Potential Toxicity of CF$_3$X Halocarbons

W.S. KOSKI,$^1$ S. ROSZAK,$^{1,3}$ J.J. KAUFMAN,$^1$ and K. BALASUBRAMANIAN$^2$

ABSTRACT

A molecular model for the carcinogenicity of carbon tetrachloride in mice has been previously suggested in which an electron is transferred from an enzyme to the CCl$_4$ molecule resulting in its dissociation into Cl$^-$ and the free radical ·CCl$_3$. Cellular damage was attributed to the free radical. In light of this model, we examined the series of one carbon halocarbons CF$_4$, CF$_3$Cl, CF$_3$Br, and CF$_3$I for their potential carcinogenic activity. The propensities of the halocarbons to produce free radicals by dissociative electron attachment were obtained by quantum chemical calculations or by physical measurements. The ability of the free radicals to abstract hydrogen atoms from the lipid was estimated from C-H bond energies in the appropriate molecules formed when the free radical combines with the hydrogen atom. Using these two parameters the potential toxicity of the halocarbons was established.

INTRODUCTION

The halocarbons have been used extensively for many years in industrial and agricultural applications and as their use increased it became clear that many of them were toxic. In 1941, the hepatocarcinogenicity in mice induced with carbon tetrachloride was reported (Edwards, 1941). In 1966, a molecular mechanism for the toxic action of CCl$_4$ was proposed (Gregory, 1966). In this proposal it was suggested that a complex is formed between CCl$_4$ and an enzyme that acts as an electron donor causing a dissociative electron attachment with the production of the free radical ·CCl$_3$

$$\text{CCl}_4 + e \rightarrow [\text{CCl}_4^-] \rightarrow \cdot\text{CCl}_3 + \text{Cl}^-$$

The highly reactive free radical was suggested as being the agent responsible for cellular damage. It is now well established that under anaerobic conditions some halocarbons are reductively dehalogenated by cytochrome P-450 (Luke et al., 1987). It has been further suggested that the halogenated free radical produced by the dissociation of CCl$_4$ can abstract hydrogen from the lipid and produce tissue damage by subsequent reactions by the newly formed free radical (Woo et al., 1985). The presence of ·CCl$_3$ is supported by the observation of CHCl$_3$ and hexachloroethane as metabolic products in CCl$_4$ toxicity studies.

Two energetic parameters play a role in this model of toxic action. They are the vertical electron affinity (VEA) and the C-H bond energy in the molecule formed when in the case of the CCl$_4$ example the ·CCl$_3$ radical abstracts a hydrogen from the lipid. The VEA is defined as
the energy difference between the ground state of the neutral halocarbon molecule and the anion of the halocarbon both at the equilibrium geometry of the neutral molecule. Both of these parameters can be calculated by quantum chemical methods or measured experimentally. In studying the correlation between energetic and toxicities of single-carbon halides (CX$_4$ and CHX$_3$) we find that if the VEA is more positive than $-1.4$ eV and if the C-H bond energy is greater than 92 kcal/mol, then one can expect that the molecule will be toxic (Kaufman et al., 1996).

The halocarbon CF$_3$Br has been widely used as a combustion inhibitor in fire extinguishers on aircrafts. Recently, a search has been initiated for a replacement and the question arises whether the compound CF$_3$I would satisfactorily serve as a nontoxic combustion inhibitor. In this connection we thought it would be of interest to examine the potential toxicity of the series of halocarbons CF$_3$X (where X is F, Cl, Br, or I) using the free radical model. We report our results in this communication.

**METHODS**

The VEAs of the molecules in question have been calculated in our laboratory and have been submitted for publication (Roszak et al., 1997) and the C-H bond strength in CF$_3$I was taken from the published calculations (Luke et al., 1989). In addition, the VEAs for CF$_3$Cl and CF$_3$I have been determined experimentally and the results agree well with the calculated VEAs (Illenberger and Momigny, 1994).

**RESULTS AND DISCUSSION**

**CF$_4$**

Carbon tetrafluoride is generally assumed to be inert and there is no experimental evidence that it is carcinogenic. Its VEA has been measured (Modelli et al., 1992) and reported to be $-7.9$ eV since it is much higher than $-1.4$ eV. Free radical production from CF$_4$ and low energy electrons is not expected. We would not expect CF$_4$ to be toxic on the basis of the free radical model.

**CF$_3$Cl**

The VEA for this molecule is $-1.2$ eV as determined experimentally and is supported by the calculated value. The C-H bond energy in CHF$_3$ is 107.1 kcal/mol (Luke et al., 1989). Although the bond strength meets the requirements of the free radical model (92 kcal/mol), the VEA is marginally close to the model requirements ($-1.4$ eV) and the toxicity is too close to call; therefore, we categorize it as equivocal as far as carcinogenicity is concerned. If any CF$_3$ free radicals are formed by reaction of CF$_3$Cl with low energy electrons they would be expected to be low in numbers.

**CF$_3$Br**

The VEA for this molecule is $-0.69$ eV as calculated in our laboratory (Roszak et al., 1997). It is considerably more positive than the required $-1.4$ eV, therefore, it would be expected to give copious amounts of free radicals on reaction with free electrons. This coupled with the 107.1 kcal/mol bond energy in CF$_3$I suggests that CF$_3$Br would give rise to toxicity in mice and rats.

**CF$_3$I**

The VEA for CF$_3$I is close to 0 eV and our calculations (Roszak et al., 1997) gave 0.1 eV. This is consistent with experimental measurements and the free radical model indicates that this compound can be expected to be carcinogenic. We have not been able to find any animal toxicity studies for CF$_3$Cl, CF$_3$Br, or CF$_3$I in the literature. In conclusion, it appears that the free radical model of toxicity of halocarbons indicates that CF$_4$ and possibly CF$_3$I are not expected to be toxic in mice and rats; whereas CF$_3$Br and CF$_3$I will be potent toxicants.

It is of interest to note that because of the similarities in mechanism of action of halocarbons in combustion inhibition and in toxicity, in many instances, but not always, the better a halocarbon is as a combustion inhibitor the more toxic it will be.
REFERENCES


Address reprint requests to:

W. S. Koski
Department of Chemistry
Johns Hopkins University
3400 N. Charles Street
Baltimore, MD 21218