The Reaction of Geminal Bromonitroalkanes with Nucleophiles. Part 1. The Decomposition of 2-Bromo-2-nitropropane-1,3-diol ('Bronopol') in Aqueous Base

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2-Bromo-2-nitropropane-1,3-diol decomposes in aqueous base to give tris(hydroxymethyl)-nitromethane, glycolic acid, formic acid, methanol and 2,2-dinitroethanol. It also releases NO_2^- and Br^- ions but not BrO^-. These products are shown to form *via* four concurrent decomposition pathways, three of which involve 2-bromo-2-nitroethanol as a reactive intermediate.

In view of the ability of a nitro group to stabilise a negative charge by conjugation, geminal bromonitroalkanes should undergo nucleophilic attack at carbon with displacement of bromide ion.[1] With weak nucleophiles, the parent compound, bromonitromethane, reacts mainly at the bromine,[2,3] yielding nitromethane after work-up; with strong nucleophiles, *e.g.* methoxide ion in methanol, deprotonation occurs and the subsequent nitronate ion is 'inert to further reaction'.[3] There are three clear examples, however, of exclusive substitution of bromide ion by weak nucleophiles in geminal halonitroalkanes in spite of Yousaf and Lewis' comment that 'there are virtually no established cases of substitution of halogen on carbon in these systems'.[1] These examples are: the reaction of bromonitromethane with dimethyl sulphide[3] to yield methyl nitromethyl sulphide and trimethylsulphonium bromide; the reaction of chloro- and bromonitromethane with nitrite ion in aqueous methanol to yield dinitromethane;[4] and the reaction of 2-bromo-2-nitroethanol with nitrite ion in aqueous methanol to yield 2,2-dinitroethanol.[5]

The nucleophilic reactions of amines with geminal bromonitroalkanes do not appear to have been examined; neither have the reactions of hydroxide ion, although the solvolysis of bromonitromethane in water is known to be very slow.[6] We have begun an investigation of the reactions of geminal bromonitroalkanes with these nucleophiles, and this paper deals with the hydroxide ion-initiated hydrolysis of 2-bromo-2-nitropropane-1,3-diol ('Bronopol'), a water-soluble geminal bromonitroalkane with broad-spectrum bacteriocidal activity.[7]

Previous work on the decomposition of Bronopol (**1**) in aqueous base is inconclusive. Bryce *et al.*[8] identified formaldehyde, 2-bromo-2-nitroethanol (**2**) and tris(hydroxymethyl)-nitromethane (**14**) (Scheme 1) as products, but did not really explain the formation of **14**. Subsequently, Schmeltz and Wenger[9] found formaldehyde, 2-nitroethanol (**17**) and **2** as products but not the triol **14**. Both sets of workers, however, did show that nitrite and bromide ions were also released, but offered no satisfactory mechanisms for their formation.

We have therefore re-examined the decomposition of Bronopol in aqueous base by ^{13}C NMR spectroscopy, HPLC and UV spectrophotometry. Both the organic and inorganic decomposition products are identified and probable pathways for their formation are discussed.

