**β-Substituted Ethylamine Derivatives As Suicide Inhibitors of Lysyl Oxidase***

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Lysyl oxidase initiates the covalent cross-linking of elastin and collagen, converting lysyl residues in these proteins to peptidyl aldehyde residues. The present study explored structural and electron withdrawing features required to generate mechanism-based inhibitors of this enzyme with antifibrotic potential. It was found that the electron withdrawing nitrite moiety of β-aminopropionitrile (BAPN), a naturally occurring syncatalytic inhibitor of lysyl oxidase, can be replaced by chlorine, bromine, or the nitro function to yield 2-haloamines or nitroethylenamine compounds which also act as mechanism-based irreversible inhibitors of this enzyme. BAPN and 2-bromo- and 2-chloroethylamine exhibit similar *K*<sub>i</sub> values of 6–10 μM. However, the enzyme becomes irreversibly inactivated significantly faster by either of the 2-haloamines than by BAPN. 2-Nitroethylenamine has by far the poorest affinity for the enzyme and inactivates much more slowly than the other amines of this series, consistent with interference with optimal enzyme-inhibitor interactions by the anionic nitro group. Unlike BAPN, 2-bromoethylamine is processed to a detectable aldehyde product upon incubation with enzyme, showing a partition ratio of 1.2 mol of acetaldehyde formed per mol of 2-bromoethylamine which becomes covalently incorporated in the enzyme. The results are consistent with the processing of 2-bromo-ethylamine to an enzyme-ethyleneamine Schiff base subject to hydrolysis to acetaldehyde or to covalent attack at carbon 2 by an enzyme nucleophile. Thus, β-haloamines represent a new series of suicide inhibitors of lysyl oxidase which can inactivate the enzyme faster than BAPN and hence may have antifibrotic potential.

Lysyl oxidase is a copper-dependent amine oxidase which initiates the biosynthesis of lysine-derived cross-linkages in elastin and collagen by oxidizing peptidyl lysine to α-amino adipic-4-semialdehyde in these proteins (1, 2). The reactive aldehyde can then form aldol condensation products, Schiff base adducts, or other types of cross-linkages (3). Lysyl oxidase can be inhibited in vivo and in vitro by lathyrogenic agents. While severe defects occur in connective tissues of growing animals exposed to lathyrogens as a result of inhibition of cross-linkage formation, lysyl oxidase is nevertheless a reasonable chemotherapeutic target for the control of fibrosis in pathologic conditions.

At least four groups of compounds, including nitriles, urides, hydrazides, and hydrazines, have been reported to have lathyrogenic activity (4). Among these, β-aminopropionitrile is one of the most potent inhibitors of lysyl oxidase since it inhibits the enzyme irreversibly in the micromolar range of inhibitor concentration (1). We have recently noted that the intact carbon chain of BAPN covalently modifies the active center of lysyl oxidase, consistent with an inactivation mechanism in which the electron withdrawing potential of the nitrite moiety is essential to the covalent derivatization and therefore the irreversible inactivation of lysyl oxidase by this lathyrogen (5). This study also revealed that the rate constant for inactivation of lysyl oxidase by BAPN is relatively slow (5). In the present study, we have explored the effect of replacing the nitrite moiety by alternative electron withdrawing functions. The results point toward the potential of β-substituted haloamines as a new class of suicide inhibitors of lysyl oxidase.

**EXPERIMENTAL PROCEDURES**

**Materials**—Lysyl oxidase was isolated from bovine aorta by a method which yields a mixture of the four species of this enzyme apparently free of other proteins, as judged by sodium dodecyl sulfate-gel electrophoresis (6, 7). Prior studies revealed the essential similarities in subunit molecular mass (32,000 daltons), peptide maps, and substrate and inhibitor profiles (7, 8) of the individual species. Preparation of the tryptate chick embryo aortic elastin substrate for assay of lysyl oxidase (1) and synthesis of 2-Br-[1,2-'<sup>14</sup>C]ethylamine hydrobromide (5) were performed as described previously. All other reagents were of the highest quality obtainable.

