FORMATION AND FATE OF REACTIVE INTERMEDIATES OF HALOALKANES, HALOALKENES, AND α-HALOACIDS

M. W. Anders

Department of Pharmacology and Physiology
University of Rochester Medical Center
601 Elmwood Avenue, Box 711
Rochester, NY 14642

INTRODUCTION

Haloalkanes, haloalkenes, and α-haloacids are important industrial chemicals and environmental contaminants. For example, 1,2-dibromoethane and 1,2-dibromo-3-chloropropane were formerly used as fumigants and nematocides, trichloroethylene is a common environmental contaminant, and dichloroacetate (DCA), which is produced during the chlorination of drinking water, is present in finished drinking water supplies in the U.S. Many haloalkanes, haloalkenes, and α-haloacids are toxic, and some are rodent or suspected human carcinogens. The toxicity of these chemicals is associated with their bioactivation to reactive intermediates by the cytochromes P450 or glutathione transferases (GSTs).

This review will focus on the glutathione- and GST-catalyzed biotransformation of haloalkanes, haloalkenes, and α-haloacids. A common feature of the glutathione-dependent bioactivation of these compounds is the formation of sulfur-containing metabolites that may undergo chemical conversion to reactive intermediates or enzymatic processing to other metabolites are enzymatically converted to reactive intermediates. In all cases, the biological effects are associated with reactive-intermediate formation.

HALOALKANES

The GSTs, particularly theta-class GSTs (GSTT1-1), catalyze the biotransformation of a range of haloalkanes. Dichloromethane (methylene chloride) is an important solvent used in many industrial processes. Dichloromethane and other dihalomethanes undergo GST-dependent biotransformation to formaldehyde (Hashmi et al., 1994). The reaction mechanism involves the GSTT1-1-catalyzed displacement of chloride from dichloromethane (Figure 1, 1) to give S-(chloromethyl)glutathione (Figure 1, 2). Hydrolysis of S-(chloromethyl)glutathione 2 gives S-
(hydroxymethyl)glutathione (Figure 1, 3), which is the hemithioacetal of formaldehyde and glutathione (Figure 1). Hemithioacetal 3 is in equilibrium with glutathione and formaldehyde (Figure 1, 4). The observed carcinogenicity of dichloromethane in mice is associated with its GSTT1-I-dependent metabolism (Sherratt et al., 1997). Although dichloromethane is not mutagenic in most in vitro assay systems, it is mutagenic in the Ames test with Salmonella typhimurium TA1535 transfected with GSTT1-1 (Thier et al., 1993).

![Figure 1. Glutathione transferase-dependent biotransformation of dichloromethane. 1, dichloromethane; 2, S-(chloromethyl)glutathione; 3, S-(hydroxymethyl)glutathione; 4, formaldehyde; GSH, glutathione; GSTT1-I, theta-class glutathione transferase.](image1)

A role for dichloromethane-derived formaldehyde, which leads to the formation of protein-DNA crosslinks, in the carcinogenicity of dichloromethane has been demonstrated (Casanova et al., 1992). Other studies implicate the reactive intermediate S-(chloromethyl)glutathione in the mutagenicity of dichloromethane (Gisi et al., 1999).

1,2-Dihaloalkanes (vicinal dihaloalkanes or ethylene halides) are an important group of chemicals. 1,2-Dibromoethane, 1,2-dichloroethane, 1,2-dibromo-3-chloropropane are examples of commercially important 1,2-dihaloalkanes. 1,2-Dibromoethane, for example, has seen considerable use as a lead scavenger in gasoline and as a fumigant. 1,2-Dibromo-3-chloropropane was formerly used extensively as a soil nematocide. Significantly, many 1,2-dihaloalkanes are mutagenic in the Ames test and some are rodent carcinogens, which has lead to restrictions in their commercial applications. The mutagenicity and, perhaps, carcinogenicity of this group of chemicals is associated with GST-dependent biotransformation to reactive intermediates. 1,2-Dihaloethanes (Figure 2, 1) undergo GST-catalyzed biotransformation to S-(2-haloethyl)glutathiones (half-sulfur mustards) (Figure 2, 2), which undergo intramolecular reactions to yield thiiranium (episulfonium) ions (Figure 2, 3). The thiiranium ions thus formed may react with nucleophilic sites in DNA to give the adduct S-[2-N7-guanyl)ethyl]glutathione (Ozawa and Guengerich, 1983) (Figure 2, 4).

![Figure 2. Glutathione transferase-dependent biotransformation of 1,2-dihaloethanes. 1, 1,2-dihaloethane; 2, S-(2-haloethyl)glutathione; 3, thiiranium ion; 4, S-[2-N7-guanyl)ethyl]glutathione; 5, S-[2-N7-guanyl)ethyl]-N-acetyl-L-cysteine; 6, S-(2-haloethyl)-L-cysteine; 7, ethylene; 8, cysteinyl glutathione disulfide; GSH, glutathione; GST, glutathione transferase; GGT, γ-glutamyltransferase; DP, dipeptidases; NAT, N-acetyltransferase.](image2)