Results

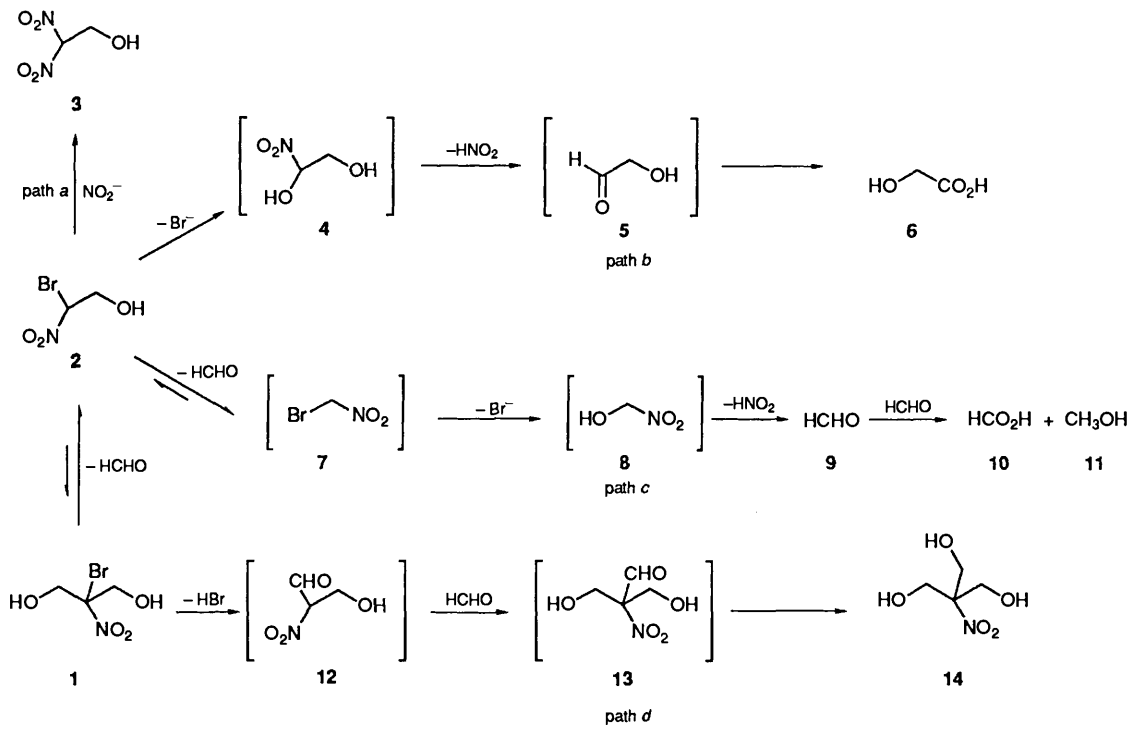
In agreement with earlier work,[8,9] the decomposition of aqueous Bronopol is accelerated on raising the pH. Addition of either Bronopol **1** or 2-bromo-2-nitroethanol **2** to KOH (0.5–2 mol dm^{-3}) at ambient temperature produces a vigorous effervescence of formaldehyde. The solutions, initially colourless, instantly turn yellow and within hours darken to a deep reddish-brown. In unbuffered solutions, decomposition of Bronopol is accompanied by a sharp fall in the pH.

Fig. 1 is a decoupled ^{13}C NMR spectrum of the decomposition products formed in aqueous base (see Experimental section for details). The major products identified from their chemical shifts and carbon multiplicities are glycolic acid **6** (CH_2 62.1 ppm; CO_2^- 178.6 ppm), formaldehyde **9** (84.5 ppm), formic acid **10** (168.2 ppm), methanol **11** (51.8 ppm) and tris(hydroxymethyl)nitromethane **14** (C 97.5 ppm; CH_2 62.6 ppm). The formaldehyde carbonyl carbon (expected at *ca.* 200 ppm)[10] is not observed because in aqueous solution formaldehyde is present exclusively (>99.95%) as the hydrate.[11] Unreacted Bronopol is also seen (C 103.0 ppm; CH_2 67.4 ppm). All of the above identities were confirmed by comparison with authentic compounds.

The ^{13}C chemical shifts of several other potential products, conspicuous by their absence from Fig. 1, were also characterised using authentic compounds. These are 2-bromo-2-nitroethanol **2** (CH 81.4 ppm; CH_2 66.4 ppm), bromonitromethane **7** (61.2 ppm), 2-nitropropane-1,3-diol **15** (CH 93.4 ppm; CH_2 62.4 ppm), 2-nitroethanol **17** (CH_2NO_2 79.9 ppm; CH_2OH 60.5 ppm) and 1,3-dihydroxyacetone **18** (CO 214.8 ppm; CH_2 67.7 ppm). Dinitromethane **19** (99.4 ppm)[12] is also absent from Fig. 1.

Fig. 2(*a*) is a reversed-phase HPLC analysis of the reaction mixture of Fig. 1 on a silica C18 column. Only two peaks are observed, corresponding to unreacted Bronopol (4.4 min) and the triol **14** (2.8 min). It is not surprising, therefore, that in a previous study[8] of the decomposition of Bronopol in aqueous base the triol **14** was the only product detected apart from formaldehyde and 2-bromo-2-nitroethanol **2**. Glycolic acid **6** and formic acid **10** elute in the solvent front on the silica C18 column [Fig. 2(*a*)], but they can be detected using a Polypore H® column [Fig. 2(*b*)].