**Enzyme Assays**—Lysyl oxidase was assayed against 125,000 cpm of the tritiated elastin substrate suspended in 0.1 M sodium borate, 0.15 M NaCl, pH 8.0, at 37 °C for 2 h. Tritiated water released during the incubation was isolated by vacuum distillation and radioactivity counted in Formula 963 (New England Nuclear) scintillation fluid. Alternatively, enzyme activity against non-peptidyl amine substrates was monitored by a horseradish peroxidase-coupled fluorescence assay for the lysyl oxidase-catalyzed release of H<sub>2</sub>O<sub>2</sub> (9).

**Synthesis of 2-Nitroethylenamine HCl**—2-Bromoethylamine hydrogen bromide (3.4 g; 16.6 mmol) was reacted with 2.3 g (33.3 mmol) of NaN<sub>3</sub> in 20 ml of dimethyl sulfoxide. The solution was stirred in the dark for 18 h at 25 °C. The reaction mixture was concentrated by evaporation, and the 2-nitroethylamine product was isolated by cation exchange chromatography on a column (0.8 × 30 cm) of 200–400 mesh AG 50W-X2 in the H<sup>+</sup> form (Bio-Rad), eluting with a linear gradient between water and 2 N HCl. Thin layer chromatography on silica gel plates developed with 1-butanolacetic acid:water (4:1:1), revealed a single yellow-orange spot with an *R*<sub>f</sub> of 0.3 after spraying the dried plate with ninhydrin reagent. The product melted with decomposition at 160 °C. Infrared spectra of the product displayed vibrational frequencies at 3100, 2600, 2000, and 1700 cm<sup>-1</sup>, consistent with NC<sub>≡</sub>N<sub>2</sub>, and at 1550 and 1370 cm<sup>-1</sup>, consistent with NO<sub>2</sub>.

**Enzyme Inhibitor Binding Studies**—Aliquots of lysyl oxidase (32 μg; 1 nmol) were incubated in the presence or absence of selected
concentrations of 2-brom0[1,2-¹⁴C]ethylamine or [1,2-¹⁴C]BAPN at 37 °C for 2 h in 16 mM potassium phosphate, pH 7.7. Unbound inhibitor was removed by extensive dialysis against this buffer at 4 °C, and enzyme-bound inhibitor was quantified by liquid scintillation spectrometry. Corrections were made as required for radioactivity retained in dialyzed enzyme-free buffer samples. Enzyme protein in dialyzed samples was quantified by the Lowry procedure (10) using bovine serum albumin to construct a standard curve of color yield.

Enzyme activity in the dialyzed samples was determined by the tritium release assay method, using tritiated elastin as the substrate. Samples of the dialyzed enzyme complexes of [¹⁴C]BAPN and of 2-Br[¹⁴C]ethylamine were also analyzed by sodium dodecyl sulfate-gel electrophoresis according to Laemmli (11) after boiling the adducts in the sample buffer containing 1% sodium dodecyl sulfate and 5% mercaptoethanol for 2 min. Seventy-five to ninety-five percent of the ¹⁴C label migrated with the 32,000-dalton enzyme band in each case, further indicating the covalent nature of the adducts formed between lysyl oxidase and these inhibitors.

