leftarrow$ N bond was calculated to be 2.04 Debye and the charge displacement 0.20 e [4]. This was interpreted by assuming that the nitrogen atom donates 10% of its electron pair to the vacant 3d orbital of the silicon atom. Quantumchemical calculations by the CNDO/2 method have shown that the contribution of the *pd* atomic dipole to the resultant dipole of the molecules is 7.7% on the average. The Wiberg indices i(Si $\Leftarrow$ N) determined for the Si $\Leftarrow$ N bond varied between 0.33 and 0.46 which indicated the existence of the chemical bond between the two atoms and the role of the d orbital of the silicon atom [3, 4].

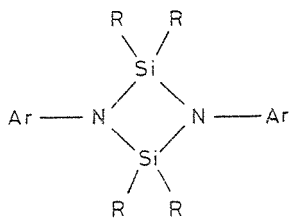
Mass spectra of silatranes have shown that fragmentation usually starts with the cleavage of the Si–R bond. A different fragmentation pattern was observed with fluorosilatrane in which, due to the strong Si–F bond, one of the rings cleaves and $(M-C_2H_3O)^+$ produces the base-peak [5]. In silatranones and in some carbasilatranes one of the rings is cleaved at first and the base-peak is formed with the splitting of CO_2 and C_2H_5 fragments, respectively [6]. These decomposition processes are in accordance with the data of X-ray diffractograms.

Finally it should be mentioned that many of the compounds synthesized were screened for biological activity. *m*- Chlorophenoxysilatrane deserves to be mentioned as a non- toxic substance with an effect similar to that of the known and efficacious chloromethylsilatrane, a drug promoting growth of hair and growth and regeneration of connective tissue

[7]. Germination experiments with white mustard seed have shown that *m*-chlorophenoxysilatrane producing (an increase of 36% compared with the control during 168 hr treatment) and ethoxytrimethylsilatrane (48% increase) are the most effective agents.

N,N′–diarylcyclodisilazanes

Cyclodisilazanes are compounds of favourable properties with an interesting structure containing a four-membered ring. Utilizing their thermal stability heat-resistant polymers are prepared from these compounds. In the present work the N,N′–diarylcyclodisilazanes shown in *Fig. 2* were synthesized for structural studies concerning mainly the structure of the four-membered ring, the spatial arrangement of the atoms bound to the nitrogens, the possibilities of delocalization and the planarity of the molecules. The structure of 8 derivatives was determined by X-ray diffraction method. With the exception of *o*–tolyl derivative all the molecules are planar, i. e. the phenyl groups bound to the nitrogen atoms are coplanar with the four-membered cyclodisilazane ring. In the *o*–tolyl derivative the plain of the four-membered ring is perpendicular to that of the phenyl group, $\rho = 89.6°$ [8]. In the case of *o*–chloro- or *o*–methoxy-substitution a planar structure is formed showing that electron effects rather than steric effects become predominant.



	Ar	R
I	C_6H_5	CH_3
II	o-$CH_3C_6H_4$	CH_3
III	m-$CH_3C_6H_4$	CH_3
IV	p-$CH_3C_6H_4$	CH_3
V	o-ClC_6H_4	CH_3
VI	C_6H_5	C_6H_5
VII	o-$CH_3OC_6H_4$	CH_3
VIII	m-$CF_3C_6H_4$	CH_3

N,N'-diaryl cyclodisilazanes

Fig. 2. The structural formula of N,N′–diarylcyclodisilazanes

Formation of five-membered rings also favours planar structure. This is also proved by the non-bonding distances: Si... Cl 313.7 pm [9], Si... OCH_3 272.3 pm [10] which are smaller than the sum of the van der Waals radii, 390 and 350 pm, respectively.

The conformation in solution was studied by NMR spectroscopy. From the deviation of the measured ^{13}C NMR data from calculated values (non-additivity) the degree of conjugation and the change in the delocalization and spatial arrangement were estimated. It was stated that the dominant conformation in solution is the same as that existing in the crystalline form for the compounds studied: with the exception of the *o*–tolyl derivative, all the molecules are planar [9, 10]. So far no biological effect has been proved for the cyclodisilazanes studied.

Silaarylalkylamines

A number of phenyl-ethyl amine derivatives are used as pharmaceuticals (e. g. adrenaline, dopamine, actedrone, etc.). If one of the carbon atoms in the skeleton is replaced by silicon, silaphenylethylamines are obtained which belong to the group of biologically active silicon compounds 'silapharmaca'. The formula of the compounds synthesized by us is shown in *Fig. 3.*

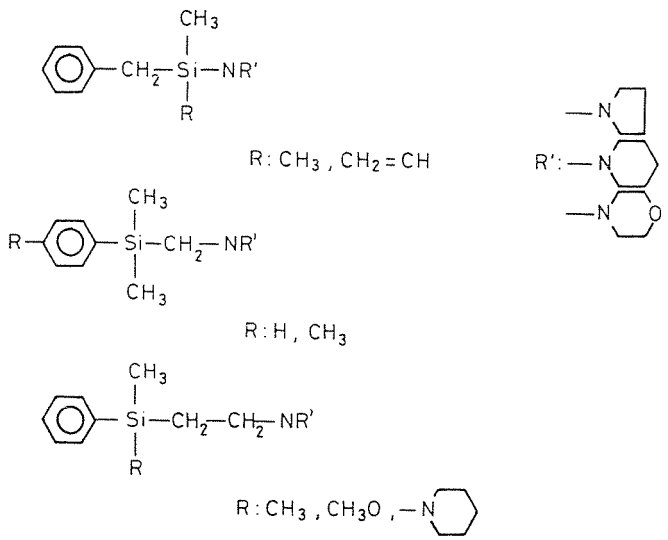


Fig. 3. The structural formula of various silaarylalkylamines

The majority of the compounds are not known in the literature, their synthesis can be considered as a new procedure [11]. The compounds were studied by spectroscopic methods (IR, ^{1}H NMR, MS), and the crystal structures of one of the compounds and that of its carbon analog were determined. (Methyl iodide salts of dimethylphenyl- piperidinomethyl silane and N–(β–phenylethyl)– piperidine [12]). No significant difference was found between the two structures.

Of the silaarylalkylamines prepared benzylaminosilanes are the least stable, since they contain the Si–N bond which is sensitive to moisture and air. The stability of the other two series was much higher.

Finally, some data concerning the activity of the research group for biologically active silicon compounds are summarized in *Table 2.*

Table 2
Scientific activity of the group of bioactive organosilicon compounds

	Publications	Books	Patents	Dissertations	Lectures
Silatranes	45	2	1	6	37
Cyclodisilazanes	16	—	—	6	12
Silaarylalkylamines	1	—	—	1	5

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