Structure–Activity Relationships of Anesthetic Ethers Using Molecular Connectivity

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Abstract □ The structure–activity relationships in the anesthetic and toxic actions of 28 aliphatic ethers were simple functions of molecular connectivity indexes. These quantitative relationships are discussed briefly in the light of theories of the mechanism of action of general anesthetics.

Keyphrases □ Structure–activity relationships—various aliphatic ethers, anesthetic activity and toxicity related to molecular connectivity indexes □ Molecular connectivity indexes—various aliphatic ethers, related to anesthetic activity and toxicity □ Ethers, various aliphatic—anesthetic activity and toxicity related to molecular connectivity indexes □ Anesthetics—various aliphatic ethers, activity related to molecular connectivity indexes □ Toxicity—various aliphatic ethers, related to molecular connectivity indexes □ Topological indexes—molecular connectivity, various aliphatic ethers, related to anesthetic activity and toxicity

In theories of the mode of action (1, 2) and structure–activity relationships (3, 4) of general anesthetics, their solubility in lipophilic media and their oil–water partition coefficients have been emphasized as important factors governing their activity (1, 4). These properties are related to molecule size, and these studies also emphasized the importance of the volume of these anesthetics (1).

In support of this latter aspect, an excellent correlation was obtained between the anesthetic potency of a mixed group of anesthetics and a molecular connectivity term plus a term for the charge on the polar hydrogens (5). To test the validity of these findings further and to gain more information, a structure–activity study of 28 aliphatic ethers was undertaken. In this group, the polarity of the hydrogens does not vary significantly; hence, this factor is approximately constant. The anesthetic AD_{50} and LD_{50} toxicity data used are from Marsh and Leake (6).

EXPERIMENTAL

Molecular connectivity indexes were calculated in the usual manner (7). A short description of the calculation of $^1\chi$ and $^1\chi^v$ is given here.

The molecular skeleton is drawn, and each nonhydrogen atom is assigned a number, δ, corresponding to the number of nonhydrogen atoms connected to it; thus, $\delta = 1, 2, 3,$ or 4. A value for each molecule bond, c_k, is computed from each pair of bonded atoms by $c_k = (\delta_i\delta_j)_k^{-1/2}$, where k is the bond between atoms i and j. Finally, $^1\chi$ is the sum of the c_k values of all bonded atoms, $^1\chi = \Sigma_k c_k$.

The valence χ term, $^1\chi^v$, is calculated similarly, except that valence δ^v values are used. They are assigned on the basis of the expression $\delta^v = Z^v - h_i$, where Z^v is the number of valence electrons and h_i is the number of attached hydrogen atoms.

The complete set of connectivity indexes was calculated for the molecules in Tables I and II and statistically analyzed with a computer program[1] to find the best set of variables. All possible linear, inverse, and quadratic equations with one and two variables were calculated. The best equations obtained for one and two variables are reported.

RESULTS AND DISCUSSION

The statistical analysis showed that $^1\chi$ is the best connectivity term to correlate with anesthetic activity. The following equations were formulated from the data in Table I:

$$\log 1/c = 4.376\ (\pm 0.05) - \frac{3.729\ (\pm 0.15)}{^1\chi} \qquad \text{(Eq. 1)}$$

$$r = 0.979 \quad s = 0.076 \quad n = 28$$

$$F_{1,26} = 606.1,\ p < 0.001$$

$$\log 1/c = -0.365\ (\pm 0.18) + 1.865\ (\pm 0.13)^1\chi - 0.230\ (\pm 0.02)(^1\chi)^2 \qquad \text{(Eq. 2)}$$

$$r = 0.986 \quad s = 0.063 \quad n = 28$$

$$F_{2,25} = 449.1,\ p < 0.001$$

where c is the AD_{50} molar concentration of anesthetic. The 95% confidence intervals of the coefficients are shown in parentheses. Equations 1 and 2 account for 96% (r^2) and 97% (r^2), respectively, of the variance in $\log 1/c$, and the standard deviations are within experimental error.

