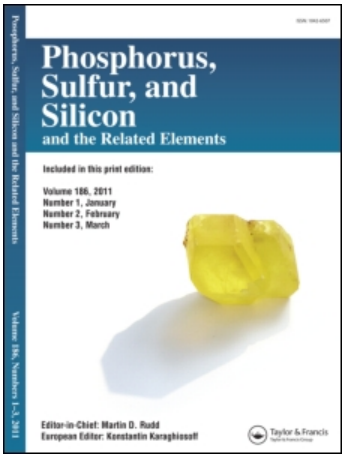

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Spyros V. Serves[a]; Demetrios N. Sotiropoulos[a]; Panayiotis V. Ioannou[a]; Henry B. F. Dixon[b]
[a] Department of Chemistry, University of Patras, Patras, Greece [b] Department of Biochemistry, University of Cambridge, Cambridge, England

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ON THE MECHANISM OF THE MEYER REACTION WITH EPOXIDES AND 2-HALOALCOHOLS AS SUBSTRATES†

SPYROS V. SERVES, DEMETRIOS N. SOTIROPOULOS and PANAYIOTIS V. IOANNOU*

Department of Chemistry, University of Patras, Patras, Greece

and

HENRY B. F. DIXON*

Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge CB2 1QW, England

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The Meyer reaction of alkaline arsenious acid with glycidol is first order in As(III) and first order in glycidol. The kinetic and stereochemical evidence shows that the reaction follows an S_N2 mechanism. The uncertainty in the pK_2 and, especially, pK_3 values for H_3AsO_3 does not distinguish between $HAsO_3^{2-}$ and AsO_3^{3-} as the actual nucleophile in the Meyer reaction with glycidol as substrate. Kinetic runs and synthetic experiments point towards AsO_3^{3-} as the most probable nucleophile. The Meyer reaction with 3-chloropropane-1,2-diol, proceeds either via glycidol or by direct displacement of chloride, in a ratio determined by the starting stoichiometry. $HAsO_3^{2-}$ does not react with the chlorodiol, thus leaving AsO_3^{3-} as the nucleophile in the Meyer reaction.

Key words: The Meyer reaction: mechanism, glycidol, 3-chloropropane-1,2-diol.

INTRODUCTION

The Meyer reaction[1] is the arsenic analogue of the Arbuzov reaction. Trialkyl arsenites, $(RO)_3As$, however, do not give this reaction[2]; indeed the equilibrium lies in the reverse direction and they can be formed by distilling $R—As(O)(OR)_2$. The "arsenite ion" gives the Meyer reaction and, based on the reactivity of the alkyl halides, the mechanism was *suggested*[3] to be S_N2:

$$RX + \text{“}Na_3AsO_3\text{”} \rightarrow R—As(O)(ONa)_2 + NaX \qquad (1)$$

With typically hydrophobic alkyl halides the reaction takes place in a two-phase system, since the halide will not dissolve in the water needed as solvent for the alkaline arsenite. Hence irreproducible results and complex kinetics, including lag periods,[4] result. This can sometimes be obviated by using water-soluble alkyl halides, e.g. 2-haloacids, R—CHX—COOH,[5] 3-chloropropane-1,2-diol,[6] or epoxides, e.g. ethylene oxide[7] and glycidols.[8,9]

†Part of this work has been presented in the NATO Advanced Study Institute, June 1994, Rhodes Island, Greece.

Another unanswered question is the nature of the nucleophile in the Meyer reaction, i.e. which species from the ones involved in the equilibria:

$$\underset{\mathbf{1}}{H_3AsO_3} \rightleftharpoons \underset{\mathbf{2}}{H_2AsO_3^-} \rightleftharpoons \underset{\mathbf{3}}{HAsO_3^{2-}} \rightleftharpoons \underset{\mathbf{4}}{AsO_3^{3-}} \qquad (2)$$

