characteristics as in the previous experiment, although the intensity of the orange compound was increased.

A solution of sodium hydrogen sulfide dihydrate (0.3146 g, 0.0034 mole) in propylene glycol (3.7 ml) and a solution of acetylacroninium perchlorate (0.0110 g, 0.000034 mole) in propylene glycol (4.7 ml) were stirred at room temperature for 1 hr. The resultant viscous, orange solution was poured into water (20 ml), and the yellow precipitate was collected and dried. TLC showed a yellow component (with similar R_f value and fluorescence properties as acronine) and an orange component, R_f 0.70, as the major product.

In a further experiment, acetylacroninium perchlorate (0.0245 g, 0.0000528 mole) was added to a stirred solution of thioacetic acid (0.4296 g, 0.00565 mole) and sodium hydroxide (0.20 g, 0.005 mole) in water (100 ml). After stirring at room temperature for 1 hr, the precipitate was collected and dried. TLC showed a yellow spot, R_f 0.39, fluorescing under UV light and an orange component, R_f 0.68, in major amount.

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Molecular Connectivity Study of Halocarbon Anesthetics

THÉRÈSE DI PAOLO *¶×, LEMONT B. KIER ‡, and LOWELL H. HALL §

Received February 3, 1978, from the **Massachusetts College of Pharmacy, Boston, MA 02115*, the ‡*Department of Pharmaceutical Chemistry, Medical College of Virginia, Richmond, VA 23298*, and the §*Department of Chemistry, Eastern Nazarene College, Quincy, MA 02169.* Accepted for publication May 19, 1978. ¶Present address: Medical Research Council Group in Molecular Endocrinology, Centre Hospitalier de l'Université Laval, Quebec G1V 4G2, Canada.

Abstract □ The structure–activity relationships of 45 halogenated hydrocarbons using molecular connectivity were studied. A very good correlation was obtained between the anesthetic activity and the molecular connectivity term ${}^0\chi^v$ in addition to the polar hydrogen factor, Q_H. The equation reported accounts for and quantifies the known structure–activity observations on general anesthetics. The results are discussed briefly with reference to the mechanisms of action of general anesthetics.

Keyphrases □ Molecular connectivity indexes—related to anesthetic activity of various halogenated hydrocarbons □ Halogenated hydrocarbons, various—molecular connectivity indexes related to anesthetic activity □ Anesthetic activity—various halogenated hydrocarbons, related to molecular connectivity indexes □ Structure–activity relationships—molecular connectivity indexes related to anesthetic activity of various halogenated hydrocarbons □ Topological indexes—molecular connectivity, related to anesthetic activity of various halogenated hydrocarbons

To derive information about the mechanism of action of anesthetic gases, some investigators attempted to relate potency to physicochemical properties, including boiling points, solubilities, partition coefficients, molar volumes, molar refractions, and van der Waals equation constants. The finding of a significant correlation indicated that mechanisms of action parallel the physicochemical property.

These property studies (1) did not give any direct insight into the structural features influencing potency. The first real effort to gain such insight used a calculation of molecular structure known as molecular connectivity (2). That study, on a diverse group of anesthetic gases, resulted in a good correlation between potency and a combination of a molecular connectivity index and an electronic charge description. The correlation (r = 0.982) was good enough

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Table I—CH Bond Polarity Indexes

Halogen	Q_H Contribution
F	0.43
Cl	0.41
Br	0.44
I	0.40
α-F	0.13
α-Cl	0.10
α-Br	0.09
β-F	0.05
β-Cl	0.05
β-Br	0.05

to permit the prediction of the potency trend in eight other anesthetic gases. Of equal importance was the utility of the relating equation for describing some important structural features influencing the anesthetic potency.

