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## Correlations between Chemical Structure and Normal Boiling Points of Halogenated Alkanes C<sub>1</sub>-C<sub>4</sub><sup>†</sup>

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Correlations were investigated between topological indexes representing the chemical structures of 532 halo- and polyhaloalkanes with 1-4 carbon atoms and their boiling temperatures at normal pressure. Effects of constitutional isomerism and replacing one halogen by another on the boiling points of mono-, di-, tri-, and tetrahaloalkanes were studied.

### INTRODUCTION

Halocarbons as a class have found many applications in modern society. They have been used as pesticides (DDT,  $\gamma$ -hexachlorocyclohexane), solvents (chloroform, carbon tetrachloride), alkylating agents (mustards), anesthetics (halothane), plastics (PVC), etc. Recently the use of chlorofluorocarbons (CFCs) in cryogenic systems and aerosols has stirred up a controversy regarding their environmental effects.<sup>1</sup> The high C-F bond energy makes these compounds extremely stable and resistant to environmental degradation. Hence, these compounds remain in the atmosphere for a long time. When they reach the stratosphere they are decomposed photochemically. The decomposition products of these CFCs catalyze the breakdown of the ozone layer, which is an important shield against the cancer-causing short-wavelength ultraviolet rays.

Many major industrial producers of CFCs are now replacing CFCs without any hydrogen atoms by CFCs with hydrogen atoms. The presence of hydrogen atoms makes these compounds degrade 20-200 times faster. However, the volatility of these compounds is also different from the CFCs without any H atoms. In this study we examine effects such as the replacement of halogen atoms by hydrogens in haloalkanes and attempt to obtain quantitative relationships relating the structure of the halocarbons to their boiling points. These equations could then be used to predict the volatility of haloalkanes.

The data used in this study were collected from several sources: Beilstein's *Handbuch der Organischen Chemie*, the *CRC Handbook of Chemistry and Physics*, Heilbron's *Dictionary of Organic Compounds*, and some other books<sup>2</sup> and primary literature sources. Since at normal pressure com-

pounds with boiling points (bps) above 300 °C cannot be distilled without decomposition, the highest number of halogens possible for C<sub>1</sub>-C<sub>4</sub> halo derivatives is ten for F, eight for Cl, four for Br, and two for I.

### BOILING POINTS OF HALOALKANES

As seen in Figure 1, boiling temperatures of all halo-methanes vary nonlinearly with increasing numbers of halogen atoms. For the heavier halogens, the curvature is less evident because the increase in molecular weight leads to a marked increase in boiling points; however, for fluorine compounds the boiling point curve versus the number of hydrogens replaced by fluorine atoms has a maximum when about half of the hydrogen atoms have been replaced. This phenomenon is encountered in higher haloalkanes even when less than half of the hydrogens have been replaced by fluorine atoms. Several other interesting trends have been observed in the boiling points of haloalkanes:

(i) As with the alkanes, branching also lowers the boiling points of the haloalkanes. Intermolecular forces are weaker for branched molecules than for linear ones, and even more so for spherically-shaped molecules. In isomeric systems this is demonstrated by the observation that in monohalo-*n*-alkanes the bp drops on moving the halogen from the terminal carbon toward the middle of the chain.

(ii) In the case of dihalo-*n*-alkanes, geminally-substituted compounds boil at lower temperatures than vicinally-substituted ones; with an *n*-butyl chain the bp increases in the sequence: 2,2- < 1,1- < 2,3- < 1,2- < 1,3- < 1,4-dihalo-*n*-butanes.

