The Relationship between Anesthetic Potency (Minimum Alveolar Concentration) and Molecular Shape; Structural Studies on Conventional Inhalational Anesthetics

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We have explored the ability of molecular mechanics energy calculation as a probe to obtain quantitative information about the molecular shape and energies of inhalational anesthetics. (Molecular mechanics is a readily accessible, nonquantum mechanical method of computing detailed molecular structure from energetical viewpoint.) From this aspect, the structure-activity relationships of ten inhalational anesthetics were studied. Using this method, stable conformers of these anesthetics are deduced with various physicochemical parameters. The importance of dipole interaction as the major determinant of stable conformation was suggested, and reasonable correlations between anesthetic potency (minimum alveolar concentration: MAC) and components of dipole moments, with reference to the specific sites of molecules, were obtained. The results indicate that there are important polar components which play a major role in anesthesia. (Key words: anesthetics, inhalational, structure-activity relationship, molecular mechanics)

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The study of the mechanism and the action of inhalational anesthesia has been the subject of much discussion. Since the work of Meyer and Overton[1,2], physicochemical properties of general anesthetics, such as oil/water partition coefficients and solubility in lipophilic media, have been emphasized as crucial factors governing their activities. Much of this wrok has been reviewed[1–3]. Physicochemical properties are the result of the structure of the molecules. However, these properties are rather all-inclusive and these property studies did not afford any direct insight into the detailed structural features influencing anesthetic potency. Over the past decades, the concepts of the molecular mechanisms of anesthesia have advanced considerably and the modern approach to the evaluation of bioactive molecules as a function of molecular structure, so-called structure-activity relationships with regard to anesthetics, has also advanced in several aspects[4]. These concepts are well docu-

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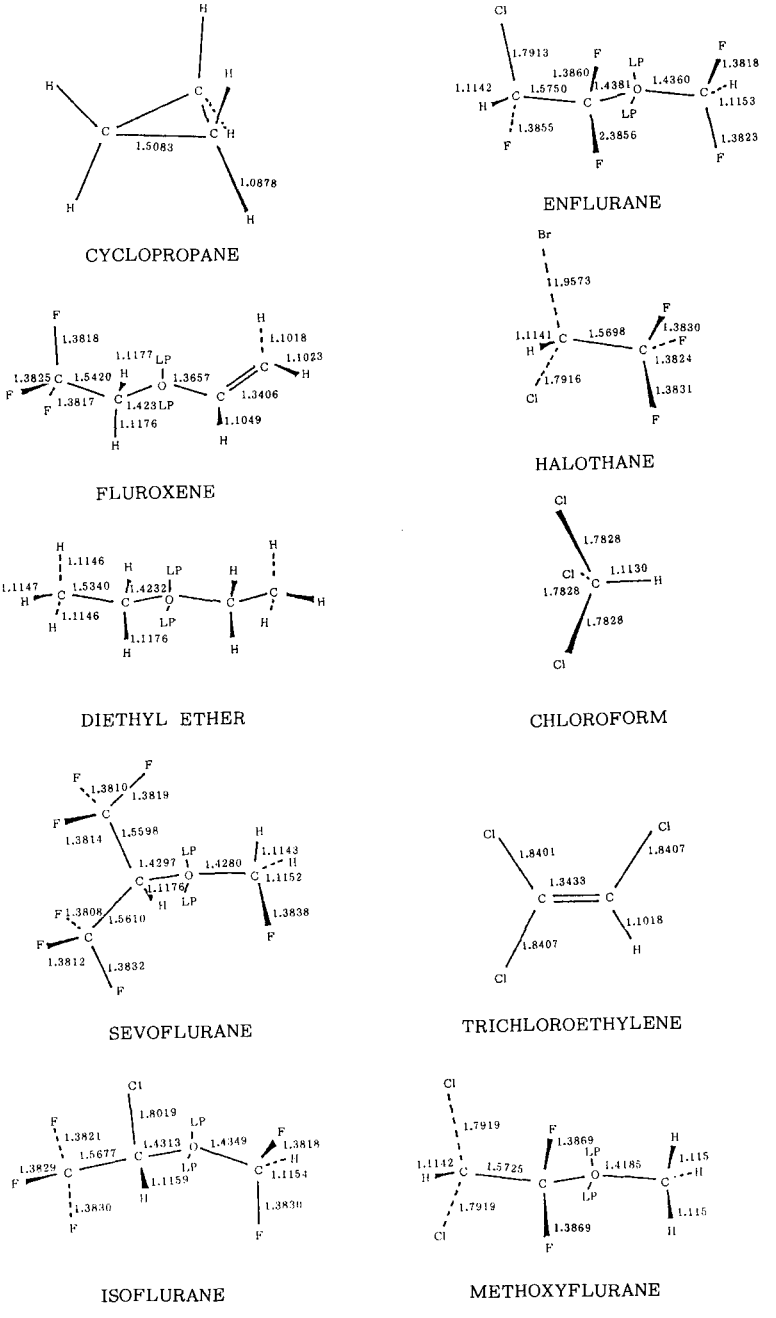

