STRUCTURE-ACTIVITY RELATIONSHIP OF 2- AND 3-CARBON HALOGENATED HALOCARBONS

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INTRODUCTION

A number of halogenated hydrocarbons, in particular CFCs and halons, are being phased out of production due to environmental concerns. Many other partially halogenated hydrocarbons exist that could be substitutes for the restricted chemicals. However, only a small number of these chemicals have known toxicities. It would be highly beneficial to predict which compounds of this chemical class possess features that contribute to lowering toxicity. The objective of this work is to develop a method for predicting the toxicity of partially halogenated hydrocarbons. The approach taken is to compile similar toxicological data on a set of isomeric halogenated hydrocarbons, then, by comparing the chemicals' structural features and corresponding toxicity endpoints, devise a list of features that contribute to either lowering or increasing the toxicity of these chemicals.

Structure-activity relationships (SARs) have been investigated in the past by this organization and others research organizations. Some of the work has focused on numerical means of estimating toxicity. Quantitative methods are preferred if one has enough information on the chemicals of interest to generate a predictive algorithm. In many cases, the chemicals of interest have no known information, but a preliminary toxicity estimation is still desired. Therefore, this work focuses on a non-quantitative SAR which would allow quick, first-cut toxicity estimations based strictly on a visual assessment of chemical structure. In addition, this analysis provides helpful information on which geometric isomers would most likely have the lowest toxic potential. This estimation work is in no way meant

to take the place of thorough toxicity testing; rather it is intended to provide a low-cost indication of which chemicals would be best to study.

METHODS

In the first step, acute toxicity data of lethality and anesthesia was compiled for a set of halogenated hydrocarbons. Only toxicity information for the same animal species, the same exposure duration, and same route of exposure could be used together to make comparisons about which chemical features influence toxicity. In addition, this work assumed that the chemicals studied all act through the same biological mechanism for a given toxic effect. This was not an unreasonable assumption based on previous work investigating the mechanism of action of halogenated hydrocarbons and given that the chemicals generally all exhibit the same toxic effects - anesthesia, cardiac sensitization, and lethality by respiratory arrest.

A data set of 51 halogenated hydrocarbons with mouse 30-minute LC_{50} (concentration to kill 50% of test population) and AD_{50} (dose required to anesthetize 50% of test population) values was used. Although rats are generally the preferred species of investigation of these toxic endpoints, insufficient data on rats were available on isomeric pairs of chemicals to formulate conclusion on structural features influencing toxicity. Of the 51 chemicals having known mouse 30-minute LC_{50}s and AD_{50}s, only 12 sets of isomers (26 chemicals) existed which allowed comparison of the atomic arrangements (Table 1). The structures of each isomer and the toxicity values were examined, and a list of structural features influencing toxicity of halogenated hydrocarbons was generated.

RESULTS

By analyzing the set of isomers, several trends in structural features influencing toxicity became apparent. The numbers presented in each of the examples are the mouse 30-minute

TABLE 1. HALOGENATED HYDROCARBON ISOMERIC CHEMICALS

CHEMICAL FORMULA	30-MINUTE MICE LC_{50}, %	30-MINUTE MICE AD_{50}, %
$CCl_2FCHClF$	2.01	0.58
$CClF_2CHCl_2$	2.03	0.80
$CClF_2CHClF$	9.03	3.00
CF_3CHCl_2	7.39	2.39
$CClF_2CH_2Cl$	4.90	1.28
$CHClFCHClF$	----	0.94
$CClF_2CHBrF$	4.14	1.20
$CBrF_2CHClF$	3.39	1.11
$CF_3CHBrCl$	3.00	0.85
$CClF_2CH_2Br$	3.71	0.80
$CBrF_2CH_2Cl$	2.61	0.74
$CClF_2CH_3$	30.0	23.10
CHF_2CH_2Cl	7.39	2.15
$CBrF_2CHBrF$	1.57	0.65
CF_3CHBr_2	1.20	0.53
$CF_3CCl_2CH_3$	9.97	4.01
$CF_3CH_2CHCl_2$	2.41	0.56
$CF_3CHClCH_2Cl$	2.20	0.39
$CF_3CH_2CF_2Cl$	16.95	5.25
$CH_2FCF_2CClF_2$	15.03	9.97
$CHF_2CH_2CClF_2$	20.10	9.97
$CHF_2CF_2CH_2Cl$	5.05	1.20
$CF_2ClCH_2CH_3$	15.96	8.00
$CH_2ClCF_2CH_3$	8.41	2.15
$CF_3CHBrCH_3$	7.61	1.70
$CF_3CH_2CH_2Br$	4.48	1.51

(Reference 1)

LC_{50}s, which are measures of percent by volume concentration. Higher numbers indicate a lower toxicity since a high concentration of chemical is required to kill the animals. Low LC_{50} values show that less agent is needed to **kill** the animals. Use of the **AD„** values also contributed to the same findings as the LC_{50} value analysis.

