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 known[1] to undergo the normal deamination reaction with nitrous acid[1] to give the corresponding alcohols. We have measured the rate constants for these reactions, and find (see Figure 1) that the reaction is *ca.* 100 times faster for the sulphides than for alanine (**3**), the model compound without the -SMe substituent.

$MeSCH_2CH_2CH(NH_2)CO_2H$
(**1**)

$MeSCH_2CH(NH_2)CO_2H$
(**2**)

$MeCH(NH_2)CO_2H$
(**3**)

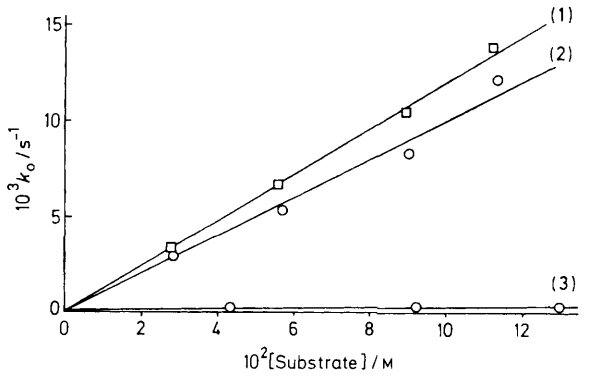
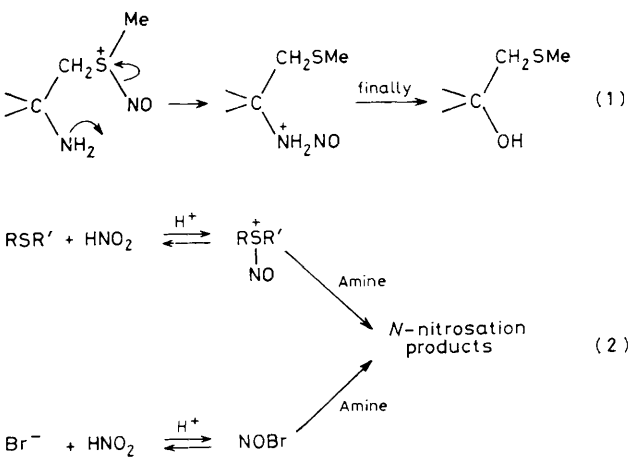


Figure 1. Variation of k_o with [substrate] for the diazotisation of (**1**), (**2**), and (**3**).

The first-order rate constants k_o in Figure 1 are defined by $-d[HNO_2]/dt = k_o[HNO_2]$, with [substrate] >> [$HNO_2$]. 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 = $k[HNO_2][substrate]$) are 0.0013, 0.109, and 0.127 l mol^{-1} 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 are[2] 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] thiourea[4] (and its methyl derivatives[5]), 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 aniline[8] 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*-methylcysteine[8] but the effect is small since there is competition between the intra- and the intermolecular processes.

It has been suggested[4] that *N*-nitrosation of thiourea which occurs at low acidity arises from an initial *S*-attack and subsequent rearrangement, but ^{15}N n.m.r. studies[9] 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 –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 –SR) be very much less reactive. The possibility arises that ethers might act in a similar way.

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