94. The Rates of Diazomethane Formation from Methylnitrosoamides. The Stability of Diazomethane Solutions towards Aqueous Alkalis

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Summary

The rate of hydrolysis of *N*-methyl-*N*-nitrosoamides by aqueous alkalis varies greatly. Methylnitrosourea (**1**) is hydrolyzed rapidly by aqueous KOH-solutions at low temperatures to give a high yield of diazomethane. Under similar conditions, *N*, *N'*-dimethyl-*N*, *N'*-dinitroso-oxamide (**3**) is hydrolyzed more slowly, but also gives a good yield of diazomethane. *N*, *N'*-Dimethyl-*N*, *N'*-dinitrosoterephthalamide (**4**), and (*N*-methyl-*N*-nitroso)-4-amino-4-methyl-2-pentanone (**5**) are less easily hydrolyzed by aqueous KOH-solutions. *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (**2**) was the least reactive out of those tested. The hydrolysis of diazomethane in toluene with aqueous bases follows first order kinetics. The hydrolysis rate is greatly influenced by the concentration and strength of the base and temperature.

Introduction. - Diazomethane is frequently prepared by the alkaline hydrolysis of *N*-methyl-*N*-nitrosoamides, *e.g.* methylnitrosourea (**1**). Numerous methods of carrying out methylnitrosoamide hydrolyses to yield diazomethane have been described in the past [1-5] but information on the reaction rates under various conditions is lacking. This work was carried out during a search for a method of preparing diazomethane solutions by simply mixing a methylnitrosoamide, solvent and base, in a system where rapid diazomethane formation was essential. Information was also obtained on the stability of the diazomethane solution so formed in the base systems.

Results and Discussion. - There is a wide choice of methylnitrosoamides that can be used for the generation of diazomethane. After careful consideration of such factors as toxicity, stability and ease of preparation, the following compounds were selected for the study: *N*-Methyl-*N*-nitroso-urea (**1**), *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (**2**), *N*, *N'*-Dimethyl-*N*, *N'*-dinitrosooxamide (**3**), *N*, *N'*-Dimethyl-*N*, *N'*-dinitrosoterephthalamide (**4**), (*N*-Methyl-*N*-nitroso)-4-amino-4-methyl-2-pentanone (**5**).

Hydrolysis Rates/Diazomethane yields. Figure 1 gives a comparison of the yields of diazomethane as a function of reaction time for the compounds **1**-**5** with aqueous KOH-solutions (30%) at 0° to −5°. The hydrolyses were carried out in the presence of toluene which was assayed at intervals for diazomethane content. It can be seen

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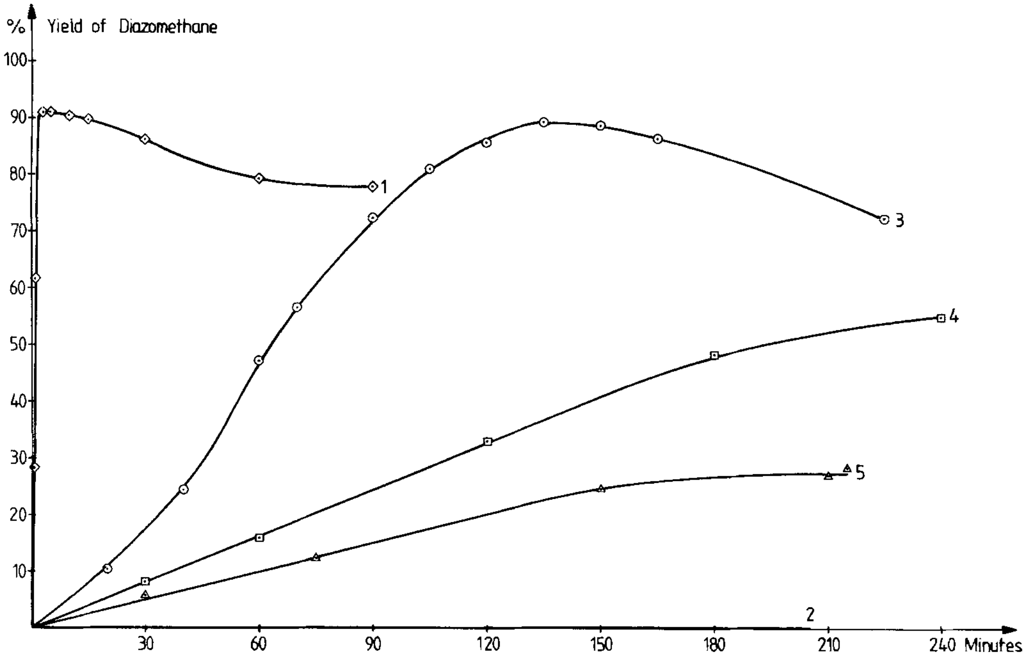

