Prophage Induction in Lysogenic *Escherichia coli* with Simple Hydroxylamine and Hydrazine Compounds

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The prophage-inducing capability of hydroxylamine sulfate and 36 of its derivatives, and of hydrazine dihydrochloride and dihydrazine sulfate and 43 of their derivatives, was determined in *Escherichia coli* W1709 (λ). Maximal nontoxic concentrations up to 1 mg/ml were tested. Hydroxylamine sulfate was active at 2.5 μg/ml and the following 17 derivatives were active at concentrations ranging up to 500 μg/ml: α-naphthylhydroxylamine, N-hydroxy-2-aminofluorene, oxamyl hydroxamic acid, O-carbamoyl hydroxylamine (isohydroxyurea), N-hydroxyurethane, N-methylhydroxylamine HCl, salicylhydroxamic acid, oxalohydroxamic acid, methoxylamine HCl, ethoxylamine HCl, N,N-diethylhydroxylamine oxalate, formaldoxime, formamidoxime, acetoxyhydroxamic acid, acetaldoxime, acetone oxide, and hydroxyguanidine sulfate. Hydrazine dihydrochloride and dihydrazine sulfate were effective inducers at 5.0 and 2.5 μg/ml, respectively, and the following nine derivatives of them were active at concentrations ranging up to 500 μg/ml: phthalic acid hydrazide, phenyldihydrazine HCl, p-nitrophenylhydrazine, p-chloro phenylhydrazine HCl, formylhydrazine, carbohydrazide, semicarbazide HCl, 1-methyl-1-phenylhydrazine sulfate, and acetic acid hydrazide. Nineteen hydroxylamine and 34 hydrazine derivatives were ineffective as inducers. Application of the prophage-induction system as a tool for detection of responsive hydroxylamino and hydrazino compounds which may be potential toxicological hazards in the environment is discussed.

There appears to be a clearly positive association (20) between a compound's ability to induce prophage in lysogenic bacteria and its ability to inhibit development of transplanted tumors in rodents. An ever-increasing list of compounds (20) capable of mutagenic, carcinogenic, and teratogenic effects in various experimental systems are also capable of prophage induction. Hydroxylamine has been shown to be mutagenic (17), chromosome-damaging (37), and teratogenic (38), and to possess weak carcinostatic (39) activities; hydrazine has been shown to be carcinogenic (6), mutagenic (26), and teratogenic (38). These properties suggest that both compounds and their analogues might also be capable of prophage induction and, if so, that this simple, in vitro test system might prove useful for detecting responsive hydroxylamino and hydrazino compounds found to be potential hazards in the environment.

Hydroxylamino and hydrazino compounds may be encountered by man and animals in the environment. Hydroxylamine is generally accepted as a logical intermediate in nitrogen fixation, nitrification, and denitrification reactions. A number of acyl derivatives of N-hydroxyamino acids commonly found as end products of microbial fermentations (31) and cyclic hydroxamic acids present in food plant sources (42) may represent unsuspected environmental, toxicological hazards. Pyridine-2-aldoxime is a hydroxylamine-derived medicinal. There has been interest recently in the potential therapeutic application (10) of acetoxyhydroxamic acid and in its use for improving animal nutrition (16). Evidence (29) that N-hydroxylation of carcinogenic, aromatic amines and amides may be a relatively general reaction by which these compounds are converted to proximal carcinogenic metabolites in vivo has focused attention on the hydroxyamino moiety as a potential carcinogen.

Hydrazine may occur as a primary product of nitrogen fixation by *Azotobacter agile* (15). Agaritine, characterized as β-N-(γ-L-(+)-glutamyl-p-hyroxymethylphenylhydrazine, has been isolated (24) from aqueous extracts of basidiomycetes of the family *Agaricaceae*. A steadily increasing array of hydrazine-derived medicinals include hydralazine, phenelzine, nialamid, iso-
carboxazid, isoniazid, several sulfa drugs, pyralazons, and hydrazones of 5-nitro-2-furaldehyde.

The number of industrial and agricultural applications of agents containing hydroxylamine (2) and hydrazine (35) moieties appears to be growing rapidly.