(iii) Isomerism leads to diagrams such as Figure 2 for polyhaloethanes or Figure 3, panels A and B for polyhalopropanes (hal = F or Cl). It can be seen that the highest bp is attained for the terminally-disubstituted dihalo derivatives. Figure 4 compares bps of  $\alpha,\omega$ -dihaloalkanes with *n* = 1-9 carbon atoms, and Figure 5 displays bps of 1-haloalkanes with *n* = 1-10. The same nonlinearity can be seen as in the dia-

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Boiling point (K)

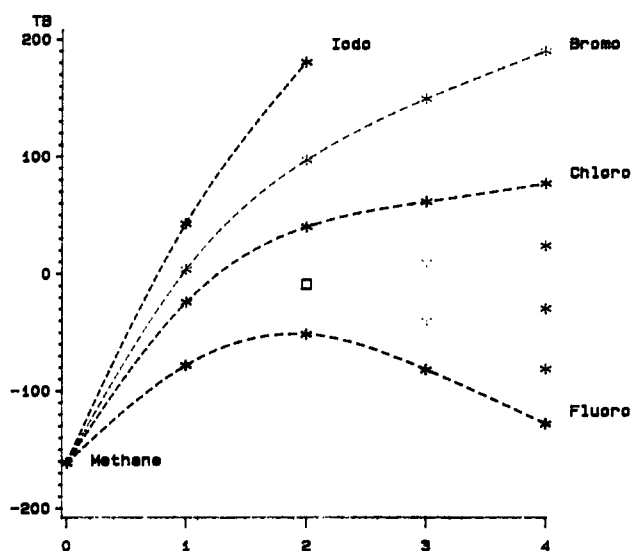


Figure 1. Graphical representation of the nonlinear variation of boiling points of halomethanes with increase in the number of halogens. Unconnected points are mixed chloro/fluoromethanes. Numbers of halogens are indicated on the abscissa.

Boiling Point (C)

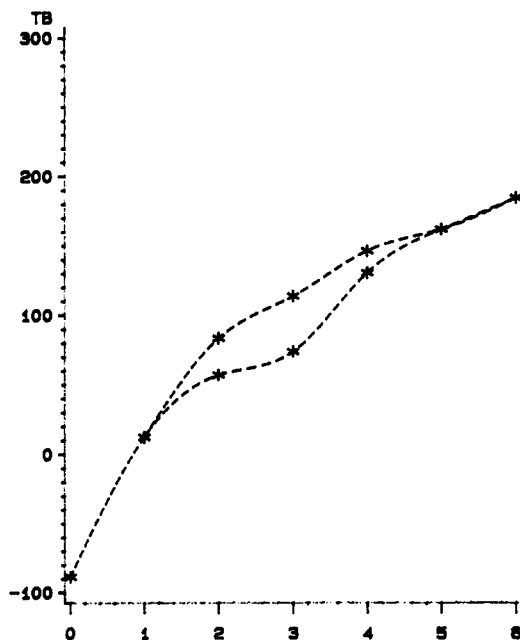
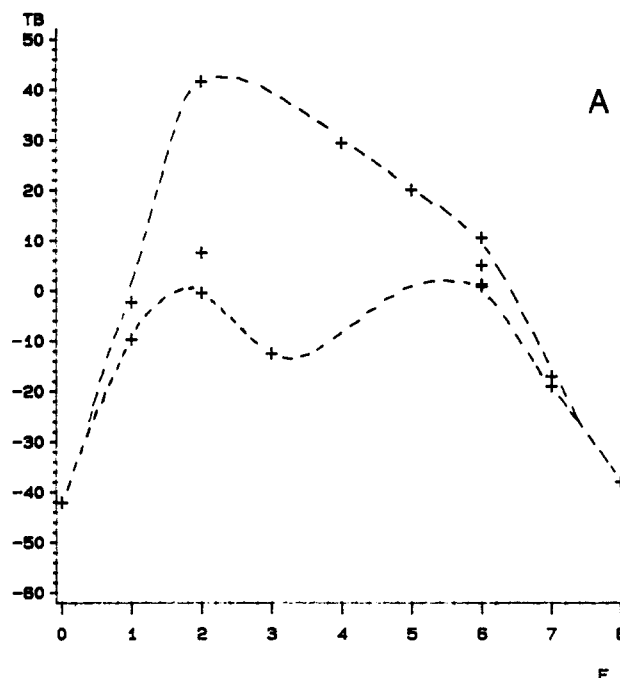


Figure 2. Boiling points of the isomers of chloroethanes. The lower curve represents the isomer with more numerous geminal halogens and the upper curve the isomer with fewer geminal pairs. Numbers of chlorine atoms are on the abscissa.

grams with halogen numbers on the abscissa, but the curvatures are much less pronounced.

