Reactions of Dipotassium Diazomethanedisulphonate in Aqueous Solution

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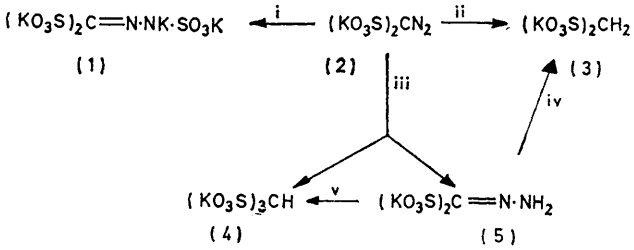
Decomposition of dipotassium diazomethanedisulphonate (2) in aqueous solution leads to the appropriate potassium salt of either hydrazonomethanedisulphonic acid (5), methanetrisulphonic acid (4), methanedisulphonic acid (3), or sulphohydrazonomethanedisulphonic acid (1), depending on the conditions employed. The relative stability of the diazo-compound at neutral pH together with its function as an alkylating agent, evidenced by the formation of dipotassium methoxymethanedisulphonate in aqueous methanol, suggests that it may have some potential as an irreversible inhibitor in biological systems.

DIPOTASSIUM DIAZOMETHANEDISULPHONATE (2), a relatively stable diazo-compound first synthesized by von Pechmann and Manck [1] in 1895 has received little attention since.[2-5] The relatively slow decomposition of the diazo-disulphonate (2) in aqueous solution at neutral pH suggests that it might be a useful irreversible inhibitor in biological systems, particularly where there is an anion-binding site adjacent to, or part of, the active site under investigation. However, the present exploratory study of the reactivity of the diazomethanedisulphonate (2) in aqueous solution shows that its behaviour is more complex than the earlier literature suggested, the nature of the methanedisulphonate derivative formed showing a striking dependence on the conditions employed (Scheme 1).

The decomposition of the diazo-compound (2) in aqueous solution was reported [3] to yield only tripotassium methanetrisulphonate (4), apart from several inorganic products [1] which have not been investigated further here. However, at room temperature and below, the major



SCHEME 1 Conditions: i, N-NaOH; ii, H_2O–NEt_3; iii, H_2O, 20°; iv, NaOH; v, H_2O, heat

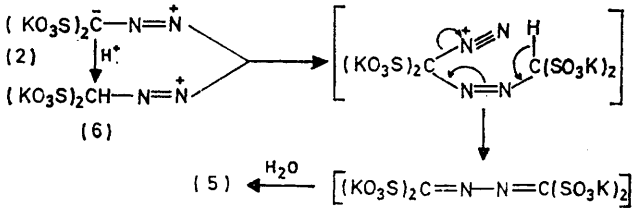
product is the hitherto unknown hydrazone (5), the trisulphonate (4) being only a minor component. The structure of the hydrazone (5) was consistent with the elemental analysis and with the i.r. spectrum. The u.v. spectrum was similar to that of the sulphohydrazone (1).

[1] H. von Pechmann and P. Manck, *Ber.*, 1895, **28**, 2374.
[2] P. Fantl and J. Fisch, *J. prakt. Chem.*, 1930, **124**, 159; F. B. Kipping, *J. Chem. Soc.*, 1931, 222; U.S.P. 2,825,747 (*Chem. Abs.*, 1958, **52**, 8610*f*).
[3] H. J. Backer, *Rec. Trav. chim.*, 1930, **49**, 1107.
[4] F. Nesh, *J. Phys. Chem.*, 1958, **62**, 566.
[5] A. P. Kottenhahn, *J. Org. Chem.*, 1963, **28**, 3433.

In N-potassium hydroxide solution at room temperature the hydrazone (5) underwent a normal Wolff–Kishner reduction, yielding dipotassium methanedisulphonate (3). On heating in aqueous solution, compound (5) decomposed giving the trisulphonate (4), indicating why the hydrazone (5) was not identified in earlier studies where higher temperatures were employed either during the reaction or during recrystallisation.

In N-potassium hydroxide at room temperature the diazo-disulphonate (2) is moderately stable, but decomposes more rapidly at higher temperatures forming the tetrapotassium salt of the sulphohydrazone (1) in high yield (88% at 70°), none of the trisulphonate (4) being detected. The change from the hydrazone (5) and the trisulphonate (4) to the sulphohydrazone (1) as products from the room temperature decomposition of 0·07M-diazomethanedisulphonate (2) solutions of increasing pH occurred on going from 0·01M- to 0·1M-potassium hydroxide, although some of the trisulphonate (4) was also isolated from the latter solution. A report [4] that in 0·005N-sodium hydroxide at 25° the diazo-compound (2) decomposes, giving, after 4 days, a quantitative yield of nitrogen is not easily reconciled with the formation of nitrogen-containing products, although the solutions of the diazomethanedisulphonate employed in the earlier study [4] were more dilute (0·005M) than those convenient to use here (0·07—0·1M). The yields of nitrogen from 0·1M-diazomethanedisulphonate (2) solutions usually correlated well with the yields of the hydrazone (5) isolated [50 and 56% of theoretical yield of N_2 in distilled water at 6°, two experiments; *cf.* 41% yield of the hydrazone (5)] and only in strongly acidic solution was the yield of nitrogen quantitative (103 and 105% yield in N-sulphuric acid at 6°).