Marsh and Leake (6) observed that, in general, as the molecular weight or molecular size increases, the activity increases and that within a group of compounds with the same total number of carbon atoms or the same molecular weight, the isomers with the longest straight chain or highest boiling point are the most active. Both Eqs. 1 and 2 account very well for these observations (Table I). Table I shows that $^1\chi$ increases as the molecules become larger, reflecting their size; for molecules with the same number of carbons, $^1\chi$ is smaller for the more branched isomers (*e.g.*, Compounds 3–8, 9–15, 16–23, 24–26, and 27–28 in Table I).

For anesthetic activity, two equations were formulated with comparable correlation statistics. In Eq. 1, the activity is inversely proportional to $^1\chi$; Eq. 2 is a parabolic relationship in $^1\chi$. These equations were derived from a limited group of molecules in a homologous series. The apex of the parabola defined by Eq. 2 is for $^1\chi = 4.05$, $\log 1/c = 3.42$. Table I shows that only two molecules are past the maximum and, in fact, are very close to it ($^1\chi = 4.26$, $\log 1/c = 3.30$, and $^1\chi = 4.20$, $\log 1/c = 3.45$). This result explains why Eqs. 1 and 2 describe equally well the variation in activity. More data points past the maximum would be required for an adequate structure–activity study.

The toxicity (LD_{50}) of these ethers also was analyzed using molecular connectivity. The statistical analysis showed that the number of edges (NEDG) is the best single variable to correlate with activity and that the best set of two variables is NEDG and $^1\chi^v$. The following equations were formulated from the data in Table II:

$$\log 1/c' = 0.311\ (\pm 0.02)\text{NEDG} + 1.034\ (\pm 0.12) \qquad \text{(Eq. 3)}$$

$$r = 0.945 \quad s = 0.132 \quad n = 25$$

$$F_{1,23} = 191.9,\ p < 0.001$$

$$\log 1/c' = 0.538\ (\pm 0.05)\text{NEDG} - 0.099\ (\pm 0.02)(^1\chi^v)^2 + 0.466\ (\pm 0.13) \qquad \text{(Eq. 4)}$$

$$r = 0.976 \quad s = 0.090 \quad n = 25$$

$$F_{2,22} = 222.2,\ p < 0.001$$

where c' is the LD_{50} molar concentration of the anesthetic. Equations 3 and 4 account for 89% (r^2) and 95% (r^2), respectively, of the variance in $\log 1/c'$, and the standard deviations are close to the experimental error. The topological designation "edge" corresponds in chemistry to a σ-bond. Thus, the NEDG variable is the number of σ-bonds in the hydrogen-suppressed molecule.

Marsh and Leake (6) reported that, in general, the toxicity increased as the molecular weight of the compounds increased, although the relationships were not exactly parallel to those of anesthetic activity. The difference in toxicity between the isomers of the same molecular weight does not show a clear pattern, although usually the asymmetric and branched chain compounds are more toxic. The very simple Eq. 3 ac-

[1] IBM REGR.