(iv) Replacing a halogen atom with another in haloalkanes leaves the hydrogen-suppressed graph unchanged. It is clear from Figure 1 that each successive replacement of F by Cl increases the bp by a nearly constant increment. A rule of thumb is that the bp increases by 45 deg on replacing geminally one F atom in a fluorocarbon with Cl, by 75 deg with Br, and by 115 deg with I. These increments (approximately 0:3:5:8 for F:Cl:Br:I) also hold for polysubstitution, indicating that one I atom has the same effect on bp as a pair Br + Cl. When replacing F atoms in vicinal substitution by other halogens, the absolute increments are smaller but the same relative ratios hold.

Boiling Point (C)



Boiling Point (C)

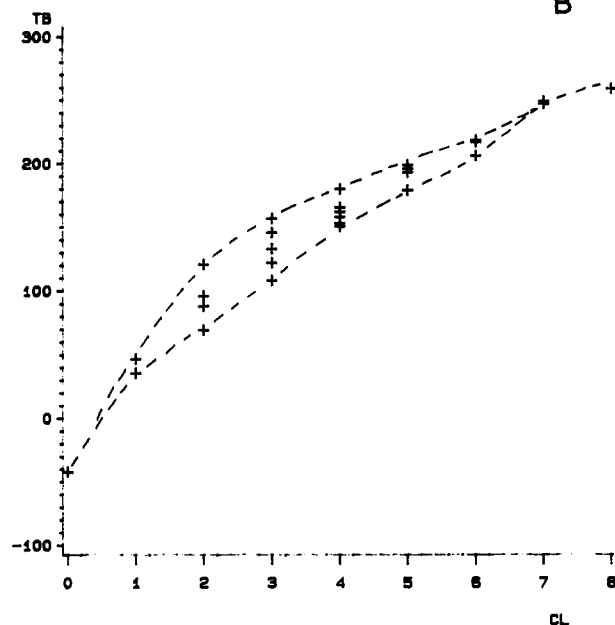


Figure 3. (A) Effect of constitutional isomerism and the boiling points of halopropanes. (B) Lower curve represents the isomer with more numerous geminal halogens and the upper curve the isomer with fewer geminal pairs. On the abscissa, the numbers of F atoms are indicated in (A) and of Cl atoms in (B).

(v) Bps of enantiomeric stereoisomers are equal, and the same holds for their racemic mixture. However, diastereomers (*meso*- and racemic 2,3-dihalobutanes, or *threo*/*erythro*-1,2-dibromo-1-chloropropane) differ in their boiling points. Thus, for *meso*- and racemic 2,3-dichlorobutane the boiling points are 115.9 °C and 119.5 °C, respectively. By taking average values, in no cases is the difference larger than 2.5 deg so that graph-theoretical indices which ignore stereochemistry do not lead to large errors. By contrast, *E/Z* diastereoisomerism in the haloalkene series leads to substantial differences in bps, these may be as large as 15 deg.

(iv) Whenever constitutional isomers differ in the branching degree of the corresponding hydrogen-depleted graphs, bps may differ markedly (20–80 °C), e.g.,  $\text{H}_3\text{C}-\text{I}_2\text{C}-\text{CH}_3$  has a

