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Thioureas as Effective Catalysts for *N*-Nitrosodimethylamine Formation

Thioureas accelerate the formation of *N*-nitrosodimethylamine more effectively than thiocyanate ion: among the compounds tested the order of effect was tetramethylthiourea> thiourea>*N*,*N*′-dimethylthiourea.

Keywords——*N*-nitrosodimethylamine; thiourea; *N*,*N*′-dimethylthiourea; tetramethylthiourea; differential pulse polarography

Dialkylnitrosamines, known as potential carcinogenic substances, are formed by the reaction of secondary amines with nitrous acid under acidic conditions. Essentially the same process involved in diazotization has been demonstrated for their formation,[1] and various anions have been found to catalyze the reaction:[1,2] especially thiocyanate ion is one of the most effective catalyst hitherto reported.[1b,2] Pronounced catalysis by a neutral species is not known.

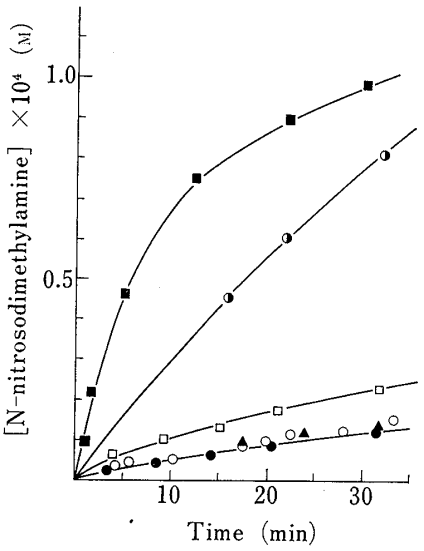

Fig. 1. Concentration-time Curve for the Reaction of Dimethylamine and Sodium Nitrite at pH 4.0

Conditions, see text: ■, with thiourea (10^{-2} M); □, with thiourea (10^{-3} M); ◑, with tetramethylthiourea (10^{-3} M); ▲, *N*,*N*′-dimethylthiourea (10^{-3} M); ○, with sodium thiocyanate (10^{-2} M); ●, without additives.

In a de-nitrosation reaction, thiourea has been reported to show a greater nucleophilicity than thiocyanate ion.[3] Since thiocyanate ion and other anions promote the nitrosamine formation as a nucleophile,[1] similar catalysis by thiourea can be supposed. However, thiourea is also known to decompose nitrous acid under acidic conditions.[4] It seems of interest to examine whether thiourea accelerates or inhibits the nitrosamine formation.

The reaction of dimethylamine and sodium nitrite was followed in aqueous acetate buffer of pH 4.0. The conditions are as follows: initial concentration of Me_2NH and $NaNO_2$, 0.01 and 0.1 M, respectively; total concentration of acetate, 2 M; μ=1.0 with $NaClO_4$; at 30±0.05°. The procedure for the determination of *N*-nitrosodimethylamine was essentially the same as described previously:[1e] differential pulse polarography was employed in place of the conventional DC polarography. The polarograms of the reaction product coincided with those of the authentic *N*-nitrosodimethylamine under the same conditions.

1) *a*) J.H. Ridd, *Quart. Rev.*, **15**, 418 (1961); A.T. Austin, *Sci. Progr.* (London), **49**, 619 (1961); *b*) S.S. Mirvish, *J. Nat. Cancer Inst.*, **44**, 633 (1970) and **46**, 1183 (1971); M. Greenblatt and S.S. Mirvish, *ibid.*, **49**, 119 (1972); S.S. Mirvish, J. Sams, T.Y. Fan, and S.R. Tannenbaum, *ibid.*, **51**, 1833 (1973); S.S. Mirvish and H. Garcia, *Z. Krebsforsh.*, **79**, 304 (1973); S.S. Mirvish, *Toxicol. Appl. Pharmacol.*, **31**, 325 (1975); *c*) T. Yamada, M. Yamamoto, and A. Tanimura, *J. Food Hyg. Soc.*, **15**, 201 and 461 (1974), **17**, 176, 182, and 363 (1976), and **18**, 509 (1977); *d*) T.Y. Fan and S.R. Tannenbaum, *J. Agr. Food Chem.*, **21**, 237 (1973); *e*) M. Masui, H. Nakahara, H. Ohmori, and H. Sayo, *Chem. Pharm. Bull.* (Tokyo), **22**, 1846 (1974).

