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REACTIVE SKIN DECONTAMINANT REACTIVITY STUDIES: THE EFFECT OF O-ACETYL 2,3-BUTANEDIONE MONOOXIME ON THE STABILITY OF 2,3-BUTANEDIONE MONOOXIMATE

by

R.G. Clewley, J.G. Purdon, and C.L. Chenier

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ABSTRACT

The reaction of acetic anhydride with 2,3-butanedione monooximate, to generate *in situ* O-acetyl 2,3-butanedione monooxime, has been examined in four solvents. In water, the initially formed O-acetyl oxime undergoes a general-base catalysed Beckmann rearrangement; if present in excess, one equivalent of oximate is consumed by every equivalent of acetic anhydride. In acetonitrile, O-acetyl 2,3-butanedione monooxime catalyses the dispropotionation of 2,3-butanedione monooximate. In RSD formulations employing polyethylene glycol monomethyl ether of average molecular weight 550 (MPEG-550) and 10% w/w water/MPEG-550 less than one equivalent of oximate is consumed by every equivalent of acetic anhydride. While O-acetyl 2,3-butanedione monooxime catalysed disproportionation of 2,3-butanedione monooximate does not occur in the medium employed for the RSD, it may place a significant constraint on the use of this nucleophile in decontaminants which employ aprotic media.

RÉSUMÉ

La réaction de l'anhydride acétique avec le butane-2,3-dione-monooximate, en vue de préparer *in situ* de l'O-acétylbutane-2,3-dione-monooxime, a été étudiée dans quatre solvants. Dans l'eau, l'oxime O-acétyl subit un réarrangement de Beckmann catalysé par une base générale; un équivalent d'oximate, si cette substance est présente en excès, est consommé par chaque équivalent d'anhydride acétique. Dans l'acétonitrile, l'O-acétylbutane-2,3-dione-monooxime catalyse la dismutation du butane-2,3-dione-monooximate. Dans les formulations RSD comprenant l'éther monométhylique d'un polyéthylèneglycol de masse moléculaire moyenne de 550 (MPEG-550) et dont le rapport massique eau/MPEG-550 est de 10%, moins d'un équivalent d'oximate est consommé par chaque équivalent d'anhydride acétique. Dans le milieu utilisé pour les formulations RSD, il n'y a pas dismutation du butane-2,3-dione-monooximate catalysée par l'O-acétylbutane-2,3-dione-monooxime, ce qui peut restreindre considérablement l'utilisation de ce nucléophile dans les décontaminants contenant des milieux aprotiques.

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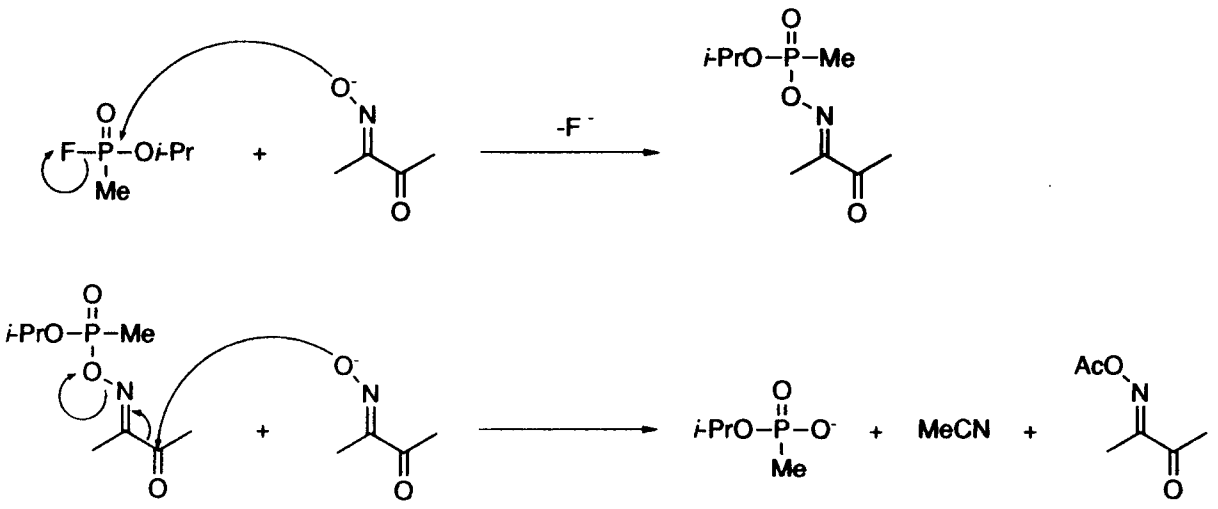
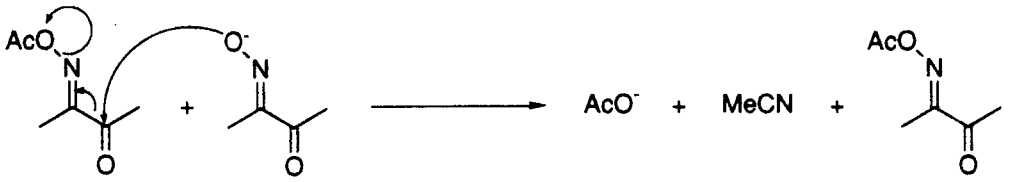
INTRODUCTION

