

Adsorption of Inhalational Anesthetics and Hydrochlorofluorocarbons on Activated Carbons as a Biological Model

Seiki TANADA,*^a Naohito KAWASAKI,^a Takeo NAKAMURA,^a and Ikuo ABE^b

Faculty of Pharmaceutical Sciences, Kinki University,^a Kowakae, Higashi-Osaka, Osaka 577, Japan and Osaka Municipal Technical Research Institute,^b Morinomiya, Joto-ku, Osaka 536, Japan.

Received August 26, 1996; accepted November 5, 1996

Chlorofluorocarbon (CFC) replacements have recently been used for their lower stability and because they have carbon-hydrogen bonds, which means that their atmospheric lifetime is expected to be much shorter than those of CFCs. The adsorption properties of 1,1,2-trichloro-1,2,2-trifluoroethane (CFC113) and its replacement compounds, 1,1-dichloro-2,2,2-trifluoroethane (HCFC123), 1,1-dichloro-1-fluoroethane (HCFC141b), and 1,1-dichloro-1,2,2,3,3-pentafluoropropane (HCFC225ca) on four kinds of activated carbons were investigated. The amount of CFC and HCFCs adsorbed on the activated carbon was concluded to depend upon the number of chloride and carbon atoms in their molecules. The adsorption isotherms of inhalational anesthetics (halothane, chloroform, enflurane, isoflurane, and methoxyflurane) on the activated carbon were measured to evaluate the action mechanism of inhalational anesthesia. The adsorption isotherms of CFC, HCFC, and the inhalational anesthetics were fitted to the Freundlich equation. The Freundlich constant N was well correlated with the minimum alveolar concentration (MAC) of the inhalational anesthetic: 1 MAC means that 50% of the patients will not move during a surgical operation. The adsorption mechanism of inhalational anesthetics on the surface of the activated carbon is concluded to be similar to the adsorption mechanism on a nerve cell. The anesthesia of CFC replacements can be estimated by the Freundlich constant N of the adsorption isotherms.

Key words inhalational anesthetic; adsorption; biological model; CFC; HCFC; activated carbon

Chlorofluorocarbons (CFCs) have an ozone depletion and global warming effect. Because hydrochlorofluorocarbons (HCFCs) and hydrofluorocarbons (HFCs) contain one or more hydrogen atoms in a molecule, HCFCs and HFCs are susceptible to attack by hydroxide radicals in the troposphere. Although HCFCs are much less destructive to the ozone layer than CFCs, they do carry some chloride atoms into the stratosphere and are classified as transitional compounds to be banned in 2030 after a gradual phase-out. We have reported the recovery and/or decomposition of CFC and CFC replacements by the surface-modified activated carbons.^{1–3)} The structure of HCFCs is very similar to that of several inhalational anesthetics; therefore, the HCFCs may have an anesthetic effect.

Activated carbon has been applied to artificial livers, in treatment for drug poisoning, and complex formation with anticancer drugs to be deposited into malignant tissues for prolonged release. We reported that the adsorption of local anesthetics on the surface of activated carbon was analyzed for its correlation with local anesthetic potency.⁴⁾ The oil-water partition coefficient has been shown to correlate with the clinical potency of various drugs^{5–12)} and has been used for quantitative structure-activity relationships (QSAR). The physicochemical theories¹³⁾ for the action of anesthesia are the lipid theory, the membrane transport and adsorption theory, the formation of a gas hydrate theory, and the release phenomenon theory. Most of these are based on the adsorption/absorption of drugs on a nerve cell.

