The Base-Catalyzed Conversion of Triphenylfluorosilane and Triphenylsilanol to Hexaphenyldisiloxane

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An observation that triphenylfluorosilane on heating with a sodium hydroxide solution yielded hexaphenyldisiloxane rather than the expected triphenylsilanol led us to perform a number of systematic experiments in order to elucidate the mechanism of this reaction. This information seemed to be of particular interest in view of the recent kinetic study of Swain[1] in which the hydrolytic behavior of trityl fluoride was critically compared to that of triphenylfluorosilane. Since in the last mentioned paper the products of hydrolysis were assumed to be the corresponding hydroxy derivatives, our initial observation suggested a possible necessity of reinterpretation of the data of Swain.

Experimental

The amounts of starting materials, reagents and products, as well as the conditions of the experiments are summarized in Table I. The products were isolated by concentration of the reaction solvents and by crystallization of the crude solids. Since the disiloxane is quite insoluble in cold benzene, the crude products were crystallized from hot benzene; the unreacted starting material or the silanol were obtained only on concentration of the benzene solution while any disiloxane could be isolated on cooling of the hot solution. The products were identified by means of mixed melting point determinations.

TABLE I

THE HYDROLYSIS OF TRIPHENYLFLUOROSILANE

Ph_3SiF, mole	NaOH mole	Medium	Reacn. conditions Time, hr.	Temp., °C.	Products Wt., g.	M. p., °C.[a]	Yields of prod., %
0.0035	....	50 cc. of H_2O–Me_2CO (30–70)	120	25	0.9	52–54[b]	*ca.* 90 Ph_3SiF
					.12	140–150[c]	*ca.* 10 Ph_3SiOH
.0035	....	50 cc. of H_2O–dioxane (30–70)	56	100	.01	135[c]	*ca.* 1 Ph_3SiOH
.0035	0.0035	500 cc. of H_2O–Me_2CO (30–70)	24	25	.5	58–60[b]	*ca.* 50 Ph_3SiF
					.08	151	8 Ph_3SiOH
.0035	.03	150 cc. of H_2O–dioxane (10–90)	96	25	.7	151	70 Ph_3SiOH
.0035	.05	50 cc. of H_2O–dioxane (30–70)	12	100	.75	220[d]	81 $(Ph_3Si)_2O$
.0025[e]	.05	50 cc. of H_2O–dioxane (30–70)	6	100	.5	219	76 $(Ph_3Si)_2O$

[a] All melting points are uncorrected. [b] Impure triphenylfluorosilane (m. p. 64°). [c] Impure triphenylsilanol (m. p. 150–151°). [d] Crude product fused partially at 143° and melted completely at 220°. Crystallization gave 0.2 g. of product melting sharply at 219°. Hexaphenyldisiloxane, m. p. 220–221°. [e] Triphenylsilanol was used in this experiment.

The results of the experiments can be summarized as follows. The hydrolysis of triphenylfluorosilane in a neutral or weakly alkaline medium produces only the expected triphenylsilanol. The conversion of the fluoride to hexaphenyldisiloxane occurs under strongly alkaline conditions and at an elevated temperature. Under these conditions triphenylsilanol is converted also to the disiloxane.

The last mentioned observation suggests the following paths of the reactions

(1) $R_3SiF + H_2O$ (or OH^-) $\longrightarrow R_3SiOH$

(2) $R_3SiOH + OH^- \rightleftharpoons R_3SiO(^-) + H_2O$

(3) $R_3SiO(^-) + R_3SiF \longrightarrow (R_3Si)_2O + F^-$

(4) $R_3SiO(^-) + R_3SiOH \longrightarrow (R_3Si)_2O + HO^-$

Reaction (1) does not require any comments.[1] The formation of the disiloxane by (3) or (4) requires the presence of the silanolate ion, and the latter is produced in sufficient concentration only when strong alkali is present. Since sodium salts of silanols are known to hydrolyze in the presence of water, it is clear that in (2) we are dealing with an equilibrium rather than with an unidirectional process. The formation of the diloxane was observed only under elevated temperature conditions. Thus, the temperature factor may be involved in the following fashion: (a) it may affect the equilibrium (2) favorably with respect to the formation of the silanolate ion; and/or, (b) it may be required to provide the energy of activation in the nucleophilic attack of the bulky triphenylsilanolate ion on the silicon atom in reaction (3) or (4). While reaction (4) is rather well substantiated, the formation of the disiloxane from triphenylfluorosilane may proceed by a sequence of reactions (1), (2) and (3), rather than through (4). The success of the last mentioned experiment in Table I provides, in our opinion, an excellent argument in favor of reaction mechanisms in which a pentacovalent silicon atom exists in the transition state.[1,2,3]