Retention times on the silica C18 column of other potential products which were not detected in either the ^{13}C NMR study or the HPLC analysis study [Fig. 2(*a*)] are 2-bromo-2-nitroethanol **2** (6.4 min), bromonitromethane **7** (8.4 min), 2-nitropropane-1,3-diol **15** (3.0 min), 2-nitroethanol **17** (3.3 min) and 1,3-dihydroxyacetone **18** (2.6 min). The absence of these products clarifies the decomposition pathways, as discussed below. Formation of 2-bromo-2-nitroethanol **2** can be observed by HPLC, however, when Bronopol is decomposed in borax buffer (pH 8.98) at 25 °C. The concentration of **2** increases over *ca.* 30 min following pseudo first-order kinetics (rate = 1.1×10^{-3} s^{-1}) then remains constant in equilibrium with Bronopol. Under these milder conditions, only small amounts (<5%) of the other products **3**, **6**, **10**, **11** and **14** are produced over 24 h.



Scheme 1

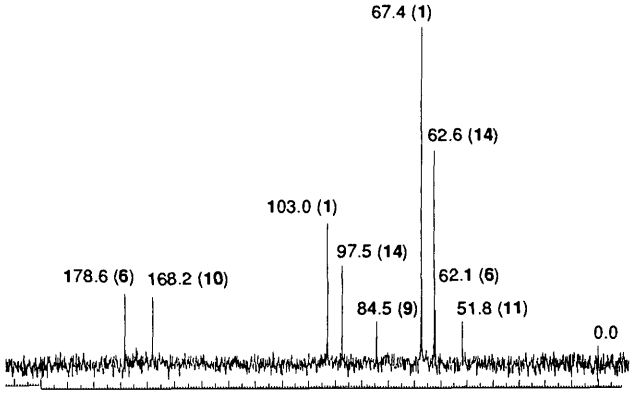


Fig. 1 ^{13}C NMR spectrum in D_2O/H_2O (1:1, v/v) of the decomposition products of Bronopol in base (*cf.* Results for interpretation). Chemical shifts are quoted relative to sodium trimethylsilylpropanoate as internal standard.

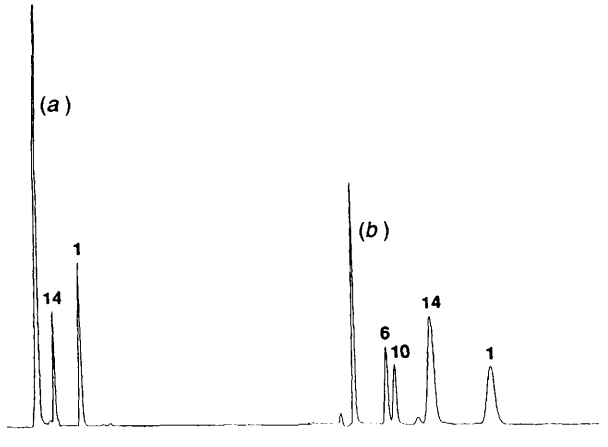


Fig. 2 Analysis of decomposition products of Bronopol in aqueous base by reversed-phase HPLC. (*cf.* Results for interpretation). (*a*) Column, silica C18 (ODS) 0.46 × 25 cm; solvent, CH_3CN–water (20:80, v/v); flow, 1 cm^3 min^{-1}; detector, UV (210 nm). (*b*) Column, Polypore H® 0.46 × 25 cm; solvent, 0.005 mol dm^{-3} H_2SO_4; flow, 0.4 cm^3 min^{-1}; detector, UV (214 nm).

Analysis of the inorganic products of the reaction (see Experimental section) confirms the formation of Br^- and NO_2^- only, as reported earlier.[8,9] Significantly, hypobromite ion (BrO^-) is not detected as a hydrolysis product. The concentration of both NO_2^- and Br^- increase asymptotically in concert with the decrease in Bronopol concentration. The concentration of Br^- does not pass through a maximum, as previously suggested.[9] It forms quantitatively, whereas only 35% of the nitrogen is expelled as NO_2^-. The significance of these findings is also discussed later.

UV analyses of alkaline aqueous solutions of Bronopol show a rapid appearance of a peak at λ_{max} 365 nm due to the anion of 2,2-dinitroethanol **3** (lit.,[13] λ_{max} 365 nm; log ε 4.19). The absence of a peak at 362 nm implies that dinitromethane anion (lit.,[14] λ_{max} 362 nm; log ε 4.30) is not formed, supporting the ^{13}C NMR product study (*vide supra*). The concentration of **3** never exceeds *ca.* 1% of the initial concentration of Bronopol. It is therefore a minor product of Bronopol hydrolysis.

