Phosphaadamantanes: Reaction with Formaldehyde in Acid Solution

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The methoacid salts of hexamethylenetetramine, 1,3,5-triaza-7-phosphaadamantane (PAA), and its oxide (PAAO) were prepared from their reaction with formaldehyde in solution containing a strong acid. The compound 2-thia-1,3,5-triaza-7-phosphaadamantane 2,2-dioxide ($PASO_2$) did not form a methoacid salt and substantiated earlier work that $PASO_2$ is chemically phosphorus oriented.

The compound 1,3,5-triaza-7-phosphaadamantane (PAA) (*1, 2*) resembles the repeating unit proposed for a well-known flame retardant polymer prepared from sodium hydroxide-neutralized tetrakis(hydroxymethyl)phosphonium chloride solutions (THPOH) and ammonia. Recently, both the THPOH–NH_3 polymer and PAA were found to "decompose" in hot formalin, whereas the oxidized polymer and 1,3,5-triaza-7-phosphaadamantane 7-oxide (PAAO) were stable to solutions of hot formalin (*3*). The only product isolated from the reaction with the polymer or PAA was tris(hydroxymethyl)phosphine oxide. We now have isolated the products from the reactions of phosphaadamantanes with formaldehyde in the presence of an acid.

Initially, hexamethylenetetramine picrate was reacted with formaldehyde. With nuclear magnetic resonance spectroscopy (NMR) the work of Foss et al. (*4, 5*) was confirmed, and a methopicrate salt was proved to be the only product from such a reaction. The product had been identified as a dimethylpentamethylenetetramine picrate (*6, 7*). The NMR spectra showed a 1:6 ratio of aromatic protons to methylene protons. The use of dimethyl sulfoxide as a solvent interfered with the integration of the methyl protons.

This same reaction with PAA and PAAO picrate also produced methopicrate salts as shown by NMR spectroscopy and chemical analyses. The highest theoretical yield of the PAA methopicrate, 45% (based upon PAA) (V), also suggested that the decomposition reaction with formaldehyde might also be operative. Yields of this reaction with hexamethylenetetramine and PAAO were 67 (IV) and 73% (VI), respectively. The reaction of PAAO with formaldehyde in the presence of another strong acid, hydrochloric, produced a methochloride salt (VII). Apparently, acid strength is important since in the presence of acetic acid, the reaction with either PAA or PAAO produced only the starting compounds.

The methopicrates of hexamethylenetetramine, PAA, and PAAO were also prepared in quantitative yield from methyl iodide salts of the three compounds and sodium picrate.

The compound 2-thia-1,3,5-triaza-7-phosphaadamantane 2,2-dioxide did not react with formaldehyde in the presence of either picric or hydrochloric acid. However, the picrate and chloride were isolated and by NMR spectroscopy shown to be ammonium salts.

This work substantiates earlier work that PAA and PAAO resemble hexamethylenetetramine in their chemistry, that is, they are nitrogen oriented and that $PASO_2$ is phosphorus oriented. Elemental analyses obtained were in agreement with theoretical values and were submitted for review.

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Experimental

General preparation of picrate salt. The picrates of hexamethylenetetramine, PAA, and PAAO were prepared by dissolving 0.02 moles of each compound in about 100 ml of methanol and 0.02 mol of picric acid in 125 ml of ethanol. The precipitates produced were collected by filtration.

1-Hydro-1-azonia-3,5,7-triazaadamantane picrate (I). Filtration yielded 6.88 g [92.7%] of crude I. The NMR spectrum (Varian A-60A spectrometer) of a deuterated dimethyl sulfoxide solution of I at 60 MHz exhibited the following bands relative to an internal standard (tetramethylsilane): a singlet at δ 4.87 and a singlet at δ 8.65 in the ratio of 6:1, respectively.

1-Hydro-1-azonia-3,5-diaza-7-phosphaadamantane picrate (II). Filtration yielded 6.55 g [84.4%] of crude II. The NMR spectrum of a deuterated dimethyl sulfoxide solution of II showed a doublet centered at δ 4.07 with a coupling constant of 9 Hz, a singlet at δ 4.78, and a singlet at δ 8.62 in the ratio of 3:3:1, respectively.

1-Hydro-1-azonia-3,5-diaza-7-phosphaadamantane-7-oxide picrate (III). Filtration yielded 7.32 g (90.6% yield) of crude III. The NMR spectrum of a deuterated dimethyl sulfoxide solution of III showed a doublet centered at δ 4.18 with a coupling constant of 11, a singlet at δ 4.63, and a singlet at δ 8.67 in the ratio of 3:3:1, respectively.

General reaction conditions of picrates I–III with formaldehyde. The picrates (0.013 mol) were dissolved in a solution in 100 ml of ethanol and formaldehyde (40 g, 37.5%, 0.50 mol); the mixture was heated on a steam bath for the time specified: I, ½ h; II, 2 h; and III, 2 h. The solution was allowed to cool slowly to room temperature, and the precipitate filtered.

1-Methyl-1-azonia-3,5,7-triazaadamantane picrate (IV). Filtration yielded 3.2 g (67.3%) of crude IV. The NMR spectrum of a deuterated dimethyl sulfoxide solution of IV showed a singlet at δ 8.67, a singlet at δ 5.01, and a complex of peaks from δ 4.82 to δ 4.33 in the ratio of 1:3:3. The spectrum also showed a singlet at δ 2.35 (CH_3 protons), but the protons of the solvent overlapped, interfering in the integration.

1-Methyl-1-azonia-3,5-diaza-7-phosphaadamantane picrate (V). Filtration yielded 2.34 g (45%) of crude V. The NMR spectrum of a deuterated dimethyl sulfoxide solution of V showed a singlet at δ 2.63, a complex of peaks from δ 3.33 to 4.75, a broad singlet at δ 4.92, and a singlet at δ 8.63 in the ratio of 3:8:4:2, respectively.