Fig. 1 *Yields of diazomethane as a function of reaction time for the compounds* **1**-**5**

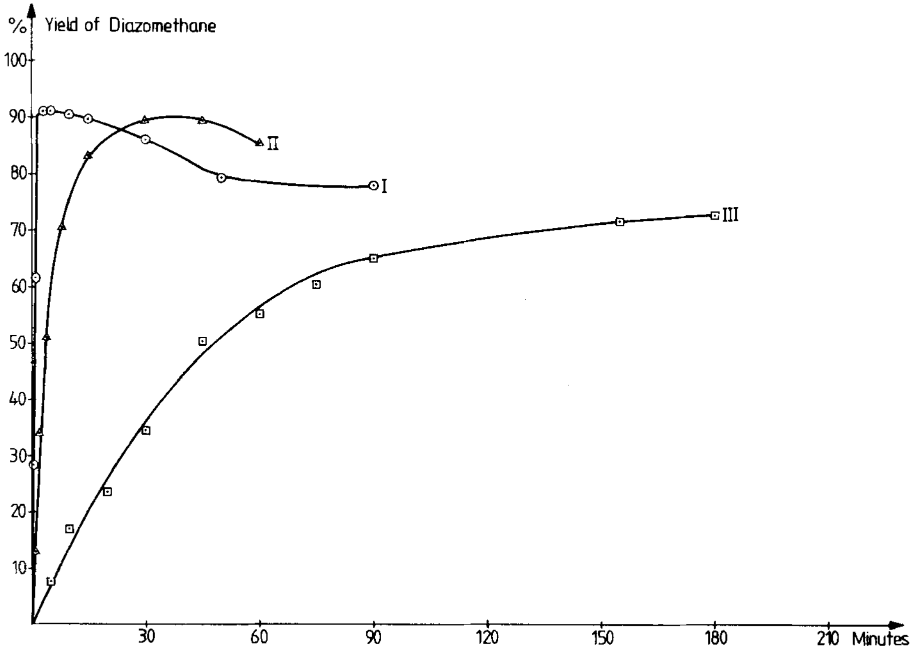

Fig. 2. *Yields of diazomethane as a function of reaction time of compound* **1** *for different concentrations of KOH-solution* (I 30%, II 40%, III 50% at 0° to −5°)

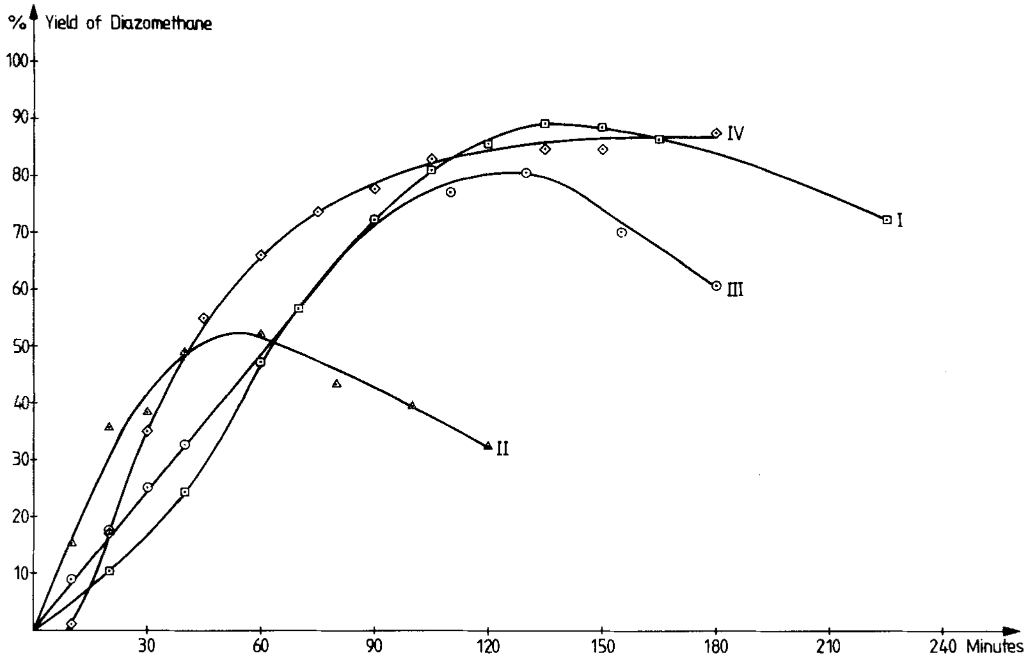

Fig. 3. *Yields of diazomethane from* **3** (I 30% KOH at 0° to −5°, II 30% KOH at 16°, III 20% KOH at 0° to −5°, IV 30% NaOH at 0°)