Structure–activity relationship studies of anesthetic activity were pursued on other groups of molecules to study and isolate the factors affecting activity. A structure–activity study on a group of anesthetic ethers where the polarity of the hydrogens is fairly constant gave very high correlations with a molecular connectivity term (3). A nonlinear structure–activity study of a group of hydrocarbon, ether, and ketone anesthetics also gave very good correlations with two molecular connectivity terms (4).

Another group of molecules with general anesthetic potency is the halocarbons. The potency of 45 halocarbons was reported (5) and served as a basis for the present study of the structure–activity relationship. This study extends the opportunity to probe the important structural features influencing anesthetic potency and, more specifically, the effect of polar hydrogens.

EXPERIMENTAL

The method of structural description, molecular connectivity, describes numerically the branching, unsaturation, cyclization, and heteroatom presence and position in a molecule (2, 6–9).

The polar nature of hydrogen atoms previously was found to be an important structural characteristic (2). Similarly, in this study, the polar hydrogen was found to influence potency. The quantification of this polarity was undertaken at a subquantum mechanical level, because the general utility of a possible structure–activity correlation lies in the general ease with which such an index may be calculated.

Accordingly, a polar hydrogen index was computed as a derivative of the Swain and Lupton F values (10, 11). The F value is the relative field effect (as opposed to the resonance effect) on an atom or group influencing the Hammet σ constant.

The F values are used directly as an index of the polarity of CH bonds. The F value (Table I) of chlorine is 0.41. This index is used to describe the polarity of the CH bond in the fragment ClCH. The total polarity index of the CH bond is a sum of the effects arising from all halogens; therefore, the CH bond polarity index in chloroform is 3 (0.41) = 1.23. In dichloromethane, the two equivalent CH bonds must be reckoned as $2 \times 0.41 = 0.82$ each.

For the influence of halogen atoms on carbon atoms attached to the primary CH fragment, a diminished influence is used in the Swain and Lupton system. From the F values for the fragment ClCCH, the influence of an α-chlorine atom on the CH bond polarity value is 0.10. Halogens on β-carbons were approximated as only contributing 0.05 each to the CH bond polarity total.

Summation of all polarity influencing values, Q_{Hi}, gives a total CH bond polarity, Q_H, which might also be used as a structural descriptor coupled with connectivity indexes in an analysis of halocarbon structure–activity relationships.

In cases where no halogen is attached to a CH fragment, the Q_H is taken as zero, as in V, VII, IX, X, XIX, XXVIII, XXX, XXXV, and XLIII–XLV. Two exceptions to this rule are XXIX and XXXIV, in which a methylene group is flanked by two halogen-substituted methyl groups. Here, the computed total Q_H value was obtained as a sum of both CH fragments.

RESULTS AND DISCUSSION

For the analysis of the data set, the molecular connectivity indexes ${}^m\chi_t$ were calculated through the third order ($m = 3$) for the path indexes ($t = P$) and for the ${}^3\chi_c$ index. Also, the corresponding valence indexes ${}^m\chi_t{}^v$ were calculated and entered into the data file. For each observation, then, there are 10 indexes as variables. Multiple linear correlations were run between the variables and the anesthetic potency, considering all possible single variables as well as all pairs and triplets.

The single χ index giving the best correlation against log AD_{50} was ${}^0\chi^v$. No other variable gave a correlation significantly close to that for ${}^0\chi^v$, $r = 0.70$. This result is consistent with that found for two other sets of general anesthetics (2, 3).

To obtain an equation that accurately represents the data, the questions to be resolved center on the characterization of the polar hydrogen atoms. Should the effects of all such hydrogens be summed? Do all polar hydrogens affect the anesthetic potency equivalently?

A plot of log AD_{50} *versus* ${}^0\chi^v$ gives some helpful indications. Compounds with nonpolar or only very slightly polar hydrogens fall along the same line as compounds with no hydrogen atoms. The compounds with polar hydrogens fall below that line; the more polar the hydrogen, or the greater the number of polar hydrogens, the further below the line they fall. This general observation suggests that there is a minimum value for polarity to activate the hydrogen atom in the physiological process.