Fig. 1. The most stable conformations for 10 anesthetic compounds with bond lengths.

mented in the literature[5].

Several studies for stereochemical considerations in the mechanism and action of inhalational anesthesia appeared in the literature[6–10]. In an attempt to understand the metabolisms of anesthetics, Lowe et al. calculated the conformational and electronic properties of three anesthetics[7]. The role

of "acidic hydrogen" for the mechanism of anesthesia has been demonstrated by Ruelle and Sandorfy on the basis of quantum chemical calculations[8]. Conformational stability of methoxyflurane by the use of vibrational spectra was discussed by Li and Durig[9].

From a viewpoint of steric or molecular shape parameter in the study of the structure-activity relationship, molecular connectivity studies resulted in a good correlation between potency and the molecular connectivity index and an electronic charge descriptor[10].

To our knowledge, mobile, structural studies of inhalational anesthetics with regard to anesthetic potency have been quite limited. We felt it necessary to carry out a more detailed examination of the conformational properties and related physical descriptors of inhalational anesthetics for the interpretation of the structure-activity relationship.

In order to substantiate structural features of anesthetic molecules and to provide some basic information for the investigation of anesthetic potency and the structure-activity relationship, it seemed to us rational to calculate stereochemical structures and energies. Taking enflurane, $CFHCl\text{-}CF_2\text{-}OCHF_2$ for example, the compound show that it can have many mobile shapes (conformers) as the C-C and C-O bonds are allowed to rotate (fig. 1). Conformations in which large groups are as far apart as possible are ordinarily most stable. In general, rotational arrangement of groups about single bonds sometimes has a profound influence on chemical reactivities and physical properties.

Molecular mechanics is a nonquantum mechanical method of computing molecular structure and energy. Although this method has been documented over the last decades[11,12], it recently became popular with a large number of chemists and pharmacologists. At present, it appears that the most widely distributed program are those of Allinger and they are readily accessible from Quantum Chemical Program Exchange (QCPE).

We feel our effort is worthwhile as it represents the application of a simple, quantitative approach that provides the kind of methodology suited for the structure-activity relationship study of halogenated anesthetics. Several points are subjects of considerable interest. a) Deducing the shape of the molecule which reflects various physical and chemical behaviors and plays an important role in anesthesia, b) Deducing the major contributing factor of potential energy, and c) Inspecting the potency which can be predicted from chemical structure.

It is the purpose of this paper to examine the evidence for the structure-activity relationship in the field of anesthesia. These results could then possibly be used to provide some basic information for the understanding of the mechanism, action and potency of inhalational anesthetics.

Methods and Materials

The following compounds were considered with respect to clinical evaluation in humans: sevoflurane $(CF_3)_2CHOCH_2F$, enflurane $CHFClCF_2OCHF_2$, fluroxene $CF_3\text{-}CH_2OCH = CH_2$, methoxyflurane $CHCl_2\text{-}CF_2OCH_3$, isoflurane $CF_3\text{-}CHClOCHF_2$, diethyl ether $(C_2H_5)_2O$, halothane $CF_3CHBrCl$, trichloroethylene $Cl_2 = CHCl$, chloroform and cyclopropane. Minimum alveolar concentration (MAC)[13,14], a measure of anesthetic potency, is the alveolar concentration of anesthetic at which 50% of patients do not move in response to a skin incision.

