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Synthesis and Structure of New Types of Organogermanium Compounds Containing α-Amino Acid or α-Aminophosphonic Acid Moieties

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ABSTRACT: *A series of germasesquioxides and germatranes containing α-amino acid or α-aminophosphonic acid moieties was synthesized by the reaction of β-trichlorogermylpropionyl chloride with α-amino acid esters or α-aminophosphonates. The structures of all products were confirmed by ^1H NMR, ^{31}P NMR, and IR spectra, and elemental analyses. The intramolecular monocyclic penta-coordinated structure of the trichlorogermyl intermediate was determined by X-ray diffraction. The X-ray analyses showed that the geometry about the germanium atom was a slightly distorted trigonal bipyramid, and a coordinate covalent bond exists between the oxygen and the germanium atoms.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 73–78, 1999

INTRODUCTION

Some amino acids and α-aminophosphonic acids possess many bioactivities, for example, antibacterial [1], antitumor [2], etc. It is reported in the recent literature that the combination of amino acids and germasesquioxides leads to higher antitumor activity than that of the original compounds [3,4]. For several years, we have focused more attention on the synthesis of new types of germanium compounds containing phosphoryl or phosphonyl groups in order to find new drugs with high efficiency and low toxicity [5–9]. Some of these compounds have been found to have anti-inflammatory or antitumor activities through the preliminary bioassays. Studies on the penta-coordinated germanium compounds are also very attractive to our group. Syntheses and structures of tricyclic and bicyclic penta-coordinated germanium compounds, in which the fifth coordinated bonds are the nitrogen–germanium bonds, have been reported in previous articles [5,6,10,11].

Research introducing the amino acid esters or α-aminophosphonates into organogermanium compounds (including germasesquioxides and germatranes) in a different way has been carried out by our group, and the bioactivities of the target products are being investigated. As part of this work, presented in this article, the preparation of these types of compounds and investigation of the monocyclic intramolecular penta-coordinated structures of β-trichlorogermyl compounds are reported.

RESULTS AND DISCUSSION

The title compounds were synthesized by the condensation of β-trichlorogermylpropionyl chlorides with amino acid esters or α-aminophosphonates in the presence of triethylamine in dichloromethane, followed by the hydrolysis with sodium hydrocar-

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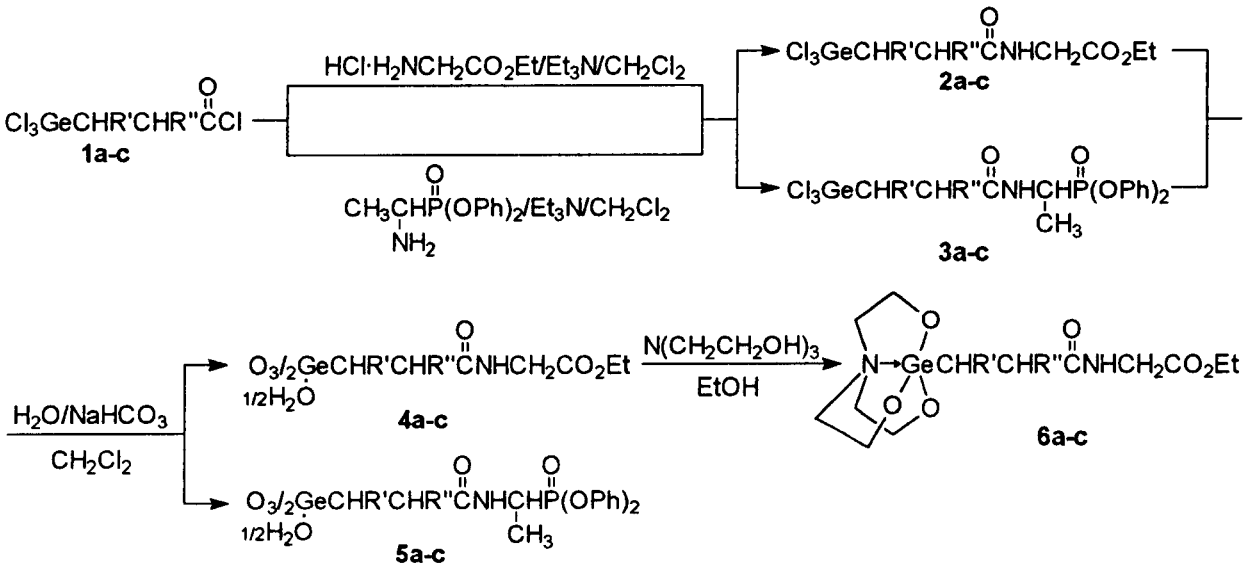
bonate as the acid-neutralizing agent in mixed solvents (Scheme 1). The germasesquioxides containing amino acid ester groups were condensed with triethanolamine to give the corresponding germatranyl derivatives.