The Reactive Skin Decontaminant (RSD) employs as its active ingredient potassium 2,3-butanedione monooximate (KBDO). This species, like many other α-nucleophiles, is a potent nucleophile (1,2). It has been found that KBDO reacts with organophosphorus chemical warfare (CW) agents in aprotic organic solvents to produce the corresponding O-phosphonylated 2,3-butanedione monooxime (3-5); if a second equivalent of 2,3-butanedione monooximate is available, the phosphonylated oxime undergoes a second-order Beckmann rearrangement to yield O-acetyl 2,3-butanedione monooxime, acetonitrile, and the phosphonate anion corresponding to the original agent (3,4):



Scheme 1

There exists the possibilty that a Beckmann rearrangement could also take place between 2,3-butanedione monooximate and the acetylated oxime so formed. If this reaction does occur, it is conceivable that, under some conditions, the oximate in the RSD could be depleted through disproportionation to acetonitrile and acetate anion in a chain reaction:



Scheme 2

Whether or not such a reaction can take place is of some interest, as it could explain the apparent stoichiometry of the reaction of nerve agents with KBDO in the RSD found in a toxicity study (6). A 1.25 molal solution of KBDO in polyethylene glycol monomethyl ether of average molecular weight 550 (MPEG-550) was reacted with GB, GD, and VX *in vitro*. The resulting product mixtures were then injected intraperitoneally into Sprague-Dawley rats. It was found that a molar ratio of agent to KBDO of 1:4 provided total protection in the cases of GB and GD, but for VX a molar ratio of 1:10 was required to entirely eliminate toxicity. As the leaving groups in VX are much poorer leaving groups than is fluoride in GB and GD, the rate of reaction of VX with 2,3-butanedione monooximate will be slower than the reaction of oximate with GB and GD (1). However, the rates for the Beckmann rearrangements of the three resulting phosphonylated oximes to produce O-acetyl 2,3-butanedione monooxime should be similar as the structures of the phosphonyl groups are very similar. It is also conceivable that the rates of the reaction of 2,3-butanedione monooximate with VX and with O-acetyl 2,3-butanedione monooxime are not significantly different. If so, the apparent stoichiometry of the reaction of KBDO with VX would be higher than the reactions with GB and GD due to the depletion of oximate through disproportionation.

To confirm whether or not O-acetyl 2,3-butanedione monooximate catalysed disproportionation of 2,3-butanedione monooximate can occur, the chemistry of these species in two simple solvent systems, water and acetonitrile, has been examined, as has

the chemistry in RSD formulations employing neat MPEG-550 and 10% w/w water/MPEG-550.