Molecular mechanics calculations (MM2)[11] were performed using FACOM M-140F computer (Fujitsu, Tokyo, Japan) to obtain energetically stable geometries and related conformational characteristics. After the energy minimization has been completed, orientation options were applied to reorient the molecule within the indicated coordinate system. At the same time, the components of the dipole moment along the principal axes were also calculated. Optimal geometries derived for possible rotamers of each compound were also considered by the use of dihedral driver option (NDRIVE). The calculated parameters retrieved in such a way were compared with those of stable conformers.

Individual structural parameters, such as

Table 1. Calculated MM2 parameters

ANESTHETICS	MAC*	T.S.**	E_D***	MOMENT OF INERTIA			DIPOLE MOMENT		
				I_X	I_Y	I_Z	μX	μY	μZ
CYCLOPROPANE; $(CH_2)_3$	9.2	4.86	0.00	4.2	4.2	6.7	0.0	0.0	0.0
FLUROXENE; $CF_3CH_2OCH{=}CH_2$	3.4	7.93	3.52	18.3	85.5	86.6	1.5	1.6	1.1
DIETHYL ETHER; $(C_2H_5)_2O$	1.9	5.49	0.00	4.7	38.2	40.7	0.0	1.3	0.0
SEVOFLURANE; $(CF_3)_2CHOCH_2F$	1.71	20.05	14.91	87.4	96.4	145.3	1.0	2.0	0.3
ENFLURANE; $CHFClCF_2OCHF_2$	1.68	33.01	25.13	45.9	115.9	129.2	0.5	0.0	0.7
ISOFLURANE; $CF_3CHClOCHF_2$	1.15	26.43	19.76	54.0	106.0	136.1	1.2	1.3	0.5
HALOTHANE; $CF_3CHBrCl$	0.76	16.59	14.64	47.0	76.7	106.9	0.0	0.1	1.6
CHLOROFORM; $CHCl_3$	0.64	0.00	0.00	26.2	26.2	50.6	0.0	0.0	1.7
TRICHLOROETHYLENE; Cl_2CCHCl	0.23	4.61	3.99	23.8	61.6	85.4	0.1	1.5	0.0
METHOXYFLURANE; $CHCl_2CF_2OCH_3$	0.16	24.07	15.29	48.7	75.2	93.5	1.3	0.0	0.6

Footnote: *MAC: Minimum Alveolar Concentration
**T.S.: Total Steric Energy
***E_D: Dipole Interaction Energy

total steric energies (E), moments of inertia (I), dipole interactions (E_D), dipole moments (μ), stretching energies (Er), bending energies (Eθ), stretch-bending energies (Erθ), van der Waals' energies (EvdW) and torsional energies (E_T) were compared with MAC. To the parameters supplied with the program were added the following constants for ethers.

Stretching: Ks = 0.56, b = 109.5
Torsion:
C-O-C-F
V1 = 0.5, V2 = –0.42, V3 = 0.0
lone pair-O-C-F
V1 = 0.0, V2 = 1.5, V3 = 0.0

The constants above are not the result of an extensive parameterization and should only be considered as crude. For methoxyflurane, most stable conformers are the trans-trans (total steric energy; 24.0659 kcal·mol^{-1}) and gauche-trans (total steric energy; 24.1669 kcal·mol^{-1}) conformers. These results agree in so far as stable forms are deduced by microwave analysis[9]. Detailed parameterization study in this field is now in progress.

The linear multiple regression analysis (Hansch method[15]) was applied to the evaluation of anesthetic potency due to the properties of molecular configurations.

Results

The most stable conformation of each compound deduced from MM2 calculation is shown in figure 1 by molecular maps. The calculated MM2 parameters of various anesthetics are listed in table 1.