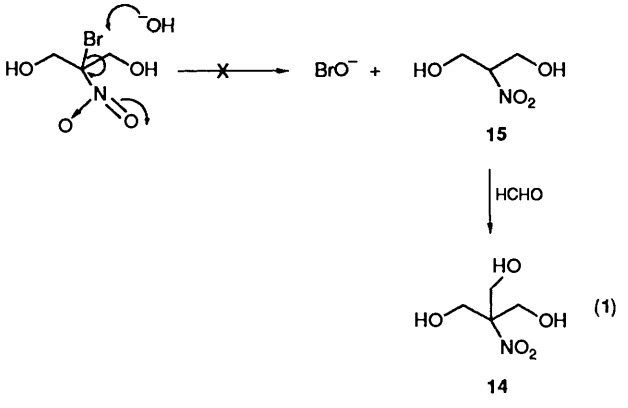
Discussion

All of the products can be rationalised by the occurrence of four concurrent pathways (*a*–*d*) for the decomposition of Bronopol in aqueous base (Scheme 1). Three of these pathways (*a*–*c*) proceed *via* 2-bromo-2-nitroethanol **2** which forms by the reversible loss of formaldehyde (retro-aldol reaction). This initial reaction is pH sensitive and accelerates with increasing pH.[8] We find that it occurs to a small extent even in mildly acidic media; thus on standing, aqueous solutions of Bronopol at pH 5–6 contain *ca.* 2–5% of **2** by HPLC assay.

Bryce *et al.*[8] reported that 2-bromo-2-nitroethanol **2** is much less stable in aqueous media than Bronopol itself, and may be viewed as a reactive intermediate vulnerable to either displacement of bromine (paths *a* and *b*) or further loss of formaldehyde (path *c*). Path *a* is displacement by nitrite ion to give 2,2-dinitroethanol **3** as previously reported.[4] Path *b* is an hydrolysis to give the unstable aldehyde **5**, which is then oxidised to glycolic acid **6**. Path *c* is a retro-aldol reaction to give bromonitromethane **7**, which is not found as a product because it hydrolyses to formaldehyde **9**. The final products, formic acid

10 and methanol **11**, are formed by the Cannizzaro reaction of formaldehyde.[15] Pathways *a–c* were confirmed by decomposing an authentic sample of 2-bromo-2-nitroethanol **2** in aqueous base. This reaction also produced Bronopol, *i.e.* formaldehyde released by path *c* reacts with starting material **2** to give Bronopol by an aldol condensation. This confirms the reversibility of the interconversion **1** ⟷ **2**.

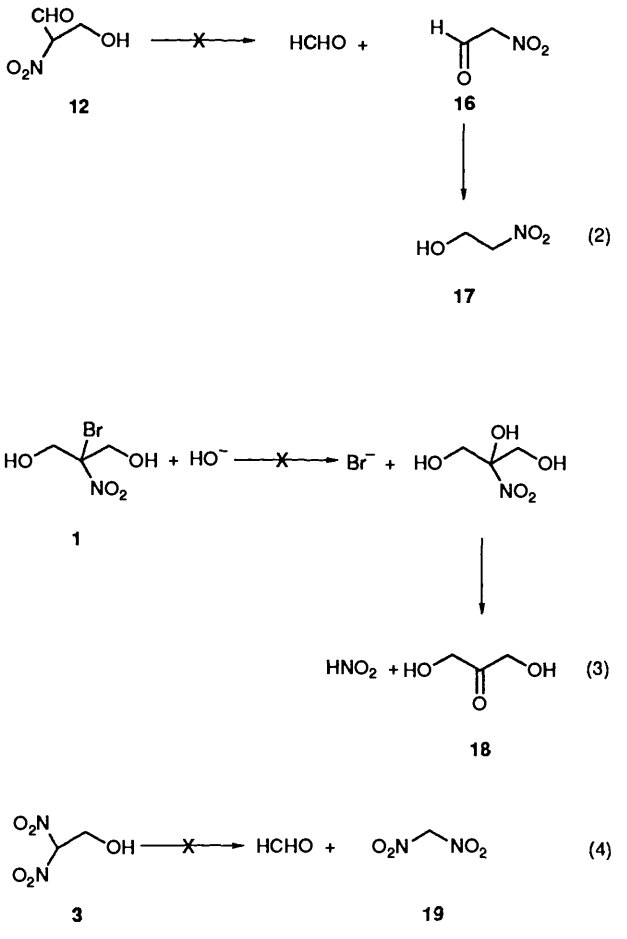
Path *d* of Scheme 1 is the irreversible conversion of Bronopol to tris(hydroxymethyl)nitromethane **14**. No mechanism was given by Bryce *et al.*[8] for this transformation, even though **14** is the major product in the base-initiated hydrolysis of Bronopol. The most likely process would be an S_N2 attack of hydroxide ion on bromine to give 2-nitropropane-1,3-diol **15** followed by an aldol condensation **15** ⟶ **14** [eqn. (1)]. This can be ruled out, however, because hypobromite ion is not formed by the decomposition reaction and the diol **15** is not detected either as