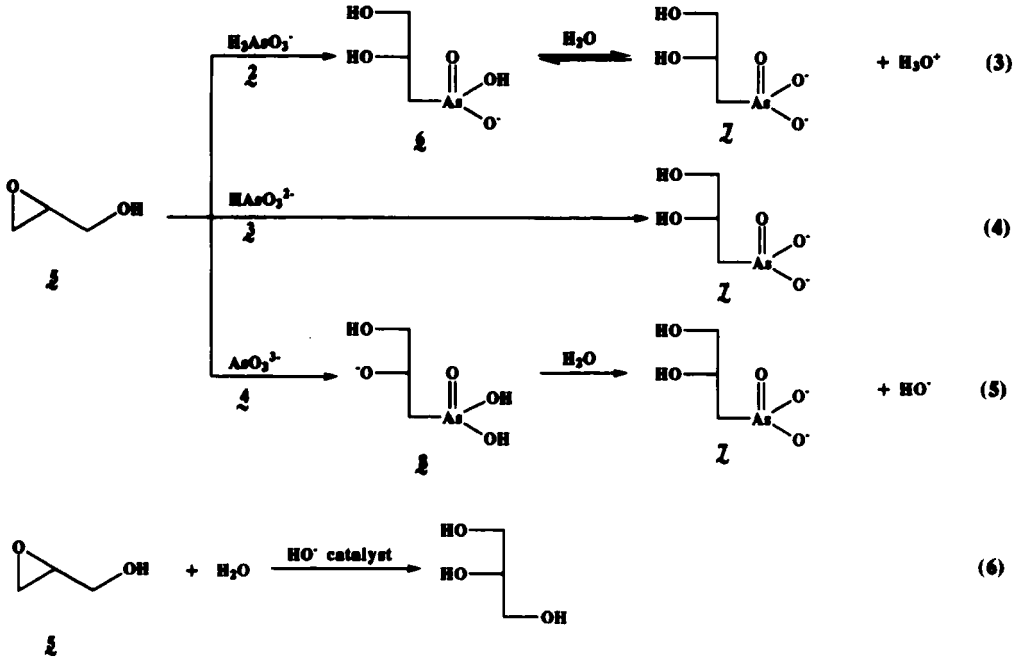
is the actual nucleophile.

Having glycidol and 3-chloropropane-1,2-diol as a water-soluble substrates for the Meyer reaction, we studied the reactions in the hope of establishing the mechanism and finding the actual nucleophile.

RESULTS AND DISCUSSION

The Meyer reaction with glycidol, **5**, can be described by the Equations 3–5, Scheme I, and, since glycerol was always found by TLC, the reaction described by Equation 6 (Scheme I) always competed. The arsonic acid must be fully ionized, as in **7**, because the pK_1 and pK_2 of the arsonic acids are 3.5–4.2 and 8.2–9.2, respectively (Reference 3, pp. 26–27).

The order of the reaction determined by the method of initial rates,[10] with respect to alkaline H_3AsO_3 is unity and with respect to glycidol is also unity, Figure 1. We could not determine the order with respect to HO^-. Therefore the Meyer reaction with glycidol follows at least second order kinetics and the mechanism is likely to be S_N2. Evidence for exclusive attack at the epoxide CH_2 came from stereochemical



SCHEME I The Meyer reaction of alkaline H_3AsO_3 with glycidol.

