0.006, it is possible to estimate the error which would have been encountered in measuring the integral increment for aspartic acid by ignoring the effect of ionization. If $\bar{c}_{\text{Asp}} = 0.03$, the degree of ionization is approximately $\sqrt{K/\bar{c}} = \sqrt{11.75 \times 10^{-5}/0.03} = 0.063$. In this case the percentage error would be 1.6%. For glutamic acid, the percentage error would undoubtedly be smaller, since glutamic is a weaker acid and has a larger integral increment. Yet, in both cases the probable error arising from the omission of ionization considerations would be less than the error encountered in the experimental method.

It is possible, at least in principle, to calculate the ionization constant for a weak acid from the variation of its constituent refractive index increment with concentration. For each concentration equation (18) relates the constituent increment $(n - n_0)/c$ to three unknown quantities k_{HA}, $k_{\text{H}^+\text{A}^-}$ and α. The ionization constant K may be considered as a third unknown in place of α, inasmuch as the two quantities are related by the equation $\alpha = (-K + \sqrt{K^2 + 4Kc})/2c$. Hence, it is possible to calculate K from measurements of $n - n_0$ at three concentrations. For oxalic acid, an ionization constant $K_1 = 0.12 \pm 0.02$ at 1° has been calculated in this manner. There is considerable uncertainty in this value of K because it is necessary in solving the three simultaneous equations to use the small differences between the constituent increments at the three concentrations. These small differences are subject to comparatively large errors which are reflected in the calculated value of the ionization constant. In general, this fact presents a serious limitation to the determination of ionization constants by this method.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DREXEL INSTITUTE OF TECHNOLOGY]

Isopropylgermanium Halides, Oxides and Hydroxide; Grignard Reaction

BY HERBERT H. ANDERSON

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In contrast with the known reaction 4 n-PrMgBr + $GeBr_4$ = n-Pr_4Ge + $4MgBr_2$, an excess of isopropylmagnesium bromide (or chloride) furnishes only partial substitution products i-PrMgBr + $GeBr_4 \rightarrow MgBr_2$ + i-Pr_2GeBr_2 + i-Pr_3GeBr and also furnishes a polymeric solid, essentially $(i\text{-PrGe})_n$. The hydrolysis of i-Pr_3GeBr produces i-Pr_3GeOH, rather than the expected $(i\text{-}Pr_3Ge)_2O$, which results in reaction of the bromide with silver carbonate in dry hexane. Only one form of $(i\text{-}Pr_2GeO)_3$ is now known. Steric effects may explain differences between n-propylgermanium and isopropylgermanium derivatives, and also differences in their formation through the Grignard reaction. New compounds include the following: i-Pr_3GeOH, i-Pr_3GeF, i-Pr_3GeCl, i-Pr_3GeBr, i-Pr_3GeI, i-$Pr_3Ge(NCS)$ and $(i\text{-}Pr_3Ge)_2O$; $(i\text{-}Pr_2GeO)_3$, i-Pr_2GeF_2, i-Pr_2GeCl_2, i-Pr_2GeBr_2 and i-Pr_2GeI_2.

Previous results with tri-n-propylgermanium[1] and di-n-propylgermanium[2] halides and oxides laid the groundwork for an investigation of diisopropylgermanium and triisopropylgermanium halides and oxides. One of the main purposes of this paper was to evaluate the steric factor of two or more isopropyl groups in germanium compounds; germanium lies between tin, which offers no steric troubles, and silicon, which offers definite steric limitations. Difficulties with diisopropyldichlorosilane and triisopropylchlorosilane, as well as failure to obtain tetraisopropylsilane,[3] evidently were due to steric factors. Isopropylgermanium trichloride[4] offered no unusual problem in the synthesis, yet the corresponding isopropyltrichlorosilane and aniline[5] reacted quite slowly, requiring a large excess of aniline and standing for several days for completion of the reaction.