from *Figure 1* that **1** underwent the most rapid hydrolysis to give over 90% of the theoretical yield of diazomethane in 3 minutes. A similar yield of diazomethane was obtained from **3**, but the hydrolysis rate was much slower. The hydrolyses of **4** and **5** were considerably slower and lower yields of diazomethane resulted. No hydrolysis was observed with **2** under the conditions of the experiment (it was shown that hydrolysis of **2** with aqueous KOH-solutions requires temperatures of around 55° or higher). When **5** was hydrolyzed with a 20% KOH-solution at 0° to −5°, a faster hydrolysis took place giving a 44% theoretical yield of diazomethane after 150 minutes. In this case, it was clear that the diazomethane was decomposed during its production.

The curves of **1** and **3** on *Figure 1* clearly show the diazomethane decomposition after having reached the maximum yields. This point will be discussed later.

Figure 2 shows the results of further hydrolysis experiments with **1**. The concentration of the KOH-solutions has a profound effect on the hydrolysis rate. The rapid hydrolysis observed with 30% KOH-solution becomes slower as the base concentration is increased. When the use of 10% KOH-solution was examined, a rapid hydrolysis took place, but no diazomethane resulted due to its rapid decomposition under the conditions of the reaction.

Figure 3 shows the results of further hydrolysis experiments with **3**. Increasing the temperature from 0° to −5° to 16° gave, as expected, an increased hydrolysis rate, but the diazomethane yield was reduced due to its more rapid decomposition at the higher temperature. Using 20% KOH-solution in place of 30% base at

Table. *Hydrolysis rates of diazomethane in toluene when mixed with various aqueous bases*

Base	°C	k (s^{-1})	$t^{1/2}$ (s) approx.
Water	20	2×10^{-2}	35
Water	0	5×10^{-3}	139
10% NaOH	20	2×10^{-3}	347
10% NaOH	0	7.7×10^{-5}	9,000
50% K_2CO_3	20	5.7×10^{-5}	12,160
50% NaOH	20	2×10^{-5}	28,880
10% KOH	20	4×10^{-4}	1,733

0° to −5° again gave an increased hydrolysis rate and a reduced diazomethane yield. NaOH-solutions (30%) gave after a short induction period a rapid hydrolysis which slowed down abruptly as a precipitate formed. The solid apparently hindered the hydrolysis. The constitution of the solid was not examined, but it was clearly inorganic salts (cyanate or carbonate) resulting from the methylnitrosourea hydrolysis.

Diazomethane Stability. Diazomethane is hydrolyzed by water to methanol and nitrogen. In order to devise a method of producing diazomethane solutions in the presence of aqueous bases, it is necessary to have information on the stability of such solutions in the presence of the bases. A study was made of the stability of solutions of diazomethane (2-3%) in toluene in the presence of some aqueous bases. The results are given in the *Table.*

The decomposition of the diazomethane solution in the presence of excess base with rapid mixing was found to be first order with respect to diazomethane. The increased stability of diazomethane in water at 0° compared with water at 20° is within the expected order of magnitude. The increased stability in 10% NaOH at 0° compared with 20° is however greater than expected.

Safety Note. Methylnitrosoamides are extremely toxic and thermally unstable. Diazomethane is highly toxic, carcinogenic towards animals and potentially explosive. This work was carried out in a special laboratory, equipped with an efficient fume cupboard. Protective clothing was worn whilst handling these substances.

Experimental Part

Preparation of the methylnitrosoamides. - N-*Methyl*-N-*nitrosourea* (**1**), following [6]. The sample used for the experiments assayed at 93.7% by titanimetry. A dried sample assayed at 99.7% and gave the following elemental analysis:

$C_2H_5N_3O_2$	Calc.	C 23.31	H 4.89	N 40.77	O 31.04%
(103.06)	Found	„ 22.99	„ 4.98	„ 40.55	„ 31.56%

N-*Methyl*-N-*nitroso*-p-*toluenesulfonamide* (**2**), following [7]. The material used for this work gave the following elemental analysis:

$C_8H_{10}SO_3N_2$	Calc.	C 44.85	H 4.71	N 13.08	O 22.41	S 14.97%
(214.24)	Found	„ 44.79	„ 4.65	„ 13.17	„ 22.42	„ 15.12%