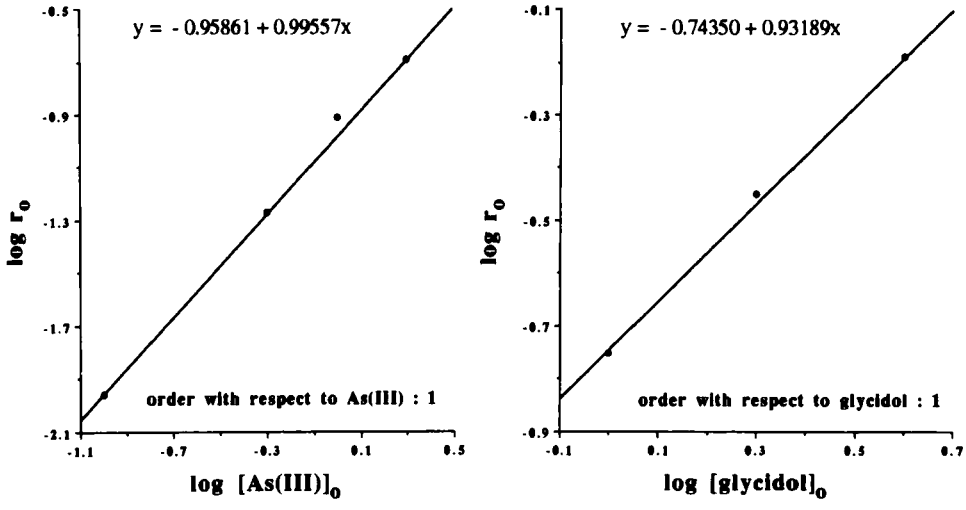


FIGURE 1 Plots of the logarithms of the initial rates against the logarithms of the initial concentrations of alkaline H_3AsO_3, As(III), and glycidol at 25°C.

studies,[8] i.e. from (*R*)-(+)-glycidol we obtained (*R*)-(−)-**7** and from (*S*)-(−)-glycidol we got (*S*)-(+)-**7**.

In order to find the actual nucleophile we have to know the pK values of arsenious acid, H_3AsO_3. The pK_1 is accurately known[11] but the pK_2 and, especially, pK_3 values are not. A published value[12] for pK_3 of 14 deviates greatly from that predicted by the Pauling[13] rules, Table I.

If $H_2AsO_3^-$, were the nucleophile then Equation 3 predicts the production of H_3O^+ which will protonate the $H_2AsO_3^-$ to H_3AsO_3. The latter, by analogy with

TABLE I

Calculated pH and concentrations of $HAsO_3^{2-}$ and AsO_3^{3-} in alkaline arsenious acid solutions using pK_2 and pK_3 values predicted by the Pauling rules[13] and those published[12]

		According to Pauling rules pK_1= 9.29, pK_2=14.3, pK_3=19.3			Published pK_1= 9.29, pK_2=13.5, pK_3=14.0		
Alkaline arsenious acid H_3AsO_3 + x NaOH	Molarity of As(III), M	pH	$[HAsO_3^{2-}]$ M	$[AsO_3^{3-}]$ M	pH	$[HAsO_3^{2-}]$ M	$[AsO_3^{3-}]$ M
x = 1	0.5	11.5	$7x10^{-4}$	~0	11.3	$3x10^{-3}$	$6x10^{-6}$
"NaH_2AsO_3"	2.0	11.6	$5x10^{-3}$	~0	11.4	$1x10^{-2}$	$3x10^{-5}$
x = 2	0.5	13.6	0.09	$2x10^{-7}$	13.4	0.19	0.04
"Na_2HAsO_3"	2.0	14.1	0.77	$5x10^{-6}$	13.6	0.91	0.35
x = 3	0.5	13.9	0.15	$7x10^{-7}$	13.7	0.24	0.12
"Na_3AsO_3"	2.0	14.5	1.18	$2x10^{-5}$	14.1	0.81	0.99

$(RO)_3As$, should not be nucleophilic towards **5**. Figure 2 shows that 5–10% of **7** is produced in the early stages of the reaction and thereafter it remains constant. Glycidol is consumed *via* Equation 6 (TLC analysis). Therefore $H_2AsO_3^-$ cannot be the nucleophile. At pH ~11.5 (Table I) very small amounts of $HAsO_3^{2-}$ exist in the solution and the production of **7** can be attributed to $HAsO_3^{2-}$.

When the values for pK_2 and pK_3 predicted by the Pauling[13] rules are used, the