The indication to be drawn from the comparison of molecular geometry of ether linkages shown in figure 2 is the presence of a conformational characteristic: each arrangement of C-C-O-C bonds proved to be antiperiplanar (150°–180°) and fairly aligned in the plane. As listed in table 2, the corresponding dihedral angles are remarkably large and ranged from 149.9° to 179.4°. The result coincides with the previous report on methoxyflurane based on vibrational spectral analyses by Durig[9]. It is noteworthy that there is a similar spatial arrangement of the

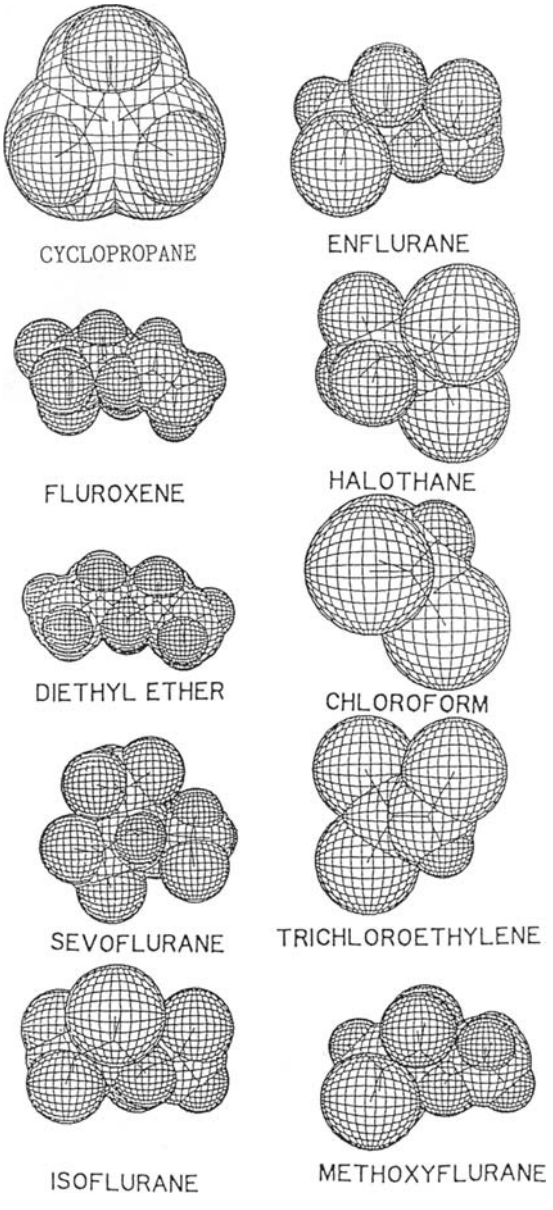

Fig. 2. The most stable conformations for 10 anesthetic compounds, space-filling models.

ether chain for the most stable conformers of anesthetics, which may possibly be related to the activity.

Comparison of the total steric energies and their components are graphed in figure 3. The major contributor of the total steric energy is the dipole interaction. The result suggested a dependence of anesthetic potency on dipole moment, which is the vector sum of individual bond and group moments and is a function of molecular structure. Therefore, it is informative to compare the relative magnitude of the dipole moments among the compounds and their detailed distribution along the indicated axes in the Cartesian coodinates. Thus, we next examined the correlation between MAC and dipole components. The moment of inertia was also considered for the quantitative evaluation of the molecular shape as shown in the table 1. ($Iz \geqq Iy \geqq Ix$).

Table 2. Calculated dihedral angles of ether anesthetics

Anesthetic Agents	C-O-C-C Dihedral Angles
Enflurane	176.6
Isoflurane	149.9
Methoxyflurane	179.3
Sevoflurane	−135.7
	98.9
Fluroxene	173.3
Diethyl Ether	−179.6

From a view point molecular shape, we thought it necessary to orient the molecule in a systematic manner and specify the coodinate axis by the use of orientation options in MM2, through examination of the results obtained from possible orientation of the class of the molecules. The following trends were revealed.

The presence of distinct types of active sites were indicated by the data analyses as follows:

1) Reorienting the molecules so that the oxygen atom is at the origin and rotating to place midpoint between C_2–C_4 in the XY plane (figs. 4,5). A reasonable correlation was obtained between MAC and the component of dipole moment μy with the correlation coefficient of $r = 0.89$ as shown in figure 6 and equation (1).

$$Y = 0.339 + 0.416\ X \qquad (1)$$

2) Reorienting the molecules so that the C_1 or C_2 atom, bearing hydrogen, at the origin

