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Synthesis and characterization of ferrocenylalkoxygermatranes and crystal structures of $FcCH_2OGe(OCH_2CH_2)_3N$ and $FcCH(CH_3)OGe(OCH_2CH_2)_3N$[1]

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Germatranes bearing a ferrocenylalkoxyl moiety have been obtained by the reaction of $HOGe(OCH_2CH_2)_3N$ with various ferrocenyl alcohols. A convenient new synthesis method of $FcCH_2OGe(OCH_2CH_2)_3N$ was reported. $FcCH_2OGe(OCH_2CH_2)_3N$ was prepared in 93% yield when $FcCH_2OH$ reacted with $HOGe(OCH_2CH_2)_3N$ in chloroform at room temperature in the presence of molecular sieves (3 Å) as a dehydrating agent. All compounds were characterized by elemental analysis, ^1H NMR and IR spectroscopy. The molecular structures of $FcCH_2OGe(OCH_2CH_2)_3N$ and $FcCH(CH_3)OGe(OCH_2CH_2)_3N$ have been determined by X-ray diffraction. The antitumor activities of $FcCH_2OGe(OCH_2CH_2)_3N$ and p-$FcC_6H_4CH_2OGe(OCH_2CH_2)_3N$ were determined. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: germatranes; crystal structure; ferrocene; ferrocenyl alcohol; bioactivity

INTRODUCTION

Since the discovery of the drug ^{132}Ge in 1970s, ^{132}Ge has been proved to obtain many bioactivities, such as antitumor activities,[1] inducing to produce interferon,[2] inhibiting falling sickness and hyperkinesias,[3] preventing and curing sugar diabetes, etc.[4] Since then, many organogermanium compounds have been investigated. The germatrane compound is an important one of these. The synthesis and properties of functionalized germatranes[5–8] have been investigated in recent years. It has been shown that the majority of organogermanium compounds possess low toxicity.[9]

Ferrocene and its derivatives have been attracting much attention for their use in catalysis, organic synthesis, and new materials (such as liquid crystals and polymers).[10] Incorporation of a ferrocene fragment into a molecule of an organic compound often leads to unexpected biological activity,[11] which is due to their different membrane-permeation properties and anomalous metabolism.[12–15] Moreover, the stability and nontoxicity of the ferrocenyl moiety are particular interesting, rendering such drugs compatible with other treatment.[16–18]

Our research group also reported the synthesis and structure of germatranes.[19,20] We found that trialkyltin β-2,8,9-trioxa-5-aza-1-germyltricyclo[3.3.3.0^{1,5}]undecanyl propionates have good acaricidal and herbicidal activities and display fungicidal activities for plant diseases.[21] Recently, we reported that 1-ferrocenecarboxysilatranes exhibit weak antibacterial activity,[22] diorganotin ferrocenoates[23] show high inhibiting activity for KB cells and Bel-7402 cells, and ferrocenoylphenylureas possess weak larvicidal activity.[24] Until now the reaction of $HOGe(OCH_2CH_2)_3N$ with ferrocenyl alkoxy has not been studied in a similar way. Therefore, we introduce a ferrocenyl alkoxyl moiety to germatranes that will give an opportunity to study their interaction. Here, we introduce the synthesis, structure and bioactivities of ferrocenylalkoxygermatranes and report a new method, which is carried out under mild conditions, to synthesize $FcCH_2OGe(OCH_2CH_2)_3N$ in good yield.

RESULTS AND DISCUSSION

The methods used for the synthesis of 1-alkoxygermatranes usually use germanium tetrachloride as a starting material. But germanium tetrachloride is expensive, unstable and the

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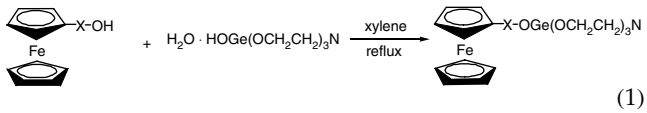
yields are low. Here, we used stable material–germanium dioxide to prepare stable 1-hydroxygermatrane.[25] A method[5] reported previously for the synthesis of 1-alkoxygermatranes was used to convert 1-hydroxygermatrane to 1-ferrocenylalkoxygermatranes (Equation (1)). A novel synthetic method of compound **I** by condensation reaction of ferrocenylmethanol with 1-hydroxygermatrane in $CHCl_3$ using molecular sieves (3 Å) as dehydrating agent at room temperature in good yield (Equation (2)) is described. This new and highly efficient method enjoys a number of advantages in which the reaction is carried out under mild conditions, starting materials are cheap and easily prepared and the experimental procedure is very simple. However, compounds **II** and **III** were not obtained when using molecular sieves (3 Å) as dehydrating agent at room temperature. It may be that the reactions for synthesizing compounds **II** and **III** occur under heating conditions.