Identification of Carbonyl Products of Amino Oxidation—Lysyl oxidase (2 nmol) was incubated with the radioactive amine substrate or inhibitor in 3 ml of 16 mM sodium borate buffer, pH 7.7, at 23 °C for 2 h in an atmosphere of air at 1 atm of pressure. Incubation tubes were sealed with rubber caps to prevent escape of volatile aldehyde products. Reactions were acidified by injection of 2 mmol of HCl and dinitrophenylhydrazine in 4 trifluoroethylamine nor 4-bromobutyronitrile inhibits the electron-withdrawing substituents on an alkyl chain lacking a phenyl group. Amine substrates or inhibitors with lysyl oxidase. The 2,4-dinitrophenylhydrazones produced by incubation of 14C-labeled aldehydes with 2 nmol of enzyme at 25 °C for 30 min. Hydrazones formed were then extracted into toluene and resolved by TLC on silica gel using as solvent benzene:ethyl acetate (95:5) as described (12). One-cm segments of the developed TLC plate were scraped off and extracted into toluene. The toluene extracts were screened by liquid scintillation counting for the presence of ¹⁴C-labeled hydrazones of authentic samples of acetaldehyde and 2-bromoacetaldelye had Rₚ values in this system of 0.49 and 0.62, respectively.

RESULTS

Comparisons were made of the effects of various substituted alkylamines on the oxidation of the elastin substrate by lysyl oxidase. As shown in Fig. 1, substitution at the β-carbon of the ethylamine structure by nitrile, bromo, chloro, or nitro moieties generates inhibitors of the activity of lysyl oxidase with I₅₀ values of 10⁻⁵-10⁻⁴ M. Ethanolamine and 3-bromopropylamine represent a second group of apparent inhibitors of elastin oxidation with I₅₀ values of 1-10 mM. Neither 2,2,2-trifluoroethylamine nor 4-bromobutyronitrile inhibits the enzyme, the latter result illustrating that the presence of electron withdrawing substituents on an alkyl chain lacking a primary amino function is insufficient to inhibit the enzyme.

Since lysyl oxidase can oxidize non-peptidyl amines in addition to elastin and collagen (9), the substrate potential of substituted alkylamines was tested to account for the possibility that these compounds inhibit by acting as competitive substrates. As shown (Table I), 2-bromo-, 2-chloro-, 2,2,2-trifluoro-, and 2-nitroethylamine are not oxidized by lysyl oxidase within the detection limits of the sensitivity of the peroxydas coupled assay, i.e., 10 or more catalytic turnovers. As previously reported, BAPN is not a productive substrate based on analyses capable of detecting less than 0.005 enzyme turnovers (5). However, 3-bromopropylamine and ethanolamine each are effective substrates for lysyl oxidase (Table I). Kinetic parameters of these substrates were compared to those of unsubstituted primary alkylamines. The K₅ values decrease as the carbon chain length of primary amines increases from 2 to 4 to 5, while the V₅₀ values increase slightly to an apparent maximum for this series of 4.3 nmol of H₂O₂/µmol of substrate. Notably, the β-hydroxy group of ethanolamine increases the V₅₀ and decreases the K₅ relative to ethylamine, making this a catalytically more efficient substrate than ethylamine. It is also of interest that 1,2-diaminoethane is not a substrate while 1,5-diaminopentane is the most effective substrate of those tested in this series of amines. The inhibition of lysyl oxidase by 2-Br-ethylamine was explored in further detail, selecting this compound as representative of that group of β-substituted derivatives of ethyla-

![Fig. 1. Inhibition of elastin oxidation. Each point represents the average of triplicate assays.](image-url)
mine with $I_0$ values between 1 and 15 $\mu$M. 2-Bromoethyamine competitively inhibits elastin oxidation (Fig. 2). Measurement by atomic absorption spectroscopy of the copper content of lysyl oxidase preincubated at 37 °C with 10 nM 2-Br-ethylamine for 1 h and then dialyzed against buffer revealed that the copper content of the native enzyme (0.7 g atom/32 kDa) does not change significantly by this treatment.