Following this line of thought, polarity variables were calculated for each hydrogen, Q_{Hi}, in a molecule as already described and regressions were run along with the variable ${}^0\chi^v$. The following equations were obtained:

$$\log_e AD_{50} = 5.14 - 0.959{}^0\chi^v - 1.53Q_{H1} \quad \text{(Eq. 1)}$$

$$r = 0.86 \quad s = 0.63 \quad F = 59 \quad n = 45$$

$$\log_e AD_{50} = 6.04 - 1.05{}^0\chi^v - 1.68Q_{H1} - 1.49Q_{H2} \quad \text{(Eq. 2)}$$

$$r = 0.96 \quad s = 0.34 \quad F = 177 \quad n = 45$$

$$\log_e AD_{50} = 6.15 - 1.06{}^0\chi^v - 1.71Q_{H1} - 1.34Q_{H2} - 0.549Q_{H3} \quad \text{(Eq. 3)}$$

$$r = 0.97 \quad s = 0.32 \quad F = 151 \quad n = 45$$

where Q_{H1} represents the most polar CH bond, Q_{H2} represents the second most polar, and so on. Examination of residuals clearly indicates that compounds with slightly polar hydrogens (V, IX, XXVIII, XXX, XXXV, and XLIII–XLV) are predicted too small, indicating that Q_{Hi} should be set to zero up to a threshold value. The Q_H values for these hydrogens range up to about 0.36. There is a significant break in the Q_H values up to about 0.67. Thus, a useful threshold value of about 0.50 can be tested. The statistical results are as follows:

$$\log_e AD_{50} = 4.78 - 0.94{}^0\chi^v - 1.30Q_{H1} \quad \text{(Eq. 4)}$$

$$r = 0.87 \quad s = 0.60 \quad F = 67 \quad n = 45$$

$$\log_e AD_{50} = 5.17 - 1.00{}^0\chi^v - 1.12Q_{H1} - 1.32Q_{H2} \quad \text{(Eq. 5)}$$

$$r = 0.97 \quad s = 0.32 \quad F = 194 \quad n = 45$$

$$\log_e AD_{50} = 5.19 - 0.993{}^0\chi^v - 1.13Q_{H1} - 1.12Q_{H2} - 0.800Q_{H3} \quad \text{(Eq. 6)}$$

$$r = 0.976 \quad s = 0.27 \quad F = 204 \quad n = 45$$

There is some improvement in the correlation statistics and achievement of a better distribution of residuals.

From Eqs. 4–6, it appears that the influence of each polar hydrogen is not greatly different. Hence, it is of interest to investigate a Q_H variable that is a summation of all the polar hydrogen terms (above the threshold).

The equation based upon ${}^0\chi^v$ and $Q_H = \Sigma Q_{Hi}$ gives the best statistical results:

$$\log_e AD_{50} = 5.229\ (\pm 0.171) - 1.026\ (\pm 0.044){}^0\chi^v - 1.054\ (\pm 0.053)Q_H \quad \text{(Eq. 7)}$$

$$r = 0.975 \quad s = 0.27 \quad F = 411 \quad n = 45\ (p < 0.001)$$

The quantities in parenthesis for each regression parameter in Eq. 7 are the standard deviations calculated in the regression routine for each parameter. The calculated values shown in Table II are based on Eq. 7.