Table I—AD_{50} Values for Anesthesia of Mice by Aliphatic Ethers

Compound	$^1\chi$	log $1/c'$ Obs.[a]	log $1/c'$ Calc.[b]	$\lvert\Delta \log 1/c\rvert$	log $1/c$ Calc.[c]	$\lvert\Delta \log 1/c\rvert$	V, cm^3/mole
1 Dimethyl	1.414	1.85	1.74	0.11	1.81	0.04	31.04
2 Methyl ethyl	1.914	2.22	2.43	0.21	2.36	0.14	41.27
3 Methyl isopropyl	2.270	2.70	2.73	0.03	2.68	0.02	51.49
4 Diethyl	2.414	2.75	2.83	0.08	2.80	0.05	51.50
5 Divinyl	2.414	2.82	2.83	0.01	2.80	0.02	44.52
6 Ethyl vinyl	2.414	2.82	2.83	0.01	2.80	0.02	48.01
7 Methyl cyclopropyl	2.432	2.85	2.84	0.01	2.81	0.04	48.06
8 Methyl propyl	2.414	2.90	2.83	0.07	2.80	0.10	51.50
9 Methyl *tert*-butyl	2.561	3.00	2.92	0.08	2.90	0.10	61.71
10 Methyl isobutyl	2.770	3.00	3.03	0.03	3.04	0.04	61.72
11 Ethyl isopropyl	2.770	3.00	3.03	0.03	3.04	0.04	61.72
12 Methyl *sec*-butyl	2.808	3.04	3.04	0.00	3.06	0.02	61.72
13 Ethyl propyl	2.914	3.10	3.10	0.00	3.12	0.02	61.73
14 Ethyl cyclopropyl	2.932	3.10	3.11	0.01	3.13	0.03	58.29
15 Methyl butyl	2.914	3.15	3.10	0.05	3.12	0.03	61.73
16 Ethyl *tert*-butyl	3.061	3.15	3.16	0.01	3.19	0.04	71.94
17 Diisopropyl	3.126	3.15	3.18	0.03	3.22	0.07	71.94
18 Ethyl isobutyl	3.270	3.22	3.24	0.02	3.27	0.05	71.95
19 Ethyl *sec*-butyl	3.308	3.22	3.25	0.03	3.29	0.07	71.95
20 Propyl isopropyl	3.270	3.26	3.24	0.02	3.27	0.01	71.95
21 Ethyl butyl	3.414	3.30	3.28	0.02	3.32	0.02	71.96
22 Methyl pentyl	3.414	3.40	3.28	0.12	3.32	0.08	71.96
23 Dipropyl	3.414	3.40	3.28	0.12	3.32	0.08	71.96
24 Ethyl *tert*-pentyl	3.561	3.40	3.33	0.07	3.36	0.04	82.17
25 Ethyl isopentyl	3.846	3.45	3.41	0.04	3.41	0.04	82.18
26 Ethyl pentyl	3.914	3.45	3.43	0.02	3.41	0.04	82.19
27 Diisobutyl	4.260	3.30	3.47	0.17	3.41	0.11	92.40
28 Di-*sec*-butyl	4.202	3.45	3.49	0.04	3.41	0.04	92.40

[a] From Ref. 6. [b] Calculated using Eq. 1. [c] Calculated using Eq. 2.

counts well for the size effect on toxicity, and Eq. 4 refines the correlation, $^1\chi^v$ distinguishing the asymmetric and branching variations.

Equation 4 also refines Eq. 3 in that it accounts for the nonlinear variation in activity. In this respect, an inverse relationship with NEDG fits slightly better the toxicity activity variations than the linear form of Eq. 3: $\log 1/c' = 3.69 - 5.04/\text{NEDG}$ ($r = 0.952$, $s = 0.124$, $n = 25$, $F_{1,23} = 220.6$, $p < 0.001$), but Eq. 4 still gives the best results.

For the same molecules, the parabolic relationship between anesthetic activity and the octanol–water partition coefficient gave the following correlation statistics: $r = 0.966$, $s = 0.101$, and $n = 26$ (4); the two unsaturated ethers were omitted. Similarly, for the toxic activity, the following correlation statistics were obtained with $\log P$ and $(\log P)^2$: $r = 0.864$, $s = 0.208$, and $n = 25$ (8). The correlations reported here with molecular connectivity are clearly superior to those obtained with the octanol–water partition coefficients.

Bondi's (9) van der Waals volumes (V) of the ethers were calculated. The volumes of the ethers and their $^1\chi$ values are highly correlated ($V = -1.54 + 22.13\ ^1\chi$; $r = 0.977$, $s = 3.22$, $n = 28$). Therefore, for these ethers, $^1\chi$ is a very simply derived size variable. In comparing computed Bondi's van der Waals volumes with the $^1\chi$ values (Table I), it is clear that $^1\chi$ differentiates better the isomers (compare Compounds 3, 4, and 8; 10–13 and 15; 17–23; 24–26; and 27–28 in Table I).