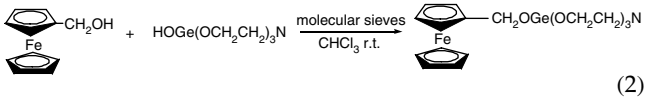
Method A:



(1)

where X = $-CH_2-$ (**I**), $-CH(CH_3)-$ (**II**), *p*-$C_6H_4-CH_2-$ (**III**).

Method B:



(2)

All compounds are yellow crystals. They are stable under ordinary conditions. The compounds are easily dissolved in organic solvents, such as chloroform, dichloromethane, acetonitrile and dimethyl sulfoxide, but do not dissolve in *n*-hexane or petroleum ether.

The IR spectra of these compounds have been recorded in the range of 400–4000 cm^{-1}. The absorption bands can be assigned on the basis of earlier publications.

The IR spectroscopic data provide further support for the molecular constitution of the title compounds. The broad absorption region at 2500–3200 cm^{-1} of O–H in the corresponding alcohol disappeared. In the spectra, medium to weak bonds in the region 2800–2950 cm^{-1} are assigned to vibration absorption of C–H. The bending vibration of C–H is observed in the 1350–1450 cm^{-1} region. The strong intense band near 1290 cm^{-1} is due to C–O vibrations. Absorption bands of the region 1000–1100 cm^{-1} are due to the stretching vibrations of C–C, C–O and C–N. Two strong, intense bands assigned to vibration of the Ge–O bond are observed, one near 903 cm^{-1} and the other near 930 cm^{-1}.

All the compounds were completely characterized by ^1H NMR spectroscopy. The ^1H NMR data of the title compounds are listed in Table 1. The signals of the methylene protons of the germatrane skeleton appear in the ^1H NMR spectra as two triplets at 2.88 ppm (NCH_2) and 3.86 ppm (OCH_2), forming an A_2X_2 system. Comparing the above protons with those of 1-hydroxygermatrane, we found an upfield shift (0.1 ppm) in the ^1H NMR spectra. On the other hand, on comparing the title compounds with the corresponding alcohols we find a downfield shift for the protons of R groups. This indicates that the ferrocenylalkoxyl group is a donor group when it combines with germatrane.

All the protons in the compounds have been identified, and the total number of protons calculated from the integration curve tallies with what was expected from the molecular formula.

Yellow, needle-like crystals of the compounds **I** and **II** were recrystallized from CH_3CN. Figure 1 shows the molecular structure of compound **I** and gives the atom numbering scheme. The molecular structure of compound **II**, along with the atom numbering scheme, is depicted in Fig. 2. Selected bond distances and angles of the two compounds are listed in Tables 2 and 3. The two compounds possess the usual skeleton containing a five-coordinate germanium atom. The N(1)–Ge(1)–O(4) angles of compounds **I** and **II** are 178.3° and 174.51° respectively. The germanium atoms of compounds **I** and **II** are displaced 0.1689 Å and 0.1783 Å respectively from the center of the plane defined by O(1), O(2), O(3) towards O(4). The stereochemistry of germanium is distorted trigonal