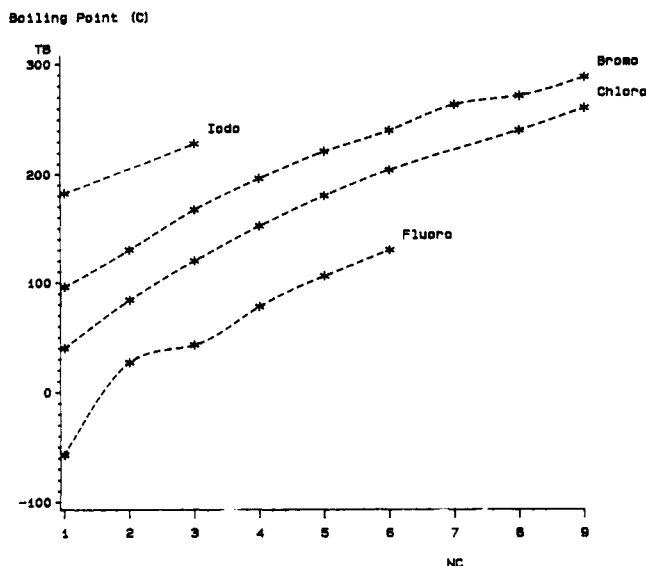


Figure 4. Boiling points of  $\alpha,\omega$ -dihaloalkanes with 1-9 carbon atoms.

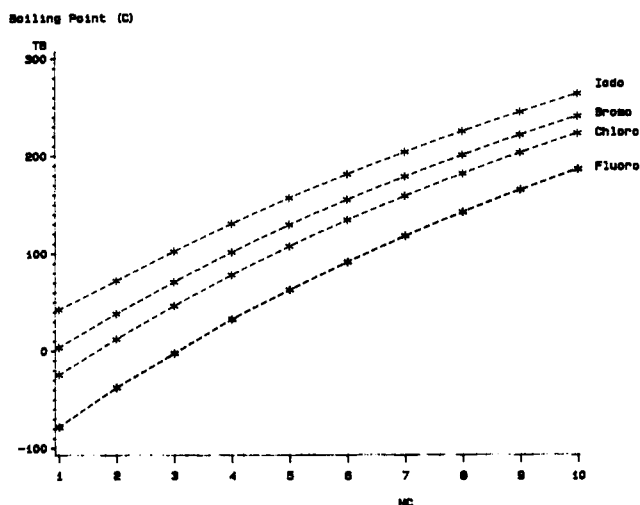


Figure 5. Boiling points of 1-haloalkanes with 1-10 carbon atoms.

bp of 148 °C and  $\text{I}(\text{CH}_2)_3\text{I}$  has a bp of 227 °C. Even if the difference involves interchange of a carbon and a halogen atom in the same graph there will be an appreciable difference as for instance between 1,1- and 1,3-dichlorobutane (bp 115 and 133 °C, respectively). On the other hand, interchange of halogens has little effect when the hydrogen-depleted graph remains unchanged, as seen in Table I.

#### QUANTITATIVE STRUCTURE-PROPERTY CORRELATIONS FOR HALOALKANES

Few QSAR analyses have been done on haloalkanes despite their numerous applications outlined above.<sup>3,4</sup> Kier and Hall<sup>5</sup> investigated correlations between bps of monohaloalkanes and molecular connectivity indices, obtaining for 24 compounds with 2-5 carbon atoms  $r = 0.992$  and  $s = 4.8$  deg in terms of  $^1\chi$  and  $^1\chi^v$ ; for 17 compounds with 3-6 carbon atoms a better correlation was obtained ( $r = 0.998$ ,  $s = 2.57$  deg) in terms of  $^1\chi^v$ ,  $^3\chi_p$ , and  $^3\chi_c^v$ .

The present study deals specifically with haloalkanes in which halogens are univalent, therefore, in hydrogen-depleted graphs these heteroatoms always act as end points (vertices of degree 1). Also, intermolecular forces such as hydrogen bonding are not explicitly considered in the analyses.

In considering first the halomethanes where only one isomer exists for each molecular formula, two striking facts emerge: (i) there is a nonlinear variation of bps versus the number of halogens, illustrated in Figure 1, and (ii) there is an additivity

