Notes

Nitrogen Ylides. III.[1] The Explosive Decomposition of Tetramethylammonium Amide

W. K. Musker

Department of Chemistry, University of California at Davis, Davis, California

Received January 30, 1967

In an earlier study[1] it was suggested that the decomposition of tetramethylammonium hydroxide to give trimethylamine and dimethyl ether proceeds by a mechanism which involves the initial removal of a proton from the quaternary ammonium salt followed by the decomposition of the resulting ylide. In another analysis of the decomposition of tetramethylammonium hydroxide, Tanaka, Dunning, and Carter[2] proposed that a nucleophilic displacement on the tetramethylammonium ion by hydroxide and, subsequently, by methoxide would be a more satisfactory explanation for the formation of dimethyl ether than the ylide intermediate. In addition, they proposed that a similar process would be expected to occur at lower temperature with the amide ion and would account for the explosive decomposition of tetramethylammonium amide observed by Parry and Schumacher.[3] However, in 1935, Franklin[4] reported that tetramethylammonium chloride reacted with potassium amide in liquid ammonia to give trimethylamine and methylamine, and the experiment was later repeated by other workers[5] who observed that only a trace of ethylene was formed. In all these studies, the products of the reaction were not thoroughly characterized and an explosive decomposition was reported only by Parry and Schumacher.[3]

During this examination of the decomposition of tetramethylammonium amide in liquid ammonia a violent explosive decomposition was observed in one case after the reaction vessel had warmed to room temperature. However, by carefully removing all the ammonia at −45° and allowing the reaction vessel to stand for several hours prior to warming to room temperature, the explosion was avoided and the reaction could be controlled. Extreme safety precautions must be taken at all times, since an explosion may occur even at low temperature under different experimental conditions.[3]

We have found that the products resulting from the reaction of tetramethylammonium fluoride with potassium amide under controlled conditions at −45° were ethylene (∼35-50%), polymethylene (18-40%), dimethylethylamine (5-10%), and trimethylamine. The yield was based on the location of the methyl group lost by the tetramethylammonium ion.

In a typical reaction 1-5 mmoles of tetramethylammonium fluoride was added to a solution of freshly prepared potassium amide in about 5 ml of liquid ammonia on a high vacuum line. The solution was stirred for 3 hr at −45° and the solvent was removed at this temperature to avoid explosion. The ammonia vapor was analyzed continuously by gas-liquid partition chromatography for the presence of the decomposition products. *No methylamine or dimethylamine was formed.* Most of the ammonia could be removed without significant decomposition and only the last 0.5 ml was subjected to a thorough product analysis. The ethylene was isolated by fractionation through a −130° cold trap, and the infrared spectrum indicated that no other hydrocarbons were present. After removal of the ethylene, the solution was treated with excess methyl iodide and shaken for 24 hr. The quaternary iodide salts were collected, converted to the hydroxides with silver oxide, and pyrolyzed. The ethylene obtained from this pyrolysis could have resulted only from the decomposition of trimethylethylammonium hydroxide formed by the methylation of dimethylethylamine with methyl iodide. The presence of dimethylethylamine in the original reaction mixture was confirmed by gas-liquid partition chromatography by a comparison of its retention time with that of an authentic sample. The polymethylene was recovered from the reaction vessel as an insoluble amorphous powder and its identity was confirmed by elemental analysis.

Since the strongly basic amide ion was not methylated by the tetramethylammonium ion, a nucleophilic attack on a carbon atom of the tetramethylammonium ion by amide ion did not occur; however, all the products resulting from this controlled reaction can be envisioned to arise from the decomposition of a nitrogen ylide which is formed after most of the ammonia solvent has been removed. The general synthesis of trimethylammonium methylide is accomplished by treatment of tetramethylammonium bromide with phenyllithium[6] in ether, and under these conditions the ylide is stabilized as a lithium bromide complex.[7] When a mixture of phenyllithium and phenylsodium was used,[8] the ylide decomposed to polymethylene (5%) and dimethylethylamine (49%), with only a trace of ethylene. When dimethylsulfonium methylide, the simplest sulfur ylide, was prepared in ether using phenyllithium, polymethylene was found,[9] but, when this sulfonium

$$\begin{array}{c}
(CH_3)_3\overset{+}{N}CH_3 + {}^{-}NH_2 \rightleftharpoons (CH_3)_3\overset{+}{N}\text{—}\overset{-}{C}H_2 + NH_3 \\
\downarrow \\
(CH_3)_3N + (\text{-}CH_2\text{-})_n + CH_2{=}CH_2 + (CH_3)_2NCH_2CH_3
\end{array}$$