an intermediate or product. The alternative process (path *d*) is a base-catalysed β-elimination to give the unstable nitroaldehyde **12** which then rapidly undergoes an aldol condensation with formaldehyde to give the aldehyde **13**. Aldehyde **13** is devoid of hydrogen on the α-carbon and in the presence of formaldehyde undergoes a cross-Cannizzaro reaction to give the triol **14**. There is no evidence that aldehyde **13** is also oxidised to the corresponding carboxylic acid, as expected.[15] Further, the failure to detect intermediates **12** and **13** on path *d* implies that the initial β-elimination is rate-limiting.

Nitrite ion is released in the processes **4** ⟶ **5** and **8** ⟶ **9** but is consumed in the conversion of 2-bromo-2-nitroethanol **2** to 2,2-dinitroethanol **3** as previously reported.[4] Bromide ion is released in the processes **2** ⟶ **3**, **2** ⟶ **4** and **1** ⟶ **12**. None of the final products contains bromine whereas both **3** and the major product **14** contain nitro groups. This accounts for quantitative formation of Br^- but only partial formation (*ca.* 35%) of NO_2^-.

Other conclusions can be drawn from the absence of certain products. Despite a report to the contrary,[9] 2-nitroethanol **17** is not detected as a decomposition product of Bronopol in aqueous base and the retro-aldol reaction **12** ⟶ **16** followed by reduction to **17** [eqn. (2)] cannot be extensive. The absence of 1,3-dihydroxyacetone **18** as a decomposition product implies that nucleophilic attack by HO^- at the quaternary carbon of Bronopol [eqn. (3)] does not occur. This is not surprising in view of the steric hindrance at the quaternary carbon, and the known reactivities of geminal halonitroalkanes towards nucleophiles.[2,3] Finally, failure to detect dinitromethane **19** implies that the retro-aldol reaction **3** ⟶ **19** [eqn. (4)], does not occur, as expected.[16]



Experimental

Chemicals.—Glycolic acid was obtained from Sigma and characterised by its ^{13}C NMR spectrum. Bronopol was obtained from Boots Microcheck and characterised by m.p. (129.7–130.0 °C; lit.,[17] 120–122 °C); HPLC; ^{13}C NMR spectroscopy; and mass spectroscopy (Table 1). All other compounds were obtained from Aldrich and were characterised by the HPLC retention times and ^{13}C NMR spectra.

2-Bromo-2-nitroethanol **2** was synthesised by the procedure of Gold *et al.*,[4] purified by vacuum distillation (62–64 °C/0.1 mmHg; lit.,[4] 83 °C/2 mmHg), and characterised by HPLC retention time and ^{13}C NMR and mass spectroscopy (Table 1). Its mass spectrum has not been previously reported.[18]

2-Nitropropane-1,3-diol **15** was synthesised and characterised *in situ* by the alkaline hydrolysis of tris(hydroxymethyl)-nitromethane **14**. KOH (0.11 g, 2 mmol) was added as pellets to a solution of the triol **14** (1 mol dm^{-3}) in a 10 mm NMR tube in H_2O/D_2O (1:1, v/v). The mixture was left overnight at 22 °C and a ^{13}C NMR spectrum was recorded. Two new peaks, at 128.1 ppm (C=N) and 60.7 ppm (CH_2) due to the nitronate ion of the diol **15** were visible (in addition to formic acid and methanol formed by the Cannizzaro reaction of formaldehyde). Acidification with conc. HCl converted the nitronate ion to the neutral diol (CH 93.4 ppm; CH_2 62.4 ppm). In aqueous solution 2-nitropropane-1,3-diol **15** is present entirely in the CH form, as confirmed by the INEPT pulse sequence. In benzene solution it exists wholly in the NH form, *i.e.* as the nitronic acid.[19]

All m.p.s were determined on an Electrothermal Digital Melting Point Apparatus and are uncorrected.