Equation 7 accounts for 95% (R^2) of the variance in $\log_e AD_{50}$. These results are in line with previous results for a mixed group of anesthetics

Table II—Correlation of Anesthetic Activity of Halogenated Hydrocarbons

Compound	$^0\chi^v$	Q_H	$\log_e AD_{50}$ Obs.	$\log_e AD_{50}$ Calc.[a]	$\lvert\Delta\log_e AD_{50}\rvert$
		Methane Derivatives			
I CHF_2Cl	1.334	1.27	3.02	2.52	0.50
II $CHFCl_2$	2.761	1.25	1.12	1.08	0.04
III CH_2Cl_2	3.115	1.64	0.49	0.30	0.19
IV $CHFClBr$	3.542	1.28	0.18	0.25	0.07
		Ethane Derivatives			
V CF_2ClCH_3	2.257	0.00	3.14	2.91	0.23
VI CF_3CHFCl	1.387	1.22	2.74	2.52	0.22
VII $CF_3CFClBr$	3.294	0.00	2.28	1.85	0.43
VIII CF_2BrCHF_2	2.167	1.21	1.94	1.73	0.21
IX $CFCl_2CH_3$	3.684	0.00	1.85	1.45	0.40
X $CF_2ClCFCl_2$	3.941	0.00	1.70	1.19	0.51
XI $CF_2ClCHFCl$	2.814	1.19	1.11	1.09	0.02
XII CF_3CHCl_2	2.814	1.20	0.87	1.08	0.21
XIII CHF_2CH_2Cl	2.041	2.30	0.77	0.71	0.06
XIV CHF_2CH_2Br	2.821	2.35	0.26	−0.14	0.40
XV CF_2ClCH_2Cl	3.168	1.54	0.25	0.36	0.11
XVI $CF_2ClCHFBr$	3.595	1.23	0.18	0.24	0.06
XVII $CF_2BrCHFCl$	3.595	1.19	0.11	0.29	0.18
XVIII $CF_3CHClBr$	3.595	1.23	−0.16	0.24	0.40
XIX $CFCl_2CFCl_2$	5.368	0.00	−0.22	−0.28	0.06
XX CF_2ClCH_2Br	3.948	1.60	−0.22	−0.51	0.29
XXI CF_2BrCH_2Cl	3.948	1.52	−0.29	−0.42	0.13
XXII $CF_2ClCHCl_2$	4.242	1.18	−0.22	−0.37	0.15
XXIII $CFCl_2CHFCl$	4.242	1.17	−0.54	−0.36	0.18
XXIV $CF_2BrCHFBr$	4.375	1.22	−0.43	−0.55	0.12
XXV CF_3CHBr_2	4.375	1.26	−0.63	−0.59	0.04
XXVI $CHFClCHFCl$	3.115	2.14	−0.60	−0.22	0.38
XXVII $CF_2ClCHClBr$	5.022	1.21	−0.78	−1.20	0.42
		Propane Derivatives			
XXVIII $CF_2ClCH_2CH_3$	2.964	0.00	2.08	2.19	0.11
XXIX $CF_3CH_2CF_2Cl$	1.793	1.48	1.66	1.83	0.17
XXX $CF_3CCl_2CH_3$	3.737	0.00	1.39	1.39	0.00
XXXI $CF_3CHBrCH_3$	3.391	0.82	0.78	0.89	0.11
XXXII $CH_2ClCF_2CH_3$	2.964	1.34	0.77	0.78	0.01
XXXIII CF_2ClCF_2CHFCl	2.867	1.25	0.69	0.97	0.28
XXXIV $CF_3CH_2CF_2Br$	2.573	1.46	0.64	1.05	0.41
XXXV $CFCl_2CH_2CH_3$	4.391	0.00	0.40	0.72	0.32
XXXVI $CH_2BrCF_2CH_3$	3.744	1.40	0.22	−0.09	0.31
XXXVII $CHF_2CF_2CH_2Cl$	2.094	2.69	0.18	0.24	0.06
XXXVIII $CF_2ClCHClCH_3$	4.038	0.77	−0.04	0.27	0.31
XXXIX $CF_2ClCHBrCH_3$	4.818	0.80	−0.58	−0.56	0.02
XL $CHF_2CF_2CH_2Br$	2.874	2.77	−0.63	−0.64	0.01
XLI $CHF_2CF_2CHClBr$	3.948	2.43	−1.66	−1.38	0.28
XLII $CF_3CHBrCH_2Br$	5.082	2.27	−2.30	−2.38	0.08
		Butane Derivatives			
XLIII $CH_3CF_2CF_2CH_3$	2.106	0.00	2.99	3.07	0.08
XLIV $CH_3CF_2CH_2CH_3$	2.760	0.00	1.79	2.40	0.61
XLV $CH_3CF_2CFClCH_3$	3.533	0.00	1.22	1.60	0.38

[a] Using Eq. 7.