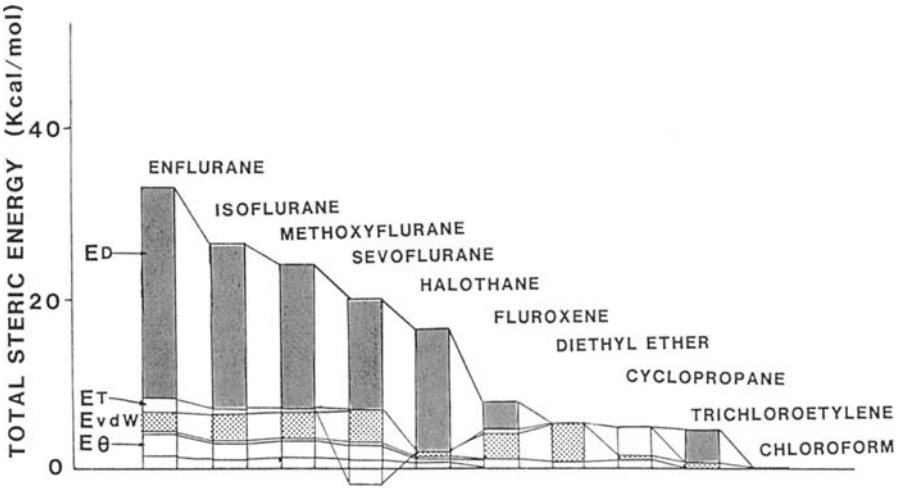

Fig. 3. Total steric energies and their components for minimum energy conformers. (E_D: dipole interactions, E_T: torsional energies, EvdW: van der Waals' energies, $E\theta$: bending energies).

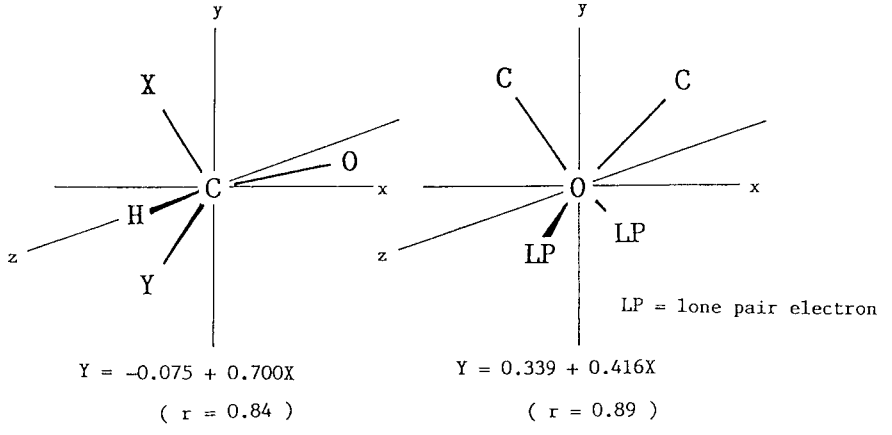

Fig. 4. The right column shows that the oxygen atom is at the origin and rotates to a place midpoint between C_2-C_4 in the XY plane (fig. 5).

The left column shows that the C_1 or C_2 atom, bearing hydrogen, at the origin then rotates the molecule to place C-H bond along Z-axis and places the oxygen atom in plane XY (fig. 7).

then rotates the molecule to place C-H bond along Z-axis and places the oxygen atom in plane XY (figs. 4,7). μyz denotes vector sum of $\mu y + \mu z$, as the square root of the sum of the squares of μy and μz component along each axes. Equation (2) express the correlation between the two sets of values with the correlation coefficient of r = 0.84 (fig. 8).

$$Y = -0.075 + 0.700\ X \qquad (2)$$

Equation (1) and (2) may suggest that particular orientation of the molecule or functional group played an important role in evaluating the action and mechanism of anesthetic potency.