2) E. Boyland, E. Nice, and K. Williams, *Food Cosmet. Toxicol.*, **9**, 639 (1971); E. Boyland and S.A. Walker, *Nature*, **248**, 601 (1974); *idem*, *Arzneim. Forsh.*, **24**, 1181 (1974).

3) D.L.H. Williams, *J. Chem. Soc. Chem. Comm.*, **1975**, 375.

4) K. Al-Mallah, P. Collings, and G. Stedman, *J. Chem. Soc. Dalton*, **1974**, 2469 and references therein.

The effects of three thioureas on the nitrosamine formation are shown in Fig. 1. Thiocyanate ion exhibited essentially no catalytic effect under the conditions. The accelerating effect of tetramethylthiourea was considerably larger than that of thiourea, while the effect of *N*,*N*′-dimethylthiourea was very small. These results suggest that some factors other than nucleophilicity are also important for a potential catalyst to be effective in the reaction. Detailed kinetic studies to confirm these factors are in progress.

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The Revised Stereostructure of Patrinoside X-Ray Crystallographic Analysis

The configuration at C-8 position of patrinoside, isolated from *Patrinia scabiosaefolia* Fischer (Valerianaceae) was revised as *S* configuration by X-ray crystallographic analysis. The absolute configurations of the other carbon atoms are also confirmed as 1*S*, 5*S*, 7*S* and 9*S* (1).

Keywords——patrinoside; absolute configuration; X-ray crystallographic analysis; direct method; orthorhombic; *Patrinia scabiosaefolia* Fischer; Valerianaceae

In the preceding communication, we reported the structure of patrinoside isolated from the root and rhizome of *Patrinia scabiosaefolia* Fischer (Valerianaceae) and its stereochemistry at C-8 position was suggested as the *R* configuration (formula 2) by the chemical and spectral studies.[1)]

However, on the basis of biogenetic considerations, it has been felt that the C-8 configuration of patrinoside should be reinvestigated. Recently, Jensen *et al.* reported the isolation of the iridoid glycosides from *Viburunum opulus* (Caprifoliaceae), which possess the similar aglycones to that of patrinoside and they proposed the stereochemistry at C-8 position of these glycosides as β-hydroxymethyl and α-hydroxyl groups.[2)] Thus, in order to establish the absolute configuration of C-8 position of patrinoside, its single crystal was subjected to X-ray crystallographic analysis by the direct method.

Pure patrinoside was obtained as colorless prisms by recrystallization from H_2O, mp 97—98°, $[\alpha]_D^{28}$ −45.4° (c=1.63, MeOH), IR ν_{max}^{KBr} cm^{-1}: 3370, 1740, 1660, *Anal.* Calcd. for $C_{21}H_{34}O_{11}\cdot H_2O$: C, 52.49; H, 7.55. Found: C, 52.44; H, 7.50. The crystals are orthorhombic, space group $P2_12_12_1$ with a=28.150(10), b=9.651(4), c=9.267(4) Å, U=2517.6 Å^3, D_x=1.266 g·cm^{-3}, Z=4. The intensity data were measured by a Philips four-circle diffractmeter using graphite monochromated Cu Kα radiation. The 2647 independent reflections were used for the structure determination. The absolute configuration was assigned by taking

1) H. Taguchi and T. Endo, *Chem. Pharm. Bull.* (Tokyo), **22**, 1935 (1974).
2) K. Bock, S.R. Jensen, B.J. Nielsen, and V. Norn, *Phytochem.*, **17**, 753 (1978).