The correlation between the anesthetic activity and Bondi's van der Waals volumes (V) is very good ($\log 1/c = 4.30 - 75.82/V$; $r = 0.959$, $s = 0.107$, $n = 28$), although inferior to Eq. 1. This result could be explained by the fact that Bondi's volume values have to be corrected for small rings and that they do not differentiate the isomeric variations as well as $^1\chi$. The correlation between the toxic activity and the volumes of the ethers gives the following statistics: $\log 1/c' = 4.00 - 80.31/V$ ($r = 0.916$, $s = 0.159$, $n = 25$). These results are superior to the quadratic $\log P$ equation but inferior to the molecular connectivity correlations.

The excellent correlations obtained for the anesthetic activity and the obvious relationship between $^1\chi$ and the molecular size for these ethers are in line with the Mullins critical volume hypothesis (1). This hypothesis

Table II—Toxicity (LD_{50}) of Ethers to Mice

Compound	NEDG	$^1\chi V$	log $1/c$ Obs.[a]	log $1/c$ Calc.[b]	$\lvert\Delta \log 1/c'\rvert$	log $1/c'$ Calc.[c]	$\lvert\Delta \log 1/c'\rvert$
1 Dimethyl	2	0.816	1.43	1.66	0.23	1.48	0.05
2 Methyl ethyl	3	1.404	1.74	1.97	0.23	1.89	0.15
3 Diethyl	4	1.992	2.22	2.28	0.06	2.23	0.01
4 Methyl isopropyl	4	1.799	2.26	2.28	0.02	2.30	0.04
5 Divinyl	4	1.288	2.33	2.28	0.05	2.45	0.12
6 Ethyl vinyl	4	1.640	2.34	2.28	0.06	2.35	0.01
7 Methyl propyl	4	1.904	2.45	2.28	0.17	2.26	0.19
8 Methyl cyclopropyl	5	1.960	2.75	2.59	0.16	2.78	0.03
9 Ethyl propyl	5	2.492	2.60	2.59	0.01	2.54	0.06
10 Ethyl isopropyl	5	2.386	2.60	2.59	0.01	2.59	0.01
11 Methyl butyl	5	2.404	2.70	2.59	0.11	2.58	0.12
12 Methyl isobutyl	5	2.260	2.79	2.59	0.20	2.65	0.14
13 Methyl *sec*-butyl	5	2.337	2.79	2.59	0.20	2.62	0.17
14 Methyl *tert*-butyl	5	2.112	2.79	2.59	0.20	2.72	0.07
15 Ethyl cyclopropyl	6	2.548	3.00	2.90	0.10	3.05	0.05
16 Dipropyl	6	2.992	2.79	2.90	0.11	2.81	0.02
17 Propyl isopropyl	6	2.886	2.82	2.90	0.08	2.87	0.05
18 Diisopropyl	6	2.781	2.82	2.90	0.08	2.93	0.11
19 Ethyl butyl	6	2.992	2.82	2.90	0.08	2.81	0.13
20 Ethyl isobutyl	6	2.847	2.82	2.90	0.08	2.89	0.07
21 Ethyl *sec*-butyl	6	2.924	2.85	2.90	0.08	2.85	0.00
22 Methyl pentyl	6	2.904	2.88	2.90	0.08	2.86	0.02
23 Ethyl *tert*-butyl	6	2.700	2.92	2.90	0.02	2.97	0.05
24 Ethyl pentyl	7	3.492	3.00	3.21	0.21	3.02	0.02
25 Ethyl *tert*-pentyl	7	3.138	3.15	3.21	0.06	3.18	0.03

[a] From Ref. 6. [b] Calculated using Eq. 3. [c] Calculated using Eq. 4.

states that anesthesia occurs when the volume of a hydrophobic region is caused to expand beyond a certain critical amount by the absorption of molecules of an inert substance. These results also are in agreement with a previous study of a mixed group of anesthetics (5) for which a size effect interpretation was proposed. More structure–activity studies of anesthetics are being completed to generalize these findings.

