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International Journal of Pharmaceutics 202 (2000) 41–45

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Relationship between potency and boiling point of general anesthetics: a thermodynamic consideration

Siavoush Dastmalchi [a,*], Mohammad Barzegar-Jalali [b]

[a] *Faculty of Pharmacy, The University of Sydney, Sydney, NSW 2006, Australia*
[b] *School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*

Received 30 June 1999; received in revised form 3 March 2000; accepted 21 March 2000

Abstract

The most important group of nonspecific drugs is that of the general anesthetics. These nonspecific compounds vary greatly in structure, from noble gases such as Ar or Xe to complex steroids. Since the development of clinical anesthesia over a century ago, there has been a vast amount of research and speculation concerning the mechanism of action of general anesthetics. Despite these efforts, the exact mechanism remains unknown. Many theories of narcosis do not explain how unconsciousness is produced at a molecular level, but instead relate some physicochemical property of anesthetic agents to their anesthetic potencies. In this paper, we address some of those physicochemical properties, with more emphasis on correlating the anesthetic potency of volatile anesthetics to their boiling points based on thermodynamic principles.

Keywords: Volatile anesthetics; Boiling point; Anesthetic potencies; Thermodynamics; Ferguson principle

The volatile anesthetics are the most important group of nonspecific drugs. Their structures vary from the noble gases such as Ar to the volatile halogenated liquids. As they are not sharing a common three-dimensional structural feature, correlations have been sought between biological potency and the physicochemical properties of these agents. Lipid solubility (Eger et al., 1969), partition coefficient (Eger et al., 1965; Hansch, 1975), molar refraction, polarizability (Pauling, 1961), van der waals *a* and *b* constants, interfacial activity (Clements and Wilson, 1962) and molal volume (Wulf and Featherstone, 1957; Koski et al., 1973) are among the physicochemical properties that have been used to evaluate the potency of volatile anesthetics. Potency of the volatile anesthetics has also been correlated to the boiling point of these compounds (Bindal et al., 1980; Katritzky and Gordeeva, 1993).

In Figs. 1–3, the natural logarithms of the isonarcotic pressure ($\ln P_{an}$) for different anesthetics are plotted against the boiling points of these agents (see Table 1 for P_{an} and boiling point values). It can be deduced from the plots that compounds with higher boiling points produce

* Corresponding author. Tel.: +61-2-93514698; fax: +61-2-93514391.
E-mail address: siavoush@pharm.usyd.edu.au (S. Dastmalchi).

0378-5173/00/$ - see front matter
PII: S0378-5173(00)00425-7

the same degree of depression at lower pressure in a given system. This observation has already been evaluated thermodynamically (Cammarata, 1975).

In the present study, we re-examine the existing empirical relationship between the potency of the volatile anesthetics and their boiling points based on classical thermodynamic equations.

The variation of the vapor pressure with temperature is governed by the well-established Clausius–Clapeyron equations, which can be written in two forms:

$$\frac{\partial \ln P}{\partial T} = \frac{\Delta H_v}{RT^2} \quad (1)$$

$$\frac{\partial \ln P}{\partial T} = \frac{\Delta S_v}{RT} \quad (2)$$

where P is the partial pressure of the gas at the absolute temperature, T, R is the gas constant, and ΔH_v and ΔS_v are enthalpy and entropy of vaporization, respectively. Eq. (1) can be rearranged and integrated between specified limits:

$$\int_{P_A}^{P} \partial \ln P = \left(\frac{\Delta H_v}{R}\right) \int_{T_{bp}}^{T_B} T^{-2}\, \partial T \quad (3)$$

$$\ln P = \ln P_A - \frac{\Delta H_v}{RT_B} + \frac{\Delta H_v}{RT_{bp}} \quad (4)$$

where P is the vapor pressure of pure liquid at human body temperature, T_B (310 K). P_A is the partial pressure of the vapor phase at boiling point, T_{bp}, which in fact is equal to atmospheric pressure. By dividing the numerator and denominator of the second and third terms at the right-hand side of Eq. (4) by T_{bp}, and having $\Delta H_v/T_{bp}$ equal to ΔS_v, Eq. (5) can be drawn.

$$\ln P = \ln P_A - \left(\frac{\Delta S_v}{RT_B}\right) T_{bp} + \frac{\Delta S_v}{R} \quad (5)$$

According to the Ferguson (1939) principle, the thermodynamic activity of the anesthetic agents, α, can be expressed as:

$$\ln P = \ln P_{an} - \ln \alpha \quad (6)$$

where P_{an} is the pressure required to produce a given state of anesthesia (isonarcotic pressure). Substitution of $\ln P$ into Eq. (5) by its equivalent from Eq. (6) leads to Eq. (7), which correlates the natural logarithm of isonarcotic pressure, P_{an}, to the boiling point, T_{bp}, of the anesthetic agents.