Table 1. ^1H NMR data of the compounds

No.	C_5H_5	C_5H_4	OCH_2	NCH_2	R [protons of corresponding alcohols]
I	4.17 (s, 5H)	4.2 (s, 2H); 4.35 (s, 2H)	3.84 (t, 6H, $^3J_{HH} = 5.4$ Hz)	2.87 (t, 6H, $^3J_{HH} = 5.6$ Hz)	4.57 (s, 2H) [4.44 (s, 2H)]
II	4.08 (s, 5H)	4.18 (s, 2H); 4.19 (s, 2H)	3.85 (t, 6H, $^3J_{HH} = 5.6$ Hz)	2.89 (t, 6H, $^3J_{HH} = 5.8$ Hz)	1.49 (d, 3H, $^3J_{HH} = 6.2$ Hz); 4.68 (tetra, 1H, $^3J_{HH} = 5.6$ Hz) [1.43 (d, 3H); 4.52 (tetra, 1H)]
III	4.03 (s, 5H)	4.26 (s, 2H); 4.61 (s, 2H)	3.89 (t, 6H, $^3J_{HH} = 5.6$ Hz)	2.13 (t, 6H, $^3J_{HH} = 5.6$ Hz)	4.87 (s, 2H); 7.32–7.40 (tetra, 4H, $^3J_{HH} = 5.6$ Hz) [4.65 (2H, s); 7.25–7.44 (4H, tetra)]
$HOGe(OCH_2CH_2)_3N$			3.94 (t, 6H)	2.98 (t, 6H)	

bipyramidal. The Ge–N lengths of the two compounds are 2.133 Å and 2.164 Å respectively. Both these figures agree with that of 1-alkoxygermatranes.[9] Compound **II** is a racemic form.

The antitumor activities of compounds **I** and **III** were determined *in vitro* against KB cells and Bel-7402 cells at a concentration of 5 μg ml^{-1}. The relative inhibitions were 7.12% and 20.20% respectively for compounds **I** and **III** against KB cells and −2.74% and −4.55% respectively for compounds **I** and **III** against Bel-7402 cells. The data indicate that compounds **I** and **III** possess potential antitumor activity against KB cells. The negative values found with Bel-7402 cells indicate that the mean optical density of the drug-treated cells was greater than that of untreated cells, i.e. the drug promoted growth of some tumor cells. Compared with compound {*n*-$Bu_2Sn[O_2CCH(2\text{-}ClC_6H_4)CH_2Ge(OCH_2CH_2)_3N]_2$}O, whose IC_{50}s against KB cells and Bel-7402 cells are 4.8 μg ml^{-1} and 6.4 μg ml^{-1} respectively,[25] the antitumor activities of the compounds **I** and **III** were lower.

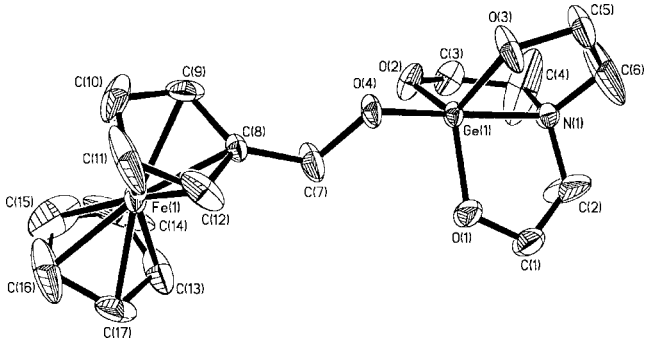


Figure 1. The molecular structure of $FcCH_2OGe(OCH_2CH_2)_3N$.

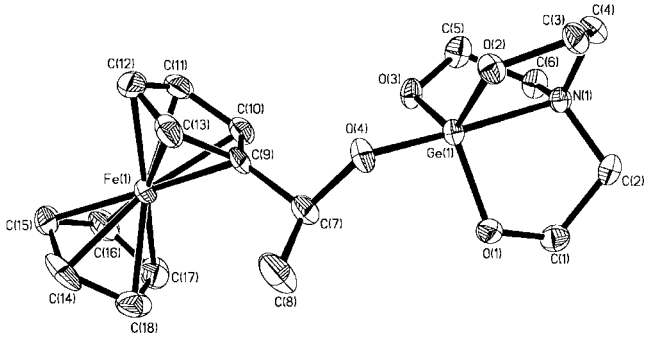


Figure 2. The molecular structure of $FcCH(CH_3)OGe(OCH_2CH_2)_3N$.