Table I. Examples of Boiling Points for Constitutional Isomers Differing by Interchange between Halogens

formula	bp, °C
$\text{Cl}_2\text{FC}-\text{CF}_3$	03.6
$\text{ClF}_2\text{C}-\text{CClF}_2$	03.8
$\text{ClF}_2\text{C}-\text{CHBrF}$	51.5
$\text{BrF}_2\text{C}-\text{CHClF}$	52.5
$\text{ClF}_2\text{C}-\text{CF}_2-\text{CF}_2-\text{CClF}_2$	64.0
$\text{F}_3\text{C}-\text{CF}_2-\text{CCl}_2-\text{CF}_3$	64.0
$\text{F}_3\text{C}-\text{CClF}-\text{CClF}-\text{CF}_3$	64.0
$\text{ClF}_2\text{C}-\text{CH}_2\text{Br}$	68.4
$\text{BrF}_2\text{C}-\text{CH}_2\text{Cl}$	70.0
$\text{F}_3\text{C}-\text{CBrCl}_2$	69.2
$\text{BrF}_2\text{C}-\text{CCl}_2\text{F}$	71.0
$\text{ClF}_2\text{C}-\text{CBrClF}$	72.0
$\text{Cl}_3\text{C}-\text{CClF}_2$	92.6
$\text{Cl}_2\text{FC}-\text{CCl}_2\text{F}$	92.6
$\text{ClF}_2\text{C}-\text{CH}_2\text{I}$	97.5
$\text{F}_2\text{IC}-\text{CH}_2\text{F}$	101.0
$\text{ClF}_2\text{C}-\text{CCl}_2-\text{CClF}_2$	112.3
$\text{Cl}_2\text{FC}-\text{CCl}_2-\text{CF}_3$	112.5
$\text{Cl}_3\text{C}-\text{CClF}-\text{CF}_3$	113.5
$\text{BrF}_2\text{C}-\text{CHBr}_2$	144.0
$\text{Br}_2\text{FC}-\text{CHBrF}$	146.0

Table II. Boiling Points of Dihaloethanes (°C)

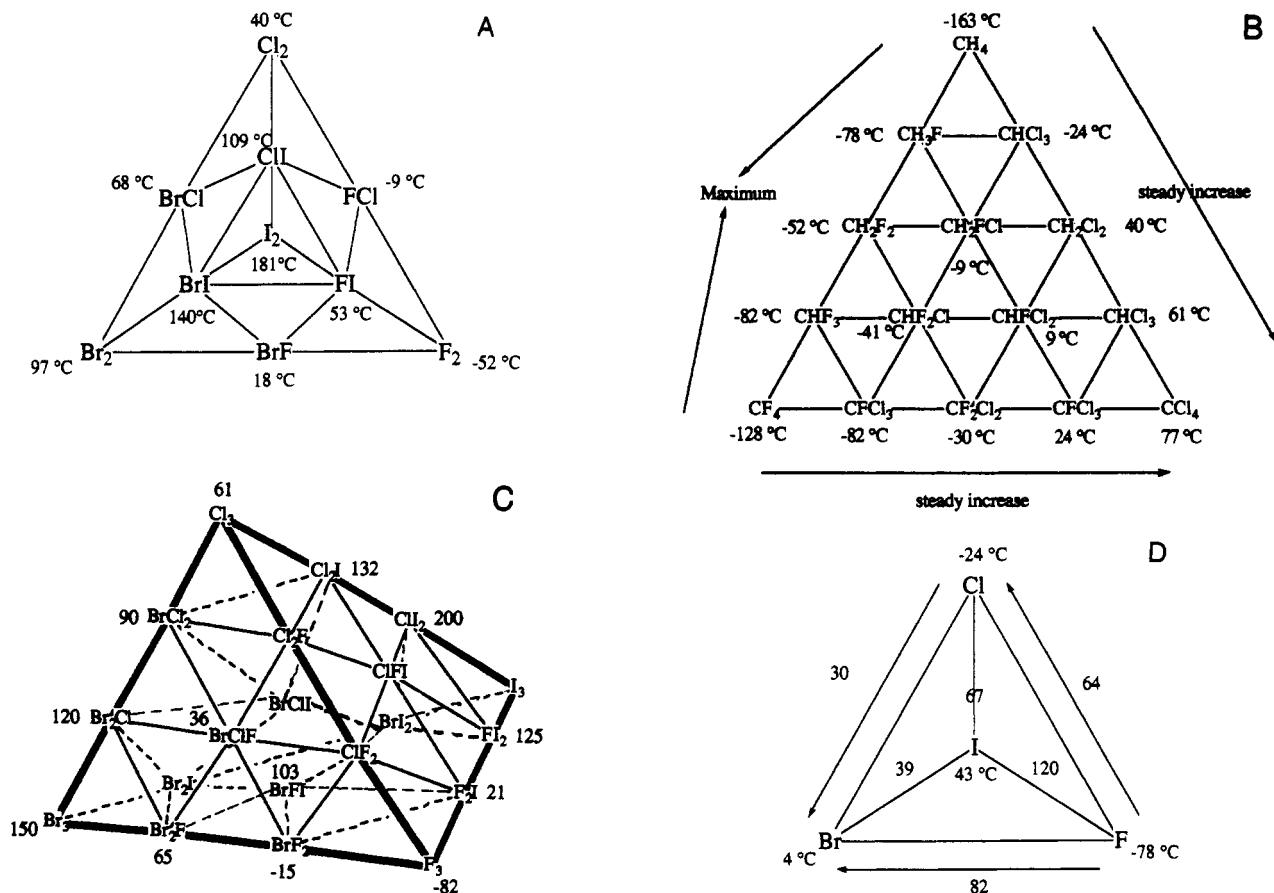
hal <sub>2</sub>	hal <sub>2</sub> CH-CH <sub>3</sub>	halCH <sub>2</sub> -CH <sub>2</sub> hal	$t_{\text{med}}$	$\Delta t$
FF	-24.7	26.0	0.7	50.7
FCI	16.1	53.0	34.6	36.9
FBr	<i>a</i>	71.6		
ClCl	57.3	83.4	70.3	26.1
FI	<i>a</i>	100.0		
ClBr	82.5	107.0	94.8	24.5
BrBr	108.0	131.4	119.7	23.4
ClI	117.0	140.1	128.6	23.1
BrI	143.0	163.0	153.0	20.0
II	180.0	<i>a</i>		