EXPERIMENTAL

2,3-Butanedione monooxime (Aldrich), acetic anhydride (Amachem), and dichloromethane and acetonitrile (BDH Omnisolve) were employed without further purification. Potassium 2,3-butanedione monooximate (Raylo Chemicals, Edmonton, Alberta, Lot 1363-A-1) was washed three times with dry ether, filtered under nitrogen, then dried under reduced pressure. Polyethylene glycol monomethyl ether of average molecular weight 550 (MPEG-550; Aldrich, Lot 00608CK) was purified in a fashion analogous to that employed previously for MPEG-350 (2). Because of the greater viscosity of MPEG-550, it was passed through activated neutral alumina at 40° C and filtered through a medium-porosity glass frit at 27° C. It was stored under nitrogen.

A 0.60 M 2,3-butanedione monooximate aqueous solution was prepared from the oxime and potassium hydroxide; the pH of the solution was 10.60. To 2.00 mL aliquots of this solution (1.2 mmol total oxime) were added 14 to 113 μL (0.15 to 1.2 mmol) aliquots of neat acetic anhydride. The reaction mixtures were stirred 14 h, then made basic and diluted to 50.0 mL. The absorbances at 360 nm of these solutions and of a 0.024 M solution of potassium 2,3-butanedione monooximate were measured to determine the amount of oximate consumed. The reported values are averages of triplicate experiments. In some cases the spectra of the reaction mixtures were examined prior to work-up with base.

To each of three stirred suspensions, each containing 139 mg (1.00 mmol) of potassium 2,3-butanedione monooximate in 3 mL acetonitrile, was added 23.5 μL (0.25 mmol) of neat acetic anhydride. The reaction mixtures were stirred 1.5 h, then they were quenched with water, made basic, and the acetonitrile was evaporated; the aqueous solutions were then diluted to 50.0 mL. The absorbance at 360 nm of these solutions and of a 0.02 M potassium 2,3-butanedione monooximate standard were measured to determine the amount of oximate that had been consumed.

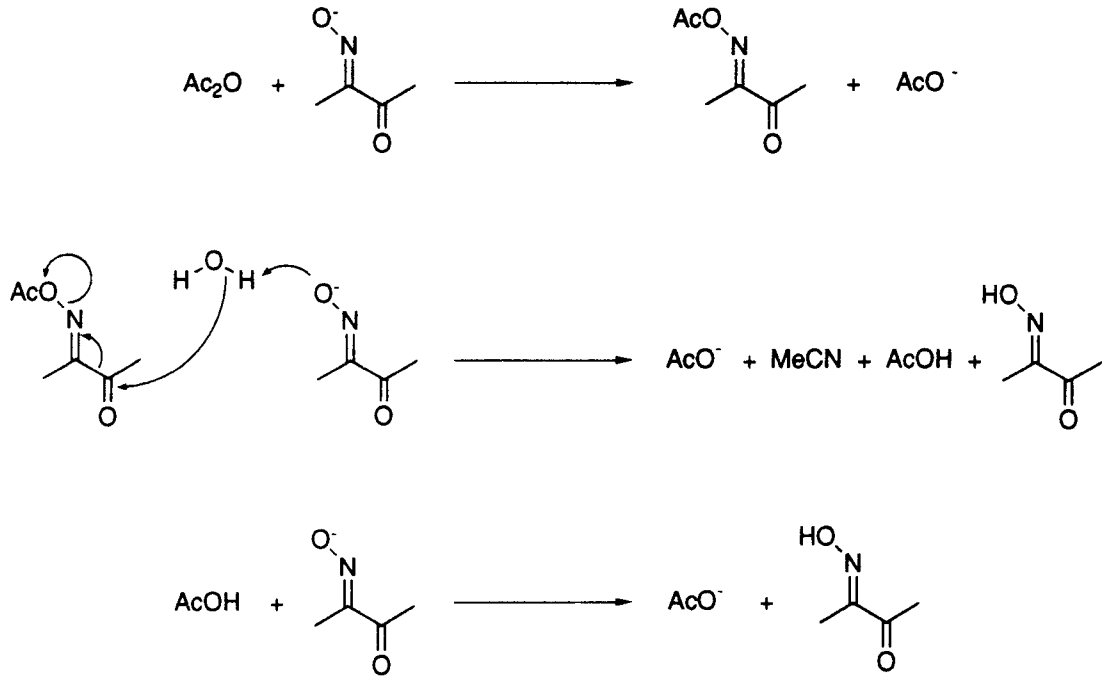
RSD formulations using neat MPEG-550 and 10% w/w water/MPEG-550 as solvent were prepared under nitrogen. To 500 g of the appropriate solvent at 55° C was added in three portions 86.9 g (0.625 mol) of KBDO (Raylo, unpurified). The mixture was stirred for 4 h, then it was allowed to cool to ambient temperature. The formulations were stored under nitrogen. Reactions were carried out using 2.00 g aliquots of these preparations (each containing 2.1 mmol of oximate). To these were added 25 to 200 μL (0.26 to 2.1 mmol) aliquots of neat acetic anhydride. After one hour, when reaction was complete, water was added to the reaction mixtures; they were made basic, and diluted to 50.0 mL. The absorbance at 360 nm of these solutions and of standards, prepared from 2.00 g aliquots of the RSD formulations made basic and diluted to 50.0 mL, were measured to determine the amount of oximate that had been consumed. The reported values are averages of triplicate experiments.

