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Density Functional Theory (DFT) based QSAR analysis of general anaesthetic analogues using quantum chemical descriptors

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ABSTRACT

An anaesthetic is a drug that causes anesthesia-reversible loss of sensation. These drugs are generally administered to facilitate surgery. A wide variety of drugs are used in modern anaesthetic practice. General anaesthetics are a category of anaesthetics which cause a reversible loss of consciousness. In this paper, QSAR study has been done with the help of DFT based quantum chemical descriptors for thirty three general anaesthetic analogues. The quantum chemical descriptors that have been used in our study are total energy, HOMO energy hardness, softness, electronegativity, electrophilicity index and molecular weight. The computational works have been performed with the help of CAChe Pro software of Fujitsu. It has been observed from our study that the best combination of quantum chemical descriptors is molecular weight, total energy, electronegativity and electrophilicity index for the QSAR study of general anaesthetics. The descriptor electrophilicity index (ω) is present in all best five regression equations thus electrophilicity index (ω) appears an important descriptor for the study of general anaesthetics.

Keywords: General anaesthetics analogues, DFT, quantum chemical descriptors, electrophilicity index.

INTRODUCTION

An anaesthetic is a drug that causes anesthesia-reversible loss of sensation. They contrast with analgesics (painkillers), which relieve pain without eliminating sensation. These drugs are generally administered to facilitate surgery. A wide variety of drugs are used in modern anaesthetic practice. Anaesthetics are categorized into two classes: general anaesthetics, which cause a reversible loss of consciousness, and local anaesthetics, which cause a reversible loss of sensation for a limited region of the body while maintaining consciousness.

General anaesthetics have acquired a most important place. They affect vital functions of all types of cells, especially those of nervous tissue. The state of general anesthesia is a drug-induced absence of perception of all sensations. General anaesthetics can depress the CNS (central nervous system) to such an extent that sensitivity to pain is completely abolished [1-7]. When used in surgery, they produce analgesia, loss of consciousness, and muscular relaxation. General anaesthetics are structurally nonspecific; i.e., they have no definite pattern of chemical structure. They are therefore classified on the basis of their method of administration. We have thus inhalation (or volatile) anaesthetics and intravenous anaesthetics.

Since general anaesthetics are structurally nonspecific, no unified theory has yet been proposed for the mechanism of their action. It is, however, admitted that they depress the CNS nonselectively by a physicochemical mechanism. Of the various theories that have been proposed, some are purely physical and some purely biochemical. Physical theories are based mainly on two physicochemical properties of anaesthetics: polarizability and volume. Among the physical theories, the most widely accepted one is the lipid theory advanced by Meyer [8] and Overton [9]. According to this theory, the potency of an anaesthetic should be directly related to its olive oil-water partition coefficient. Miller et al [10, 11] suggested that there is a very high correlation between anaesthetic potency of

anaesthetic gases and olive oil-gas partition coefficient. For the same anaesthetic gases Hansch et al [12] tried to correlate the potency with the octanol-water partition coefficient. The anaesthetic potency of a series of aliphatic ethers was found by Glave and Hansch [13] to depend upon the octanol-water partition coefficient. For the same aliphatic ethers Di Paolo [14] related the anaesthetic potency with Kier's molecular connectivity index χ. This index signifies the degree of branching or connectivity in a molecule and is derived from the numerical extent of branching or connectivity in the molecular skeleton (hydrogen-suppressed graph).

In recent years quantum chemical descriptors has successfully been used in the study of various compounds. In this paper, QSAR study has been done with the help of quantum chemical descriptors for thirty three general anaesthetic analogues. The quantum chemical descriptors that have been used in our study are total energy [15], HOMO energy, hardness [16, 17], softness [18], electronegativity [19, 20], electrophilicity index [21, 22] and molecular weight.

EXPERIMENTAL SECTION

The study material of this paper is thirty three general anaesthetic analogues given in Table-1 along with their observed biological activities in terms of Log(1/C). The 3D modeling and geometry optimization of all the compounds and evaluation of values of descriptors have been done with the help of CAChe Pro software of Fujitsu, using the DFT Methods [23, 24] and semiemperical PM3 Hamiltonian [25]. The Project Leader program has been used for multi linear regression (MLR) analysis. The statistical parameters have been calculated by Smith's Statistical Package (version 2.80).