Some salient difficulties with di- and triisopropylgermanium compounds and some differences from the corresponding n-propylgermanium analogs are listed in the following sentences. First, an excess of isopropylmagnesium halide and a smaller amount of germanium tetrahalide produced a mixture of diisopropylgermanium dihalide and triisopropylgermanium halide, also an unexpected, difficultly-redissolvable solid polymer, essentially $(i\text{-PrGe})_n$; tetraisopropylgermanium was absent. Second, the hydrolysis of triisopropylgermanium bromide furnished only triisopropylgermanium hydroxide (which lost water slowly below 200°), unlike the hydrolysis of a tri-n-propylgermanium halide, probably 2 n-Pr_3GeBr + 2 H_2O = 2 n-Pr_3GeOH and then 2 n-Pr_3GeOH = $(n\text{-}Pr_3Ge)_2O$ + H_2O. Third, only one crystalline form of trimeric diisopropylgermanium oxide appeared; this may be due either to steric factors or to a melting point above room temperature. Fourth, esterification with organic acids such as acetic gave impure products; in the successful preparation of triisopropylgermanium acetate (to be reported later separately) esterification with acetic acid cannot be the process. This is unlike the reactions with halogen acids reported herein. Fifth, antimony trifluoride fluorinated diisopropylgermanium dibromide completely and rapidly, while it fluorinated triisopropylgermanium bromide only slightly in an apparently novel approach to the separation problem. Sixth, as expected, the more compact isopropylgermanium compounds generally had lower boiling points and often had higher melting points

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[1] H. H. Anderson, THIS JOURNAL, **73**, 5440 (1951).

[2] H. H. Anderson, *ibid.*, **74**, 2370 (1952).

[3] C. D. Hurd and W. A. Yarnall, *ibid.*, **71**, 755 (1949). Grignard method. For more successful lithium method see H. Gilman and R. W. Clark, *ibid.*, **69**, 1499 (1947).

[4] E. G. Rochow, R. Didtschenko and R. C. West, Jr., *ibid.*, **73**, 5486 (1951).

[5] H. H. Anderson, *ibid.*, **73**, 2351 (1951).

than the corresponding *n*-propylgermanium derivatives. The isopropylgermanium oxides seemed less stable at the normal boiling point than the *n*-propyl analogs were.

All-in-all, perhaps the separation of $i\text{-Pr}_2\text{GeCl}_2$ and $i\text{-Pr}_3\text{GeCl}$ through distillation may be the best method. Distillation of $i\text{-Pr}_3\text{GeOH}$ and $(i\text{-Pr}_2\text{GeO})_3$ under one mm. pressure has recently given fairly pure hydroxide; distillation at higher pressures yielded some $(i\text{-Pr}_3\text{Ge})_2\text{O}$ in each run, thus contaminating the trimeric oxide. This paper relied on the fluoride method, which is not smooth and clean-cut.

Four Grignard reactions reported herein indicated that the smallest amount of polymeric organogermanium solid formed during the addition of isopropylmagnesium chloride to germanium tetrachloride, while addition of germanium tetrabromide to excess isopropylmagnesium bromide furnished the largest amount of polymer. By extrapolation, difficulties should be severe with iodides and inconsequential with fluorides.

Experimental

Grignard Reactions.—Gradual addition of 142 g. of germanium tetrabromide to 1400 ml. of 1.2 *M* isopropylmagnesium bromide in diethyl ether, followed by three hours of reflux at the end, then treatment with excess aqueous sodium hydroxide and next drying over calcium oxide yielded 30 g. of diisopropylgermanium oxide trimer (called trimeric oxide herein), 30 g. of triisopropylgermanium hydroxide and 9 g. of solid polymeric $(i\text{-PrGe})_n$. Similarly, gradual addition of 1200 ml. of 1.1 *M* isopropylmagnesium bromide to 120 g. of germanium tetrabromide ultimately furnished 26 g. of trimeric oxide, 18 g. of hydroxide and 5.5 g. of solid polymer. Similarly, gradual addition of 60 g. of germanium tetrachloride in 350 ml. of benzene to one liter of 2 *M* isopropylmagnesium chloride after standing 40 hours ultimately yielded 14 g. of trimeric oxide, 21 g. of hydroxide and 3 g. of solid polymer. Similarly, the best way consisted of gradual addition of one liter of 1.4 *M* isopropylmagnesium chloride to 40 g. of germanium tetrachloride at 0°, followed by standing a day; the final yield was 15 g. of trimeric oxide, 20 g. of the organogermanium hydroxide and only 1 g. of solid polymer.