Recently there has been increasing interest in the possibility that various N-nitrosamines may have etiological significance in human cancer (25). Many of these same N-nitrosamines are also potent mutagens (27). Although much evidence has demonstrated (27) that carcinogenic N-nitrosamines alkylate cellular constituents of the tissues of treated animals, no direct evidence of the production of a diazoalkane or carbonium ion has been presented. The possible formation of other biologically active metabolites, including hydroxylamines and hydrazines which are reactive with nucleic acids, has not been excluded.

In this report, the results of testing 37 hydroxylamine and 45 hydrazine derivatives for prophage-inducing capability are presented. The minimal inducing concentrations for the effective agents, as well as a listing of the inactive compounds, are reported. Positive findings in this test system are considered in relation to a limited number of published results obtained in experimental systems demonstrating mutagenic, chromosome-damaging, carcinogenic, carcinostatic, and teratogenic effects.

MATERIALS AND METHODS

Minimal concentrations of test agent required to induce bacteriophage in streptomycin-dependent Escherichia coli W1709 (λ) were determined by use of the technique described in detail by Price et al. (33). Test sample activity is reported in terms of the ratio of the number of plaque-forming λ phage in the test sample (T) to that in a control (C). All phage present in the control sample are produced spontaneously. An analysis of test results indicates that the minimal concentration of compound having a T/C value of 3.0 (three times the spontaneous phage count), or greater, could be considered with some assurance (P < 0.05) to be effectively inducing the lytic cycle in E. coli W1709 (λ) cells.

To minimize changes in the test agent resulting from bacterial metabolism, induction was carried out in the absence of streptomycin, resulting in a transitory starving of the cells during the 1.5-hr induction period at 37 C. Similarly, to minimize chemical reactions, induction was carried out in a synthetic medium at pH 7.2.

Preparation of test materials. Compounds were dissolved in deionized water or, when necessary, in solvents just before use in the test to minimize activity losses. The highest final concentrations of solvents that could be employed without effect in the induction test were as follows: ethyl alcohol, 8%; acetone, 8%; and dimethylacetamide, 2%. Agents were tested at final concentrations up to 1.0 mg/ml when they proved to be sufficiently soluble and without toxicity for the bacterial cells.

Isohydroxyurea was provided by H. S. Rosenkranz, Columbia University; N-hydroxycyclohexylamine, by Abbott Laboratories, North Chicago, Ill.; acetyhydroxamic acid, 3-phenyl-1-hydroxyurea, 1-acetyl-2-picolinoyl hydrazine, and 1-methyl-2-(p-isopropylcarbamoyl)benzyl hydrazine HCl, by Cancer Chemotherapy National Service Center, Washington, D.C.; N-hydroxy-2-aminofluorene, N-acyetoxy-2-acylamino fluorene, and 4- and β-naphthylhydroxylamine, by J. A. Miller, University of Wisconsin; N-hydroxy-2-acetylamino fluorene, by H. L. Falk, National Institute of Environmental Health Sciences; oxamyl hydroxamic acid, by G. R. Gale, Medical University of South Carolina; phenelzine sulfate, by the Warner-Lambert Research Institute, Morris Plains, N.J.; N-acetyl-N-hydroxyl-1-naphthylamine, by S. Belman, New York University; and L-aspartic acid β-hydroxyamine, and L-β- aspartohydroxamic acid, by I. Chibata, Tanabe Seiyaku Co., Ltd., Osaka, Japan. The remaining test compounds were purchased from commercial sources.

RESULTS

The relative capabilities of the 37 hydroxylamines tested to induce lambda bacteriophage formation in a lysogenic strain, E. coli W 1709, are shown in Table 1. The inducing activities of these compounds fell into three groups. Ten compounds were classified as active (minimal inducing concentration, <100 μg/ml): α-naphthylhydroxylamine, N-hydroxy-2-aminofluorene, hydroxylamine sulfate, oxamyl hydroxamic acid, O-carbamoyl hydroxylamine (isohydroxyurea), N-hydroxurethane, N-methylhydroxylamine HCl, salicylhydroxamic acid, oxalohydroxamic acid, and methoxymine HCl. Eight were weakly active (minimal inducing concentration, 100 to 500 μg/ml): ethoxymine HCl, N,N-diethylhydroxylamine oxalate, formaldoxime HCl, formamidoxime, acetoxyhydroxamic acid, acetaldoxime, hydroxyguanidine sulfate, and acetone oxime. Nineteen derivatives were inactive at their highest nontoxic concentration up to 1,000 μg/ml.