RESULTS AND DISCUSSION

To generate in various media O-acetyl 2,3-butanedione monooxime *in situ*, acetic anhydride was reacted with 2,3-butanedione monooximate. The amount of oximate that underwent chemical transformation, that is to say was not merely protonated, was determined spectrophotometrically by taking up the reaction products in dilute aqueous potassium hydroxide. It was established, at the concentrations employed, that at 360 nm 2,3-butanedione monooximate obeys Beer's law. Of the starting materials, including 2,3-butanedione monooxime, only MPEG-550 absorbs significantly at this wavelength. In an analogous fashion to the procedures described in the experimental section, reactions were carried out in which a dilute acid work-up was employed. It was found that in dilute acid there was no absorbance at 360 nm due to reaction products, although in the case of media containing MPEG-550 there was absorbance equal to that expected from the amount of MPEG-550 present. Thus, it is a reasonable assumption that the absorbance at 360 nm (corrected, where appropriate, for the absorbance of the MPEG-550 present) of the reaction products in dilute base is proportional to the concentration of 2,3-butanedione monooximate present, allowing ready determination of how much

oximate had undergone chemical transformation.

The reaction of acetic anhydride with aqueous 2,3-butanedione monooximate was investigated in 0.60 M 2,3-butanedione monooxime at pH 10.60. The literature value of the pK_a is 9.34 (7); consequently, the fraction of the total oxime present as the oximate anion at pH 10.60 is 0.95. The results of representative experiments are given in Table I. It was found in these and other experiments in water that addition of less than one-third equivalent of acetic anhydride destroyed the same quantity of oximate on a molar basis. Addition of greater than one-third equivalent of acetic anhydride resulted in the disappearance of the characteristic absorbance of the oximate from the spectra of the reaction mixtures. These results can be explained by attack of 2,3-butanedione monooximate on acetic anhydride to yield the O-acetyl oxime followed by general base catalysis by the oximate of the Beckmann rearrangement of the O-acetyl oxime:



Scheme 3

Thus, addition of one equivalent of acetic anhydride to excess oximate will result in the disproportionation of one equivalent of oximate, and the protonation of two more. This is entirely analogous to the reaction of acetic anhydride with 2-oxopropanal 1-oximate in water (8). Subsequent to this process when there is less than a threefold excess of oximate is the formation of O-acetyl 2,3-butanedione monooxime through general base catalysed attack of 2,3-butanedione monooxime on acetic anhydride, although hydrolysis competes with this reaction.

In acetonitrile the situation is quite different. Potassium 2,3-butanedione monooximate is only slightly soluble in this solvent, so heterogenous conditions were employed. Addition of 0.25 mmol of acetic anhydride to a suspension of 1 mmol of oximate was found to have destroyed 0.38 ± 0.02 mmol of oximate after a reaction period of only 1.5 h; given the heterogenous conditions, the rate of reaction is high. This result is only explicable in terms of a chain reaction as depicted in Scheme 2.