Separation Methods.—Before any substantial progress could be made, the non-volatile solid polymer had to be removed from the liquid organogermanium compounds. As actually done the method consisted of distilling a mixture of the triisopropylgermanium hydroxide and the trimeric oxide at 1 mm. pressure. The *ideal method* would have been distillation of the two corresponding organogermanium chlorides under reduced pressure—since the chlorides are the most volatile compounds that are easily prepared (the more volatile fluorides involve aqueous hydrofluoric acid). Once given a polymer-free mixture of chlorides, these chlorides could either have been distilled in a column with at least fifteen theoretical plates, or they could have been converted into the mixture of trimeric oxide and the hydroxide, followed by distillation in a column with five theoretical plates at *one* mm. pressure. (Distillation of the hydroxide under 100 mm. pressure yielded a product accompanied by small amounts of water.)

Heating 150 g. of mixed diisopropylgermanium dibromide and triisopropylgermanium bromide with 200 g. of antimony trifluoride for an hour yielded a distillate at 160–220°. Careful redistillation in a total reflux, variable takeoff column (packed for a height of 500 mm. and a diameter of 8 mm. with tiny squares, 2 mm. on edge, of cut-up stainless steel Stedman packing; with electrical heating provided) furnished 6 ml. of diisopropylgermanium difluoride boiling at 172° flat (uncor., at 760 mm.); then 4 ml. at 172–175°; next about 10 ml. at 190–200° mainly, a mixture; and finally at 234° approximately 55 g. of unaltered triisopropylgermanium bromide. Melting points showed the two chief constituents to be rather pure compounds.

Because of experimental difficulties the fluoride method is not to be recommended; either the chloride method or the hydroxide–trimeric oxide method, the latter at 1 mm. pressure, seemed likely to be better.

Crude Polymer.—This substance made complete recovery of the trimeric oxide difficult. As yet the only known good solvent for the polymeric solid was carbon tetrachloride; after removal of nearly all the trimeric oxide using a mercury vapor pump at very low pressure, the crude polymer was dissolved in boiling carbon tetrachloride. Recrystallization was impossible because of high solubility, despite a slow rate of solution. After cooling and then the addition of a fivefold volume of (60–120°) petroleum ether, the solution was allowed to stand and evaporate spontaneously. Two small first crops of light-orange solid were contaminated. Three center crops of nearly-colorless material amounted to nearly half the total weight, and bore about 57% germanium; the solid did not dissolve in molten camphor. A solution of bromine in carbon tetrachloride converted the polymer into impure isopropylgermanium tribromide, bearing a higher and a lower boiling impurity. Surprisingly, the end fractions of the polymer, upon crystallization from the mixture of carbon tetrachloride and petroleum ether, were strongly contaminated by organogermanium oxides.

Diisopropylgermanium difluoride, as above, had a rather sharp melting point of −24° and a musty, penetrating, obnoxious odor; the 6-ml. sample served in the preparation of the trimeric oxide.

Triisopropylgermanium bromide, also as above, shown qualitatively to be a bromide and shown by m.p. to be rather pure, was finally redistilled once under one mm. pressure. This colorless compound, as well as the corresponding hydroxide and fluoride, had a penetrating, nauseating odor.

Trimeric Diisopropylgermanium Oxide.—Seven grams of pure diisopropylgermanium difluoride and excess hot 3 *M* aqueous sodium hydroxide furnished some emulsion upon shaking for 15 minutes; however, extraction with carbon tetrachloride and then distillation of solvent yielded the organogermanium oxide essentially quantitatively. Distillation of this oxide under 1 mm. pressure at 138–139° produced a center fraction of fine crystals or supercooled liquid. This oxide decomposed slightly at the normal boiling point, turning light-red. No higher-melting crystalline form has appeared in three months of standing.

Diisopropylgermanium Dichloride, Dibromide and Diiodide.—In each case 4 g. of the trimeric oxide and 20 ml. of concentrated aqueous halogen acid were heated to 85° and shaken vigorously for five minutes. After cooling two hours it was possible to separate the organogermanium iodide mechanically from the acid layer; the chloride and bromide both required extraction with (30–60°) petroleum ether, then drying over sodium sulfate and finally distillation of the solvent. Table I lists the distillations; all yields were nearly quantitative.