The reversible or irreversible character of the inhibition by 2-Br-ethylamine was explored by diluting aliquots of enzyme-inhibitor mixtures preincubated at 37 °C into the peroxidase-coupled assay mixture. As shown (Fig. 3A), enzyme activity decreases irreversibly following pseudo-first order kinetic patterns. A double reciprocal plot (Fig. 3B) of the $k_{\text{act}}$ values against inhibitor concentration yields a $K_i$ value of 7 $\mu$M and a limiting inactivation rate constant, $k_0$, of 1.07 min$^{-1}$. These results are consistent with the reversible formation of an $E-I$ complex followed by the rate-determining enzyme-assisted processing of the prebound inhibitor to form a covalent complex at the active site, the covalent modification being governed by $k_2$ and where $k_{-1}/k_1 = K_i$ (13), as in Equation 1.

$$E + I \overset{k_1}{\rightleftharpoons} [E-I] \overset{k_2}{\rightarrow} [E-I]^* \text{ (inactivated enzyme)} \quad (1)$$

Thus, 2-bromoethylamine fulfills these criteria as a suicide inhibitor of lysyl oxidase.

Since the inhibition model shown in Equation 1 predicts at least partial processing of 2-Br-ethylamine by the enzyme, the possibility that this haloamine was processed to 10 or fewer mol of an aldehyde product/mol of enzyme was tested, this limit being derived from the negative results obtained when 2-Br-ethylamine was tested as a substrate in a peroxidase-coupled assay (see Table I). As shown in Fig. 4, thin layer chromatography of the 2,4-dinitrophenylhydrazone of acetaldehyde treated incubation mixture of lysyl oxidase and bromo[1,2-14C]ethylamine reveals the presence of the 2,4-dinitrophenylhydrazone of acetaldehyde but not of 2-bromoacetaldehyde. Duplicate analyses yielded a value of 0.59 ± 0.03 nmol of acetaldehyde produced in the presence of 2.9 nmol (92 $\mu$g) of lysyl oxidase in 2 h at 37 °C representing a turnover number of 0.20 mol/mol of enzyme.

Lysyl oxidase covalently incorporates radioactivity when incubated with 2-bromo[1,2-14C]ethylamine (Fig. 5). Loss of activity parallels the incorporation of label with an extrapolated incorporation of 0.165 mol/mol of lysyl oxidase protein (Fig. 5, inset). Additional label (1.2 mol/mol) is incorporated when the enzyme is preincubated with 1 mM 14C-labeled 2-Br-ethylamine, thus exceeding by 10-fold the concentration of inhibitor required for full inhibition (Fig. 5). This pattern and extent of labeling follows that of [14C]BAPN previously reported (5). The higher level of labeling presumably reflects modification of a site or sites distinguishable from the active site.

The incorporation of label and substrate potential of [14C]BAPN or bromo[14C]ethylamine are compared in Table II. The moles of BAPN and 2-Br-ethylamine incorporated at full inactivation approximate each other. As previously reported, each of the three carbons of BAPN is incorporated into lysyl oxidase, negating a mechanism involving departure of the nitrile moiety upon enzyme processing. Furthermore, there is no detectable production of aldehyde from BAPN by lysyl oxidase (5). It is of interest, therefore, that 2-Br-ethylamine is processed to an aldehyde product. However, the turnover number for [14C]-labeled 2-Br-ethylamine closely approximates the molar covalent incorporation of the carbons of bromoethylamine into lysyl oxidase, indicating a partition ratio between product release and covalent modification which approximates unity.

Kinetic, inhibitor, and Hammett $\sigma$ constants (14) for BAPN and 2-bromo-, 2-chloro-, and 2-nitroethylamine are compared in Table III. BAPN, 2-Br-ethylamine, and 2-Cl-ethylamine have comparable affinities for lysyl oxidase, judging from the $K_i$ values, while the nitro compound has the lowest affinity by far. Both the 2-Cl- and 2-Br-ethylamine inhibitors irreversibly inactivate lysyl oxidase more rapidly than does BAPN, while inactivation occurs most slowly with 2-nitroethylamine. Although the presence of an electrophilic substituent at the $\beta$ position appears important to the expression of inhibitor potential, there appears to be an inverse correlation of the $k_2$ values with the $\sigma$ constants relevant to the specific $\beta$ substituents. It is likely, therefore, that steric and charge factors, as well as the tendency of the $\beta$ substituent to fragment from the ethylamine carbon structure upon enzyme processing, are more important in dictating the rapidity of the inactivating events.