---

[1] W. K. Musker, *J. Am. Chem. Soc.*, **86**, 960 (1964).

[2] J. Tanaka, J. E. Dunning, and J. C. Carter, *J. Org. Chem.*, **31**, 3431 (1966).

[3] H. Schumacher and R. W. Parry, personal communication.

[4] E. C. Franklin, "The Nitrogen System of Compounds," Reinhold Publishing Corp., New York, N. Y., 1935, p 63.

[5] D. A. Hazlehurst, A. K. Holliday, and G. Pass, *J. Chem. Soc.*, 4653 (1956).

[6] G. Wittig and M. H. Wetterling, *Ann.*, **557**, 193 (1947).

[7] G. Wittig and R. Polster, *ibid.*, **599**, 1 (1956).

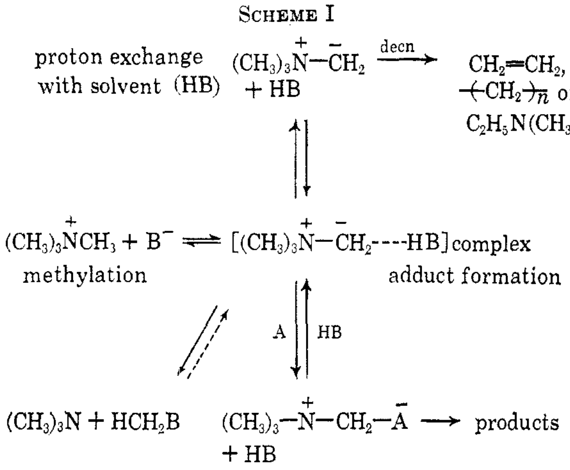
[8] G. Wittig and D. Krauss, *ibid.*, **679**, 34 (1964).

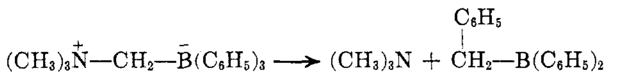
[9] G. Wittig and H. Fritz, *ibid.*, **577**, 39 (1952).

ylide was generated in dimethyl sulfoxide,[10] only ethylene was reported.

On the basis of product analyses it is suggested that all reactions of the tetramethylammonium ion with strong bases (B^-) proceed by way of a nitrogen ylide. The effective base strength determines whether an ylide will be formed at all; however, when the ylide is formed, the course of its decomposition can be summarized as shown in Scheme I. Rapid proton exchange with solvent may occur when $\equiv\overset{+}{N}-\overset{-}{C}H_2$ bond rupture is reduced by complexation. Thus, ylides stabilized by coordination with Lewis acids (A) or Brønsted acids (BH) may be present in equilibrium with the tetramethylammonium ion. Unstable ylides decompose rapidly, and the products which are formed depend on the species near the site. If insertion processes are favorable, the decomposing ylide will react with BH, A, or the solvent "pool." Methylation of the base is a well-known process,[6] and we have recently shown that the methylene group is inserted into a boron–carbon bond during an attempt to stabilize the the ylide by coordination with trihexyl- and triphenylboron (A).[11]

SCHEME I





$$(CH_3)_3\overset{+}{N}-CH_2-\overset{-}{B}(C_6H_5)_3 \longrightarrow (CH_3)_3N + \overset{C_6H_5}{\overset{|}{C}}H_2-B(C_6H_5)_2$$

In the absence of intermolecular insertion processes, the ylide may undergo an intramolecular insertion process to give dimethylethylamine *via* a Stevens rearrangement.[12] Polymerization processes occur as secondary alternatives to the other modes of decomposition. The factors leading to ethylene or polymethylene formation from sulfur ylides[13] and nitrogen ylides[8] have been discussed, but the mechanism of these reactions is uncertain.