Experiments were carried out in two possible media for the RSD: MPEG-550 and 10% w/w water/MPEG-550, using the same concentration of potassium 2,3-butanedione monooximate as is to be employed in the RSD. The results are listed in Tables II and III. In both media, at all proportions of acetic anhydride, for every equivalent of acetic anhydride added less than one equivalent of oximate was found to have been consumed after basic work-up. That less than one equivalent of oximate becomes acetylated may be due to partitioning of acetic anhydride between nucleophilic attack by oximate and general base catalysed solvolysis. More likely, it is due to inefficient macroscopic diffusion of acetic anhydride resulting in local depletion of oximate followed by potassium acetate general base catalysed solvolysis:

Scheme 4

In both media, as the ratio of acetic anhydride to oximate approaches 1:1, the proportion of oximate consumed rises sharply. It is not immediately obvious what is the cause of this effect and it warrants further study.

Physical changes observed upon addition of acetic anhydride to the RSD formulations are consistent with chemical modification of the solvent. The mixed solvent RSD formulation became somewhat less viscous, but addition of even small amounts of acetic anhydride to the formulation in neat MPEG-550 resulted in it becoming a semisolid Bingham plastic (9), likely due in large part to precipitation of the salts present in solution upon acylation of the solvent. If macroscopic diffusion is also significantly slower than chemical reaction with the organophosphorus CW agents, then the formation of a non-Newtonian fluid of this type may be responsible for the finding that KBDO in neat MPEG-550 is a somewhat less effective decontaminant in animal studies than is KBDO in 10% water/MPEG-550 (10), as the formation of a Bingham plastic layer at the point of contact between the RSD and contaminated skin would reduce the rate of diffusion of agent from the skin into the RSD.

Addition of 0.25 equivalents of acetic anhydride resulted in conversion of only 11% and 17% of the oximate in the MPEG-550 and 10% w/w water/MPEG-550 RSD formulations, respectively, to O-acetyl 2,3-butanedione monooxime. At the completion of reaction, free oximate remained in the reaction mixtures of both formulations. Consequently, it is clear that O-acetyl 2,3-butanedione monooxime catalysed disproportionation of 2,3-butanedione monooximate similar to that proposed for acetonitrile cannot occur to any significant extent in these media.

CONCLUSIONS

These experiments have confirmed that disproportionation of the active ingredient of the RSD in a chain reaction catalysed by O-acetyl 2,3-butanedione monooxime will not occur when the RSD is used to decontaminate organophosphorus CW agents. However, O-acetyl 2,3-butanedione monooxime does catalyse the disproportionation of 2,3-

butanedione monooximate in acetonitrile. This is likely a general result for KBDO in aprotic media, where there can be no partitioning between solvolysis of O-acetyl 2,3-butanedione monooxime and its reaction with 2,3-butanedione monooximate, although the rate of reaction will depend on the medium. This reaction may place a significant constraint on the extension of the use of KBDO to other decontamination systems employing aprotic media.

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Table I

Reaction between Acetic Anhydride and Potassium 2,3-Butanedione Monoximate in Water

Equivalents of Acetic Anhydride Added	Equivalents of Oximate Consumed
0.12	0.12 ± 0.01
0.25	0.24 ± 0.01
0.38	0.32 ± 0.01
0.50	0.36 ± 0.01
1.00	0.46 ± 0.01

Table II

Reaction between Acetic Anhydride and Potassium 2,3-Butanedione Monoximate in MPEG-550

Equivalents of Acetic Anhydride Added	Equivalents of Oximate Consumed
0.12	0.05 ± 0.02
0.25	0.11 ± 0.02
0.50	0.15 ± 0.03
0.75	0.22 ± 0.03
1.00	0.58 ± 0.01

Table III

Reaction between Acetic Anhydride and Potassium 2,3-Butanedione Monoximate in 10% Water/MPEG-550

Equivalents of Acetic Anhydride Added	Equivalents of Oximate Consumed
0.12	0.09 ± 0.01
0.25	0.17 ± 0.01
0.50	0.29 ± 0.01
0.75	0.38 ± 0.01
1.00	0.76 ± 0.01

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