$$\ln P_{an} = \left(\ln \alpha + \ln P_A + \frac{\Delta S_v}{R}\right) - \frac{\Delta S_v}{RT_B} T_{bp} \quad (7)$$

According to the to the Trouton rule (Atkins, 1995), the entropy of the vaporization, ΔS_v, is constant for different gases. T_B, R, and P_A are also other constants in Eq. (7). It can be deduced

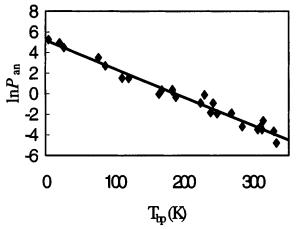

Fig. 1. Plot of ln P_{an} (righting reflex test) versus boiling point of different anesthetics. The ΔS_v value calculated from the slope using Eq. (7) equals 16.99 ± 0.65 cal/deg mol (data from Cammarata, 1975; see also Table 1).

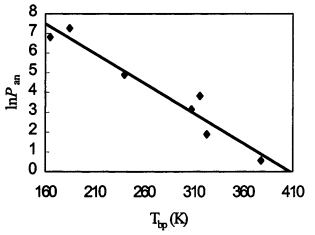

Fig. 2. Plot of ln P_{an} versus boiling point of different anesthetics. The ΔS_v value calculated from the slope equals 18.65 ± 2.14 cal/deg mol (data from Eger et al., 1965; see also Table 1).

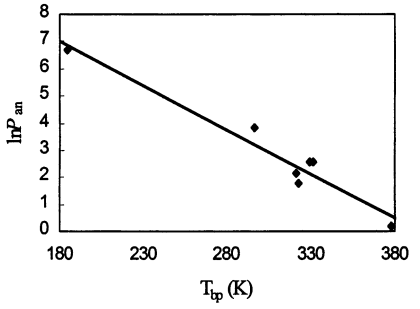

Fig. 3. Plot of ln P_{an} versus boiling point of different anesthetics. The ΔS_v value calculated from the slope equals 20.10 ± 2.17 cal/deg mol (data from Stoeltin and Miller, 1994; see also Table 1).

Table 1
Boiling points (T_{bp}) and logarithm of the pressure (P_{an}, mmHg) required to produce a certain level of depression in different tests

Compounds	T_{bp} (K)	Log P_{an}	ln P_{an}		
		Righting reflex[a]	Righting reflex[a]	Gross movement[b]	General anesthesia[c]
Helium	4.5	2.28	5.250	–	–
Hydrogen	20.6	2.14	4.928	–	–
Neon	27.1	1.94	4.467	–	–
Nitrogen	77.3	1.52	3.500	–	–
Hexafluoroethane	194.1	1.19	2.740	–	–
Tetrafluoroethane	145.4	1.24	2.855	–	–
Argon	87.5	1.18	2.717	–	–
Methane	111.6	0.66	1.520	–	–
Krypton	121.1	0.65	1.497	–	–
Nitrous oxide	184.6	0.18	0.414	7.265	6.673
Ethylene	169.4	0.15	0.345	–	–
Ethane	184.5	0.11	0.253	–	–
Xenon	165.1	−0.02	−0.046	6.807	–
Propane	231	−0.05	−0.115	–	–
Acetylene	189.5	−0.15	−0.345	–	–
Dichlorodifluoromethane	243.3	−0.4	−0.921	–	–
Propylene	225.4	−0.4	−0.921	–	–
Cyclopropane	239.6	−0.8	−1.842	4.890	–
Trichloromonofluoromethane	269.8	−0.82	−1.888	–	–
Fluoromethane	351.3	−0.85	−1.957	–	–
Chloromethane	249.1	−0.85	−1.957	–	–
Idomethane	315.5	−1.15	−2.648	–	–
Ethyl chloride	285.4	−1.4	−3.224	–	–
Ethyl bromide	311.5	−1.4	−3.224	–	–
Diethyether	307.7	−1.52	−3.500	3.140	–
Dichlorodifluoromethane	313.8	−1.52	−3.500	–	–
1,1-Dichloroethane	330.5	−1.59	−3.661	–	–
Chloroform	334.4	−2.08	−4.789	–	–
Fluroxene	316.3	–	–	3.818	–
Halothane	323.2	–	–	1.889	1.767
Methoxyflurane	378.0	–	–	0.558	0.196
Enflurane	329.5	–	–	–	2.559
Isoflurane	321.5	–	–	–	2.168
Sevoflurane	331.5	–	–	–	2.565
Desflurane	296.5	–	–	–	3.820

[a] Pressure required in mice to inhibit the righting reflex (Cammarata, 1975).
[b] Pressure required in dogs to prevent gross movement in response to a painful stimulus (Eger et al., 1965).
[c] Pressure required in humans (35–55 years old) to produce general anesthesia (Stoeltin and Miller, 1994).

from the Ferguson principle that the thermodynamic activity, α, of nonspecific drugs should be a constant value for a given biological activity. Thus, the plot of logarithm of isonarcotic pressure against boiling point would be linear with the slope of $-\Delta S_v/RT_B$ and intercept of $\ln(\alpha P_A) + \Delta S_v/R$. As the slope is negative, the higher the boiling point, the lower the isonarcotic pressure, which means the higher the potency.