Inducing activity was observed with hydroxylamine sulfate, with all 3 of the O-substituted hydroxylamines, with 4 of 7 N-substituted hydroxylamines, with 1 of 4 N,N-disubstituted hydroxylamines, with 4 of 9 monoximes, with 4 of 10 monohydroxamic acids, and with the single dihydroxamic acid tested. Neither of the single members of the O,N-disubstituted hydroxylamines or dioximes which were tested exhibited activity.

The observation that N-hydroxyurethane, which may be formed in vivo from urethane (30), induced prophage at 25 μg/ml is of interest in that urethane failed to induce prophage (34) at 1,000 μg/ml.
### Table 1. Prophage induction in Escherichia coli W1709 (λ) by hydroxylamine and its derivatives

| Compound tested                          | Minimal inducing concn (μg/ml) | No induction at highest concn tested (μg/ml) |
|------------------------------------------|--------------------------------|------------------------------------------|
| Hydroxylamine sulfate H₂NOH             |                                |                                          |
| O-substituted R—ONH₂ Methoxyamine HCl    | 100                            | —                                        |
| Ethoxyamine HCl                          | 200                            | —                                        |
| O-carbamyl hydroxylamine (isohydroxyurea)| 15                             | —                                        |
| N-substituted R—HNOH N-methylhydroxylamine HCl | 50                | —                                        |
| Hydroxyguanidine sulfate                 | 500                            | —                                        |
| N-hydroxycyclohexylamine                 | —                              | 1,00                                     |
| N-phenylhydroxylamine                    | —                              | 0.8                                      |
| a-Naphthylhydroxylamine                  | 0.5                            | —                                        |
| β-Naphthylhydroxylamine                  | —                              | 3.1                                      |
| N-hydroxy-2-amino-fluorene               | 0.5                            | —                                        |
| N,N-N-substituted R—NOH N-formyl-N-hydroxyglycine (Hadamidin) | —              | 1,00                                     |
| N,N-diethylhydroxylamine oxalate         | 200                            | —                                        |
| N-hydroxy-2-acetylaminofluorene          | —                              | 62                                       |
| N-hydroxy-N-acetyl-1-naphthylamine       | —                              | 100                                      |
| O,N-N-substituted R—NHO—R N,N-dimethylhydroxylamine HCl | —            | 1,00                                     |
| Oximes                                   |                                |                                          |
| Monoximes R=NOH                         |                                |                                          |
| Formaldoxime HCl                        | 250                            | —                                        |
| Acetaldoxime                             | 500                            | —                                        |
| Formamidoxime                           | 250                            | —                                        |
| Acetamidoxime                           | —                              | 1,00                                     |
| Acetone oxime                           | 500                            | —                                        |
| Cyclohexanone oxime                     | —                              | 500                                      |
| Benzaldoxime                            | —                              | 100                                      |
| 2,3-Butanedione monoxide                | —                              | 1,00                                     |
| Pyridine-2-aldoxime methiodide          | —                              | 1,00                                     |
| Dioximes                                |                                |                                          |
| HON=R—NOH                               | —                              | 1,00                                     |
| Glyoxime                                | —                              | 1,00                                     |
| Hydroxamic acids                         |                                |                                          |
| Monohydroxamic acids R—CONHOH            | 1,000                          |                                          |
| Acetohydroxamic acid                    | 250                            | —                                        |

It is also of interest that the hydroxylamine derivative hydroxyurea failed to induce prophage in the test at 1,000 μg/ml, whereas isohydroxyurea (O-carbamoyl hydroxylamine), its possible isomeric metabolite (36), was active at 15 μg/ml. Hydroxyurea induced prophage at a concentration of 0.005 m when tested in a complete medium with an actively metabolizing strain of E. coli λ-28 (19).