<sup>a</sup> Not reported in the literature; predicted bp in the text.

in bps on replacing one halogen by another. This latter effect is best seen in following the bp increase along the edges of the tetrahedra depicting the various di-, tri-, and tetrahalomethanes (Figure 6A-C): the increment for substitution of F by Cl is about 45 deg, for F by Br it is 75 deg, and for F by I it is 115 deg. For substitution of Cl by Br it is 30 deg, for Cl by I it is 70 deg, and for Br by I it is 40 deg. These values agree fairly well with differences in bps of monohaloalkanes (Figure 6D). It will be observed in this last figure that on all four triangles forming the faces of the tetrahedron, summation of increments for two edges yields approximately the increment for the third edge.

Turning now to dihaloethanes, we have to consider vicinal versus geminal isomerism, in addition to the effects encountered with halomethanes. Large differences are observed in bps for these isomers, as seen in Table II. On plotting the difference  $\Delta t$  in boiling points between the two isomers against the median boiling temperature ( $t_{\text{med}}$ ) of the two isomers, one observes a steady asymptotic decrease of  $\Delta t$  versus  $t_{\text{med}}$ , which allows the prediction of the three missing compounds in Table II: 42 °C for 1-bromo-1-fluoroethane, 76 °C for 1-fluoro-1-iodoethane, and 196 °C for 1,2-diiodoethane. This prediction is based on the assumption that the nature of halogens does not influence  $\Delta t$ , which is believed to depend mainly on  $t_{\text{med}}$ .

Conventional reasoning might lead one to think that the symmetrically 1,2-disubstituted (vicinal) dihaloethane would have a lower bp than its 1,1-disubstituted (geminal) isomer because of dipole moment differences. Actually the opposite holds due to differences in graph topology, i.e., in branching of the hydrogen-suppressed graphs. Just as in the case of



**Figure 6.** (A) Effect of replacing one halogen by another on the boiling points of dihalomethanes. Lines indicate replacement of one halogen atom by another. (B) Effect of replacing one halogen by another on the boiling points of trihalomethanes. Lines indicate replacement of one halogen atom by another. (C) Effect of replacing one halogen by another on the boiling points of tetrahalomethanes. Lines indicate replacement of one halogen atom by another. (D) Contributions of different halogen atoms to the boiling points of monohaloalkanes. Lines indicate replacement of one halogen atom by another.

alkane isomers, where branching decreases boiling points relative to less branched isomers, in the case of geminally-substituted polyhaloalkanes the higher branching leads to lower bps than for their vicinally-substituted isomers.