**DISCUSSION**

As shown in the present study, a new series of suicide inhibitors of lysyl oxidase is generated by substituting a
variety of electron withdrawing functions at the β-carbon of ethylamine. It is of concern that the covalent incorporation of 2-Br-ethylamine or BAPN accompanying full inactivation is considerably less than 1 molar equivalent of enzyme. A similarly low incorporation of a suicide inhibitor has been noted in at least one other enzyme system (15). In the present case, it appears reasonable to assume that the low molar ratio of covalently incorporated inhibitor may reflect a significant content of inactive enzyme protein in the otherwise homogeneous enzyme preparation. Since lysyl oxidase becomes syn-catalytically inactivated within 100-150 turnovers during the oxidation of non-peptidyl amines (16), it is feasible that a significant fraction of the population of enzyme molecules has experienced such syn-catalytic events in vivo. It is also possible that site-site interactions between monomers sterically restrict access of the inhibitors to the active site, since the 32,000-dalton monomers of lysyl oxidase can aggregate in the absence of urea (7). Nevertheless, the similar molar ratios of incorporation of 2-Br-ethylamine and BAPN and the kinetic characteristics of the modification support the conclusion that these agents are suicide enzyme inhibitors and may be used as titrants of functional active site concentration.

The initially competitive interaction of 2-Br-ethylamine with the enzyme as well as the kinetics of enzyme inactivation are consistent with the enzymatic processing of the haloamine to a species which can covalently derivatize and thus inactivate the active site. The formation of the acetaldehyde rather than the Br-acetaldehyde product demonstrates that lysyl oxidase can catalyze the elimination of hydrogen bromide from the inhibitor and implies an enzyme-ethyleneamine intermediate, as illustrated in Scheme 1. This reaction mechanism proposes the initial formation of a Schiff base between an enzyme carbonyl and the inhibitor amino group (Reaction a), presumably following the course of productive catalysis. Recent evidence supports a cofactor role for pyridoxal phosphate in chick aortic lysyl oxidase (17), while inhibition by carbonyl reagents (18, 19) and spectral studies (20) also point...
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toward the presence of a reactive carbonyl cofactor in the bovine aortic enzyme, although the spectral studies (20) are not completely consistent with its identity as pyridoxal phosphate. We have previously noted that pretreatment of lysyl oxidase with either 2,4-dinitrophenylhydrazine or 2-Br-ethylamine prevents labeling of lysyl oxidase by $[^4C]$BAPN, indicating that both inhibitors likely bind to a common site and presumably form a Schiff base adduct with a carbonyl cofactor. A Schiff base intermediate may then undergo proton abstraction, electron migration, and departure of the cofactor.

