Reaction of a Nitrosamine with Thiourea - A Direct *S*-Nitrosation

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Summary Thiourea reacts with *N*-methyl-*N*-nitrosoaniline without the intermediacy of a free nitrosating agent, to form an *S*-nitroso-compound; thiourea shows comparable nucleophilic reactivity to iodide ion in this reaction.

RECENTLY[1] we have established the mechanism for the de-nitrosation in aqueous acid solution of *N*-methyl-*N*-nitrosoaniline (I) brought about by Cl^-, Br^-, I^-, SCN^-, and H_2O, and find the expected order of reactivity of the nucleophiles. The reverse reaction (*N*-nitrosation of *N*-methylaniline, NMA) was prevented by removing the free nitrosating agent (NOCl *etc.*) by reaction with sulphamic acid, urea, hydrazoic acid, or hydroxylamine, *etc.* The results were interpreted in terms of a rate-determining attack by the nucleophile at the nitroso-nitrogen centre of the protonated form of the nitrosamine. There was no direct reaction between (I) (or its protonated form) and any of the nitrite traps used.

TABLE[a]

10^3[Thiourea]/M	10^3[NMA]/M	10^4[HN_3]/M	$10^4k_0/s^{-1}$
—	—	2·7	17
1·01	—	—	92
1·01	—	2·7	88
1·01	1·0	2·7	75
1·01	4·0	2·7	51
2·02	—	2·7	155
3·03	—	2·7	233
4·04	—	2·7	273
1·01 (2·46M-HCl)	—	2·7	67
1·01 (3·64M-HCl)	—	2·7	129

[a] [(I)] = 1×10^{-4}M. In all cases except where stated [HCl] = 3·05M.

We now report preliminary results of a study of the reaction of (I) with thiourea. The Table shows that the rate constant for denitrosation increases with increasing thiourea concentration, and is much greater than the limit of 17×10^{-4} s^{-1} observed for reaction at the same acidity (HCl) using added urea, sulphamic acid, hydroxylamine, aniline, hydrazoic acid, or hydrazine as the nitrite trap. Similar results have been obtained for reaction in sulphuric acid. This reaction with thiourea is first-order in thiourea (bearing in mind that there is a competing chloride-ion reaction with k_0 17×10^{-4} s^{-1}) as demonstrated by the linear plot of k_0 *vs.* [thiourea]. The reaction is also acid-catalysed and slightly retarded by the addition of NMA. The results are consistent with a mechanism whereby thiourea reacts directly with the protonated form of the nitrosamine, and cannot be interpreted in terms of reaction of thiourea with a free nitrosating agent such as nitrosyl chloride or nitrous acid. If we assume a Hammett acidity dependence for the initial protonation, then the observed first-order rate coefficient k_0 is given by k_1Kk_0[thiourea], resulting in a value for this reaction of 0·55 for k_1K. This compares with[1] values of $0{\cdot}42 \times 10^{-4}$ for Cl^-, 22×10^{-4} for Br^-, 0·22 for SCN^-, and 0·63 for I^-. Thiourea shows a greater nucleophilic reactivity than thiocyanate ion and one almost as large as that of iodide ion. From the scale of nucleophilic constants n of the Swain–Scott equation,[2] it appears that thiourea is about 70 times more reactive towards the protonated nitrosamine than is predicted by the Swain-Scott equation. Later values of n given by Pearson[3] suggest that thiourea lies between thiocyanate and iodide ions in its nucleophilic reactivity, but log k_1K *vs.* n now gives a markedly less linear plot.

The n values, of course, were obtained originally from kinetic results of a typical S_N2 reaction at a carbon centre, and so may not apply for reaction at nitrogen. Further work is in progress with other sulphur nucleophiles in order to establish whether these nucleophiles generally show such remarkable reactivity towards nitrosamines.

Stedman and his co-workers[4] have recently examined the nitrosation of thiourea by nitrous acid, and have measured the equilibrium constant of the initially formed (but somewhat unstable) $>S^+$–NO intermediate. We observe a similar species spectrophotometrically at concentrations rather higher than those used in our kinetic studies (where we followed the rate of disappearance of the nitrosamine), so feel confident that this is a case of *S*-nitrosation. Urea does not react directly with the protonated nitrosamine.

The formation of the $>S^+$–NO species is somewhat reversible for, even though k_0 is little changed by the presence of hydrazoic acid (which rapidly decomposes $>S^+$–NO), k_0 is decreased by the addition of NMA, which thus competes with hydrazoic acid for reaction with $>S^+$–NO either directly, or with the free nitrous acid with which it is in equilibrium. From the variation of k_0 with [NMA] (*cf.* ref. 5) the former seems the more likely possibility.

Direct *S*-nitrosation of this type brought about by nitrosamines, may well play an important part in the mechanism of carcinogenesis. It is well known that nitrosamines themselves are carcinogenic,[6] and that sulphur sites (particularly–SH) are important in the metabolism of cell division.[7] Interaction between thiols and *N*-alkyl-*N*-nitrosourethane have been reported,[8] although the mechanisms of the reactions have not been established.

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$$\mathrm{PhNMeNO} + \mathrm{H^+} \overset{K}{\rightleftharpoons} \mathrm{PhNHMeNO^+}$$

$$\mathrm{PhNHMeNO^+} + \mathrm{SC(NH_2)_2} \overset{k_1}{\rightarrow} \mathrm{PhNHMe} + \mathrm{NO\text{-}SC(NH_2)_2^+}$$

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[1] I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107.
[2] C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.
[3] R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, 1968, **90**, 319.
[4] K. Al-Mallah, P. Collings, and G. Stedman, *J.C.S. Dalton*, 1974, 2469.
[5] D. L. H. Williams, *J.C.S. Chem. Comm.*, 1974, 324.
[6] P. N. Magee and J. M. Barnes, *Adv. Cancer Res.*, 1967, **10**, 163.
[7] J. S. Harington, *Adv. Cancer Res.*, 1967, **10**, 247.
[8] R. Schoental and D. J. Rive, *Biochem. J.*, 1965, **97**, 466.