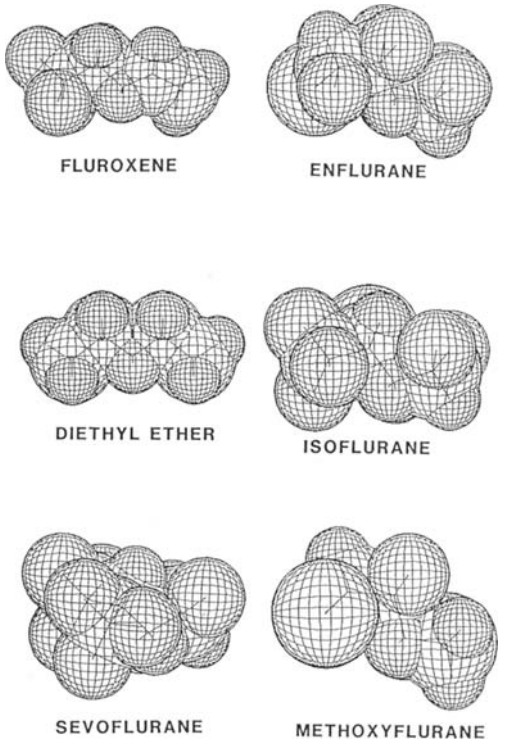

Fig. 5. Reorienting the molecules so that the oxygen atom is at the origin and rotates to a place midpoint between C_2-C_4 in the XY plane.

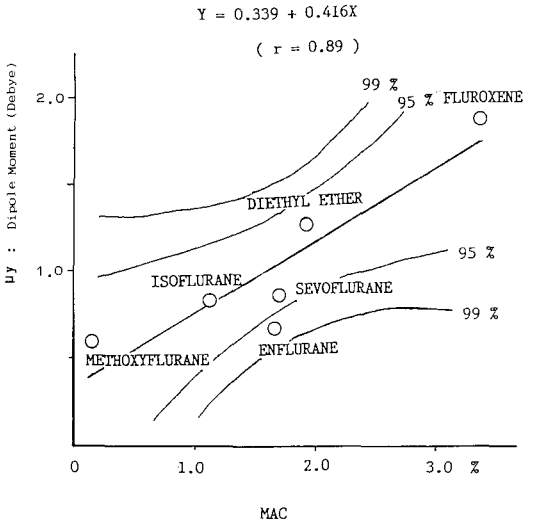

Fig. 6. A reasonable correlation between the anesthetic potency (MAC) and the component of dipole moment μy (r: correlation coefficient, 95% and 99% confidence intervals are shown).

The inclination was followed by Hansch analyses[14] using the same series of descriptors, and the results are consistent with each other. Additional evidence derived from the Hansch method is that there is a remarkable increase in anesthetic potency as the volume of C_4 unit attached to the oxygen in the C_1-C_2-O-C_4 moiety decreases.

The above results demonstrated a dependence of bioactivity on the electric field of the molecule. Components of dipole moment may largely be affected by molecular conformation, especially by the geometry of C-halogen bonds. In order to look into the relationship between structural features and anesthetic potency in more detail, energetic behavior of possible rotamers around C_1-C_2, C_2-C_3, C_3-O and O-C_4 bonds were examined by the use of MM2 optional program, dihedral driver. As a result, when the dihedral angle related to C_1-C_2-O-C_4 was rotated

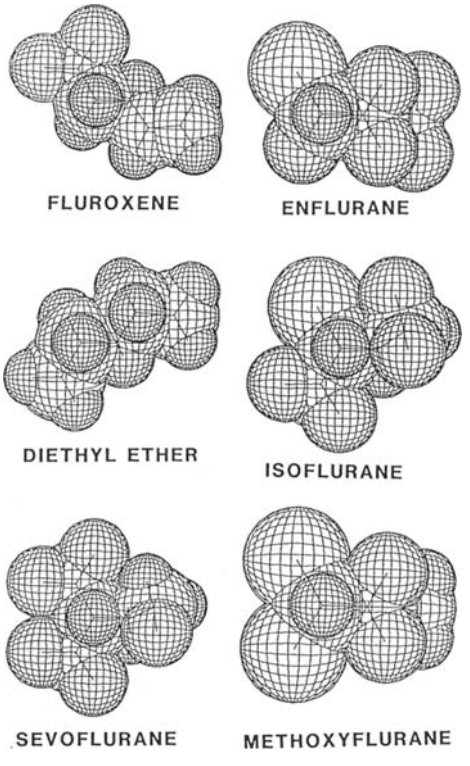

Fig. 7. Reorienting the molecules so that the C_1 or C_2 atom, bearing hydrogen, at the origin then rotates the molecule to a place C-H bond along Z-axis and places the oxygen atom in plane XY.

starting from the most stable conformation, all compounds exhibited a remarkable increase in total steric energies.