Because the surface of the activated carbon is hydrophobic, the adsorption of inhalational anesthetics on activated carbon may correlate with the anesthetic action of these anesthetics. The adsorption of activated carbon often follows the Freundlich adsorption isotherms, in

which the logarithm of the amount adsorbed bears a linear relationship to the logarithm of the free adsorbent concentrations. The reciprocal of the slope ($1/N$) of the Freundlich adsorption isotherm¹⁴⁾ measures the interaction between the activated carbon and the adsorbates, while the intercept (k) denotes both the interaction and the amount adsorbed. In this present study, the adsorption mechanism of CFC and HCFC on activated carbon in the liquid phase and the relationships between the Freundlich constant N and the minimum alveolar concentration (MAC) of the anesthetics were examined in order to evaluate the anesthetic activity of the HCFCs and to use activated carbon as a biological model.

Materials and Methods

Materials The four activated carbons used as adsorbents in this paper were DS-Z-100 prepared from coconut shell (AC-1), CAL (Calgon, Pittsburgh, PA) prepared from coal (AC-2), Diahope 006 (Mitsubishi Chemical Ind., Ltd.) prepared from coal shell (AC-3), and SA prepared from charcoal treated with zinc chloride (AC-4). Activated carbons were dried in a vacuum for 3 h at 110 °C. 1,1,2-Trichloro-1,2,2-trifluoroethane (CFC113) and its replacement compounds, 1,1-dichloro-1-fluoroethane (HCFC141b), 1,1-dichloro-2,2,2-trifluoroethane (HCFC123), and 1,1-dichloro-1,2,2,3,3-pentafluoropropane (HCFC-225ca) standard solutions were used and diluted with methanol and distilled water. 2-Bromo-2-chloro-1,1,1-trifluoroethane (halothane), trichloromethane (chloroform), 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether (enflurane), 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether (isoflurane), and 2,2-dichloro-1,1-difluoromethyl methyl ether (methoxyflurane) were used as the inhalational anesthetics. The nitrogen isotherms were determined volumetrically at liquid nitrogen temperature with a Sorptomatic series 1800 (Carlo Erba Co., Ltd.). The specific surface area (S) and the pore volume (V) of the B.E.T. equation¹⁵⁾ and Cranston-Inkley method¹⁶⁾ were calculated from the nitrogen adsorption isotherms on the activated carbons. The mean pore diameter (D) of the activated carbons was calculated as $4V/S$.

Adsorption Isotherms of CFC, HCFC, and Inhalational Anesthetics The amounts of adsorbed CFC, HCFCs, and inhalational anesthetics were measured by the headspace method. The amount adsorbed was

* To whom correspondence should be addressed.

measured in a Hitachi 263-30 gas chromatograph equipped with a Hitachi electron capture ionization detector and a Hitachi D-2000 chromatointegrator (Hitachi Ltd., Tokyo, Japan). Operating conditions were: glass column, 300-cm 3.0-mm packed with 20% Silicon DC-550 Uniport HP 60:80 mesh (GL Sciences Inc., Tokyo, Japan); carrier gas, nitrogen; column oven, 70 °C; injection temperature, 250 °C; injection volume, 5 μ l. The calibration curve for the CFC, HCFCs, and inhalational anesthetics was found to be linear in the range of approximately 1500 μ g/l. Adsorption was measured by adding various quantities of each activated carbon to the 70-ml alumi-seal vials. A 40 ml aliquot of the solution of known solute concentration was added to the alumi-seal vials, and the vials were tightly capped with a Teflon seal, butyl gum septa, and an alumi-seal by hand crimper and shaken in the water bath maintained at 15 or 25 °C. The amount adsorbed on the activated carbons at equilibrium was calculated by equation $X = (C_0 - C) \cdot V/M$ where X is the amount adsorbed per unit gram of activated carbon (mg/g), C_0 is the initial concentration of the adsorbate (mg/g), C is the equilibrium concentration of the adsorbate (mg/g), V is the solvent quantity (ml), and M is the weight of the activated carbon (mg).