1-Methyl-1-azonia-3,5-diaza-7-phosphaadamantane-7-oxide picrate (VI). Filtration yielded 3.95 g (73%) of crude VI. The NMR spectrum of a deuterated dimethyl sulfoxide solution of VI showed a doublet centered at δ 2.88 with a coupling constant of 3 Hz, a complex of peaks from δ 3.95 to δ 4.35, a broad singlet at δ 4.95, and a singlet at δ 8.67 in the ratio of 3:8:4:2, respectively.

1-Methyl-1-azonia-3,5-diaza-7-phosphaadamantane-7-oxide chloride (VII). PAAO (6.92 g, 0.04 mol) was dissolved in a solution of 100 ml of ethanol, hydrochloric acid (3.89 g, 37.5%, 0.04 mol), and formalin (18.0 g, 37.5%, 0.225 mol), and refluxed for 1¾ h. Evaporation of the solution at room temperature and washing of the solid produced 5.5 g (61.5% yield) of crude VII.

Alternative preparation of IV–VI. Compounds IV–VI were prepared by dissolving the methyl iodide salt of hexamethylenetetramine, PAA, and PAAO, respectively (0.001 mol), in methanol (60 ml) and sodium picrate (0.001 mol) in methanol (10 ml). The precipitate produced was filtered and dried. Infrared and NMR spectra of each of the compounds were identical to those of samples prepared by the other method. The methyl chloride salt of PAAO with sodium picrate also produced VI.

Reaction of 2-thia-1,3,5-triaza-7-phosphaadamantane 2,2-dioxide ($PASO_2$) with formaldehyde and acid. Reaction conditions were the same as for the preparation of VII: $PASO_2$ (2.07 g, 0.01 mol), picric acid (2.52 g, 90%, 0.01 mol), and formalin (3.0 g, 37.5%, 0.033 mol) in ethanol (150 ml). Evaporation to half volume and filtration produced 4.0 g (92.8% yield) of 5-hydro-5-azonia-2-thia-1,3-diaza-7-phosphaadamantane-2,2-dioxide picrate (VIII).

The same procedure with hydrochloric acid in lieu of picric acid produced 2.0 g (82.3% yield) of 5-hydro-5-azonia-2-thia-1,3-diaza-7-phosphaadamantane-2,2-dioxide chloride (IX). The NMR spectrum of a deuterated dimethyl sulfoxide solution showed a singlet at δ 6.83 which appears to be a mixture of water protons and N—H since it did exchange with D_2O. A doublet caused by a P—H proton was not found.

	I	II	III	IV	V
Mp	179[6]	182–3	184–5	196[6]	197–8
Solvent		H_2O–EtOH	H_2O–EtOH	...	H_2O–EtOH

	VI	VII	VIII	IX
Mp	203–4	217.5–8.5	139–40	202–3
Solvent	H_2O–EtOH	EtOH–EtOAc	EtOH	EtOH–EtOAc

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Received for review May 27, 1975. Accepted October 20, 1975.

Preparation of Diethyl Formamidomalonate

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A rapid and convenient synthesis of diethyl formamidomalonate is described.

Diethyl acetamidomalonate (*3*) is an important intermediate in the synthesis of a large number of amino acids. Diethyl formamidomalonate is even more suitable for this purpose owing to the much more facile hydrolysis of the formyl group. Several derivatives of tryptophan cannot be made via the acetamidomalonate, because the compounds are not stable enough to withstand the conditions required for the hydrolysis of the acetyl groups, but are smoothly synthesized using diethyl formamidomalonate. Unfortunately, the preparation of this material without high-pressure hydrogenation has been unsatisfactory.

In accordance with results obtained earlier (*1*), we found that the procedure described by Galat (*2*) gave erratic results. Although the reduction of the intermediate diethyl isonitrosomalonate took place, the formylation mostly failed. Therefore, it was decided to remove the water formed in the course of the reduction. The removal was carried out by azeotropic distillation with benzene. The use of benzene has the additional advantage of maintaining the reaction temperature at the desired level.

This method has also been carried out on much larger scales and secures 68–70% yields of the formylated ester.

Experimental

A solution of 621 g (9 mol) of commercial sodium nitrite in 750 ml of water is added through a separating funnel to a well-stirred mixture of 480.5 g (3 mol) of commercial diethyl malonate and 525 ml of glacial acetic acid below 5°. After the addition the cooling is terminated, and the mixture stirred for 6 h. The aqueous layer is then separated and extracted with three 300-ml portions of ether. The ethereal extracts are combined with the main fraction, and the water is separated again. The solution is dried over anhydrous magnesium sulfate, and, after filtration, concentrated on a water bath at 20 mm. The oily residue (about 530 g) is dissolved in 2200 ml of formic acid (90% or better) and placed in a 5-l. three-neck flask equipped with an efficient stirrer and a Dean-Stark water trap.

Benzene (600 ml) and 10 g of zinc powder are added, and the mixture is stirred and heated to reflux. After the reaction has started, the heating is terminated, and 405 g of zinc powder are added rapidly enough to maintain a steady reflux. The water formed is collected and removed through the trap. The hot solution is filtered 15 min after the last addition, and the solvents are removed on a water bath under reduced pressure. The residue is dissolved in 150 ml of methanol and placed in a refrigerator.

The diethyl formamidomalonate separates in the form of white crystals, mp 51–52°. The yield is 400–410 g (68–70%). The material may be distilled in vacuo (bp 130° at 2 mm), but there is danger of decomposition.

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Received for review May 27, 1975. Accepted September 27, 1975.