(5) where $^0\chi^v$ was also the best connectivity term to correlate with activity. This correlation also accounts well for the qualitative structure–activity relationships of the general anesthetics (12, 13):

1. Halogenation of hydrocarbons increases potency in the following order: F < Cl < Br (Table III). Compare also XII and XXII, XVI and XXIV, XVIII and XXVII, XV and XX, XV and XXI, V and IX, XIII and XIV, XXXIV and XXIX, XXXVII and XL, XXXI and XXXIX, XXXVIII and XXXIX, XXXII and XXXVI, and XLIII and XLV. In all of these cases, this structure–activity observation is quantitatively accounted for by Eq. 7.

2. Fluorination usually decreases potency, as can be seen in the examples in Table III for halogen substitution.

3. Compounds substituted as dibromides and dichlorides tend to be more potent than their monosubstituted analogs. The dibromo compounds are more potent than the dichloro derivatives. Compare, for example, XII and XV.

4. Increased potency in a homologous series is observed. This result is quantified in the homologous pairs V and XXVIII and IX and XXXV.

5. The polar hydrogen factor Q_H accounts well for the structure–activity observations that compounds containing CHFCl, CHFBr, and CHClBr produce good anesthesia and that one or more hydrogen atoms in the molecule are necessary for effective central nervous system depression. Equation 7 shows that a fully activated acidic hydrogen increases anesthetic activity by 1.4 $\log_e$ units and that the influence of more than one acid hydrogen can be well approximated by a simple additive relation.

The predictive value of the structure–activity equation is demonstrated by its ability to predict activities not in the original data (Table IV). One iodo compound is included and well predicted. With Eq. 7, the predicted anesthetic activity for the convulsant $CF_3CH_2OCH_2CF_3$ (indoklon) (14) is 4.66; for its anesthetic isomer $(CF_3)_2CHOCH_3$ (14), it is 3.67. Equation 7 predicts an extremely low anesthetic activity for indoklon and a value and order of magnitude higher for its anesthetic isomer.

The equation obtained in this study is analogous to equations obtained previously with a mixed group of anesthetics (5), and it can be interpreted similarly in the light of theories of anesthesia. In this study, polar hydrogens were evaluated with a term derived from the Swain and Lupton (10) field-based F. Experimentally, these polar hydrogens were better donors in a hydrogen bond than aliphatic CH (14, 15). Halogenated hydrocarbon anesthetics also break hydrogen bonds of the NH···N, OH···O, and NH···O=C types in solution (16–21). Thus, the polar hydrogens can contribute to anesthetic activity because of their hydrogen bonding ability and their ability to perturb existing hydrogen bonds. These results are consistent with the observed disordering effect of anesthetics on membranes and protein structure (1) and the concepts of the critical volume hypothesis.

Only one other structure–activity study on this data set was reported (5). A nonpolar term, P_0, was appropriately related to van der Waals interaction terms by an approximate additivity scheme (5). In addition,

