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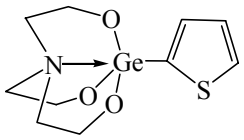
DISORDERING IN THE CRYSTAL STRUCTURES OF THIENYLGERMATRANES

E. Lukevics, L. Ignatovich, and S. Belyakov

*The crystal structure of a series of thienylgermatranes has been studied using X-ray diffraction. Disorder of the thiophene ring in a 2-thienylgermatrane has been established. In the same positions of the unit cell of the crystal there are found both molecules with an O(2)–Ge–C–S torsional angle of -166.8(4)° and molecules in which this angle is 14.0(4)°. The lengths of the transannular N→Ge bonds (2.183-2.283 Å) agrees in value with the values of crystalline germatrane structures with a Ge–C bond. The length of the transannular N→Ge bond (2.248 Å) in 4-(2-thienyl)phenylgermatrane (molecule **A**) is the largest amongst germatranes with a Ge–C_{ar} bond. Introduction of a second thiophene ring into the 2-thienylgermatrane molecule lowers the acute toxicity of the compound by about 27 times (LD_{50} for the 2,2' -bithienylgermatrane = 447 mg/kg).*

Keywords: thienylgermatranes, thienylphenylgermatrane, molecular structure, synthesis, toxicity.

Germanium compounds with an enhanced coordination (germatranes) attract the attention of investigators as model compounds for theoretical organic chemistry on the one hand and as biologically active materials on the other. Hence analysis of the Cambridge crystallographic database has shown that about 50 germatrane structures have been studied and recorded to this time [1-13]. The biological activity of germatranes are governed by the nature of the substituent on the germanium atom, e.g. 2-thienylgermatrane is a highly toxic material with a mean lethal dose in white mice LD_{50} of 16.5 mg/kg whereas its furan analog (2-furylgermatrane) is virtually nontoxic (LD_{50} 2050 mg/kg) [14-19].



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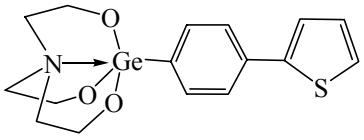

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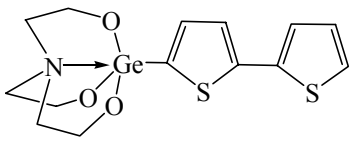

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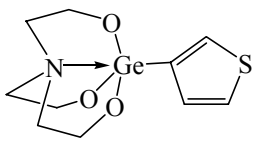

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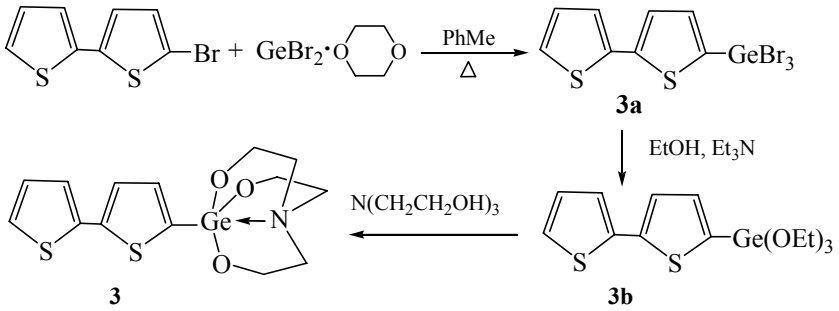
In continuing our stereochemical and crystallographic study of germatranes we have carried out an X-ray analysis of crystals of 2-thienylgermatrane (**1**), 4-(2-thienyl)phenylgermatrane (**2**), 5-(2,2'-bithienyl)-germatrane (**3**), and 3-thienylgermatrane (**4**).

The synthesis and biological activity data for the germatranes **1, 2** and **4** have been reported by us before [13, 17-19]. The bithienylgermatrane **3** was prepared similarly in 48% yield by refluxing 2-bromobithienyl with germanium dibromide dioxanate in toluene for 9 h with subsequent work up of the tribromogermane **3a** with ethanol in the presence of triethylamine and then transetherification of the triethoxy derivative **3b** with triethanolamine:



The basic geometric characteristics of germatranes **1-4** are given in Table 1. Figures 1-4 show the steric models for germatrane molecules with their thermal vibration ellipsoids and atomic numbering. The lengths of the transannular N→Ge bonds agree with those in the crystal structures of germatranes with a Ge–C bond [1, 3].