Integrating the second form of the Clausius–Clapeyron equation (Eq. (2)) and applying the assumptions already made, it is possible to relate $\ln P_{an}$ to the logarithm of T_{bp}:

$$\ln P_{an} = \left(\ln \alpha + \ln P_A + \frac{\Delta S_v}{R} \ln T_B\right) - \frac{\Delta S_v}{R} \ln T_{bp} \quad (8)$$

Based on Eqs. (7) and (8), the existing empirical positive relationship between the potency and the boiling point of the anesthetic agents is justified. From these equations, it can be inferred that, as the attraction forces between the molecules of the anesthetic agents become stronger, they are less volatile and, thus, they have more propensity to be soluble in the biophase. So, to achieve a certain concentration of the anesthetic agent in the biophase, lower pressure is required for the less volatile agent. The importance of attractive forces between molecules of anesthetics has already been suggested in terms of van der Waals *a* constant (Koski et al., 1973).

Table 2
Thermodynamic activities[a] of some gaseous anesthetics

Compounds	Thermodynamic activity, $\log(P_{an}/P^{o})$	Boiling point (K), T_{bp}
Helium[b]	1.255	4.2
Hydrogen	−0.018	20.4
Neon	−1.377	27
Nitrogen	−1.306	77
Tetrafluoromethane	−1.118	145
Hexafluoroethane	−0.408	195
Argon	−1.628	87
Methane	−1.778	112
Krypton	−1.719	121
Nitrous oxide	−1.725	184
Ethylene	−1.744	169
Ethane	−1.578	184
Xenon	−1.883	165
Propane	−1.026	231
Propylene	−1.567	225
Cyclopropane[b]	−6.270	114
Chloromethane	−1.734	249

[a] Data from Cammarata (1975).

[b] These anesthetics were not included in the analysis shown in Fig. 4.

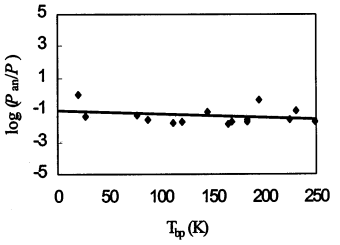

Fig. 4. Plot of $\log(P_{an}/P)$ versus boiling point of different anesthetics. The slope and regression coefficient (r^2) of the line are 0.00217 ± 0.00201 and 0.081756, respectively (data from Cammarata, 1975; helium and cyclopropane were not included in the analysis; see Table 2).

Applying Eqs. (7) and (8) to the experimental data taken from the literature confirms the correlation we have drawn. The returned values of ΔS_v for different sets of experimental data (see Figs. 1–3) are fairly close to the 20 cal/deg mol value proposed for entropy of evaporization cited in different sources (Atkins, 1995). A similar linear correlation has been used by Cammarata to relate the $\ln P_{an}$ of anesthetics to a parameter derived from the boiling point called reduced temperature, T_r, which is equal to T_B/T_{bp} (Cammarata, 1975). The slope of the line of a plot of $\ln P_{an}$ versus $1/T_r$, is taken to be ΔH_v. However, according to Eq. (7), the slope of the plot of $\ln P_{an}$ versus $1/T_r$ corresponds to ΔS_v. In addition, P_{an} was considered by Cammarata to be equal to the thermodynamic activity of the anesthetic agents, which also led to the conclusion that the Ferguson principle was in error. It can be seen from Fig. 4 that the slope of $\log(P_{an}/P)$ versus T_{bp} is not significantly different from zero, which shows that the Ferguson principle can be applied to the activity of volatile anesthetics.

In summary, we have established two equations that correlate the potency and boiling point from the liquefied phase for anesthetic gases. These equations provide thermodynamic justification for the observed relationship between $\ln P_{an}$ and the boiling point for volatile anesthetics. Also, the equations are consistent with the concept that the same level of biological effect for a set of nonspecific drugs can be achieved when the thermodynamic activities in the biophase are the same.

Acknowledgements

The authors would like to thank the Tabriz University of Medical Sciences, Tabriz, Iran for providing financial support to carry out this project.

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