Thus, the difference between the Cope and the Doering solvent exchange processes as discussed by Tanaka, Dunning, and Carter[2] involves the effective base strength of the anion toward a *hydrogen* atom of the tetramethylammonium ion. Since all the products of these reactions can be envisioned to arise from the nitrogen ylide, nucleophilic attack on the carbon atom of the tetramethylammonium ion by the anion may be relatively unimportant.

Experimental Section

Tetramethylammonium fluoride was prepared by treating a solution of tetramethylammonium hydroxide with an equivalent amount of a solution of hydrofluoric acid. The solution was evaporated to dryness and then heated at 140° on the vacuum line for 48 hr. The sample decomposed slightly at this temperature, as evidenced by the presence of methyl fluoride, trimethylamine, and water in a liquid-nitrogen trap.

Potassium amide was prepared by treating a small amount of potassum metal with liquid ammonia in a high vacuum line. The yield of potassium amide was determined by measuring the amount of hydrogen evolved during the reaction. The solution was then filtered on the vacuum line to give a slightly yellow solution.

The Decomposition Reaction.—A reaction tube containing a magnetic stirring bar and 2.60 mmoles of KNH_2 in 5 ml of liquid ammonia was frozen with liquid nitrogen, and 119 mg (1.29 mmoles) of Me_4NF was added. The tube was evacuated and the solution was warmed to −45° (chlorobenzene cold bath) and stirred for 3 hr. Most of the tetramethylammonium fluoride dissolved, but the solution was turbid and slightly yellow throughout the stirring process. In addition, a solid formed at the interface of the solution and the wall of the tube during this interval. After 3 hr, the vapor above the solution was removed slowly and shunted through the gas-injector port of a gas chromatograph equipped with a hydrogen flame detector. An Aerograph 600-D gas chromatograph containing a 10-ft column (9% THEED–3% TEP on Chromosorb W) was used to separate low molecular weight aliphatic amines.[14] The slight sensitivity of ammonia did not interfere with the methylamines. The vapor was sampled repeatedly while the solvent was being removed, and small amounts of trimethylamine and a volatile hydrocarbon were detected indicating that some reaction was occurring. However, the amount of trimethylamine and hydrocarbon increased enormously during the removal of the last traces of solvent and only the last 0.5 ml of solvent was subjected to a thorough product analysis. During the entire chromatographic analysis no methylamine or dimethylamine was detected. However, a compound having the same retention time as dimethylethylamine was observed. After all the solvent had been removed at −45°, the sample tube was kept at this temperature for an additional 3 hr before slowly warming to room temperature. While the last traces of solvent were being removed and the reaction mixture was warming to room temperature, the sample tube was well shielded and extreme safety precautions were taken at all times.

The last 0.5 ml of solvent was passed through a −130° trap (*n*-pentane) and 2.1 mmoles of ethylene was collected. The infrared spectrum indicated that ethylene was the only low molecular weight hydrocarbon present. The remaining ammonia solution was treated with a large excess of methyl iodide in a sealed tube and shaken for 24 hr. After this time the solid was collected, treated with an aqueous suspension of silver oxide,[15] and filtered. The water was removed by means of a rotary evaporator and the remaining solid was pyrolyzed on the vacuum line, giving 0.14 mmole of ethylene and confirming that dimethylethylamine was formed in the original reaction.

The original sample tube was removed from the vacuum line and carefully treated with water. The solution was filtered and 7.2 mg of the amorphous white solid which remained was washed with alcohol and acetone. The analysis corresponded closely to polymethylene.

Anal. Calcd for $(-CH_2-)_n$: C, 85.63; H, 14.37. Found: C, 83.69; H, 14.10.

Registry No.—Tetramethylammonium amide, 13422-81-6.

---

(10) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

(11) W. K. Musker and R. R. Stevens, *Tetrahedron Letters*, 995 (1967).

(12) T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. McNicol, *J. Chem. Soc.*, 3193 (1928).

