

Intramolecular S- to N-Nitrosation

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Diazotisation of L-methionine and of S-methyl-L-cysteine occurs *ca.* 100 times faster than that of alanine, suggesting that initial S-nitrosation occurs, followed by an internal S- to N-rearrangement of the nitroso group.

L-Methionine (1) and S-methyl-L-cysteine (2) are both known¹ to undergo the normal deamination reaction with nitrous acid² to give the corresponding alcohols. We have measured the rate constants for these reactions, and find (see Figure 1)

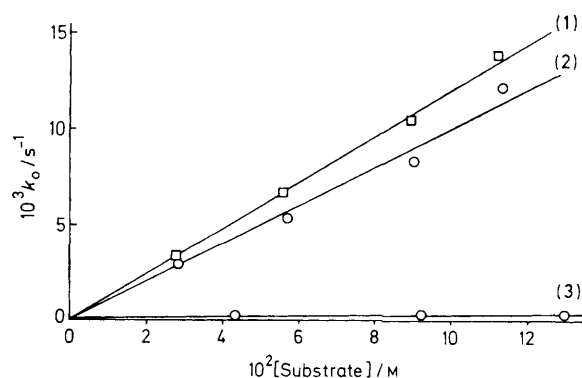
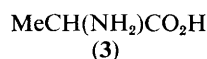
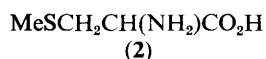
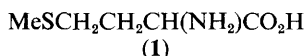
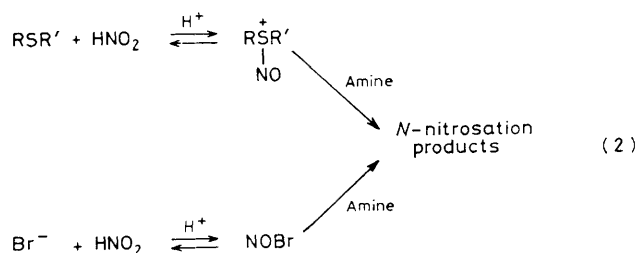
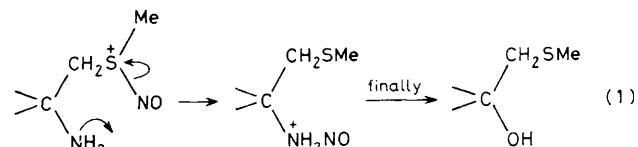


Figure 1. Variation of k_0 with [substrate] for the diazotisation of (1), (2), and (3).

that the reaction is *ca.* 100 times faster for the sulphides than for alanine (3), the model compound without the $-\text{SMe}$ substituent.

The first-order rate constants k_0 in Figure 1 are defined by $-\text{d}[\text{HNO}_2]/\text{d}t = k_0[\text{HNO}_2]$, with $[\text{substrate}] \gg [\text{HNO}_2]$. All the experiments were carried out in aqueous solution at pH 1.4 at 25 °C in the presence of sodium bromide (0.07 M). The bromide ion-catalysed reaction was chosen because the non-catalysed reaction of alanine is inconveniently slow, and the rate is comparable with the decomposition rate of nitrous



acid. The second order rate constants k (for the equation rate = $k[\text{HNO}_2][\text{substrate}]$) are 0.0013, 0.109, and 0.127 $\text{l mol}^{-1} \text{s}^{-1}$ for (3), (2), and (1), respectively. Part of the large rate constant differences for the sulphides can be attributed to the different pK_a values of the reactants. The literature values are² 9.77, 8.89, and 9.22 respectively for (3), (2), and (1). Our k values necessarily include K_a for N -protonation if reaction is assumed to occur *via* the free-base form. This effect then can account only for factors of 3.6 and 7.6 in the reactivities of (1) and (2) respectively relative to (3) (apart from predicting the order incorrectly). There remains a rate constant ratio of 27 for (1) and 11 for (2) compared with (3). The results strongly suggest that for both (1) and (2) reaction occurs initially at the sulphur atom, followed by an intramolecular S - to N -nitrosation (equation 1).

S -Nitrosation, although not as widely known as N - (or O -) nitrosation, has recently been studied mechanistically in the reaction of *t*-butyl thiol,³ thiourea⁴ (and its methyl derivatives⁵), cysteine,⁵ and N -acetylpenicillamine.⁶ Preparatively the reaction has been known for a long time although the S -nitrosation products are only stable in a few cases.⁷ Rate measurements have shown^{3,5,6} that S -nitrosation of thiols is a very rapid process, and is not inhibited by protonation as is the case for basic amines. Thus it is likely in many cases that the overall rate of S -nitrosation exceeds that of N -nitrosation, particularly for the more basic aliphatic amines.

There is some evidence that S -nitroso ions can act directly as nitrosating agents (in an intermolecular fashion). Thus the spectacular catalysis by thiourea of nitrosation of morpholine and diazotisation of aniline⁸ is readily explained by the formation of an equilibrium concentration of the S -nitroso ion which effects nitrosation, just as *e.g.* bromide ion catalysis occurs by the intermediate formation of nitrosyl bromide (equation 2). Some catalysis of diazotisation of aniline has been observed by S -methyleysteine⁸ but the effect is small

since there is competition between the intra- and the intermolecular processes.

It has been suggested⁴ that N -nitrosation of thiourea which occurs at low acidity arises from an initial S -attack and subsequent rearrangement, but ¹⁵N n.m.r. studies⁹ on the same system argue in favour of a direct attack at nitrogen.

Our results show that facile N -nitrosation can occur if the molecule contains the $-\text{SR}$ group arranged so that a 1,4- or 1,5-shift of the nitroso group can occur. This will allow rapid nitrosamine formation to occur in a system (with a secondary amine group) which would otherwise (in the absence of $-\text{SR}$) be very much less reactive. The possibility arises that ethers might act in a similar way.

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