Possible rotamers of C_1-C_2 bond and O-C_4 bond were also investigated. The results parallel those of C_2-O rotamers aforementioned.

Therefore, it is suggested that the most stable conformation and corresponding physical parameters can preferentially be considered as an index making it possible to evaluate anesthetic potency.

Discussion

In the series of studies on structure-activity relationships of general inhalational anesthetics, it has been emphasized that anesthetic potency correlates satisfactorily with solubility in lipophilic media and the oil-gas partition coefficient[1-3]. On the other hand, it should be pointed out that the these properties of the molecule, bearing highly electronegative halogens, are greatly affected by its conformation. The steric requirement of the compound is directly related to physical and chemical properties which in turn are the important parameters in the mechanism of anesthetic action.

Previously, Loew calculated the electronic properties of isoflurane, enflurane, methoxyflurane and halogenated hydrocarbons with reference to biodegradation[7,16]. Y.S. Li and J.R. Durig[9] reported detailed conformational studies on methoxyflurane by the use of vibrational spectra. However, the structure-activity relationship has not been discussed. Ruelle[8] pointed out the importance of "acidic hydrogen", on the basis of molecular orbital calculation of halogenated anesthetics. It has been generally agreed that there is no single spatial arrangement of atoms in a molecule which explains anesthetic potency.

In view of these results, we have introduced molecular mechanics calculation for the structural analyses based on potential energy of various inhalational anesthetics which seemed to provide sufficient information with regard to stable structure and physical properties.

Table 3. Dipole moments (Debye)

Compound	MM2	CNDO/S	Observed
$CHCl_3$	1.706	0.425	1.20
Et-O-Et	1.293	1.639	1.16
CHF_3	1.844	1.554	1.64
TCE	1.507	2.376	0.90

While the molecular mechanics calculations have been highly successful for hydrocarbons and related compounds, rather little has been studied on compounds containing ethers[17] and halogens[18]. In order to examine the reliability of the program toward the evaluation of a physical constant, dipole moment has been considered. Dipole moment calculations on $CHCl_3$, diethyl ether, $CClF_3$ and trichloroethylene are in reasonable agreement with the reported values. Table 3 compares calculated and experimental values. Most available data are reproduced with a demonstrable accuracy that was achieved by experimental methods.

Calculations on methoxyflurane are of interest. Comparison of the results with that of vibrational analyses reported by Y.S. Li and J.R. Durig[9] showed that the results agree in part so far as the trans-trans conformer corresponds to large dihedral angles as cited in table 2 and the gauche-trans conformer is predicted for the most stable conformation.

The role of the structural feature is indicated as follows;

1) As the result of the molecular mechanics calculation of halogenated inhalational anesthetics, the major component of steric energy is the dipole interaction.

2) In a series of halogenated alkyl ethers, reasonable correlations were obtained between anesthetic potency (MAC) and the specified components of dipole moments based on the use of partial reference to substructure.

3) It was showed in a series of ether compounds that planar C-C-O-C conformers proved to be the most stable. When the bond, either C-O or C-C, was rotated starting from the planar conformation, all compounds showed a remarkable increase in

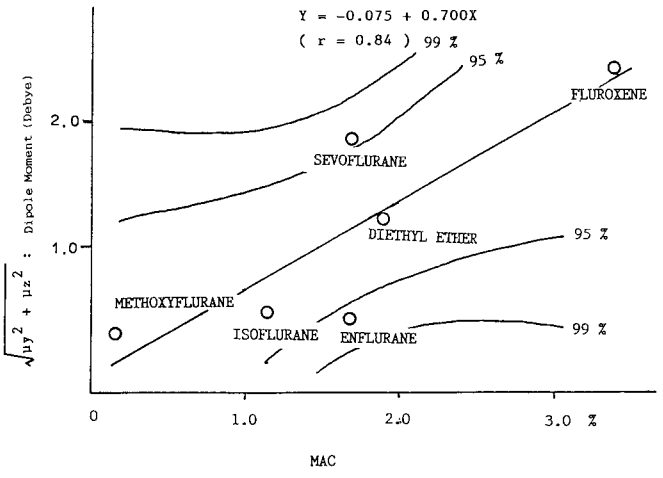

Fig. 8. A correlation between MAC and the μyz, which denotes vector sum of $\mu y + \mu z$, as the square root of the sum of the squares of μy and μz component along each axis (r: correlation coefficient, 95% and 99% confidence intervals are shown).

total steric energies.