On heating in aqueous solutions of organic bases the diazo-disulphonate (2) decomposed to give dipotassium methanedisulphonate (3), the yields at 70° being in the range of 70—83%. At lower temperatures the yields of the disulphonate (3) were lower, *e.g.* 45% from 2% aqueous triethylamine at room temperature. The disulphonate (3) was also the product when the hydrazone (5) was heated in aqueous triethylamine at 70°, but whether this is the reaction pathway is unknown, as is the mechanism of the formation of the hydrazone (5) itself. The reduction of diazo-compounds by ammoniacal hydrogen sulphide to give hydrazones is well known,[6] but there is no indication that the hydrazone (5) arises from the action of some inorganic decomposition product of the diazo-disulphonate (2). Potassium hydrogen sulphite added to solutions of the diazo-compound (2) in 0·2M-acetate buffer, pH 5·2, at room temperature approximately tripled the amount of the trisulphonate (4) formed but had no significant effect on the yield of the hydrazone (5). Interestingly a hydrazone has recently been reported [7] as a by-product of a synthetic route to bisarylsulphonyldiazomethanes and a mechanism similar to that suggested there can be proposed for the formation of the hydrazone (5) (Scheme 2). The involvement of a protonated intermediate (6) is consistent with the observed pH dependence of hydrazone formation. The formation of the sulphohydrazone (1) in alkali and the trisulphonate (4) in more acidic solutions presumably reflects the position of the hydrogen sulphite–sulphite equilibrium, the ion formed on decomposition of one molecule of the diazo-disulphonate (2) then reacting with



SCHEME 2

the parent compound (2) is known fashion [1,3] to give the appropriate product. It is probably also a consequence of the position of this equilibrium that at room temperature the products isolated from the reaction of the diazo-disulphonate with added hydrogen sulphite were the hydrazone (5) and the trisulphonate (4), while at 70° the products were the trisulphonate (4) and the sulphohydrazone (1). Interestingly, potassium chloride, which reduces the rate of decomposition of the diazo-disulphonate (2) in aqueous solution [4] markedly alters the proportions of the products at 70°, nucleophilic attack by hydrogen sulphite to give the trisulphonate (4) being decreased (65 ⟶ 24%) at the expense of electrophilic attack on sulphite forming the sulphohydrazone (1) (21 ⟶ 78%).

In contrast to the thermal decomposition, irradiation of the diazo-disulphonate (2) in N-potassium hydroxide solution yields the disulphonate (3), while in 0·5M-potassium acetate the only product isolated was the trisulphonate (4), in low yield. The mechanisms of these reactions have not been investigated but attempts to trap a carbene intermediate were unsuccessful.

Despite the competing decomposition processes, diazomethanedisulphonate (2) can be employed successfully in reactions in aqueous solution. Cycloadditions to activated olefins have been described by Kottenhahn,[5] but of particular relevance for the projected use of the diazo-compound (2) in biological systems is the observation that it also shows alkylating activity. An attempt to use aqueous methanol to improve the solubility of organic substrates led to the isolation of the methyl ether (7), which was subsequently shown to be formed in aqueous

$(KO_3S)_2CH{\cdot}OMe$
(7)

methanol alone. Limited solubility may in any case not be unduly disadvantageous providing reaction with the soluble portion is sufficiently rapid.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 21 spectrophotometer, and u.v. spectra on a Cary model 14 instrument.

[6] H. Staudinger, L. Hammet, and J. Siegwart, *Helv. Chim. Acta*, 1921, **4**, 228.
[7] G. Heyes and G. Holt, *J.C.S. Perkin I*, 1973, 189.

^{1}H N.m.r. spectra were recorded on a Varian HA-100 spectrometer for solutions in D_2O. Chemical shifts are reported as p.p.m. downfield from external hexamethyldisiloxane. The presence of water was determined from the i.r. spectrum, since in some compounds it could be removed only by extended drying *in vacuo* at high temperatures. Some of the reactions described above are not given in detail in this section, the procedures and separation techniques used being analogous to those of other reactions described below. Known compounds had i.r. spectra identical with samples prepared by alternative literature methods.[1,3,8]

Dipotassium Diazomethandisulphonate (2).—This was prepared by the method of von Pechmann and Manck[1] and purified by recrystallisation from N-KOH (*ca.* 5 ml per g of compound), warming being kept to the minimum necessary to effect dissolution. Contrary to the literature[1] pure samples of the diazo-disulphonate (2) contain no water of crystallisation (Found: C, 4·4; H, 0·2; N, 9·85; S, 22·9. Calc. for $CK_2N_2O_6S_2$: C, 4·3; H, 0·0; N, 10·1; S, 23·1%), $\nu_{max.}$ (KBr) 2101s (diazo), 1271s, 1250s, 1224s, 1196s, 1060s, 1037s, 987w, and 681s cm^{-1}, $\lambda_{max.}$ (N-KOH) 233 and 412 nm (ε 5630 and 10·4).