Results and Discussion

Specific Surface Area, Pore Volume, and Mean Pore Diameter of Activated Carbons The specific surface area, the pore volume, and the mean pore diameter of the activated carbons are shown in Table 1. The specific surface area increases in the order AC-2, AC-3, AC-1, and AC-4, while the pore volume increases in the order AC-2, AC-1, AC-3, and AC-4. The larger the specific surface area and pore volume of the activated carbon, the larger the amount of organic compounds adsorbed, because the organic compounds are adsorbed in the pores. The specific surface area, the pore volume, and the mean pore diameter of AC-4 were the largest. This result indicated that the zinc chloride treatment affects the structure of the activated carbon.

Adsorption Isotherms of CFC and HCFCs on Activated Carbon HCFCs have been developed as substitutes for CFCs. Their hydrophilicity is greater than that of CFCs because they contain a hydrogen atom in molecule. It is assumed that the use of HCFCs will cause a serious problem of groundwater pollution; those which have an anesthetic effect must therefore be recovered and/or removed from the atmosphere or tap water. The adsorption isotherms of CFC and HCFCs on an activated carbon in the liquid phase were measured; the isotherms of CFC113 at 25 °C and HCFC141b at 15 °C on four kinds of activated carbons are shown in Figs. 1 and 2, respectively. The amount of CFC113 and HCFC141b adsorbed increased in the order AC-4, AC-3 or AC-2, and AC-1, and the amount adsorbed on the activated carbon decreased with increasing mean pore diameter. This result indicates that CFC and HCFCs are adsorbed in the micropores. The adsorption isotherms of the CFC and HCFCs on AC-3 at 15 °C are shown in Fig. 3; the amount

of HCFC225ca adsorbed on was the largest, which the amounts of HCFC141b and HCFC123 adsorbed were the same. The amount of CFC and HCFCs adsorbed on the activated carbons will depend upon the atom species in their molecules. The adsorption mechanism on the activated carbon was determined by calculating the Freundlich constants N and k to apply the Freundlich equation. The B.E.T. equation and the Freundlich equation represent multilayer and monolayer models, respectively; former can be applied to the adsorption isotherm on non porous adsorbents, and the latter to the

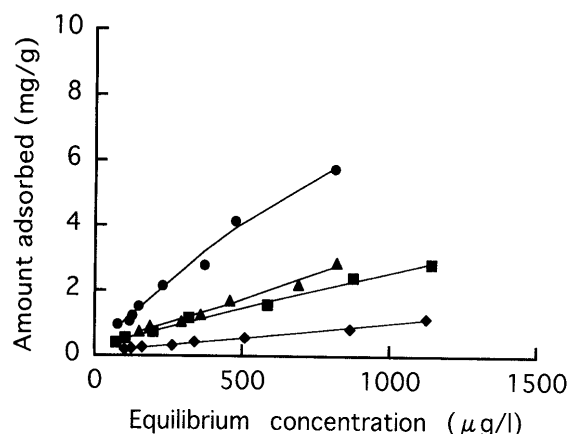


Fig. 1. Adsorption Isotherms of CFC113 on AC-1—AC-4 at 25 °C
●, AC-1; ■, AC-2; ▲, AC-3; ◆, AC-4.

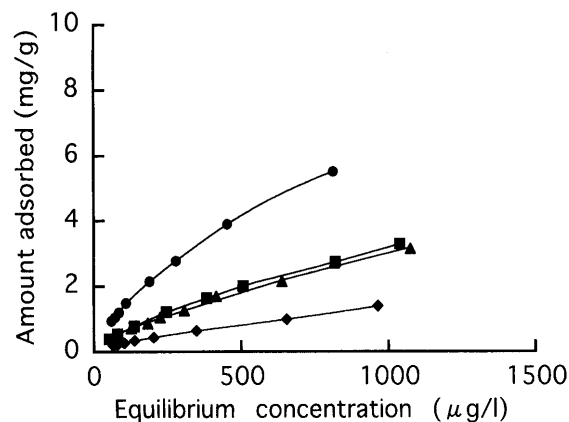


Fig. 2. Adsorption Isotherms of HCFC141b on AC-1—AC-4 at 15 °C
●, AC-1; ■, AC-2; ▲, AC-3; ◆, AC-4.