N,N′-*Dimethyl*-N,N′-*dinitroso-oxamide* (**3**), following [2]. The sample used for the work assayed at 82.1% (UV.) against a purified sample which gave the following elemental analysis:

$C_4H_6N_4O_2$	Calc.	C 27.60	H 3.48	N 32.18	O 36.76%
(174.12)	Found	„ 27.5	„ 3.5	„ 32.01	„ 37.0 %

N,N'-Dimethyl-N,N'-dinitrosoterephthalamide (**4**), following [8]. The sample used for the work gave the following elemental analysis:

$C_{10}H_{10}N_4O_4$	Calc.	C 48.00	H 4.03	N 22.39	O 25.58%
(250.21)	Found	„ 48.07	„ 4.01	„ 22.26	„ 25.87%

(N-Methyl-N-nitroso)-4-amino-4-methyl-2-pentanone (**5**), following [4]. The sample used for the work was distilled, the fraction boiling between 82-85°/0.12 Torr was collected. The product gave the following elemental analysis:

$C_7H_{14}N_2O_2$	Calc.	C 53.15	H 8.92	N 17.71	O 20.23%
(158.20)	Found	„ 52.97	„ 8.97	„ 17.75	„ 20.46%

The hydrolysis of the methylnitrosoamides. The experiments were carried out in a 0.5 l jacketed and stirred vessel. Coolant was circulated round the jacket in order to maintain the temperature at the required level. The vessel was vented through a gas scrubber charged with acetic acid to prevent any possible escape of diazomethane. Two variations of the method were used depending on the solubility of the methylnitrosoamide in toluene.

Variation 1 (Methylnitrosourea and dimethyldinitrosoterephthalamide). A suspension of methylnitrosoamide (0.083 mol-equiv.) in toluene (200 g) was cooled to −5°. A 30% (*w/w*) KOH-solution (100 ml) was pre-cooled to −5°, then added rapidly to the toluene suspension. Samples of the organic phase (*ca.* 5 g) were taken at intervals and immediately added to a solution of benzoic acid in toluene (10 ml, *ca.* 5%). The mixture was then titrated against 0.2N NaOH to phenolphthalein end-point. The diazomethane content of the toluene was calculated from the amount of unreacted benzoic acid.

Variation 2 (Methylnitroso-*p*-toluenesulfonamide, dimethyl-dinitroso-oxamide, and (*N*-methyl-*N*-nitroso)-4-amino-4-methyl-2-pentanone). A mixture of KOH (100 ml, 30%) and toluene (150 g) was cooled to −5° in the reactor. A solution of methylnitrosoamide (0.083 eq) in toluene (50 ml) was added rapidly to the mixture. Samples of the organic phase were withdrawn and assayed as in variation 1 above.

Diazomethane hydrolyses. A solution of diazomethane in toluene (2-3%) was prepared by dissolving diazomethane gas in solvent cooled in an ice/acetone bath. The diazomethane was generated by the method described by *Reinlinger* [2]. The diazomethane solution in toluene was added to the base under test (25 ml) whilst maintaining rapid stirring. The temperature was maintained constant by means of a water or ice/water bath. The progress of the hydrolysis was monitored by observing the nitrogen evolution *via* a water displacement system. The equipment was calibrated by injecting a known volume of nitrogen. The measured correction factor was applied to the results before rate constant calculations were made.

The total amount of nitrogen collected in the experiment was usually better than ±10% of the calculated quantity for the amount of diazomethane being decomposed.

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REFERENCES

[1] *T. De Boer & H. Backer,* Org. Synth. *36,* 16 (Coll. Vol IV, 250 (1963)).
[2] *H. Reinlinger, N,N'*-Dinitroso-*N,N'*-dimethyloxamid als Ausgangsprodukt für Diazomethan. European Research Associates Brüssel, March 30, 1961.
[3] *J. H. Moor & D. Reed,* Org. Synth. *41,* 16 (1961) (Coll. Vol.V, 351, 1973).
[4] *C. E. Redmann, F. O. Rice, R. Roberts & H. P. Ward,* Org. Synth., Coll. Vol.III, 244 (1955).
[5] *O. Desaux & M. Durand,* Bull. Soc. chim. France *1963,* 41.
[6] *F. Arndt,* Org. Synth., Coll. Vol.II, 461 (1944).
[7] *J. De Boer & H.J. Backer,* Org. Synth. Coll. Vol.IV, 943 (1963).
[8] *M. Fuller,* Ind. Eng. Chemistry *49,* 722 (1957).