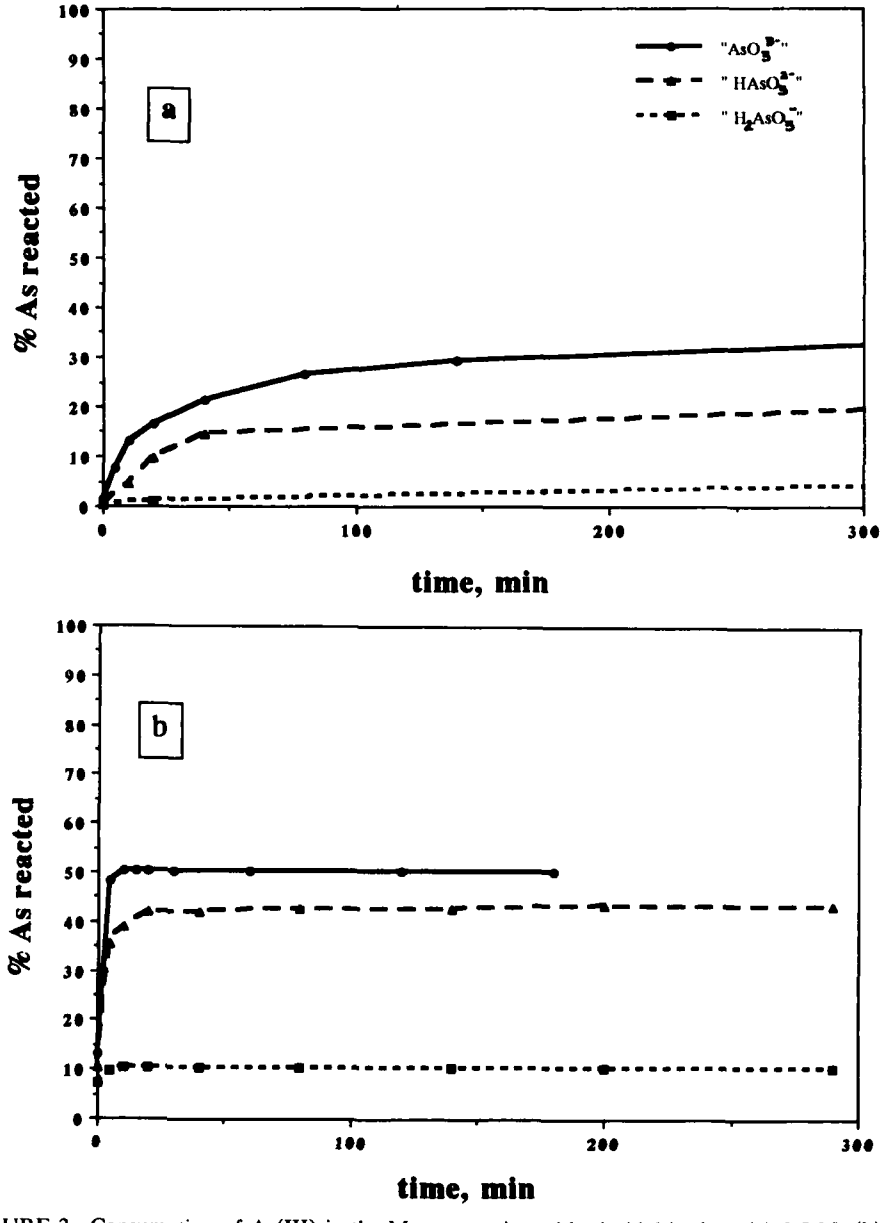


FIGURE 2 Consumption of As(III) in the Meyer reaction with glycidol both at (a) 0.5 M, (b) 2.0 M.

calculated concentrations of AsO_3^{3-} are analytically insignificant for the ratios of H_3AsO_3:NaOH of 2 and 3, Table I. In both cases the concentration of $HAsO_3^{2-}$ increases as the analytical concentration of As(III) increases and, accordingly, the rate of the Meyer reaction should increase. Figure 2 shows that the rate is indeed faster with 3NaOH per H_3AsO_3, but the yield is not greatly increased, presumably because of competing hydrolysis of the glycidol (Equation 6).

Since the reaction proceeds well with a 2:1 ratio of NaOH to H_3AsO_3, where $HAsO_3^{2-}$ predominates, this seems to be a species capable of reaction, unless AsO_3^{3-}, although in negligibly small analytical concentration by comparison, is a vastly more powerful nucleophile.