A disordering of the thiophene ring is seen in the crystalline structure of the 2-thienylgermatrane (**1**) (see Fig. 1). The same position of the crystal unit cell contains both molecules with an O(2)–Ge–C–S torsional angle of -166.8(4)° and those in which this angle is 14.0(4)°. According to data in the Cambridge structural database for compounds containing a 2-thienyl substituent a disordered structure is very typical. Ignoring this effect leads to an artificial lowering (in several case an overestimate) of the bond lengths with the disordered atoms and to high values for the difference factors. Compound **1** is relatively simple and so is a convenient example for the study of this negating effect for structural studies. The conformation of the molecule **1** with the torsional angle of -166.8(4)° is somewhat more favourable than the second conformer. According to data calculated by the molecular orbital method in the MNDO approximation the difference in the energy of the molecules in the first and second conformations is only 0.574 kcal/mol. Rotation of the thienyl ring by 180° causes the sulfur atom and the C(13)–H group to change places, the C(14)–H converting to C(15)–H and *vice versa*. Bearing in mind that the van der Waal volume of the C–H group is close the volume of a sulfur atom both conformations can be realized in the same crystallographic position. This leads to a static disordering in the

TABLE 1. Important Geometric Characteristics of the Molecules **1-4**

Compound	*l*, Å			N→Ge–C angle, deg.
	N→Ge	Ge–C	Ge–O (mean)	
1	2.187(5)	1.945(5)	1.789(4)	177.7(2)
2A	2.248(4)	1.948(5)	1.790(4)	178.8(2)
2B	2.219(4)	1.938(5)	1.787(3)	178.2(2)
3A	2.194(2)	1.948(3)	1.779(2)	179.7(3)
3B	2.183(2)	1.952(3)	1.784(2)	179.2(2)
3C	2.183(2)	1.937(3)	1.782(2)	179.1(2)
4	2.203(2)	1.946(2)	1.798(1)	178.06(7)

crystal structure. The values of the *g*-factors which identify the population densities of the atoms are 0.65 for S(16) and C(13) and 0.35 for atoms S(16') and C(13').

A similar disordering can also be seen in other 2-substituted thiophenes if the energy of the two conformations differing in the value of the torsional angle S–C–atom1–atom2 by 180°C are about the same.

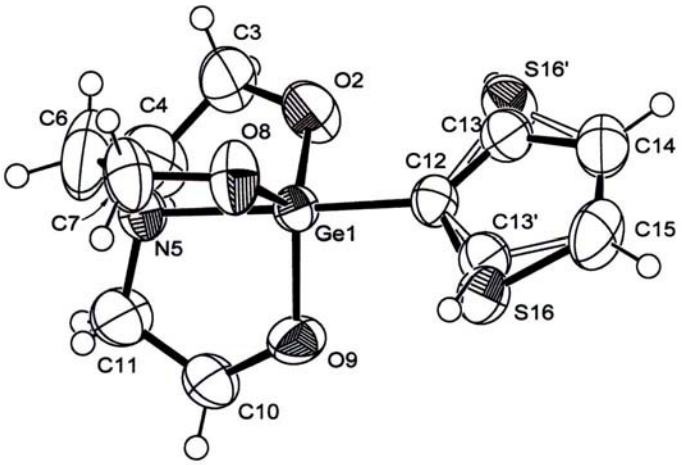


Fig. 1. X-Ray structure of the 2-thienylgermatrane molecule **1** with atomic numbering.