(13) A. W. Johnson, "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, p 322.

(14) Y. L. Sze, M. L. Borke, and D. M. Ollenstein, *Anal. Chem.*, **35**, 240 (1963).

(15) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 380 (1960).

Acknowledgment.—The author wishes to thank the National Science Foundation (GP-1704) and the National Institutes of Health (GM-14062) for supporting this research.

Chemistry of Aliphatic Disulfides. XIV. The Preparation of Disulfide Sulfoxides by Selective Oxidation[1-3]

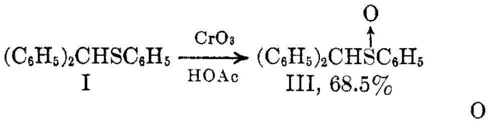
RICHARD G. HISKEY AND MICHAEL A. HARPOLD[4,5]

The Venable Chemical Laboratory,
The University of North Carolina, Chapel Hill, North Carolina

Received May 3, 1967

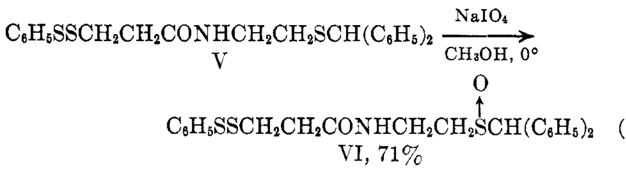
As part of an over-all program designed to produce and study unsymmetrical disulfides and related sulfur-containing peptide derivatives [1,6] it became desirable to investigate the selective oxidation of substrates containing a thio ether group and a disulfide bond. Although numerous examples of sulfoxide formation *via* oxidation of appropriate thioethers are found in the chemical literature [7-9] no report has appeared in which such an operation was successfully carried out in the presence of a disulfide bond within the same molecule.

Preliminary experiments indicated that chromium trioxide in acetic acid solution was satisfactory for the oxidization of simple diaryl thioethers such as benzhydryl phenyl sulfide (I) and benzhydryl benzyl sulfide[1] (II) to the corresponding sulfoxides, III and IV (eq 1). However, when N-(2-benzhydrylthioethyl)-5-phenyl-4,5-dithiapentanoic amide[1] (V) was treated with this reagent, extensive decomposition occurred. Attempts to oxidize V with either hydrogen peroxide or *m*-chloroperbenzoic acid also resulted in decomposition of the starting material. N-(2-benzhydrylsulfinylethyl)-5-phenyl-4,5-dithiapentanoic amide (VI) was eventually prepared in 71% yield by treating a methanolic solution of V with an aqueous solution of sodium metaperiodate[10] (eq 2). The disulfide sulfoxide, VI, could also be prepared independently as outlined in eq 3 and 4. 2-Benzhydrylthioethylammonium chloride[1] (VII) was treated with sodium metaperiodate in aqueous methanol to produce 2-benzhydrylsulfinyl ethylammonium chloride (VIII). This chromatographically pure foam was coupled with 5-phenyl-4,5-dithiapentanoic acid[6] (IX) in the presence of 1 equiv of triethylamine and WSC to give a 55% yield of VI.

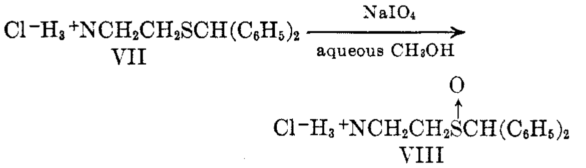


$$\underset{\text{I}}{(C_6H_5)_2CHSC_6H_5} \xrightarrow[\text{HOAc}]{\text{CrO}_3} \underset{\text{III, 68.5\%}}{(C_6H_5)_2CH\overset{\overset{O}{\uparrow}}{S}C_6H_5}$$

$$\underset{\text{II}}{(C_6H_5)_2CHSCH_2C_6H_5} \xrightarrow[\text{HOAc}]{\text{CrO}_3} \underset{\text{IV, 58\%}}{(C_6H_5)_2CH\overset{\overset{O}{\uparrow}}{S}CH_2C_6H_5} \quad (1)$$