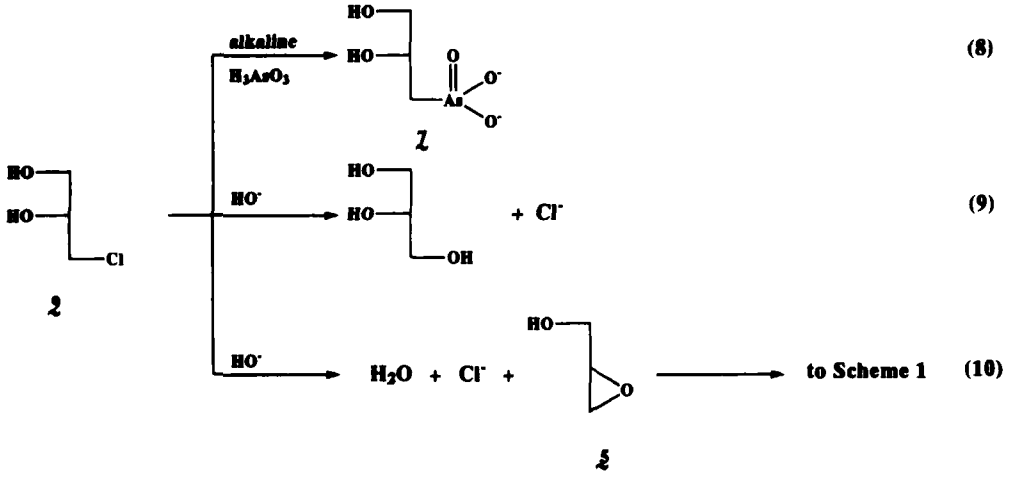
If we were to take the published[12] assignments of pK_2 and, especially, pK_3, the concentrations of $HAsO_3^{2-}$ and AsO_3^{3-} again would rise with the analytical concentration of As(III) at both 2:1 and 3:1 ratios (Table I). However, it is only the concentration of AsO_3^{3-} that would rise consistently on changing from the 2:1 to the 3:1 ratio with this assignment of pK values, suggesting that, as expected, if the pK values where such as to make the concentration of the AsO_3^{3-} appreciable, it would be the main active species in the reaction.

In deciding on the true nucleophile, with glycidol as substrate we are inclined towards AsO_3^{3-} based on preparative runs using more concentrated H_3AsO_3 + 3NaOH solutions where the yields of **7** are in the 80% region.[8,9] In such solutions the concentration of $HAsO_3^{2-}$ should be lower than those calculated in Table I thus not accounting for the increased yield of **7**.

The Meyer reaction with 3-chloropropane-1,2-diol, **9**, is more complicated because several reactions can simultaneously take place, Scheme II.

The graphs in Figure 3 are best explained if we assume that under certain conditions reactions 8 and 9 are slower than 10. Then cyclization produces HCl which is neutralized by $H_2AsO_3^-$ producing the non nucleophilic H_3AsO_3. We observed precipitation of As_2O_3 in the case of **9** + **2** (both at 2.0 M).

The system "$HAsO_3^{2-}$" + glycidol gives the Meyer reaction in respectable yields,



SCHEME II The Meyer reaction of alkaline H_3AsO_3 with 3-chloropropane-1,2-diol.