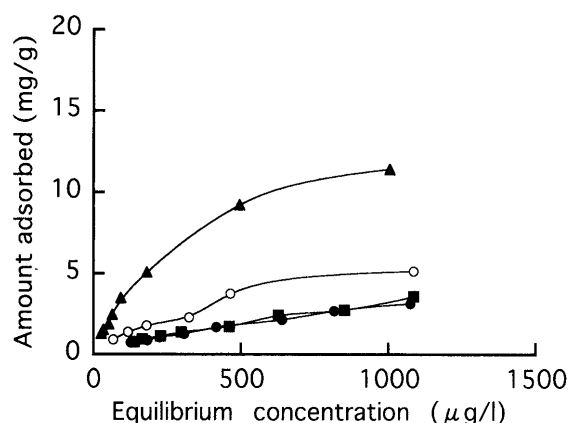


Fig. 3. Adsorption Isotherms of CFC and HCFCs on AC-3 at 15 °C
○, CFC113; ●, HCFC141b; ■, HCFC123; ▲, HCFC225ca.

Table 1. Physical Properties of Activated Carbons

Activated carbon	Specific surface area (m ² /g)	Pore volume (ml/g)	Mean pore diameter (nm)
AC-1	1359	0.344	1.01
AC-2	790	0.276	1.40
AC-3	1068	0.379	1.42
AC-4	1370	1.033	3.02

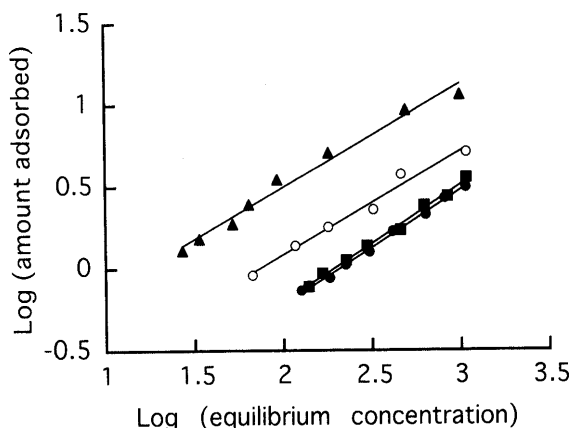


Fig. 4. Freundlich Plot of CFC and HCFCs on AC-3 at 15°C
○, CFC113; ●, HCFC141b; ■, HCFC123; ▲, HCFC225ca.

Table 2. Freundlich Constant N and k of CFC113 and HCFC141b

Refrigerant number	Freundlich constant		r	
	N	k		
CFC113	AC-1	1.240	0.026	0.991
	AC-2	1.440	0.023	0.986
	AC-3	1.310	0.015	0.985
	AC-4	1.397	0.007	0.993
HCFC141b	AC-1	1.468	0.059	0.999
	AC-2	1.421	0.025	1.000
	AC-3	1.420	0.023	0.998
	AC-4	1.372	0.009	0.999

Table 3. Freundlich Constant N and k of CFC and HCFCs onto AC-3

Refrigerant number	Freundlich constant		r
	N	k	
CFC113	1.582	0.066	0.990
HCFC141b	1.420	0.023	0.998
HCFC123	1.395	0.023	0.997
HCFC225ca	1.591	0.174	0.991

adsorption isotherm on porous adsorbents. The adsorption isotherms of CFC and HCFCs on the activated carbon in the liquid phase were fitted to the Freundlich equation.