#### CORRELATIONS FOR SUBSET HALOMETHANES

Taking into account that for any molecular formula of a halomethane there is only one compound (no constitutional or diastereo isomers are possible), it is interesting to investigate correlations for the halomethanes whose bps at normal pressure are known. With the halogen counts as parameters for 48 halomethanes, a poor correlation was obtained with all monohalomethanes as outliers. However, on including only the 44 halomethanes with two or more halogen atoms, the following equation resulted:

$$\text{bp} = -38.08(\pm 1.09)N_F + 14.60(\pm 1.12)N_{Cl} + 42.18(\pm 1.21)N_{Br} + 75.78(\pm 1.81)N_I + 18.73(\pm 3.46) \\ s = 5.26, n = 44, r^2 = 0.99, F = 2204$$

This result shows that, notwithstanding the marked non-linearity of bp variation versus the number of fluorine atoms, one can obtain as a first approximation a fair correlation. We shall therefore continue in the following study to present linear correlations and shall discuss correlations with nonlinear functions in a future paper.

#### CORRELATIONS FOR HALOALKANES C<sub>1</sub>-C<sub>4</sub>

With the large database for haloalkanes C<sub>1</sub>-C<sub>4</sub> one has to solve the problem of constitutional isomerism by adequate topological descriptors. The following structural parameters

were included as possible variables: total number of non-hydrogen atoms,  $N$ ; numbers of C, F, Cl, Br, or I denoted by  $N$  with the corresponding subscripts; fluorine fraction of non-hydrogen atoms,  $FF = N_F/N$ . As topological descriptors, we included the number of pairs of germinal halogens  $P$  (1 for -CHAl<sub>2</sub>-, 3 for -CHAl<sub>3</sub>-, 6 for CHAl<sub>4</sub>); the number of geminal fluorine atoms  $GF$  and its ratio to the number of carbon atoms,  $GFC$ ; the molecular connectivity parameter developed by Randić;<sup>6</sup> the extended and valence-weighted molecular connectivity indices developed by Kier and Hall;<sup>7</sup> the  $J$  index developed by Balaban;<sup>8</sup> the  $\kappa$  shape and the molecular flexibility  $\phi$  indexes developed by Kier;<sup>9</sup> and the difference connectivity indexes of Kier and Hall.<sup>10</sup>

All different combinations of the above variables were tried using the PROC RSQUARE in the SAS<sup>11</sup> package. A list of the 20 best regression equations for one through six variables was obtained. These equations were ranked in the order of their regression coefficients and the root mean square errors. The best three QSAR equations with six linearly independent variables are given below:

$$\text{bp} = 33.21(\pm 2.21)[^1\chi^v - ^0\chi^v] - 64.06(\pm 0.79)^D\chi^0 + 98.46(\pm 2.11)^1\chi - 20.65(\pm 0.66)N_{Br} - 22.18(\pm 1.30)N_I + 6.36(\pm 0.83)[^2\chi^v - ^1\chi^v] - 73.648(\pm 1.98) \quad (1)$$

$$s = 10.94, n = 532, r^2 = 0.97, F = 2953$$

$$\text{bp} = 26.85(\pm 1620)[^1\chi^v - ^0\chi^v] - 64.06(\pm 0.79)^D\chi^0 + 98.46(\pm 2.11)^1\chi - 20.65(\pm 0.66)N_{Br} - 22.18(\pm 1.30)N_I + 6.36(\pm 0.83)[^2\chi^v - ^0\chi^v] - 73.65(\pm 1.98) \quad (2)$$