The hydrolysis of compounds **2a–c** and **3a–c** must be carried out at pH = 7–8 in order to avoid incompleteness of the reaction when the acidity is too strong, and the formation of a by-product when the basicity is too strong. The pH value of the solution may also affect the degree of polymerization (DP) and solubility of the product. The proper conditions, for example, pH = 7–8, use of mixed solvents, low temperature, etc., led to easy isolation and high purity of the products. After the condensation of **1a–c** with amino acid esters or α-aminophosphonates, washing of the reaction mixture with concentrated hydrochloric acid is very important to purify the products. The ^{1}H NMR, ^{31}P NMR, and IR spectra, and elemental analyses data of compounds **2–6** are listed in Tables 1–3.

We have performed an X-ray single-crystal study on compound **3c**. Essential bond angles and lengths are listed in Table 4, and the molecular structure is shown in Figure 1. The bond length, Ge(1)–O of 2,287(6) Å, is obviously shorter than the intramolecular distance (3.67 Å) calculated by Van der Wall's method [12], which indicates the existence of a Ge–O coordinated bond. The germanium atom has adopted the sp^3d hybridization. The bond angle of O-Ge(1)-Cl(3) is 177.5(2)°. The sum of the three angles, Cl(1)-Ge(1)-C(2), Cl(2)-Ge(1)-C(2), and Cl(1)-Ge(1)-Cl(2), is 353.8°. The six atoms, Ge(1), O, Cl(1), Cl(2), Cl(3), and C(2), form a distorted trigonal bipyramid with the germanium atom as the center. The bond length of Ge(1)–Cl(3) [2.209(3) Å] is a little longer than that of Ge(1)–Cl(1) [2.126(4) Å] and Ge(1)–Cl(2) [2.115(3) Å], and the Cl(3) atom is located at one apical position of the TBP with an oxygen atom at the other. It is different from the fifth coordinated bonds in the tri- or bicyclic [5,6,10,11] penta-coordinated germanium compounds that we have reported previously in that the single cyclic penta-coordinated germanium compounds formed the fifth bond by the interaction of an oxygen atom of the carbonyl group instead of a nitrogen atom with a germanium atom. Single cyclic penta-coordination of the germanium atom can only be achieved when the germanium atom is linked to one or more strongly electron-withdrawing atoms or groups, for example, a chlorine atom, bromine atom, etc. [12,13]. Among the three kinds of penta-coordinated germanium compounds, the tricyclic one has the shortest length of the fifth coordinated bond (2.246 Å) [6,11], indicating the strongest coordination in that kind of compound.