Notably, conversion of enzyme-bound ethylimine to ethyleneimine intermediate (Reaction b). An ethyleneamine Schiff base could then undergo one of two alternative fates. Thus, hydrolysis of the Schiff base would release ethyleneamine (Reaction c'). The ethyleneamine product could then tautomerize to ethylymine, hydrolysis of which would yield acetaldehyde and ammonia. Notably, conversion of enzyme-bound bromoethylamine to the ethylymine intermediate is a net oxidation occurring by departure of an electron pair with the leaving bromide ion. This contrasts with the route of oxidation presumably followed by productive substrates in which electrons from the carbon bearing the amino function, may be transferred to the carbonyl cofactor eventually to be transferred to and reduce molecular oxygen to hydrogen peroxide. Alternatively (Reaction c), the Schiff base-linked ethyleneamine would be susceptible to Michael addition by an enzyme nucleophile, residue $X$ in Scheme 1, yielding the covalently derivatized inactivated enzyme. This mechanism of inhibition is consistent with that proposed for BAPN (5) in that enzyme-assisted proton abstraction may yield enzyme-bound unsaturated derivatives of BAPN or 2-Br-ethylamine, respectively, as potential enzyme-alkylating agents. Unlike 2-Br-ethylamine, however, inactivation of lysyl oxidase by BAPN does not involve departure of the electron withdrawing nitrile substituent of the inhibitor. The alkylation form of BAPN was proposed to be an enzyme-bound ketenimine derivative, i.e., $\text{NH-}^\ominus\text{CHCH=CH-N}(-)\text{CH-enzyme}$, most susceptible to nucleophilic attack on carbon 3 (denoted by asterisk), whereas carbon 2 would be most susceptible to nucleophilic attack in the ethyleneamine derivative. It is possible, therefore, that the faster rate of inactivation of lysyl oxidase by 2-Br-ethylamine may reflect both a more favorable orientation between an attacking enzyme nucleophile and the $\beta$-carbon of an enzyme-bound derivative of 2-Br-ethylamine, as well as entropic gain accompanying departure of the bromide ion. Both plasma amine oxidase (21) and fungal amine oxidase (12) each are synthetically inactivated by 2-bromoethylamine, although plasma amine oxidase is not inactivated by 2-Cl-ethylamine but does use this haloamine as a substrate (21). Each of these enzymes is copper-dependent and inhibited by carbonyl reagents, similar to lysyl oxidase. Fungal amine oxidase has a turnover/inactivation ratio of 600 when incubated with 2-Br-ethylamine (12) while that of the plasma enzyme is 9 with this haloamine (21), each yielding the Br-actetaledehyde product. Clearly, lysyl oxidase is least predisposed among these enzymes to productively oxidize these haloamines, seemingly consistent with the tendency of this enzyme to become synacatalytically inactivated while processing unsubstituted primary alkylamine or diamine substrates (16). Such restricted catalytic efficiency may be important to the restriction of the activity of this enzyme to its collagen and elastin substrates in vivo.

Increasing the carbon chain length of primary alkyl-, mono-, or diamines increases substrate efficiency, suggesting that the substrate-binding pocket of lysyl oxidase has a minimum hydrophobic requirement of two to three apolar methylene functions, interference with which, by an ionically charged component as the $\beta$-amino function in 1,2-diaminoethane, prevents functional enzyme-substrate interaction. This model of the substrate-binding site can be related to the apparently anomalous behavior of nitroethylamine. Thus, this compound carries the most electronegative substituent of the potential inhibitors examined, yet has the lowest affinity; it is not a substrate and inactivates lysyl oxidase most slowly. Nitroethylamine would be expected to have two prominent resonance forms, as shown.

$$\text{O}=\text{N-CH}_2\text{CH}_2\text{NH}_{2\ominus}\quad \text{O}=\text{N-CH}_2\text{CH}_2\text{NH}_2$$

Hence, the formal negative charge of the nitro moiety may interfere both with initial binding to lysyl oxidase and, once bound, with the processing of the nitro compound to an irreversibly linked derivative. Furthermore, the options for resonance in the nitro group should make this a poor leaving group, further retarding the formation of an electrophilic enzyme-ethyleneamine intermediate. Similarly, steric restrictions may underlie the inability of 2,2,2-trifluoroethylamine to inhibit lysyl oxidase.

In summary, $\beta$-haloethylamine compounds represent a new class of suicide inhibitors for lysyl oxidase which inactivate the enzyme more rapidly than does BAPN. Manipulation of the electron withdrawing substituent of $\beta$-substituted ethylamine derivatives appears to provide a new approach to the development of antibiotic agents which may have selectivity for lysyl oxidase in vivo.

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