From the facts described above, the following points can be reasoned:

1) As for particular parameters of the structure, it has been suggested that the molecular mechanics calculation may be used for evaluating the potency of inhalational anesthetics.

2) With this simple approach based on structural analysis, other classes of molecules of equal interest in anesthesia may be treated, and physiological properties such as metabolism, myocardial suppression, visceral toxicity, teratogenicity, may be discussed.

3) Our results clearly indicate that the presence of polar structural sites play a major role in anesthesia.

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References

1. Overton E: Studien under die Narkose zugleich ein Beitrag zur allgemeinen Pharmakologie. Jena: Verlag von Gustav Fischer. 1901
2. Meyer H: Welche Eigenschaft der Anaesthetica bedingt ihre narkotische Wirkung? Naunyn-Schmiedebergs Arch. Exp Pathol Pharmakol 42:109–118, 1899
3. Targ AG, Yasuda N, Eger EI II, Huang G, Vernice GG, Terrell RC, Koblin DD: Halogenation and anesthetic potency. Anesth Analg 68:599–602, 1989
4. Halsey MJ: A reassessment of the molecular structure-functional relationships of the inhaled general anesthetics. Br J Anaesth 56:9s–25s, 1984
5. Osawa E, Musso H: Molecular mechanics calculations in organic chemistry: Examples of the usefulness of this simple nonquantum mechanical model. Angev Chem 22:1–68, 1983
6. Hellberg S, Wold S, Dunn WJ III, Gasteiger J, Hutchings MG: The anesthetic activity and toxicity of halogenated ethyl methyl ethers, a multivariate QSAR modelled by PLS. Quant Struct-Act Relat 4:1–11, 1985
7. Loew G, Motulsky H, Trudell J, Cohen E, Hjelmeland L: Quantum chemical studies of the metabolism of the inhalation anesthetics methoxyflurane, enflurane, and isoflurane. Mol Pharmacol 10:406–418, 1974
8. Ruelle P, Sandorfy C: Electrostatic potential around halogenated anesthetics. Acidic hydrogen; chlorine vs. fluorine. Inter J Quant Chem 21:691–707, 1982
9. Li YS, Durig JR: Microwave, infrared and Raman spectra, conformational stability and vibrational assignment of methoxyflurane. J Mol Struc 81:181–194, 1982
10. Di Paolo T, Kier LB, Hall LH: Molecular connectivity and structure-activity relationship of general anesthetics. Mol Pharmacol 13:31–37, 1977
11. Allinger NL: Conformational analysis. 130. MM2. a hydrocarbon force field utilizing V_1 and V_2 torsional terms. J Am Chem Soc

99:8127–8134, 1977
12. Burkert U, Allinger NL: Molecular mechanics. Washington, D.C.: American Chemical Society. 1982
13. Katoh T, Ikeda K: The minimum alveolar concentration (MAC) of sevoflurane in humans. Anesthesiology 66:301–303, 1987
14. Sanjo Y, Ikeda K: A small bypass mixing chamber for monitoring metabolic rate and anesthetic uptake: The bymixer. J Clinic Monitor 4:235–243, 1987
15. Hansch C, Fujita T: ρ-σ-π Analysis. A method for the correlation by biological activity and chemical structure. J Am Chem Soc 86:1616–1626, 1964
16. Goldblum A, Loew GH: Quantum chemical studies of anaerobic reductive metabolism of halothane by cytochrome p-450. Chem Biol interactions 32:83–99, 1980
17. Allinger NL, Chang SHM, Glaser DH, Honig H: An improved molecular mechanics force field for alcohols and ethers. Israel J Chem 20:51–56, 1980
18. Meyer AY: Molecular mechanics of organic halides. part 6. Modified Del Re electrostatics and the force field. J chem Soc Perkin Trans 2:1199–1204, 1982