EXPERIMENTAL

^{1}H NMR and ^{31}P NMR spectra were taken on a Bruker AC-P200 spectrometer. ^{1}H chemical shifts are reported in parts per million relative to internal tetra-



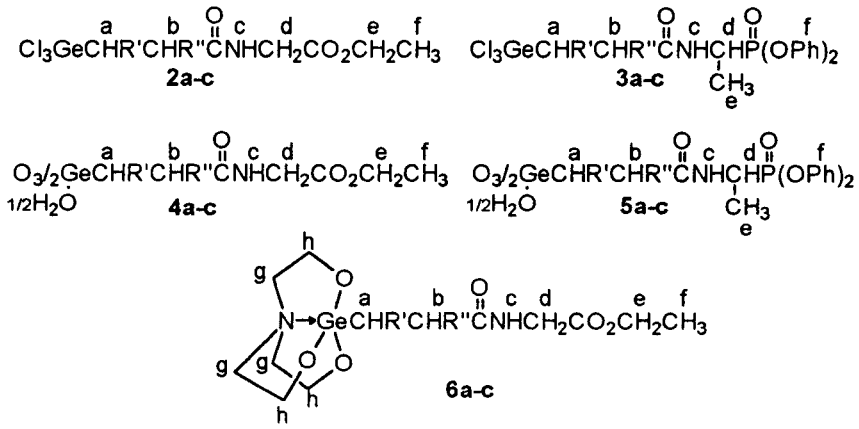
a R'=R"=H; b R'=H, R"=Me; c R'=Me, R"=H.

SCHEME 1

TABLE 1 Yields, Melting Points, ^{31}P Chemical shifts, and Elemental Analyses of Compounds **2–6**

				Elemental Analyses (%)					
				Calculated			*Found*		
Compd.	*M.p. (°C)*	*Yields (%)*	*δp*	*C*	*H*	*N*	*C*	*H*	*N*
2a	sticky liquid	71.3	—	24.97	3.59	4.16	24.56	3.72	4.34
2b	sticky liquid	82.4	—	27.37	4.02	3.99	27.11	4.15	4.02
2c	sticky liquid	73.0	—	27.37	4.02	3.99	27.09	4.09	4.25
3a	173–175	58.6	17.89	39.94	3.75	2.74	39.86	3.79	2.71
3b	166–188	72.0	18.01	41.16	4.03	2.67	41.13	4.03	2.40
3c	158–160	59.7	17.67	41.16	4.03	2.67	41.03	4.05	2.64
4a	>300	51.1	—	31.88	4.97	5.31	32.05	4.52	4.69
4b	>300	70.4	—	34.60	5.44	5.04	34.49	4.96	4.56
4c	>300	63.0	—	34.60	5.44	5.04	34.40	5.15	4.54
5a	>300	69.4	17.17	46.64	4.60	3.20	47.02	4.51	2.86
5b	>300	74.7	17.20	47.85	4.91	3.10	47.56	4.73	2.70
5c	>300	73.5	17.32	47.85	4.91	3.10	48.11	4.55	2.89
6a	148–150	72.4	—	41.43	6.42	7.43	41.58	6.91	7.70
6b	143–145	60.8	—	43.02	6.70	7.17	42.75	6.56	7.21
6c	146–148	58.6	—	43.02	6.70	7.17	42.84	6.25	7.16