Triisopropylgermanium Hydroxide.—Fifteen minutes shaking of 12 g. of pure triisopropylgermanium bromide and an excess of warm 6 *M* aqueous sodium hydroxide furnished an organogermanium layer floating on top. Separation of layers and a double extraction of the aqueous layer with (30–60°) petroleum ether followed; distillation of the ether left a nearly quantitative yield of organogermanium hydroxide. Distillation of the hydroxide at 65–66° under 1 mm. yielded a center fraction of some unusual properties; the hydroxide reacted slowly with metallic sodium. At 25° the hydroxide was a clear, colorless liquid of more than average viscosity, but at −15° the hydroxide was ordinarily a highly viscous fluid which changed into the crystalline form only under vigorous stirring. The presumably monomeric liquid formed by melting the crystalline solid was much less viscous than the presumably dimeric "glassy" form. A gas density at 250° indicated a monomer, while the value in camphor showed a dimer.

Triisopropylgermanium Fluoride, Chloride and Iodide.—In each case 5 g. of hydroxide and 15 ml. of concentrated halogen acid were shaken vigorously for 10 minutes at 50° or more; the fluoride was stirred vigorously in a clear plastic container. Light (30–60°) petroleum ether served as an extracting agent in each case; after drying the fluoride with sodium fluoride and sodium sulfate, the organogermanium fluoride was fractionally distilled. Table I lists b.ps. of center fractions.

Bis-(triisopropylgermanium) Oxide.—A suspension of 8 g. of triisopropylgermanium iodide and 12 g. of silver carbon-

TABLE I

PROPERTIES OF NEW ISOPROPYLGERMANIUM DERIVATIVES

Compound[a]	B.p., °C.	M.p., °C.	d^{20}_4	n^{20}	Mol. wt. (camphor) Calcd.	Mol. wt. (camphor) Found	Halogen, % Calcd.	Halogen, % Found	Distilled at °C.	Distilled at Mm.
$(i\text{-}Pr_2GeO)_3$	321	44	...	....	524	540	(41.5	41.3% Ge)	138–139	1
$i\text{-}Pr_2GeF_2$	174	−24	1.222	1.414_6	196.8	202	19.3	19.2, 19.2	173.5	760[b]
$i\text{-}Pr_2GeCl_2$	203	−52	1.268	1.473_8	229.7	235	30.9	31.1, 30.9	203–204	756
$i\text{-}Pr_2GeBr_2$	234	−22	1.670	1.519	318.5	314	50.2	50.3, 50.5	60–61	1
$i\text{-}Pr_2GeI_2$	268	− 9	2.008	1.597	412.6	390	61.5	61.7, 61.4	84–86	1
$i\text{-}Pr_3GeOH$	216	−15	1.077	1.472	218.9	420[c]	(33.1	32.6% Ge)	65–66	1
$i\text{-}Pr_3GeF$	198	−65	1.069	1.440	220.9	225	8.6	8.3, 8.4	197–198	761
$i\text{-}Pr_3GeCl$	222	..	1.110	1.472	237.2	248	15.0	15.3, 15.4	221–222	761
$i\text{-}Pr_3GeBr$	234	−45	1.231	1.485_2	281.8	285	28.4	28.5, 28.4	234–235	751[d]
$i\text{-}Pr_3GeI$	254	4	1.446	1.524	328.8	320	38.5	38.8, 38.6	79–80	1
$i\text{-}Pr_3Ge(NCS)$	277	18	1.112	1.512	260.0	262	22.3	22.2, 22.3	84–86	1[e]
$(i\text{-}Pr_3Ge)_2O$	315 dec.	..	1.112	1.483_6	419.7	407	(34.4	34.6% Ge)	119–120	1

[a] All compounds are colorless. [b] B.p. of fluoride at 760 mm. is uncorrected. [c] Dimeric in camphor; Dumas mol. wt., 236. Later redistilled at 63–64° under 1 mm. [e] Later purified by fractional freezing.

ate in 30 ml. of benzene slowly evolved carbon dioxide. An hour of electromagnetic stirring and gentle reflux followed; after filtration, washing and distillation of solvent, 4.5 g. of crude organogermanium oxide resulted, a yield of 87%. Distilled at 1 mm. pressure, the end fraction was a clear liquid much more viscous than carbon tetrachloride and somewhat more so than triisopropylgermanium hydroxide. This oxide had little odor, formed a glass below 0° without a true m.p.; the oxide turned medium red at 315°.