Table III—Anesthetic Potency as a Function of Halogen

Compound	$\log_e$ AD_{50} Obs.	Calc.[a]
VI CF_3CHFCl	2.74	2.52
XII CF_3CHCl_2	0.87	1.08
XVIII $CF_3CHClBr$	−0.16	0.24
XXV CF_3CHBr_2	−0.63	−0.59
VIII CF_2BrCHF_2	1.94	1.73
XVII $CF_2BrCHFCl$	0.11	0.29
XXIV $CF_2BrCHFBr$	−0.43	−0.55
XI $CF_2ClCHFCl$	1.11	1.09
XVI $CF_2ClCHFBr$	0.18	0.24
XXII $CF_2ClCHCl_2$	−0.22	−0.37
XXVII $CF_2ClCHClBr$	−0.78	−1.20
VI $CHFClCF_3$	2.74	2.52
XI $CHFClCF_2Cl$	1.11	1.09
XVII $CHFClCF_2Br$	0.11	0.29
XXIII $CHFClCFCl_2$	−0.54	−0.36
I CHF_2Cl	3.02	2.52
II $CHFCl_2$	1.12	1.08
III CH_2Cl_2	0.49	0.30
IV $CHFClBr$	0.18	0.25

[a] Using Eq. 7.

an additivity scheme was employed for estimating the acidity of hydrogen atoms by taking the contribution to the electron demand by each halogen as a constant. The total electron demand on the ith hydrogen is called H_{ai}. The developed relation (5) was a six-parameter equation with an unusual form for multiple regression:

$$\log_e AD_{50} = a_1 + a_2P_0 + a_3\delta_1H_{a1} + a_4\delta_1 + a_5\delta_2H_{a2} + a_6\delta_2 \quad \text{(Eq. 8)}$$

Table IV—Predicted Anesthetic Activity

Compound	$^0\chi^v$	Q_H	$\log_e$ AD_{50} Obs.[a]	Calc.[b]
CF_3CH_3	0.829	0.00	3.91	4.38
CF_3CH_2Cl	1.740	1.60	2.08	1.76
CF_3CH_2Br	2.520	1.66	1.03	0.89
CF_3CH_2I	3.101	1.58	0.22	0.38
$CF_3CH{=}CH_2$	1.114	0.00	4.09	4.09
$CF_3CH_2CH_3$	1.536	0.00	3.91	3.65
$CF_3CH_2CH_2Cl$	2.247	1.12	1.10	1.54
$CF_3CH_2CH_2Br$	3.227	1.18	0.41	0.67
$CF_3CHClCH_2Cl$	3.521	2.22	−0.92, −0.69	−0.72
$CF_3CH_2CF_3$	0.365	1.56	2.40	3.21
$CHF_2CHClCH_3$	2.911	1.63	0.53	0.52
$CF_3CH_2CHCl_2$	3.521	0.97	−0.58	0.59
$CF_2ClCH_2CH_2Cl$	3.875	1.12	−0.11	0.07
$CF_2ClCHClCFCl_2$	5.722	1.10	−0.51	−1.80
$CH_3CF_2CH{=}CH_2$	2.337	0.00	2.12	2.83
$CF_3CH_2CF_2CH_3$	1.589	1.30	1.61	2.23
$CH_3CFClCH_2CH_3$	4.187	0.00	0.59	0.93
$CH_3CF_2CH_2CHCl_2$	4.745	0.92	−1.05	−0.61
$CH_3CF_2CHClCH_2Cl$	4.745	1.99	−1.61	−1.74

[a] From Ref. 22. [b] Calculated using Eq. 7.

where the terms a_1–a_6 are the regression parameters and the δ_i's are Kronecker deltas used to introduce the threshold idea. However, the threshold variable δ_i is also entered separately in two places in the equation, affecting two pairs of regression parameters: a_3 and a_4 and a_5 and a_6.

The correlation of P_0 with log AD_{50} yields $r = 0.69$. Equation 8 leads to $r = 0.988$ and $s = 0.20$, the only statistics reported for Eq. 8. Therefore, it is rather difficult to compare Eqs. 7 and 8 because of the differing number of regression parameters, 3 compared to 6, and the rather peculiar manner in which the threshold variable influences the regression. Equation 7 is a more readily applied form of analysis and was used in two other anesthetic structure–activity studies.

In addition to statistical analysis, Eq. 7 is capable of structural interpretation and prediction as already discussed.

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