TABLE 2 ^{1}H NMR Spectral Data of Compounds **2–6**



Compd.	*Solvent*	δ_H (position, number of peaks)
2a	$CDCl_3$	2.33 (a, t), 2.77 (b, t), 6.70 (c, s), 3.98–4.45 (d and e, m), 1.26 (f, t)
2b	$CDCl_3$	0.98–1.85 (R″ and f, m), 1.98–2.75 (a, m), 2.90–3.20 (b, m), 6.65 (c, s), 3.90–4.50 (d and e, m)
2c	$CDCl_3$	1.00–1.58 (R′ and f, m), 2.38–3.25 (a and b, m), 6.50 (c, s), 3.94–4.40 (d and e, m)
3a	$CDCl_3$	1.90–2.38 (a and b, m), 4.67–4.92 (d, m), 1.41 (e, d of d), 6.82–7.60 (f, m)
3b	$CDCl_3$	1.08–1.25 (R″, m), 1.99–2.30 (a and b, m), 7.66 (c, s), 4.67–4.92 (d, m), 1.40 (e, d of d), 7.00–7.40 (f, m)
3c	$CDCl_3$	1.06–1.24 (R′ime, m), 2.04–2.60 (a and b, m), 8.26 (c, s), 4.66–4.90 (d, m), 1.40 (e, d of d), 6.84–7.46 (f, m)
4a	CF_3CO_2D	3.01–3.36 (a, m), 2.25–2.40 (b, m), 8.38 (c, s), 4.10–4.72 (d and e, m), 1.33 (f, t)
4b	CF_3CO_2D	1.46 (R″, d), 2.78–2.90 (a, m), 3.30–3.52 (b, m), 4.05–4.80 (d and e, m), 1.33 (f, t)
4c	CF_3CO_2D	1.52 (R′, d), 3.38–3.57 (a, m), 2.46–2.92 (b, m), 8.20 (c, s), 4.10–4.65 (d and e, m), 1.34 (f, t)
5a	CF_3CO_2D	2.30–2.41 (a, m), 3.10–3.29 (b, m), 8.70 (c, s), 4.86–5.26 (d, m), 1.60–1.90 (e, m), 6.75–7.75 (f, m)
5b	CF_3CO_2D	1.20–1.92 (R″ and e, m), 2.25–2.47 (a, m), 3.33–3.58 (b, m), 8.51 (c, s), 4.87–5.23 (d, m), 6.75–7.75 (f, m)
5c	CF_3CO_2D	1.54–1.95 (R′ and e, m), 3.05–3.75 (a and b, m), 8.75 (c, s), 5.01–5.25 (d, m), 7.00–7.62 (f, m)
6a	DMSO-d_6	0.60–1.72 (a and f, m), 2.73–3.20 (b and g, m), 3.48–4.61 (d, e, and h, m)
6b	DMSO-d_6	0.71–1.82 (R″, a, and f, m), 2.72–3.19 (b and g, m), 3.50–4.48 (d, e, and h, m)
6c	DMSO-d_6	0.65–1.75 (R′, a, and f, m), 2.70–3.15 (b and g, m), 3.45–4.35 (d, e, and h, m)

TABLE 3 IR Spectral Data of Compounds **2–6**

Compound	*IR(KBr, cm^{-1})*
2a	3315.0, 3090.0, 2947.5, 1732.7, 1623.2, 1559.1, 1405.6, 1375.4, 1289.6, 1207.0, 1094.3, 1018.3, 953.7, 707.8, 598.8
2b	3294.5, 2966.0, 1731.8, 1616.6, 1557.5, 1456.2, 1403.3, 1372.6, 1284.8, 1202.6, 1105.4, 1012.5, 856.8
2c	3310.5, 3076.0, 2965.5, 1731.8, 1621.6, 1546.9, 1444.9, 1407.0, 1374.9, 1292.2, 1086.0, 1015.6, 855.0, 683.8, 558.6
3a	3390.0, 3207.5, 3064.0, 1717.9, 1615.7, 1588.0, 1486.3, 1426.8, 1363.6, 1256.9, 1202.9, 1180.1, 1157.2, 1066.9, 1018.8, 941.0, 767.2, 688.0, 574.3, 538.6
3b	3395.0, 3214.0, 3070.0, 1716.4, 1614.9, 1588.4, 1486.8, 1396.2, 1350.2, 1255.2, 1206.0, 1181.6, 1158.0, 1084.2, 1020.2, 945.2, 761.7, 687.3, 574.4, 536.6
3c	3379.0, 3205.5, 3061.5, 1621.0, 1587.0, 1504.5, 1367.8, 1254.0, 1201.8, 1178.0, 1156.6, 1083.3, 1018.4, 947.1, 763.0, 684.8, 612.8, 534.9
4a	3300.0, 3073.5, 1741.4, 1646.3, 1546.3, 1410.3, 1375.4, 1204.1, 1099.2, 1027.6, 923.9, 795.9, 605.6, 527.6
4b	3280.0, 3062.5, 1732.6, 1641.3, 1536.9, 1394.3, 1321.3, 1194.6, 1103.5, 1017.2, 890.0, 798.4, 750.1, 573.5
4c	3296.0, 2954.0, 1745.7, 1643.0, 1543.5, 1395.5, 1321.7, 1200.4, 1089.1, 1021.2, 891.6, 794.0, 687.3, 597.7
5a	3406.5, 3233.0, 3044.5, 1644.0, 1589.2, 1531.8, 1485.5, 1240.2, 1204.9, 1181.1, 1156.0, 1020.9, 926.9, 888.3, 793.5, 754.9, 682.8, 571.6
5b	3405.5, 3258.0, 3091.5, 1645.8, 1530.7, 1506.0, 1396.2, 1262.5, 1206.9, 1183.9, 1157.7, 1043.9, 928.7, 890.0, 800.2, 753.1, 700.2, 573.9
5c	3404.5, 3250.5, 3046.5, 1640.9, 1589.7, 1485.2, 1394.2, 1251.6, 1205.0, 1180.4, 1155.2, 1020.4, 925.8, 888.6, 754.0, 682.0, 557.0
6c	3387.0, 3264.0, 2955.0, 1741.6, 1634.8, 1552.6, 1452.2, 1419.4, 1357.3, 1274.1, 1196.7, 1102.8, 1073.1, 1019.5, 985.5, 926.5, 897.7, 867.6, 616.3, 585.5, 533.2, 507.7