Freundlich Plot of Adsorption Isotherms of CFC and HCFCs Their are physical adsorption and chemical adsorption mechanisms. The adsorption of organic compounds on activated carbon is physical adsorption, because the amount of CFC113 adsorbed on AC-3 at 25°C was smaller than that at 15°C. The Freundlich plots of CFC and HCFCs on AC-3 are shown in Fig. 4. The reciprocal of the slope ($1/N$) of the Freundlich plot indicates the interaction between the surface of the activated carbon and the adsorbates, while the intercept (k) indicates both the interaction and the amount adsorbed.¹⁶⁾ The correlation coefficient and the constants N and k of the Freundlich plot of CFC113 at 25°C and HCFC141b at 15°C are shown in Table 2. That of CFC and HCFCs on AC-3 at 15°C is shown in Table 3. The Freundlich plots of CFC and HCFCs on AC-3 were a straight line. The Freundlich constants N and k of CFC113

and HCFC141b, except for the adsorption of CFC113 on AC-3, decreased with increasing mean pore diameter. The constant N of CFC113 on AC-3 at 15°C is larger than that at 25°C. This indicates that the interaction between the CFC113 and the surface of the activated carbon increases at lower temperature because the molecular kinetics decreases with decreasing temperature.

The constant k was not correlated to the specific surface area or the pore volume of activated carbons but to the mean pore diameter. The surface of the activated carbon is hydrophobic and the adsorption of organic compounds on the activated carbon is mainly due to van der Waals forces and the dispersion force. The dispersion force increases with decreasing intermolecular distance. The smaller the mean pore diameter, the shorter is the distance between the pore surface and the adsorbent molecule. As a result of the adsorption force increasing with decreasing distance, the amount of CFC and HCFCs adsorbed on activated carbon increases. The constant k is believed to depend upon the kinds of atoms in the molecule because indicates both the interaction and the amount adsorbed. The correlation between the number of each atom and the Freundlich constant k was elucidated. The Freundlich constant k was tabulated by Eqs. 1 and 2:

$$\log k = 0.88(N_C) + 0.46(N_{Cl}) + 0.030(N_H) - 4.3 \quad (1)$$

$$\log k = 0.89(N_C) + 0.46(N_{Cl}) + 0.030(N_F) - 4.3 \quad (2)$$

where N_C is the number of carbon atoms, N_{Cl} is the number of chlorine atoms, N_H is the number of hydrogen atoms, and N_F is the fluorine atoms. The coefficient of N_F and N_H was lower than that of N_C and N_{Cl} . The numbers of hydrogen and fluorine atoms do not affect the amount adsorbed on the activated carbon. The constant k is consequently indicated by Eq. 3:

$$\log k = 0.88(N_C) + 0.46(N_{Cl}) - 4.3 \quad (3)$$

($n=4$, $r=0.999$, $S=0.004$)

The coefficient of N_C was twice that of N_{Cl} . The amount adsorbed on the activated carbon depended upon the number of carbon atoms in the molecule. Hence, the amount of HCFC123 and HCFC141b adsorbed on the activated carbon was less than that of CFC113 because of the decreasing number of chlorine atoms. The amount of HCFC225ca adsorbed on the activated carbon increased with the number of carbon atoms.

Adsorption Isotherms of Inhalation Anesthetics on Activated Carbon The adsorption isotherms of the inhalational anesthetics on AC-3 at 15°C are shown in Fig. 5. Methoxyflurane was adsorbed in the largest amount because its saturated vapor pressure was the lowest. The amounts of enflurane and isoflurane adsorbed on AC-3 were the same because they are structural isomers. The adsorption isotherms of inhalational anesthetics on activated carbon in the liquid phase can be fitted to the Freundlich equation. The Freundlich plot of the adsorption isotherms of inhalational anesthetics on AC-3 is shown in Fig. 6. The correlation coefficient and the constants N and k of this plot are shown in Table 4. The Freundlich plot for inhalational anesthetics was a straight line. The constants N of enflurane and isoflurane