The relative capabilities of the 45 hydrazines to induce bacteriophage are shown in Table 2. The inducing activities of these compounds also fell into three groups. Active compounds (minimal inducing concentration, <100 μg/ml) were hydrazine dihydrochloride, dihydrazine sulfate, phthalic acid hydrazide, phenylhydrazine HCl, p-nitrophenylhydrazine, p-chlorophenylhydrazine HCl, formylhydrazine, and carboxyhydrazide; weakly active (minimal inducing concentration, 100 to 500 μg/ml) compounds were semicarbazide HCl, 1-methyl-1-phenylhydrazine sulfate, and acetic acid hydrazide; and 34 compounds were inactive at their highest nontoxic concentration, up to 1,000 μg/ml.

Dihydrazine sulfate, hydrazine dihydrochloride, and phthalic acid hydrazide, with minimal inducing concentrations of 2.5, 5.0, and 5.0 μg/ml, respectively, proved to be the most active agents in this series of compounds. Inducing activity was also observed with 3 of 14 1-substituted hydrazines, with 1 of 3 1,1-disubstituted hydrazines, with 3 of 10 monohydrazides, and with 2 of the 5 dihydrazides tested. None of the eight 1,2-disubstituted hydrazines or the single representatives in each of the dihydrazine, cyclic hydrazide, or hydrazone categories was active.
### Table 2. Prophage induction in *Escherichia coli* W1709 (X) by hydrazine and its derivatives

| Compound tested                        | Minimal inducing concn (µg/ml) | No induction at highest concn tested (µg/ml) |
|----------------------------------------|-------------------------------|---------------------------------------------|
| Hydrazine dihydrochloride              | 5.0                           | —                                           |
| Dihydrazine sulfate                    | 2.5                           | —                                           |
| Hydrazines                             |                               |                                             |
| 1-Substituted                          |                               |                                             |
| R—NHNH₂                                |                               |                                             |
| Methyl hydrazine sulfate               |                               |                                             |
| β-Hydroxyethyl hydrazine               |                               |                                             |
| Cyclohexylhydrazine                    |                               |                                             |
| Phenylhydrazine HCl                    |                               |                                             |
| p-Nitrophenyldihydrazine               |                               |                                             |
| p-Chlorophenyldihydrazine HCl          |                               |                                             |
| 2,4-Dinitrophenyldihydrazine           |                               |                                             |
| 2,5-Dichlorophenyldihydrazine          |                               |                                             |
| Phenelzine sulfate                     |                               |                                             |
| p-Hydrazinobenzoic acid HCl            |                               |                                             |
| p-Hydrazinobenzene-sulfonic acid HCl   |                               |                                             |
| 1-Naphthyldihydrazine HCl              |                               |                                             |
| 2-Hydrazinopyridine                    |                               |                                             |
| Aminoguanidine sulfate                 |                               |                                             |
| 1,1-Disubstituted                     |                               |                                             |
| R N—NH₂                                |                               |                                             |
| 1,1-Dimethylhydrazine                  |                               |                                             |
| 1-Methyl-1-phenylhydrazine sulfate      |                               |                                             |
| 1,1-Diphenylhydrazine HCl              |                               |                                             |
| 1,2-Disubstituted                     |                               |                                             |
| R—NHNH₂—R symmetry                   |                               |                                             |
| 1,2-Diformylhydrazine                  |                               |                                             |
| 1,2-Dicarboxyldihydrazine              |                               |                                             |
| sym-Dibenzyol hydrazine                |                               |                                             |
| Iproniazid                             |                               |                                             |
| Isatin β-thiosemicarbazone             |                               |                                             |
| 1-Methyl-2-(p-isopropyl-carbamoyl)ben- |                               |                                             |
| zyl hydrazine HCl                      |                               |                                             |
| 1-Acetyl-2-picolinoyl hydrazine        |                               |                                             |
| Dihydrazines                            |                               |                                             |
| H₂NHN=C—(R)—                                |                               |                                             |
| sym—Dihydrazine HCl                    |                               |                                             |
| Hydrazones                              |                               |                                             |
| Carbohydrazide                         |                               |                                             |
| Oxalyl dihydrazide                     |                               |                                             |
| Adipic acid dihydrazide                |                               |                                             |
| Phthalic acid dihydrazide              |                               |                                             |
| Sebacic dihydrazide                    |                               |                                             |
| Cyclic                                  |                               |                                             |
| Maleic acid hydrazide                  |                               |                                             |
| Hydrazonaledehyde hydrazone            |                               |                                             |