All UV spectra were taken on a UVIKON 810P Spectrophotometer in 1 cm matched stoppered quartz cells.

NMR Spectra.—^{13}C NMR spectra were taken on a JEOL FX90Q Spectrometer at 22.5 MHz (2.11 T) in 10 mm i.d. NMR tubes (from Fluorochem) using D_2O/H_2O (1:1, v/v) as solvent and internal lock, with the sodium salt of trimethylsilyl-

Table 1 Mass spectral analysis[a] of Bronopol **1** and 2-bromo-2-nitroethanol **2**

Compound	Base peak	*m/z* (%)	*m/z* (%)	*m/z* (%)	*m/z* (%)
Bronopol **1**	31	107(59)	135, 137(57)	123, 125(38)	169, 171(36)
Bromo-2-nitroethanol **2**	43	28(65)	123, 125(55)	139, 141(12)	151, 153(10)

[a] The M^+ peaks are absent from both spectra, as expected.[21]

propanoic acid (TPA) as internal standard. The bromonitromethane **7** spectrum was taken in $CDCl_3$ as solvent, internal lock and internal standard. All spectra, unless otherwise stated, were taken at ambient probe temperatures (20–22 °C) using a 5.3 kHz spectral window with 29 μs pulse width (90°), 2 s pulse delay, 0.772 s acquisition time, and 8K data acquisition, giving a digital resolution of 1.6 Hz pt^{-1}. For the relatively high concentrations used, good signal:noise ratios (>50:1) were obtained within *ca.* 500 scans. Carbon multiplicities were assigned using the two INEPT pulse sequences previously described.[20]

HPLC Analyses.—All organic HPLC analyses were carried out on a Waters Delta Prep 3000 using a Waters 712 WISP Injector and a Waters 484 Tunable Absorbance UV Detector. Chromatograms were generated by a Waters 745B Data Module. Separation was achieved using either a silica C18 (0.46 × 25 cm) or Polypore H® (0.46 × 25 cm) column. Typical operating conditions are given in Fig. 2. The NMR samples were diluted (×100) with water prior to the HPLC analyses.

Inorganic HPLC analyses were carried out on a VYDAC® resin column (0.46 × 5 cm) using a borate–phthalate (0.002 mol dm^{-3}) buffer pH 5.1 as mobile phase and a Milton Roy Conducto Monitor® III conductivity detector. Typical operating conditions were: flow rate 2 cm^3 min^{-1}; pressure 800 psi; sensitivity 3 μs; injection volume 5 nm^3. Under these conditions typical retention times were NO_2^- (1.9 min) and Br^- (2.6 min). The buffer pH was raised to 9.5 and the buffer concentration to 0.02 mol dm^{-3} to elute BrO^- (6 min). Under these conditions NO_2^- and Br^- are not retained on the column.

Reactions.—Most reactions were carried out in 10 mm NMR tubes by adding KOH pellets to a solution of Bronopol or 2-bromo-2-nitroethanol **2** in D_2O/H_2O (1:1, v/v). The concentration of KOH and reactants varied in the range 0.5–2 mol dm^{-3}. Best results were obtained using a *ca.* two fold excess of base. For Fig. 1, $[Bronopol]_0$ = 1 mol dm^{-3}; $[OH^-]_0$ 2.2 mol dm^{-3}; initial pH > 14; final pH *ca.* 8 (after *ca.* 24 h at 22 °C). The addition of KOH to Bronopol and 2-bromo-2-nitroethanol **2** results in the vigorous effervescence of formaldehyde. The solutions, initially colourless, instantly turn yellow and within hours darken to a deep reddish-brown. This colour change has been described previously,[8] and is due to 2,2-dinitroethanol anion.

Acknowledgements

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