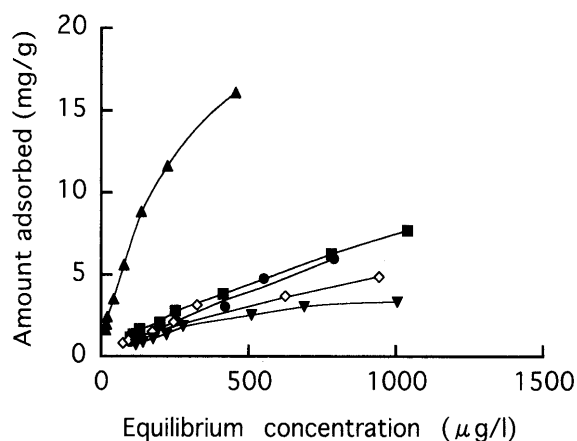


Fig. 5. Adsorption Isotherms of Inhalational Anesthetics on AC-3 at 15°C

●, enflurane; ■, isoflurane; ◆, halothane; ▲, methoxyflurane; ▼, chloroform.

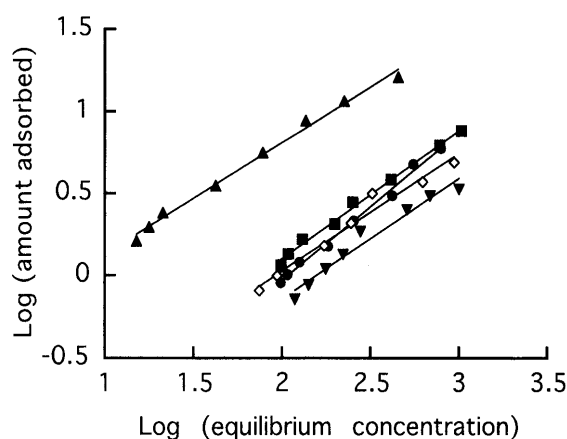


Fig. 6. Freundlich Plot of Inhalational Anesthetics on AC-3 at 15°C

●, enflurane; ■, isoflurane; ◆, halothane; ▲, methoxyflurane; ▼, chloroform.

Table 4. Freundlich Constant N and k of Inhalational Anesthetics onto AC-3

Adsorbate	Freundlich constant		r
	N	k	
Halothane	1.406	0.040	0.985
Chloroform	1.360	0.024	0.982
Enflurane	1.109	0.015	0.996
Isoflurane	1.277	0.034	0.997
Methoxyflurane	1.472	0.282	0.996

were larger than those of halothane, chloroform, and methoxyflurane. Enflurane, isoflurane, and methoxyflurane contain an ether group in the molecule, while halothane and chloroform are halogenated hydrocarbons. The interaction between the inhalational anesthetics and the surface of the activated carbon was larger in the order: enflurane or isoflurane, which contained an ether group in their molecule; chloroform or halothane, which did not contain an ether group but had five fluoride atoms in their molecules; and methoxyflurane, which contained an ether group and four hydrogen atoms in the molecule. In spite of the fact that the amount of enflurane and isoflurane adsorbed on AC-3 was the same, their Freundlich constant k was different. Thus, the interaction between the

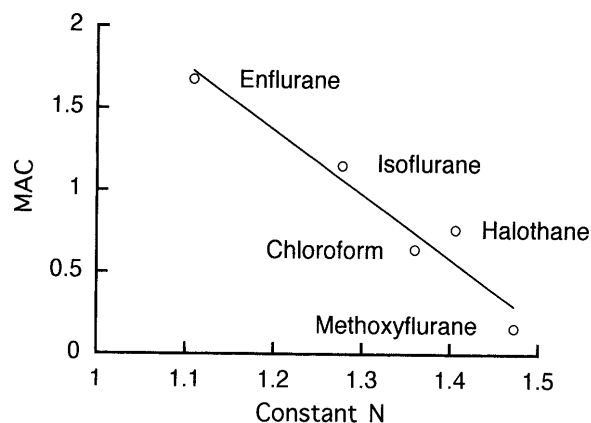


Fig. 7. Relationship between the Freundlich Constant N and the MAC of Inhalational Anesthetics

isoflurane and the surface of the activated carbon is larger than that between the enflurane and the activated carbon.