It is conceivable in those cases where inducing activity was observed only at 100 µg/ml, or greater, that induction could be the result of small amounts of undetermined impurities present in the test compound or of conversions produced during preparation of test solution or during the induction period.

### DISCUSSION

Biological activities of interest both from the view of environmental toxicology and human pathology have been observed so far in experimental systems with a number of prophage-inducing hydroxylamine and hydrazine derivatives. Chromosome-damaging properties have been demonstrated with oxalohydroxamic acid (9) and with both *N*-hydroxyurethane and *N*-methylhydroxylamine (8); mutagenic activities (18), with *N*-methylhydroxylamine and methoxyamine; teratogenic activities (11), with acetoxyhydroxamic acid and *N*-hydroxyurethane; carcinogenic (4) activity, with *N*-hydroxyurethane;...
and carcinostatic activity, with N-hydroxyurethane (1) and with acetohydroxamic acid (39).

The potent carcinogen (28) N-hydroxy-2-acetylaminofluorene failed to induce prophase at a concentration of 62 μg/ml. Similarly, its ester, N-acetoxy-2-acetylaminofluorene, an even stronger carcinogen (29) at sites of application, failed to induce at 125 μg/ml, its highest nontoxic concentration (unpublished results). It has been postulated (22) that biotransformation of N-hydroxy-2-acetylaminofluorene to N-hydroxy-2-aminofluorene, which induces prophase at 0.5 μg/ml and which may be the ultimate carcinogen, occurs.

α-Naphthylhydroxylamine was capable of inducing E. coli prophase at a concentration of 0.5 μg/ml and has exhibited both greater carcinogenicity (3) and mutagenicity (32) than its β-isomer which failed to induce at 3.1 μg/ml, its highest nontoxic concentration.

Carcinogenic properties have been demonstrated with phenylhydrazine (12), and teratogenic activity, with semicarbazide (38).

The possibility that hydroxylamine and hydrazine compounds which are potential toxicological hazards may be transformed in vivo to prophase-inducing derivatives must be considered. Hydroxamates may be directly hydrolyzed (5), releasing hydroxylamine which induces prophase at 2.5 μg/ml and which has been shown to be mutagenic (17), chromosome-damaging (37), and teratogenic (38), and to possess weak carcinostatic (39) activities. Formation of hydrazine, or its derivatives, upon breakdown of isonicotinic acid hydrazide by liver (40) and bacterial (41) enzymes has been reported. It has been suggested that the carcinogenic action of isoniazid in mice is mediated through liberation of free hydrazine (7), which induces prophase at 5.0 μg/ml and for which carcinogenicity (6), mutagenicity (26), and teratogenicity (38) have been observed. The possible role of the hydrazine function has been considered (13) in the carcinogenesis of five 2-hydrazinothiazole compounds.

The prophase-induction system has already shown utility (23) when employed to select potential carcinostatic agents present in complex fermentation broths and as an assay procedure for following the extraction and isolation of active agents from such broths. A bioautographic technique that has proven useful for identification of purified prophase-inducing agents has also been developed (21).

Unfortunately, sufficient test data regarding mutagenicity, carcinogenicity, and teratogenicity, in experimental systems, are not yet available to establish a clearly positive association of these effects with the prophase-inducing capability of hydroxylamino and hydrazino compounds. Additional testing will determine whether such associations exist. Evidence supporting a relationship between an agent’s prophase-inducing capability and its mutagenic and carcinogenic activities has already been obtained (14) in a series of 16 nitroquinolines and hydroxyminoquinolines. It is hoped that the simple, in vitro, prophase-induction system may prove useful for detecting responsive hydroxylamino and hydrazino compounds which may be potential hazards in the environment.

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