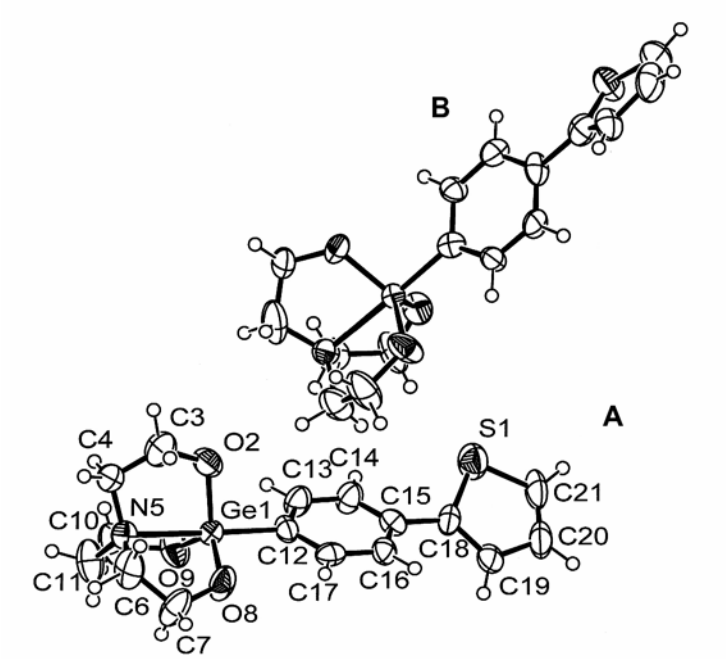


Fig. 2. X-Ray structure of the 4-(2-thienyl)germatrane molecule **2** with atomic numbering (numbering scheme for the atoms of the molecule **B** similar to molecule **A**).

Two molecules are found in the independent part of the unit cell of the crystals of the thienylphenylgermatrane **2**. In the case of the bithienylgermatrane **3** there are three molecules and one of these (molecule **A**) is disordered. In the crystal structure **2** the dihedral angles between the planes of the thiophene and benzene ring are 145.4(9)° (molecule **A**) and -36.0(9)° (molecule **B**).

However, these molecules occupy different crystallographic positions and are not disordered in the given structure. The length of the transannular N→Ge bond (2.248(4) Å) in structure **2** (molecule **A**) is the largest amongst germatranes with a Ge–C_{ar} bond.

In the crystal structure **3** the torsional angles S–C(15)–C(16)–S(2), characterizing the conformation of the bicyclic system, are -175.3(8)° (molecule **B**), and -143.3(9)° (molecule **C**). In the disordered molecule **A**, where both transoid and cisoid conformations are observed, these angles are 136.0(9)° (transoid) and -43.3(14)° (cisoid).

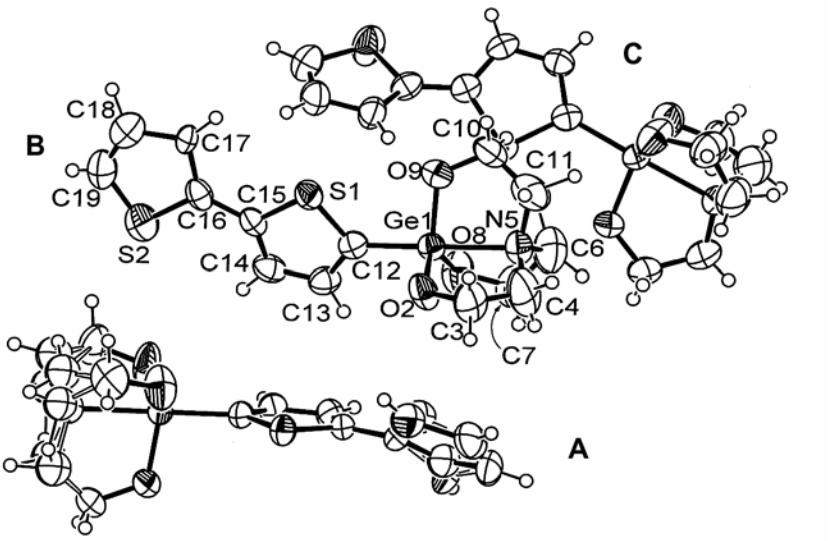


Fig. 3. X-Ray structure of the 5-(2,2'-bithienyl)germatrane molecule **3** with atomic numbering (numbering scheme for the atoms of the molecules **A** and **C** similar to molecule **B**).

A literature review [21] indicates that the typical conformation of bithiophenes is transoid. This is also confirmed in compound **3** in whose crystal structure the fraction of transoid configuration is 88% with only 12% cisoid. According to MNDO type quantum-chemical calculations the energy of the molecule **A** in the cisoid conformation exceeds that in the transoid conformation by 3.479 kcal/mol. This can explain the predominance of the transoid conformation.