Table 2. Selected bond lengths (Å) of compound **I** and **II**

	I	II
Ge(1)–O(1)	1.762(6)	1.804(3)
Ge(1)–O(2)	1.782(6)	1.794(3)
Ge(1)–O(3)	1.750(6)	1.793(3)
Ge(1)–O(4)	1.773(5)	1.783(3)
Ge(1)–N(1)	2.133(6)	2.164(3)
O(1)–C(1)	1.371(10)	1.428(5)
O(2)–C(3)	1.379(10)	1.422(5)
O(3)–C(5)	1.390(10)	1.418(5)
O(4)–C(7)	1.412(10)	1.450(5)
N(1)–C(2)	1.397(12)	1.485(5)
N(1)–C(4)	1.428(13)	1.486(5)
N(1)–C(6)	1.408(13)	1.469(5)

Table 3. Selected bond angles (°) of compound **I** and **II**

	I	II
N(1)–Ge(1)–O(1)	85.8(3)	84.85(13)
N(1)–Ge(1)–O(2)	83.9(3)	83.92(13)
N(1)–Ge(1)–O(3)	83.9(3)	84.18(13)
N(1)–Ge(1)–O(4)	178.3(3)	174.15(13)
O(1)–Ge(1)–O(2)	118.7(3)	118.97(14)
O(1)–Ge(1)–O(3)	119.1(4)	115.48(14)
O(1)–Ge(1)–O(4)	95.2(3)	97.57(14)
O(2)–Ge(1)–O(3)	119.5(4)	122.63(14)
O(2)–Ge(1)–O(4)	96.9(3)	90.60(14)
O(3)–Ge(1)–O(4)	94.4(3)	99.13(14)
Ge(1)–O(1)–C(1)	117.8(6)	116.4(3)
Ge(1)–O(2)–C(3)	118.2(5)	118.6(3)
Ge(1)–O(3)–C(5)	119.0(6)	116.7(3)

EXPERIMENTAL

Instruments

The title compounds were synthesized under a nitrogen atmosphere. Proton NMR spectra were obtained at 200 MHz using a Bruker AC-P200 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shift values (δ) are given in parts per million. IR spectra were recorded on a Bruker Equinox 55 spectrometer in KBr discs. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas-Hoover melting-point apparatus and were uncorrected.

Reagents

1-Hydroxygermatrane·monohydrate was prepared by the method of Mironov *et al.*[26] The compound is a transparent flake crystal. After recrystallization in $CHCl_3$, the compound changed to a white prism crystal and lost water of hydration. Ferrocenylmethanol and α-ferrocenylethanol were obtained from formyl- and acetyl-ferrocene by reduction at room temperature with sodium borohydride; the two alcohols were yellow needles after they were recrystallized from $CHCl_3$–petroleum ether and had melting temperatures of 74–76 °C (lit. 74–74 °C)[27] and 77–78 °C (lit. 73–75 °C)[28]

respectively, and the yields of the two compounds were 84.3% and 75.3% respectively. *p*-Ferrocenyl-benzyl alcohol was synthesized by reducing *p*-ferrocenyl-benzoic acid with lithium aluminum hydride in tetrahyydrofuran and refluxing for 9 h. The melting temperature and yield of *p*-ferrocenyl-benzyl alcohol were 108–110 °C and 77.7% respectively.

Synthesis of the title compounds

Compound **I** *(method A)*

Under a nitrogen atmosphere, ferrocenyl methanol (0.22 g, 1 mmol) was added to the hot stirred suspension solution of 1-hydroxygermatrane·monohydrate (0.24 g, 1 mmol) in xylene (13 ml). The resulting mixture was stirred and refluxed for 1 h. The water formed was continuously removed by azeotropic distillation. The residue was filtered and the precipitate was washed with *n*-pentane and recrystallized in CH_3CN.

Compounds **II** *and* **III**

These were prepared analogously.

Method B: a mixture of ferrocenyl methanol (0.22 g, 1 mmol), anhydrous 1-hydroxygermatrane (0.24 g, 1 mmol), molecular sieves (3 Å, 2 g) and chloroform (20 ml) was stirred at room temperature for 24 h. The residue was filtered off and the solution was dried. The solid was recrystallized from CH_3CN.

The yields, melting temperatures, state and elemental analyses for the obtained compounds are given in Table 4.