$$s = 10.94, n = 532, r^2 = 0.97, F = 2953$$

$$\text{bp} = 6.29(\pm 1.12)\phi - 53.46(\pm 1.50)^{\text{D}}\chi^0 + 71.76(\pm 3.10)^1\chi - 19.43(\pm 0.70)N_{\text{Br}} - 22.15(\pm 1.33)N_{\text{I}} + 10.03(\pm 2.16)[^1\chi^{\text{v}} - ^0\chi^{\text{v}}] - 81.57(\pm 2.03) \quad (3)$$

$$s = 11.20, n = 532, r^2 = 0.97, F = 2814$$

An alternate expression in terms of  $N_{\text{F}}$ ,  $N_{\text{Cl}}$ ,  $N_{\text{Br}}$ ,  $N_{\text{I}}$ , and  $^1\chi$  gives a slightly inferior correlation but makes the interpretation of the equation much easier:

$$\text{bp} = 138.62(\pm 5.63)^1\chi - 15.35(\pm 1.33)N_{\text{H}} - 76.35(\pm 3.45)N_{\text{F}} - 37.21(\pm 3.48)N_{\text{Cl}} - 14.29(\pm 3.54)N_{\text{Br}} + 14.45(\pm 3.73)N_{\text{I}} - 53.78(\pm 3.27) \quad (4)$$

$$s = 11.59, n = 532, r^2 = 0.97, F = 2620$$

In the halomethanes where there are no constitutional or steric isomers possible, the boiling point in general increases with addition of Cl, Br, or I atoms. This increase is in the order  $\text{I} > \text{Br} > \text{Cl}$ , F. In cases where  $N_{\text{C}} > 1$ , the constitutional isomerism and topology further complicate the picture. We have used topological indexes to explain some of these variations. Although these indexes are somewhat complicated and may present some difficulty in their interpretation, they can be used in predicting the boiling points of proposed compounds. This can make these equations useful in the design of new halocarbons with boiling points in a certain range.

### SUMMARY

Here we have accumulated the largest data set of haloalkanes in the open literature that we are aware of (see table in supplementary material). The data is presented as SMILES strings to permit optical scanning and loading onto a computer diskette for further study. The boiling point data presented here was collated from the literature. In some cases the precision of the data was not known since this information was often not stated in early literature.

To predict the boiling points, we have derived modestly good linear equation models in six easily calculated nonempirical variables. In three of the equations the counts of I and Br appear as equation variables. Thus, the deletion of molecules containing Br and I permits the analysis of the boiling point QSAR of fluorocarbons with the remaining fewer variables. The analysis of these halocarbons, 280 in number, with the four remaining variables gives an equation of statistical quality comparable to the six-variable equation.

Although the linear models we have derived here explain the variance in the data set reasonably well, it may be that the structure-activity relationships operating here are completely nonlinear. We continue our studies on this data set to explore this possibility.

We have also studied the effects of constitutional isomerism and the replacement of one halogen by another on the boiling points. These effects we have summarized in the Figure 6A-D.

**Supplementary Material Available:** Table containing SMILES strings and boiling points of compounds used in this study (6 pages). Ordering information is given on any current masthead page.

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## Correlations between Chemical Structure and Normal Boiling Points of Acyclic Ethers, Peroxides, Acetals, and Their Sulfur Analogues

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Boiling points at normal pressure for a set of 185 acyclic saturated compounds with one or two divalent oxygen or sulfur heteroatoms devoid of hydrogen bonding were correlated with chemical structures using two or three topological descriptors. The standard error is 8.2 °C, and the correlation coefficient  $r^2$  is 0.971. For subsets (only 72 monoethers or only 44 monosulfides) the standard error is 4-5 °C and  $r^2$  is about 0.98.

### INTRODUCTION

Along with the accompanying paper<sup>1</sup> which deals with correlations involving univalent halogens, we also investigated

correlations between boiling points at normal pressure (BPs) and chemical structures of 185 saturated acyclic compounds possessing divalent oxygen or sulfur (chalcogen) atoms, and devoid of hydrogen bonding, namely, 73 ethers, 17 diethers (with heteroatoms at least three bonds apart), 21 acetals, 6 peroxides, as well as their sulfur analogues: 45 sulfides (thioethers), 6 bis-sulfides, 4 thioacetals, and 13 disulfides,

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