The molecule **A** shows a dynamic disordering of the atrane system (see Fig. 3) where the C(4), C(6), and C(11) atoms are found in two crystallographic positions with $g = 0.5$. Thus in agreement with the results of work in [20], in molecule **A** the N→Ge bond length is somewhat greater than in molecules **B** and **C**.

The crystalline structure of the 3-thienylgermatrane (**4**) in the investigated compounds is characterized by the highest density and packing coefficient. In such structures a dynamic disordering is unlikely hence the atoms of the atrane system in **4** are not disordered. Structure **4** also does not show a static disordering of the thiophene ring even though free rotation of the thiophene ring around the Ge(1)–C(12) bond can occur in the isolated molecule **4**. As a result of MNDO calculations for rotation of the thiophene ring around Ge(1)–C(12) the molecular energy changes only within the range 0.487 kcal/mol. The C(14)–H(14) does not coincide with atom S(1), however, with rotation around this bond by 180° hence the molecular form is different and the molecules cannot be found in the same crystallographic positions in the crystal lattice. This conclusion can persist in other 3-substituted thiophenes. Hence in these compounds a static disordering in thiophene rings is not observed.

Study of the acute toxicity of the 5-(2,2'-bithienyl)germatrane (**3**) showed that the introduction of a second thiophene ring into the 2-thienylgermatrane ring lowers the acute toxicity of the compound by about 27 times (LD_{50} = 447 mg/kg). The acute toxicities (LD_{50}, mg/kg) for the studied compounds were found to be in the order: 2-thienyl- (16.5) > 3-thienyl- (89) > 4-(2-thienyl)phenyl- (324) > 5-(2,2'-bithienyl)germatrane (447).

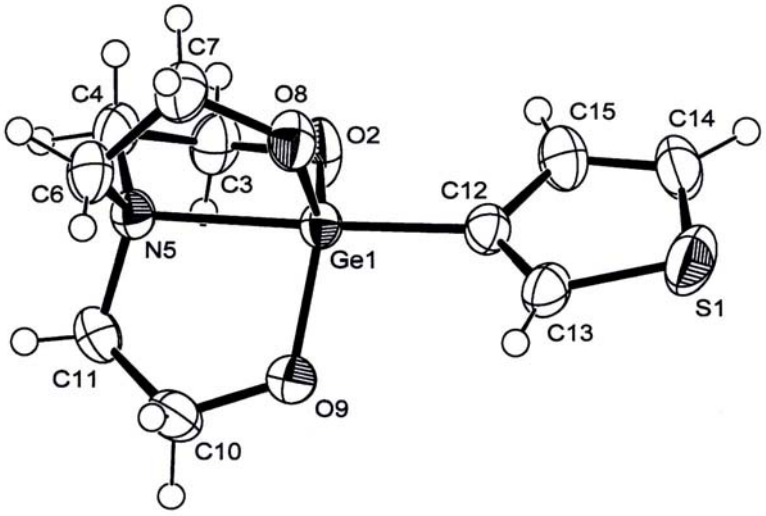


Fig. 4. X-Ray structure of the 3-thienylgermatrane molecule **4** with atomic numbering.

TABLE 2. Crystallographic Data and Refinement Parameters for the Crystalline Structures of **1-4**