Table 4. Yields and elemental analyses of the title compounds

	Compound	Formula for calc.	State	Yield (%)	M.p. (°C)	Elemental analysis, found (calc.) (%) C	H	N
I	(xylene)	$C_{17}H_{23}FeGeNO_4$	Yellow flakes	90.2	269–270	47.03 (47.07)	5.16 (5.34)	3.27 (3.23)
	($CHCl_3$)			93.0				
II	$C_{18}H_{25}FeGeNO_4$	Yellow needles	78.3	202–203	48.22 (48.28)	5.40 (5.63)	3.30 (3.13)	
III	$C_{23}H_{27}FeGeNO_4$	Red flakes	85.3	233–234	53.99 (54.18)	5.28 (5.34)	2.89 (2.75)	

Table 5. Crystallographic data for the compound **I** and **II**

	II	**II**
Empirical formula	$C_{17}H_{23}FeGeNO_4$	$C_{18}H_{25}FeGeNO_4$
Crystal system, space group	Orthorhombic, *Pbca*	Monoclinic, $P2_1/c$
Unit cell dimensions		
a (Å)	11.210(5)	13.013(4)
b (Å)	26.060(11)	13.521(5)
c (Å)	11.510(5)	11.274(4)
α (°)	90	90
β (°)	90	114.089(5)
γ (°)	90	90
V(Å^3)	3363(2)	1810.9(10)
Z	8	4
D_{calc}(mg mm^{-3})	1.714	1.643
Absorption coefficient (mm^{-1})	2.672	2.483
F (0 0 0)	1776	920
Crystal size (mm^3)	0.30 × 0.20 × 0.10	0.30 × 0.25 × 0.20
θ range for data collection (°)	2.36–25.33	1.71–25.03
Limiting indices	$-8 \le h \le 13$, $-28 \le k \le 31$, $-13 \le l \le 12$	$-5 \le h \le 15$, $-15 \le k \le 16$, $-13 \le l \le 12$
Reflections collected	12 834	6341
Independent reflections	2941 ($R_{int} = 0.0745$)	3184 ($R_{int} = 0.0451$)
Completeness to $\theta = 25.33°$ (%)	95.9	99.5
GOF	1.024	1.021
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0679$, $wR_2 = 0.1386$	$R_1 = 0.0391$, $wR_2 = 0.0844$
R indices (all data)	$R_1 = 0.0950$, $wR_2 = 0.1500$	$R_1 = 0.0722$, $wR_2 = 0.0946$

X-ray crystallography

Crystals of the compounds **I** and **II** were obtained from acetonitrile solutions. Diffraction measurements of the compounds **I** and **II** were carried out on a Bruker SMART 1000CCD diffractometer operating at 50 kV and 20 mA using Mo Kα radiation ($\lambda = 0.71073$ Å). Data collection at 293 K and reduction were performed using the SMART and SAINT software.[29] An empirical absorption correction (SADABS) was applied to the raw intensities.[30] The crystal structures were determined by direct methods and refined by full-matrix least squares using the SHELXTL-PC program package.[31] Non-hydrogen atoms were subjected to anisotropic refinement. All hydrogen atoms were generated geometrically (C–H lengths fixed at 0.96 Å), assigned appropriate isotropic thermal parameters, and included in structure factor calculations in the final stage of F^2 refinement. A summary of the crystal data is given in Table 5.

Antitumor activities

All cell lines were derived in the Institute of Materia Medica of Chinese Academy of Medical Science and Peking Union Medical College and grown in RPMI 1640 medium with 10% fetal bovine serum, in 5% CO_2 atmosphere. The antitumor activity was assayed by the methylthiazoletetrazolium (MTT) method.[32] The cell lines, human hepatocellular carcinoma (Bel-7402), human nasopharyngeal carcinoma (KB) were used for the screening. All cell lines were seeded into 96-well plates at a concentration of about 40 000 cells/ml and were incubated in 5% CO_2 atmosphere at 37 °C for 24 h. Then the sample (dissolved in dimethylsulfoxide (DMSO) and diluted by water) was added and further incubation was carried out at 37 °C for 72 h. 100 µl of 0.5 mg ml^{-1} MTT was added to each well. After 4 h incubation, the culture medium was removed, and 200 µl DMSO was added to dissolve the insoluble blue formazan precipitates produced by MTT reduction. The plate was shaken for 20 min on a plate shaker to ensure complete dissolution. The optical density of each well was measured at a wavelength of 544 nm. The cytotoxicity was determined by expressing the mean optical densities for drug-treated cells as a percentage of that of untreated cells.

Supplementary material

Crystallographic data for the structures of the compounds **I** and **II** have been deposited with the Cambridge Crystallographic Data Centre, CCDC nos. 220 441 and 220 442 respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-1223-336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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