TABLE 4 Important Molecular Parameters of Compound **3c**

Atoms	*Ge(1)–O*	*Ge(1)–Cl(3)*	*Ge(1)–C(2)*	*Ge(1)–Cl(1)*	*Ge(1)–Cl(2)*	*Cl(1)–Ge(1)–Cl(2)*	*Cl(1)–Ge(1)–C(2)*	*Cl(2)–Ge(1)–C(2)*	*0–Ge(1)–Cl(3)*
bond lengths (Å)[a]	2.287 (6)	2.209 (3)	1.944 (10)	2.216 (4)	2.115 (3)				
bond angles (degree)[a]						112.5 (1)	118.3 (3)	123.0 (3)	177.5 (2)

[a]Numbers in parentheses are estimated standard deviations in the least significant digits.

methylsilane. ^{31}P chemical shifts are reported in parts per million relative to 85% phosphoric acid (external). In both cases, the nuclei that are deshielded relative to their respective standards are assigned a positive chemical shift. IR spectra were taken on a DS-301 spectrometer. Quantitative elemental analyses were carried out on a Yana MT-3 instrument.

A colorless single crystal with approximate dimensions of 0.2 × 0.3 × 0.5 mm was mounted on a glass fiber in a random orientation. The determination of unit cell and the data collection were performed with Mo$K\alpha$ radiation (λ = 0.71073 Å) on an Enraf-Nonius CAD4 diffractometer equipped with a graphite crystal monochromator. A total of 3131 independent reflections were collected in the range of $2 < \theta < 23°$ by $\omega - 2\theta$ scan technique at room temperature, of which 1981 reflections with $I > 3\sigma(I)$ were considered to be observed and used in the succeeding refinement. The correction for *Lp* factors was made. The structure was solved by direct methods (SHELXS 86 and SHELXS 93). Most of the non-hydrogen atoms were located from an *E*-map. The others were determined by successive difference Fourier syntheses. The final refinement by the full-matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms was converged with unweighted and weighted agreement factors of 0.068 and 0.072 with unit weights. The hydrogen atoms were resolved by the theoretical method. The highest peak on the final difference Fourier map had a height of 0.62 e/Å^3. S = 1.07; Δ/σ = 0.438. All calculations were performed on PDP 11/44 and IBM 486 computers using SDP-PLUS program system.

Compounds **1a–c** were prepared according to the literature account [14].