Decomposition of Dipotassium Diazomethanedisulphonate.—(a) *In water.* A solution of the diazo-compound (2) (3·3 g) in water (100 ml) was kept at 4° until it had become colourless (*ca.* 2 h). Methanol was added until a slight cloudiness was present, and the solution was allowed to stand at 4°. The fine needles of tripotassium methanetrisulphonate (4) (0·3 g) which separated were recrystallised from water and N-hydrochloric acid (Found: C, 3·1; H, 0·8; S, 24·4. Calc. for $CHK_3O_9S_3,H_2O$: C, 3·1; H, 0·8; S, 24·75%), $\nu_{max.}$ (Nujol) 3559m, 3484m and 1645w (H_2O), 1261s, 1235vs, 1037s, 1027s, 833m, 821m, and 759m cm^{-1}. The initial filtrate was further treated with methanol to incipient precipitation and allowed to stand in the cold, when fine needles of *dipotassium hydrazonomethanedisulphonate* (5) formed. Further treatments of the filtrate with methanol yielded more product (total yield 1·35 g), which was recrystallised from water–methanol, the temperature at no time rising above ambient (Found: C, 4·4; H, 0·8; N, 9·8; S, 23·0. $CH_2K_2N_2O_6S_2$ requires C, 4·3; H, 0·7; N, 10·0; S, 22·9%), $\nu_{max.}$ (KBr) 3472m, 3322m, and 3236w (NH_2), 1631w, 1552m, 1232vs, 1182s, 1058s, 978w, and 686m cm^{-1}, $\lambda_{max.}$ (H_2O) 230 and 247 nm (ε 7950 and 7200).

(b) *In N-potassium hydroxide.* A solution of the diazo-disulphonate (2) (3·45 g) in N-potassium hydroxide (60 ml) was maintained at 70° for 17 h and the warm solution was then treated with methanol. On cooling, white needles of the tetrapotassium salt of sulphohydrazonomethanedisulphonic acid (1) (3·1 g) separated, which were further purified by recrystallisation from dilute potassium hydroxide (Found: C, 2·7; H, 0·65; K, 34·4; N, 6·4; S, 21·1. Calc. for $CK_4N_2O_9S_3,H_2O$: C, 2·6; H, 0·4; K, 34·4; N, 6·2; S, 21·1%), $\nu_{max.}$ (KBr) 3413m and 1626w (H_2O), 1460m, 1212vs, 1160s, 1086m, 1048m, 1010s, 988s, 831m, 696s, and 669m cm^{-1}, $\lambda_{max.}$ (H_2O) 231·5 nm (with shoulder at *ca.* 245 nm) (ε 10,000).

(c) *In aqueous piperidine.* A solution of the diazo-compound (2) (2·0 g) in aqueous piperidine (50 ml; 4·1, v/v) was heated at 70° for 8 h and the orange solution was then treated while still warm with methanol. White needles of dipotassium methanedisulphonate (3) (1·4 g) separated on cooling and were recrystallised from water (Found: C, 4·5; H, 0·75; S, 25·1. Calc. for $CH_2K_2O_6S_2$: C, 4·8; H, 0·8; S, 25·1%), $\nu_{max.}$ (KBr) 3448vw, 3049w, 2959w, 1386w, 1272s, 1220vs, 1203s, 1078m, 1024s, 811s, and 774m cm^{-1}. Further treatment of the initial filtrate with methanol yielded more of the disulphonate (3) (0·1 g) mixed with the sulphohydrazone (1) (0·04 g, amount determined from u.v. absorption).

(d) *On u.v. irradiation.* A solution of the diazo-disulphonate (2) (1·0 g) in N-potassium hydroxide, bubbled with nitrogen, was irradiated at 20° with a high-pressure mercury-vapour source (water cooled, quartz immersion apparatus) until the solution was colourless (*ca.* 1 h). Treatment of the solution with methanol yielded crystals of dipotassium methanedisulphonate (3) (0·2 g).

Dipotassium Methoxymethanedisulphonate (7).—A solution of the diazo-compound (2) (1·75 g) in water (30 ml) was treated with methanol (10 ml) and allowed to stand overnight at room temperature. The small quantity of crystals which had formed were discarded and the filtrate was treated with methanol to incipient precipitation. *Dipotassium methoxymethanedisulphonate* (7) (0·4 g, 20%) crystallised out on standing and was recrystallised twice from water–methanol (Found: C, 7·5; H, 1·95; S, 20·65; $C_2H_4K_2O_7S_2$, $2H_2O$ requires C, 7·5; H, 2·5; S, 20·1%), $\nu_{max.}$ (Nujol) 3521m, 3425m, and 1661w (H_2O), 1316m, 1271s, 2141vs, 1220vs, 1119w, 1057s, 1026s, 958w, 833w, 777w, and 661m cm^{-1}, δ 5·20 (1H, s, CH) and 4·09 (3H, s, OMe).

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[8] H. J. Backer, *Rec. Trav. chim.*, 1929, **48**, 949.