(1) Swain, Esteve and Jones, THIS JOURNAL, **71**, 965 (1949).

(2) Price, *ibid.*, **69**, 2600 (1947).

(3) Gilman and Dunn, *ibid.*, **72**, 2178 (1950).

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Pyrithiamine and Neopyrithiamine

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The pyridine analog of thiamine (2-methyl-4-amino-5-pyrimidylmethyl-[2-methyl-3-(β-hydroxyethyl)]-pyridinium bromide hydrobromide) was first prepared by Tracy and Elderfield[2] by condensing 2-methyl-4-amino-5-bromomethylpyrimidine hydrobromide with 2-methyl-3-(β-hydroxyethyl)-pyridine. The product gave acceptable analysis for C and H provided that a molecule of water of crystallization was assumed. A substance

(1) With the technical assistance of N. Smith and E. A. Singer.

(2) A. H. Tracy and R. C. Elderfield, *J. Org. Chem.*, **6**, 54 (1941).

made according to these directions was called pyrithiamine,[3] and was used to demonstrate that typical signs of thiamine deficiency of animals could be elicited by feeding it. Other biological investigations subsequently were conducted with such preparations.[4a,b] However, Wilson and Harris[5] observed that such material did not give correct analytical values for N. By modifying the temperature and solvent of the condensation, and by using an excess of the pyridine component they were able to prepare an apparently pure compound which gave correct analytical values for all of its constituent elements. This substance showed two absorption maxima in the ultraviolet region at 270 mμ, and at 237 mμ, whereas that of Tracy and Elderfield exhibited a rather broad region of absorption between these values, but without the two maxima. Furthermore, recrystallization of the latter material did not yield an analytically pure substance. Wilson and Harris therefore concluded that their material differed in structure from what had been named pyrithiamine, and proposed a new name, neopyrithiamine, for the compound. Because this conclusion tended to call in question the biological work which had been done with pyrithiamine, and because this work was the first unequivocal demonstration of the production of a deficiency disease of animals with an antimetabolite, the nature of the biologically active substance called pyrithiamine has been studied further, with the following results.

When the biological activity of pyrithiamine was compared to that of neopyrithiamine[6] no qualitative difference between them could be found. Quantitatively, neopyrithiamine was about four times as active.[7] Neopyrithiamine called forth the typical signs in mice which were seen with pyrithiamine administration.[3] The lag phase required between the time of first dosing, regardless of size of dose, and the appearance of symptoms was noted with both materials. Furthermore, 1 mg. of neopyrithiamine per mouse, given in one dose, resulted in the delayed appearance, 7–8 days later, of the typical pharmacological signs of thiamine deficiency. This unusual delayed effect was previously observed with pyrithiamine.[3] The cumulative nature of the action of these materials makes quantitative evaluation of their relative potencies difficult. Prior experience with pyrithiamine had shown clearly that even minute daily doses, continued long enough, would result in the production of disease. While the daily intake of thiamine is not appreciably stored, that of pyrithiamine appeared to be retained, so that the inhibition index became smaller as the length of the experiment was increased from 14 to 29 days. This index based on the ratio of daily intake of pyrithiamine to thiamine decreased from about 40, in a 14 day experiment, to about 10 in a 21 day experiment. In order to circumvent this uncertainty, pyrithiamine and neopyrithiamine were compared by giving groups of 4 weanling mice single oral doses of each of the two materials, and noting the gain in weight, the onset of pharmacological signs, and incidence of death over a three-week period. The animals were fed a highly purified diet,[3] and received 4 gamma of thiamine per day. Under these conditions, 0.5 mg. of neopyrithiamine caused typical convulsions and death in all mice, whereas 0.17 mg. did not do so in any, and only caused reduction of growth rate to about half that seen in untreated controls (average weekly gain 1.7 g. compared to 3.4 g.). When pyrithiamine was similarly assayed, 2 mg. was the minimal dose which caused death, and one-third this amount merely retarded growth during the test period. Neopyrithiamine was therefore concluded to be four times as active as pyrithiamine for mice.