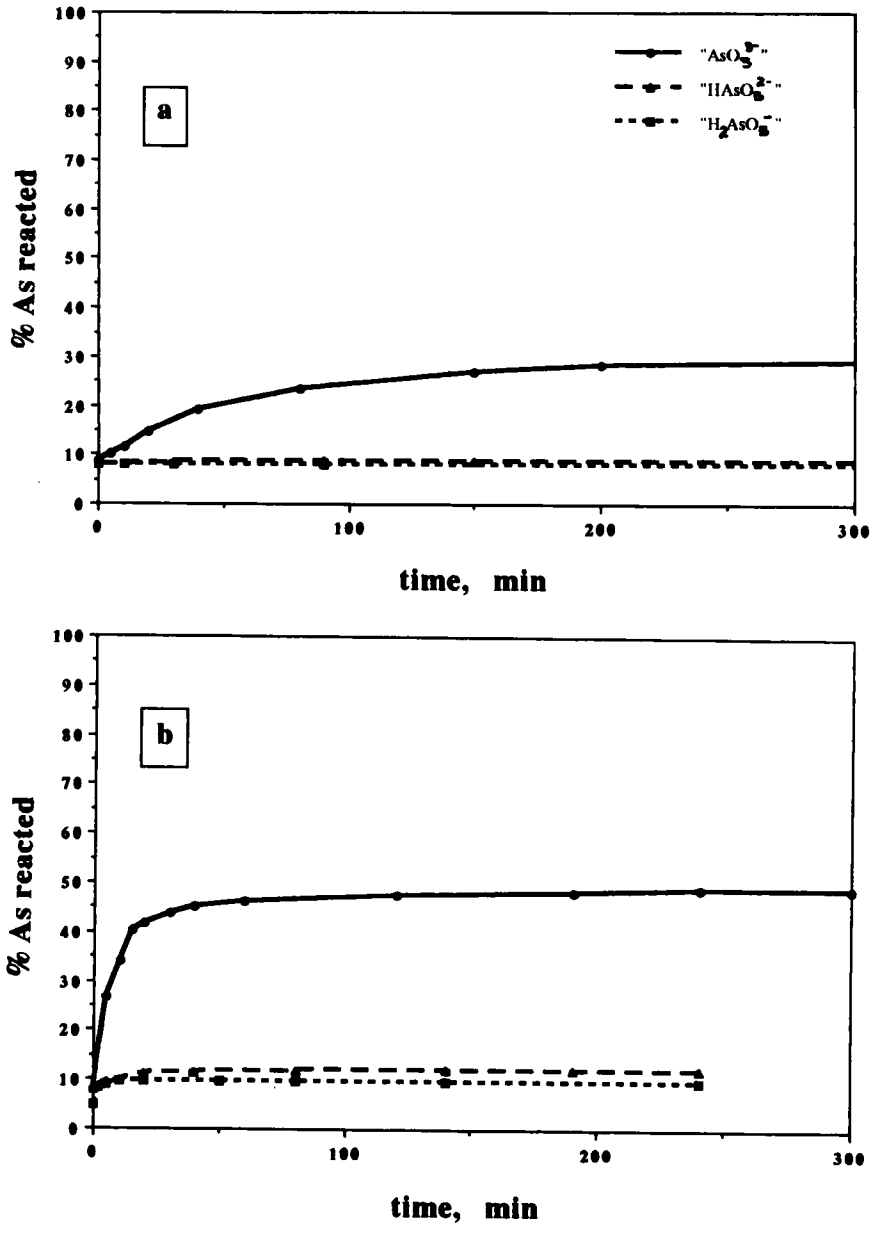


FIGURE 3 Consumption of As(III) in the Meyer reaction with 3-chloropropane-1,2-diol both at (a) 0.5 M, (b) 2.0 M.

(Figure 2), but the system "$HAsO_3^{2-}$" + **9** does not give more than 10% of **7** although the —Cl in **9** is a better leaving group than —O^- in **5**. Under these conditions cyclization is faster than the Meyer reaction and $HAsO_3^{2-}$ is converted into the inactive $H_2AsO_3^-$. Since 10% of the reaction diminishes the concentration of the $HAsO_3^{2-}$ by only 10%, this should not halt the reaction, but the minute concentration of the AsO_3^{3-} is diminished by a much greater factor by a such a

drop of pH. This set of experiments shows that $HAsO_3^{2-}$ does not have an appreciable nucleophilic character.

In the case of "Na_3AsO_3" + **9** if cyclization were faster than the direct Meyer (Equation 8) we would expect yields of **7** similar to those obtained by "$HAsO_3^{2-}$" + **5**, Figure 2. However, the yields are higher than expected (Figure 3). Therefore under these conditions **7** is obtained *via* **5** and by direct displacement of —Cl in **9** (reaction 8). This displacement must be effected by AsO_3^{3-} because we saw above that $HAsO_3^{2-}$ does not have appreciable nucleophilic characted towards **9**.

From the synthetic point of view an equimolar ratio of **9**:"Na_3AsO_3":NaOH gave the best yields (80% by titration, 45% isolated) of **7**.[6]

EXPERIMENTAL

The kinetic runs were done at 25°C. As(III) was determined iodometrically and glycidol was determined by the alcoholic magnesium chloride hydrochlorination method.[14]

Oxidation of As(III) by atmospheric O_2 was not observed. The calculations of pH and of concentrations of the various species were done by solving the equations for mass balance, charge balance, pK_w and the pertinent pK equations using a computer program.

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