Relationship between MAC and Freundlich Plot Constant N It is assumed that the activated carbon has been used for QSAR because the structure of activated carbon is very complicated and the numbers of adsorption sites for inhalational anesthetics on activated carbon correspond to the number of protein receptors in the membranes. The mechanism of action of the inhalational anesthetics in humans is not clear.

The MAC is based on the anesthetic potential. The MAC s of halothane, chloroform, enflurane, isoflurane, and methoxyflurane are 0.75, 0.64, 1.68, 1.15, and 0.16, respectively.^{17,18)} Basically, the action mechanism of inhalational anesthetics is both adsorption on nerve cell membrane and absorption in the cell membrane. The adsorption mechanism of inhalational anesthetics on activated carbon also was both adsorption on the surface of the activated carbon and condensation (absorption) in the pores. The anesthetic potential is thought to be correlated to the adsorption affinity on the activated carbon. The MAC versus constant N is shown in Fig. 7. The MAC was correlated to the Freundlich constant N , because the latter indicates the interaction between the surface of the activated carbon and the inhalational anesthetic. The greater the hydrophobicity of the drug, the greater the affinity of the drug for the cell membrane. The inhalational anesthetic molecule is first adsorbed on the adsorption site of the activated carbon surface like the surface of a nerve cell. The molecules then form a gas hydrate in the pores of the activated carbon like the cell membrane, and these are absorbed in the pores like the cell membrane. The surface of a nerve cell and the cell membrane are like the surface and the porosity structure of the activated carbon, respectively. The activated carbon can thus be utilized as a biological model for anesthetic potency.

References and Notes

- 1) Kawasaki N., Tanada S., Nakamura T., Abe I., *J. Colloid Interface Sci.*, **72**, 368—373 (1995).
- 2) Tanada S., Kawasaki N., Nakamura T., Abe I., *Chem. Lett.*, **1995**, 143—144.
- 3) Tanada S., Kawasaki N., Nakamura T., Abe I., *J. Colloid Interface Sci.*, **77**, 329—334 (1996).

- 4) Abe I., Kamaya H., Ueda I., *J. Colloid Interface Sci.*, **77**, 166—168 (1988).
- 5) Meyer K. H., Hemmi H., *Biochem. Z.*, **277**, 39—71(1935).
- 6) Leo A., Hansch C., Elkins D., *Chem. Rev.*, **71**, 525—616 (1971).
- 7) Fujita T., Iwasa J., Hansch C., *J. Am. Chem. Soc.*, **86**, 5175—5180 (1964).
- 8) Hansch C., Clayton J. M., *J. Pharm. Sci.*, **62**, 1—21 (1973).
- 9) Ostrenga J. A., *J. Med. Chem.*, **12**, 349—352 (1969).
- 10) McFarland J. W., *J. Med. Chem.*, **13**, 1192—1196 (1970).
- 11) Nys G. G., Rekker R. F., *Eur. J. Med. Chem.*, **9**, 361—375 (1974).
- 12) Kier L. B., O'Brien R. D., *J. Pharm. Sci.*, **64**, 1971—1974 (1974).
- 13) Hagita K., Yoneda Y., *Yakkyoku*, **39**(10), 11—19 (1988).
- 14) Freundlich H., "Colloid and Capillary Chemistry," Methuen, London, 1926.
- 15) Brunauer S., Emmett P. H., Teller E., *J. Am. Chem. Soc.*, **60**, 309—319 (1938).
- 16) Cranston R. W., Inkley F. A., *Adv. Catalysis*, **9**, 143—154 (1957).
- 17) Eger E. I., *Anesthesiology*, **26**, 756—763 (1965).
- 18) Stevens W. C., Dolan W. M., Gibbons R. T., *Anesthesiology*, **42**, 187—200 (1975).