$$\underset{\text{V}}{C_6H_5SSCH_2CH_2CONHCH_2CH_2SCH(C_6H_5)_2} \xrightarrow[\text{CH}_3\text{OH, 0°}]{\text{NaIO}_4} \underset{\text{VI, 71\%}}{C_6H_5SSCH_2CH_2CONHCH_2CH_2\overset{\overset{O}{\uparrow}}{S}CH(C_6H_5)_2} \quad (2)$$



$$\underset{\text{VII}}{Cl^-H_3{}^+NCH_2CH_2SCH(C_6H_5)_2} \xrightarrow[\text{aqueous CH}_3\text{OH}]{\text{NaIO}_4} \underset{\text{VIII}}{Cl^-H_3{}^+NCH_2CH_2\overset{\overset{O}{\uparrow}}{S}CH(C_6H_5)_2} \quad (3)$$

$$\underset{\text{IX}}{C_6H_5SSCH_2CH_2CO_2H} + \text{VIII} \xrightarrow[\text{WSC}]{\text{Et}_3\text{N}} \text{VI, 55\% (2 steps)} \quad (4)$$

The application of this specific oxidative procedure to a bisdisulfide thioether was made possible by the availability of N-[N-carboxy-3-[[2-[3-(phenyldithio)-propionamido]ethyl]dithio]-L-alanyl]-DL-methionine N-benzyl ethyl ester (X).[11] The oxidation of X under conditions similar to those used to prepare VI yielded N-[N-carboxy-3-[[2-(3-(phenyldithio)propionamido]ethyl]dithio]-L-alanyl]-DL-methionine-*dl*-sulfoxide N-benzyl ethyl ester (XI). This reaction, as well as an alternate route to XI, is presented in Scheme I. Ethyl DL-methionate hydrochloride (XII) was prepared from DL-methionine by treatment with anhydrous hydrogen chloride in ethanol. The oxidation of XII with sodium metaperiodate was conducted in the usual manner, but the hydrochloride could not be isolated in a pure form. Consequently, the oxalate salt was prepared; ethyl DL-methionate-*dl*-sulfoxide oxalate (XIII) was isolated following treatment of the crude hydrochloride with triethylamine in ethyl acetate and addition of an equivalent of oxalic acid. Coupling N-carboxy-3-[[2-[3-(phenyldithio)propionamido]ethyl]dithio]-L-alanine N-benzyl ester[6] (XIV) and the free amine (which had been liberated from XIII by treatment with barium hydroxide solution) in the presence of WSC produced XI.

In addition to the novelty of the disulfide sulfoxides and the unique methods of preparation, the stability of VI and XI indicates that intramolecular interactions between sulfoxide and disulfide species are probably insignificant. This could not be firmly established prior to the synthesis of materials containing both functions.

The successful preparation of these sulfoxides stimulated an attempt to reverse the procedure and reproduce the starting thioethers, V and X, by a selective reduction process. Initial studies involving the established reduction methods disclosed no report of a sulfoxide which was selectively reduced in the presence of a disulfide bond. Although Iselin[12] had demonstrated

---

(1) Part XIII of this series: R. G. Hiskey and M. A. Harpold, *Tetrahedron*, in press.

(2) Supported by Research Grant RG-7966 from the National Institute of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service.

(3) The following abbreviations have been incorporated into the text: WSC = 1-ethyl-3-(3-N,N-dimethylaminopropyl)carbodiimide hydrochloride, and Ox⁻ = oxalate.

(4) Abstracted in part from a dissertation submitted by M. A. Harpold to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June 1967.

(5) National Science Foundation Cooperative Fellow, 1964–1966.

(6) R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.*, **87**, 3965 (1965).

(7) R. Knoll, *J. Prakt. Chem.*, **113**, 40 (1926).

(8) S. Hünig and O. Boes, *Ann. Chem.*, **579**, 23 (1953).

(9) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(10) Essentially the method previously used by Leonard and Johnson;[9] only slight modifications in this original procedure were required.

(11) R. G. Hiskey and M. A. Harpold, manuscript in preparation.

(12) B. M. Iselin, *Helv. Chim. Acta*, **44**, 61 (1961).