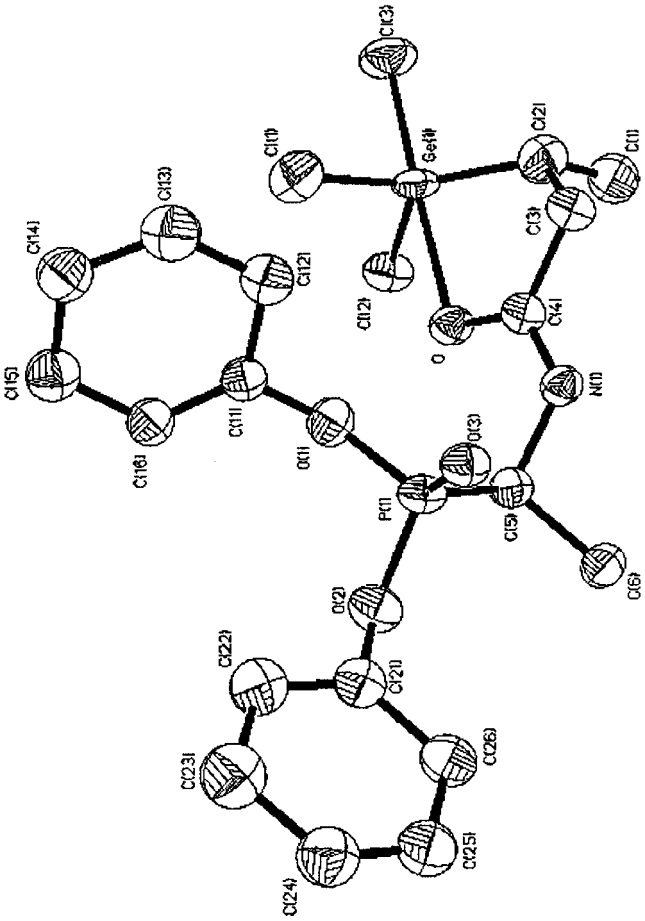


FIGURE 1 The molecular structure of compound **3c**.

General Procedure for the Preparation of Compounds **2a–c**

To a stirred mixture of ethyl glycinate hydrochloride (5 mmol) in dichloromethane (50 mL), triethylamine (10 mmol) was added slowly at −10°C, and after 2 hours, compound 1 (5 mmol) was added. The mixture was stirred at room temperature for 8 hours and then washed with concentrated hydrochloric acid (20 mL). The organic phase was dried with magnesium sulfate overnight and concentrated under vacuum to yield compound **2** as a light yellow liquid.

General Procedure for the Preparation of Compounds **4a–c**

To a solution of compound **2** in dichloromethane (20 mL), a saturated solution of sodium hydrocarbonate was added with vigorous stirring during 8 hours. The pH value of this mixture should be controlled at 7–8 when the hydrolysis has been completed. The precipitate formed was filtered off and washed with water, ethyl ether, and acetone, eventually to yield compound **4** as a white solid.

General Procedure for the Preparation of Compounds **6a–c**

Triethanolamine (3.0 mmol) and compound **4** (2.5 mmol) were mixed in absolute ethanol (30 mL). The mixture was refluxed for 20 hours. Undissolved solid was filtered off, and the filtrate was concentrated to half its volume. A white solid that crystallized from the solution was dried under vacuum to yield compound **6**.

General Procedure for the Preparation of Compounds **3a–c**

Diphenyl α-aminoethylphosphonate (2.5 mmol) and triethylamine (3.0 mmol) were mixed in dichloromethane (40 mL). The mixture was added to compound **1** (2.5 mmol) in dichloromethane (10 mL) at −15–10°C and was then stirred at room temperature for 5–6 hours. After having been washed with concentrated hydrochloric acid (10 mL), the organic phase was dried with magnesium sulfate overnight and concentrated under vacuum. The residue was recrystallized from a mixture of dichloromethane and petroleum ether to yield compound **3** as colorless crystals.

General Procedure for the Preparation of Compounds **5a–c**

The procedure for the preparation of compounds **5a–c** was the same as that used for **4a–c**.

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