The two substances were compared quantitatively for ability to inhibit growth of *Saccharomyces cerevisiae* under the conditions previously described.[4a] Neopyrithiamine was found to be 3.5 times as active as pyrithiamine. The toxic properties of both materials were overcome competitively by thiamine. Cocarboxylase was more active in this respect than was the vitamin, and this was true for neopyrithiamine as has been noted previously for pyrithiamine.[4b]

These marked similarities in biological behavior suggested that the active principle of pyrithiamine was probably what has been called neopyrithiamine, and that pyrithiamine was impure neopyrithiamine in which a relatively large amount of impurity was present and biologically inactive. In support of this idea, it has been possible to isolate from pyrithiamine a substance with the characteristic absorption maxima of neopyrithiamine (at 270 and 237 mμ), and which has the biological activity. A biologically inert material (*Saccharomyces* test) was left behind which absorbed ultraviolet light in the manner described for pyrithiamine.[5] The separation was done on a paper strip chromatogram, using benzyl alcohol saturated with 0.1 *N* HCl as solvent. After development, the solvent was washed out thoroughly with ether, the paper was cut into uniform small sections, and each was eluted with water and the eluates were examined for biological activity and absorption spectrum. Neopyrithiamine moved as a single spot of R_F 0.23. The biological activity of pyrithiamine moved as a single spot with the same R_F. Inert material which absorbed ultraviolet light remained at the starting line, and a small amount also moved rapidly (R_F between 0.4 and 0.5).

These observations would suggest that neo-

(3) D. W. Woolley and A. G. C. White, *J. Biol. Chem.*, **149**, 285 (1943).

(4) (a) D. W. Woolley and A. G. C. White, *J. Exp. Med.*, **78**, 489 (1943); (b) H. P. Sarett and V. H. Cheldelin, *J. Biol. Chem.*, **156**, 91 (1944).

(5) A. N. Wilson and S. A. Harris, THIS JOURNAL, **71**, 2231 (1949).

(6) Neopyrithiamine was very kindly supplied by Dr. S. A. Harris of Merck & Co., Inc.; Pyrithiamine was a freshly prepared specimen.

(7) Wilson and Harris mentioned that Dr. G. A. Emerson found neopyrithiamine to be at least four times as active as pyrithiamine.

pyrithiamine is pure pyrithiamine, and that the substance described by Tracy and Elderfield was grossly contaminated with biologically inert material.

Because confusion has arisen in the interpretation of the biological experiments with neopyrithiamine and pyrithiamine, some clarification might result if the name pyrithiamine were retained for the biologically active substance, in view of the facts just described. Possibly a designation such as pyrithiamine (neopyrithiamine) would indicate that the pure substance was employed rather than the old, impure preparation.

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The Preparation of New Compounds of Trivalent Nickel[1]

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Introduction

The stabilization of unusual valency states by coördination is a well-known phenomenon in organic chemistry. Numerous examples of this phenomenon exist, such as di- and trivalent silver when coördinated with pyridine, trivalent cobalt in the stable ammines, etc. Illustrations of compounds of metals at stabilized lower states of oxidation are the nickel and manganese complex cyanides. A characteristic of this phenomenon is the specificity of coördinating groups for various metals.

There is some evidence that coördination with the oxime group may be a stabilizing factor for the higher valency states of nickel. Hofmann and Ehrhardt[3] prepared the complex compound, trisodium hexaformoximonickelate(III), and Dubsky and Kuras[4] the red crystalline compound, nickel(III) tribenzamidoxime. Feigl and Kulka[5] considered the red solution formed by nickel salts and dimethylglyoxime in ammoniacal solution in the presence of oxidizing agents such as bromine, nitrates, lead peroxide, etc., to be a solution of a compound of tetravalent nickel, dimethylglyoximonickelic(IV) oxide. They were able to isolate this compound by precipitation upon careful neutralization of its solution.