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Molecular Connectivity in Quantitative Structure–Activity Relationship Study of Anesthetic and Toxic Activity of Aliphatic Hydrocarbons, Ethers, and Ketones

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Abstract □ The nonempirical molecular connectivity indexes of 27 aliphatic hydrocarbons, ethers, and ketones were calculated. Very good correlations were obtained between anesthetic (AD_{100}) and toxic (LD_{100} and LD_{50}) activities of these compounds and their molecular connectivity indexes. These quantitative structure–activity relationships are discussed briefly in the light of general anesthesia theories.

Keyphrases □ Molecular connectivity indexes—various aliphatic hydrocarbons, ethers, and ketones, related to anesthetic activity and toxicity □ Structure–activity relationships—various aliphatic hydrocarbons, ethers, and ketones, anesthetic activity and toxicity related to molecular connectivity indexes □ Anesthetics—various aliphatic hydrocarbons, ethers, and ketones, activity related to molecular connectivity indexes □ Toxicity—various aliphatic hydrocarbons, ethers, and ketones, related to molecular connectivity indexes □ Topological indexes—mclecular connectivity, various aliphatic hydrocarbons, ethers, and ketones, related to anesthetic activity and toxicity

Molecular connectivity is a method of quantitating the topological structure of organic molecules. This method derives numerical descriptors encoded with information about the number and kind of atoms and their bonding relationships to each other. It has been used successfully to arrive at structure–activity relationships with many classes of biological agents (1).

In a previous study with a mixed group of anesthetics, an excellent correlation was obtained between the relative anesthetic potency and a molecular connectivity term in addition to a term for the charge on the polar hydrogens (2).

To test further the validity of these findings and to gain more information for the interpretation of these results, structure–activity relationships of 27 anesthetic aliphatic hydrocarbons, ethers, and ketones were studied. Anesthetic and toxicity data for this group of molecules had been measured previously (2), and confidence limits of the experimental values are given. In this group, the polarity of the hydrogens does not vary much, so the effect of this factor on activity is fairly constant. In going to higher congeners of each alkane, ether, and ketone, the anesthetic and toxic activity increases, reaches a maximum, and then decreases. A parabolic relationship was found between the activity and the logarithm of the octanol–water partition coefficient or the molecular weight (3).

This group of compounds is a good example of nonlinear structure–activity relationships and will broaden the study of anesthetic activity. Since there are many measurements beyond the maximum, it can be determined accurately whether the structure–activity relationship is parabolic. Previous work on a series of ethers could not confirm this hypothesis (4).

EXPERIMENTAL

Molecular connectivity indexes were calculated, in the usual manner (1), for the molecules in Tables I and II and statistically analyzed with a system of programs developed to find the best set of variables.

The anesthetic (AD_{100}) and toxic (LD_{50} and LD_{100}) activities of the compounds studied are those of Jeppsson (3). The alkanes, ethers, and ketones were dissolved in an emulsion and administered intravenously to mice. The confidence limits given at $p = 0.05$ for the experimental data were used to compute the experimental standard error. Expressed as log $1/c$, these are values 0.17 for the AD_{100} activity and 0.13 and 0.06 for LD_{100} and LD_{50} activities, respectively.

RESULTS

The statistical analysis shows that ${}^1\chi$ and ${}^4\chi_p{}^v$ are the best connectivity terms to correlate with the AD_{100} anesthetic activity. The following equation was formulated from the data in Table I:

$$\log {}^1/c' = +2.895\ (\pm 0.324) - \frac{8.539\ (\pm 0.875)}{{}^1\chi} - 1.487\ (\pm 0.114){}^4\chi_p{}^v \quad \text{(Eq. 1)}$$

$$r = 0.943 \quad s = 0.170 \quad n = 27$$

$$F = 96.5,\ p < 0.001$$