Triisopropylgermanium Isothiocyanate.—Eighteen ml. of ethereal 3 *M* isothiocyanic acid and 3.5 g. of the hydroxide gave a product still containing soluble thiocyanuric acid; the sodium sulfate method was used.[6] Boiling at 84–86° under 1 mm. pressure, the product contained only 21.3% titratable NCS. Double purification of 1.8 g. of impure product by fractional freezing, with removal of the lower-melting portion, furnished 0.52 ml. of pure triisopropylgermanium isothiocyanate, m.p. 18 ± 1°, with the properties in Table I. An actual d^{30}_4 of 1.100 was the source of a calculated d^{20}_4 in the table. A rejected 1.20 ml. of material melted in the range 5–10°.

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(6) H. H. Anderson, THIS JOURNAL, **73**, 5439 (1951).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Electrostatic Effects in the Combination of Cobalt with Amino Acids[1,2]

BY CHARLES TANFORD AND WILLIAM S. SHORE

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The association constants for complexing of cobalt with glycine, alanine, asparagine and arginine have been obtained from glass electrode measurements by Bjerrum's method. The difference between the results for arginine and alanine can be successfully treated by the Kirkwood–Westheimer theory on the basis of the electrostatic influence of the positively-charged guanidine group of arginine. The data for asparagine cannot be explained in this way, and indicate that the structure of the chelating group ($H_2N–CHR–COO^-$) in this molecule is abnormal. There is an appreciable difference between the association constants for glycine and those for alanine, for which no obvious explanation exists.

Numerous studies have been made comparing the affinity of related substances for hydrogen ion. It has been found that the majority of the results can be satisfactorily explained by the Kirkwood–Westheimer theory[3] involving electrostatic interaction between charged or dipolar substituents and the reacting proton. In the present paper an attempt is made to extend this treatment to the affinity of four amino-acids, all containing the chelating group $H_2N–CHR–COO^-$, for cobaltous ion.

Experimental

The amino acids used in this work were C.P. or the equivalent. Glycine and alanine were Dow Chemical Co. products, asparagine monohydrate and arginine (free base) were obtained from Pfanstiehl Chemical Co. The amino-acids were carefully dried and stock solutions of them in their zwitterion form ($^+H_3N–CHR–COO^-$) were prepared. Arginine was converted into this form by the addition of one equivalent of nitric acid.

Acid dissociation constants of the amino groups were obtained from complete titration curves at constant ionic strength of 0.15. CO_2-free potassium hydroxide[4] was used. These curves served also as criteria of purity for the amino-acids, all of which were judged to be at least 99% pure.

Metal complexing was studied by the method of Bjerrum,[5] involving *p*H measurements on solutions containing known concentrations of the zwitterion form of amino-acid, of added base, and of $Co(NO_3)_2$, with sufficient KNO_3 to bring the ionic strength to 0.15. The removal of ions from solution by complexing was not taken into account in computing ionic strength, since the error introduced in this way was shown by computation to be very small. A Beckman model G *p*H meter with external electrodes was used to make the measurements. All measurements were made at 25.15 ± 0.02°, under a stream of purified nitrogen, to avoid oxidation of the cobalt and contamination by CO_2.

Values of $\bar{n}$, the average number of amino-acid molecules associated with each cobalt ion, were computed from the *p*H readings in the customary manner,[6] using the acid dissociation constants previously determined. The results

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(2) This investigation was supported by a research grant from the National Institute of Health, Public Health Service.

(3) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938); F. H. Westheimer and J. G. Kirkwood, *ibid.*, **6**, 513 (1938).

(4) I. M. Kolthoff, *Z. anal. Chem.*, **61**, 48 (1922).

(5) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941.