The present paper contains the description of stable compounds of higher valent nickel derivatives of oximes. The method of formation of the tetravalent oxide prepared by Feigl and Kulka suggested the possibility of forming a salt of higher valent nickel by the interaction of bromine and nickel dimethylglyoxime in an inert solvent.

When bromine is added to the suspension of nickel dimethylglyoxime in carbon tetrachloride, a black solid is formed. When this product is filtered and allowed to dry, it decomposes slowly and reverts to nickel dimethylglyoxime. The black solid dissolves in concentrated ammonium hydroxide to give a deep red solution such as is described by Feigl and Kulka.

A generalization that has been made concerning the stabilization of valance is that if a given coördinating group stabilizes a valence state, than the more negative the group the greater is the stabilization effect. To restate this in different form, certain strongly coördinating groups will displace the oxidation–reduction potential of an ion, and this displacement is greater with more negative groups.

Therefore, the bromine reaction was tried with nickel α-benzildioxime and a trivalent nickel derivative was formed which was stable at room temperature and decomposed slowly at 100°. A stable iodide has also been prepared. The reaction of chlorine with nickel α-benzildioxime in carbon tetrachloride results in the formation of a purple solution which is unstable.

Experimental

α-Benzildioximonickelic(III) Bromide.—Three grams of nickel α-benzildioxime (recrystallized from benzyl alcohol) was placed in 200 ml. of carbon tetrachloride. Five grams of bromine was added with stirring for ten minutes. A dark brown product was formed which was filtered, washed with carbon tetrachloride and air-dried.

The compound is insoluble in water and in all organic liquids such as benzene, alcohols, ethyl ether, acetone and carbon tetrachloride except pyridine. It forms a red-violet solution in pyridine, from which it can be precipitated by the addition of water, or will crystallize upon slow evaporation of the solvent. Concentrated ammonium hydroxide, dilute sodium hydroxide and sodium methylate in alcohol react to form a dark red compound which is insoluble in water but soluble in alkaline media.

The compound slowly decomposes at 100° to revert to the original orange-colored nickel α-benzildioxime. The loss in weight of the compound upon heating to constant weight was 13.58%, which is a measure of the bromine content.

Anal. Calcd. for $NiC_{28}H_{22}N_4O_4Br$: Ni, 9.51; Br, 12.95; C, 54.5; H, 3.59. Found: Ni, 9.34; Br, 13.02; C, 54.6; H, 3.62.

α-Benzildioximonickelic(III) Iodide.—Three grams of recrystallized nickel α-benzildioxime was dissolved in 20 ml. of hot benzyl alcohol, 3 g. of iodine was added and the mixture heated until crystallization started. The reaction mixture was cooled immediately and the product separated as glistening, bronze crystals. The solubility and stability characteristics are the same as the bromide.

Anal. Calcd. for $NiC_{28}H_{22}N_4O_4I$: Ni, 8.85; I, 19.11; C, 50.64; H, 3.34. Found: Ni, 8.98; I, 19.30; C, 51.80; H, 3.48.

Action of Chlorine on Nickel α-Benzildioxime.—Chlorine gas was passed for five minutes through a suspension of 5 g. of recrystallized nickel α-benzildioxime in 200 ml. of carbon tetrachloride. A dark-colored solid and a purple solution formed. The reaction mixture was filtered.

(1) Presented before the Division of Physical and Inorganic Chemistry of the American Chemical Society at the New York Meeting, September 1947.

(2) Dental Research Associates, Inc., 608 California Avenue, Pittsburgh 2, Penna.

(3) Hofmann and Ehrhardt, *Ber.*, **46**, 1467 (1913); *C. A.*, **7**, 2577 (1913).

(4) Dubsky and Kuras, *Chem. Zentr.*, 102, I 2045 (1931); *C. A.*, **25**, 1708 (1931).

(5) Feigl and Kulka, *Ber.*, **57**, 958 (1924); *C. A.*, **18**, 2663 (1924); A. Okac and M. Polster, *Coll. Czechoslov. Chem. Commun.*, **13**, 561 (1948).