CHF_2CH_2Cl	CHF_2CH_2Br
7.39	4.57

CF_3CHFCl	CF_3CHCl_2	$CF_3CHBrCl$
44.70	7.39	1.20

$CF_2ClCHFCl$	$CF_3CHCl_,$
9.03	7.39

$CF_2ClCHFBr$	$CF_2BrCHFCl$	$CF_3CHBrCl$
4.14	3.39	3.00

$CF_2BrCHFBr$	CF_3CHBr_2
1.57	**1.20**

TREND #3) For halopropanes, a -CF_3 groups adjacent to an acidic hydrogen increases the toxicity. Therefore, $CF_3CH_2CHX_2$ is preferred over CF_3CHXCH_2X (X's can be identical or dissimilar and follow trend #1).

$CF_3CH_2CHCl_2$	$CF_3CHClCH_2Cl$
2.41	2.20

TREND #4) For halopropanes, -CH_3 groups reduce the toxicity by reducing the number of acidic hydrogens in the molecule. Thus, CF_3CXRCH_3 **is** preferred over CF_3CRHCH_2X, where R can be either a halogen or hydrogen

Examples:

$CF_3Cl_2CH_3$	$CF_3CH_2CHCl_2$	$CF_3CHClCH_2Cl$

$CF_3CHBrCH_3$	$CF_3CH_2CH_2Br$
7.61	***4.48***

TREND #5) -CH_2X groups increase toxicity regardless of the other structural features of the molecule.

Examples:

$CHF_2CH_2CClF_2$	$CHF_2CF_2CH_2Cl$
20.10	5.05

$CH_3CH_2CF_2Cl$	$CH_3CF_2CH_2Cl$
15.96	8.41

$CF_3CHBrCH_3$	$CF_3CH_2CH_2Br$
7.61	***4.48***

DISCUSSION

The list of structural features presented above is only valid for the acute toxicity endpoints investigated, lethality and anesthesia. Although cardiac sensitization is an acute phenomenon, the complete mechanism of action for this response is unknown and possibly different than that of anesthesia or lethality due to respiratory arrest. For lethality and especially anesthesia, the theory of acidic hydrogens influencing the toxic response is well known. The observed trends support the theory that the presence of acidic hydrogen enhances toxicity.

HALOCARBON NUMBER	FORMULA	NAME	MW[1]	BP[2], °C
HBFC-124aBl	$CBrF_2CHF_2$	1-bromo-1,1,2,2-tetrafluoroethane	180.93	25
HBFC-133bB1	$CBrF_2CH_2F$	1-bromo-1,1,2-trifluoroethane	162.94	31
HBFC-142bBl	$CBrF_2CH_3$	1-bromo-1.1-difluoroethane	144.95	49
HBFC-226baB1	$CF_3CBrFCHF_2$	2-bromo-1,1,1,2,3,3-hexafluoropropane	230.94	31
HBFC-235faB1	$CBrF_2CH_2CF_3$	1-bromo-1,1,3,3,3-pentafluoropropane	212.94	40
HBFC-244ccB1	$CBrF_2CF_2CH_3$	1-bromo-1,1,2,2-tetrafluoropropane	194.95	50
HBFC-253ecB1	$CBrF_2CHFCH_3$	1-bromo-1,1,2-trifluoropropane	116.96	60

However, environmental regulations preclude further consideration of these compounds. Hydrobromofluorocarbons (HBFCs) are listed as regulated chemicals under the 1992 Copenhagen Amendments to the Montreal Protocol.

CONCLUSIONS

Structure-activity relationships can be derived for sets of halocarbons given that a sufficiently large number of similar chemicals have known toxicity information. This same analysis can be performed on any class of chemicals that have toxicity information known on a selected number. In this particular analysis, a list of trends has been derived which would allow one to predict which chemicals or chemical isomers might have sufficiently low toxicity to be considered as CFC and halon replacements. Several HBFCs have been identified as being potentially low in toxicity; however, all of these brominated compounds are regulated and cannot be considered further for that reason.

Unfortunately, the data set used herein to develop the trends influencing toxicity is limited and, in some case, lacks vital information to fully validate other trends. Additional data are needed on other isomeric pairs to fully validate these trends.

RECOMMENDATIONS

Research indicates that bromine or iodine is necessary to make a highly effective halon replacement agent. Since no currently identified, viable brominated alkane exists, a similar analysis as above should be performed on other chemical classes in order to identify possible low-toxicity, high-efficiency 2nd generation candidates (2). For some chemical families, this analysis may simply mean a collection of existing data as was done here. This preliminary, low-cost screen will aid in the selection of candidates for future halon replacement evaluation.

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