Parameter	Structure			
	1	**2**	**3**	**4**
Empirical formula	$C_{10}H_{15}GeNO_3S$	$C_{16}H_{19}GeNO_3S$	$C_{14}H_{17}GeNO_3S_2$	$C_{10}H_{15}GeNO_3S$
M	301.89	377.99	384.01	301.89
Crystal color	Colorless	Colorless	Yellowish	Colorless
Size, mm	0.09×0.18×0.33	0.18×0.25×0.27	0.12×0.43×0.49	0.19×0.26×0.27
Crystal symmetry	Rhombic	Rhombic	Rhombic	Monoclinic
Crystal lattice parameters				
a, Å	9.4852(2)	20.7296(4)	14.4450(1)	8.6030(2)
b, Å	12.4244(3)	6.6956(1)	20.3395(2)	12.5280(3)
c, Å	10.3087(2)	23.4483(5)	32.8724(4)	11.0178(3)
β, deg	90	90	90	127.207(1)
V, Å^3	1214.86(5)	3254.6(1)	9658.0(2)	1187.20(5)
Space group	*P na*2$_1$	*P na*2$_1$	*P bca*	*P* 2$_1$/*c*
Z	4	8	24	4
F(000)	616	1552	4703	616
Density, d, g/cm^3	1.651	1.543	1.585	1.689
μ, mm^{-1}	2.68	2.02	2.17	2.75
$2\theta_{max}$	60.0	55.0	60.0	55.0
Number of reflections				
measured	3552	7359	24974	5162
independent	1982	4188	14981	2834
used	1410 ($I > 2\sigma(I)$)	2273 ($I > 3\sigma(I)$)	8647 ($I > 2\sigma(I)$)	2283 ($I > 3\sigma(I)$)
Number of refinement parameters	145	397	580	166
R-factor	0.052	0.053	0.049	0.030
*wR*2	0.124	0.124	0.222	0.086

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WH-90/DS (90 MHz) instrument using DMSO-d_6 and with TMS as internal standard. Mass spectra were recorded on an HP 6890 GC-MS spectrometer with an electron ionization energy of 70 eV.

Conformational quantum chemical calculations using the self consistent field method in the MNDO approximation [22] were carried out using the method described in [20].

The X-ray analysis of compounds **1-4** was carried out using a Nonius KappaCCD automatic diffractometer (accumulated at room temperature, molybdenum irradiation with λ = 0.71073 Å, graphite monochromator, φ and ω scanning). A correction for the absorption of the X-rays after indexing all of the facets of the crystal polyhedron was carried out for good, cut edged crystals of **3**. The NUMABS program in the maXus package [23] was used for the calculation. The structure was solved by a direct method with refinement in a full matrix least squares analysis using the maXus package [23] for compounds **2** and **4** and SHELXL [24] for compounds **1** and **3**. The basic crystallografic cheracteristics, accumulation conditions, and refinement parameters are given in Table 2.

Crystals of the germatranes **1**, **2**, and **4** for X-ray analysis were grown from chloroform and the germatrane **3** from ethyl acetate.

5-(2,2'-Bithienyl)germatrane (3). A mixture of 5-bromo-2,2'-bithienyl (0.24 g, 1 mmol) and germanium dibromide dioxanate (0.42 g, 1.3 mmol) in absolute toluene (1.5 ml) were placed in a 5 ml "Pierce" microreactor in a stream of argon, tightly closed, and refluxed for 9 h to give the 5-(2,2'-bithienyl)-tribromogermane whose formation was monitored by chromato-mass spectrometry. Mass spectrum of **3a**, *m/z* (*I*, %): 476 $[M]^+$ (47), 399 $[M^+$-Br] (27), 246 (32), 232 [$GeBr_2$] (10), 153 [GeBr] (74), 121 (100), 107 (14), 93 (12), 69 (44), 45(45). Without separation from the reaction mixture the **3a** obtained was treated with ethanol (0.2 g, 4.3 mmol) in the presence of triethylamine (0.45 g, 4.5 mmol) in absolute diethyl ether (4 ml) under an argon atmosphere at 0 to -5°C. The temperature was raised to room temperature for 2 h, cooled to 0°C, and the Et_3N·HBr salt was filtered off. Transetherification of the 5-(2,2'-bithienyl)triethoxygermane with triethanolamine (0.15 g, 1 mmol) gave compound **3** (0.18 g, 48%) as white crystals with mp 169-171°C. Recrystallization from ethyl acetate gave mp 170-171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.86 (6H, t, *J* = 6.6, NCH_2); 3.67 (6H, t, *J* = 6.6, OCH_2); 7.00-7.24 (4H, m, SC_4H_3, SC_4H_2); 7.47 (1H, m, SC_4H_3). Found, %: C 43.70; H 4.37; N 3.60; S 16.60. $C_{14}H_{17}GeNO_3S_2$. Calculated, %: C 43.79; H 4.46; N 3.65; S 16.70.

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