Table-1: Thirty three general anaesthetic analogues under study

S. No.	Compound	log(1/C)
1	ethyl vinyl ether	2.82
2	methyl cyclopropyl ether	2.85
3	diethyl ether	2.75
4	methyl propyl ether	2.9
5	ethyl cyclopropyl ether	3.1
6	ethyl isopropyl ether	3
7	methyl *sec*-butyl ether	3.04
8	Methyl butyl ether	3.15
9	diisopropyl ether	3.15
10	ethyl *tert*-butyl ether	3.15
11	ethyl isobutyl ether	3.22
12	propyl isopropyl ether	3.26
13	Methyl amyl ether	3.4
14	ethyl isoamyl ether	3.45
15	diisobutyl ether	3.3
16	pentane	1.052
17	hexane	0.941
18	heptane	0.458
19	octane	0.391
20	decane	0.613
21	undecane	0.81
22	dodecane	1.124
23	tridecane	1.119
24	tetradecane	1.294
25	pentadecane	1.516
26	hexadecane	1.5661
27	heptadecane	1.538
28	3-pentanone	0.657
29	4-heptanone	0.121
30	6-undecanone	0.076
31	7-tridecanone	0.978
32	8-pentadecanone	1.127
33	9-heptadecanone	1.455

RESULTS AND DISCUSSION

The thirty three general anaesthetic analogues along with their observed biological activities are given in Table-1. The values of eight descriptors of compounds have been calculated and presented in Table-2. For the development of QSAR models multi linear regression (MLR) analysis has been performed. Various QSAR models, using descriptors in different combinations, have been developed but only best five models are reported here.

Table-2: Values of quantum chemical descriptors and observed activities of thirty three general anaesthetic analogues

C. No.	LogP	MW	E_{HOMO}	E_T	η	χ	S	ω	Obs. Activity
1	1.047	72.107	-5.195	-232.443	2.504	-2.691	0.2	1.445	2.82
2	0.409	72.107	-5.655	-232.426	3.733	-1.922	0.134	0.495	2.85
3	0.698	74.122	-5.704	-233.673	3.792	-1.913	0.132	0.482	2.750
4	0.824	74.122	-5.729	-233.668	3.661	-2.067	0.137	0.584	2.900
5	0.752	86.133	-5.518	-271.744	3.734	-1.784	0.134	0.426	3.100
6	1.111	88.149	-5.638	-272.987	3.758	-1.88	0.133	0.47	3.000
7	1.237	88.149	-5.636	-272.98	3.722	-1.914	0.134	0.492	3.040
8	1.220	88.149	-5.721	-272.98	3.67	-2.051	0.136	0.573	3.150
9	1.524	102.176	-5.581	-312.3	3.693	-1.889	0.135	0.483	3.150
10	1.189	102.176	-5.554	-312.298	3.613	-1.941	0.138	0.522	3.150
11	1.569	102.176	-5.676	-312.298	3.746	-1.93	0.133	0.497	3.220
12	1.580	102.176	-5.633	-312.299	3.713	-1.919	0.135	0.496	3.260
13	1.617	102.176	-5.716	-312.293	3.678	-2.038	0.136	0.565	3.400
14	1.893	116.203	-5.664	-351.609	3.685	-1.979	0.136	0.531	3.450
15	2.441	130.23	-5.657	-390.923	3.71	-1.947	0.135	0.511	3.300
16	2.486	72.15	-7.516	-197.765	4.804	-2.711	0.104	0.765	1.052
17	2.882	86.177	-7.346	-237.078	4.702	-2.644	0.106	0.743	0.941
18	3.278	100.203	-7.223	-276.39	4.622	-2.601	0.108	0.732	0.458
19	3.674	114.23	-7.125	-315.703	4.558	-2.567	0.11	0.723	0.391
20	4.467	142.284	-6.984	-394.328	4.466	-2.518	0.112	0.71	0.613
21	4.863	156.311	-6.932	-433.64	4.433	-2.499	0.113	0.704	0.810
22	5.260	170.337	-6.893	-472.953	4.406	-2.487	0.113	0.702	1.124
23	5.656	184.364	-6.859	-512.265	4.382	-2.476	0.114	0.7	1.119
24	6.052	198.391	-6.823	-551.578	4.361	-2.462	0.115	0.695	1.294
25	6.448	212.418	-6.801	-590.89	4.346	-2.455	0.115	0.693	1.516
26	6.845	226.445	-6.782	-630.203	4.333	-2.449	0.115	0.692	1.5661
27	7.241	240.471	-6.76	-669.516	4.321	-2.439	0.116	0.688	1.538
28	1.636	86.133	-5.579	-271.796	2.043	-3.537	0.245	3.062	0.657
29	2.428	114.187	-5.521	-350.42	2.029	-3.492	0.246	3.006	0.121
30	4.014	170.294	-5.499	-507.671	2.026	-3.473	0.247	2.978	0.076
31	4.806	198.348	-5.493	-586.296	2.022	-3.471	0.247	2.979	0.978
32	5.599	226.401	-5.484	-664.921	2.024	-3.461	0.247	2.959	1.127
33	6.391	254.455	-5.478	-743.546	2.022	-3.456	0.247	2.954	1.455

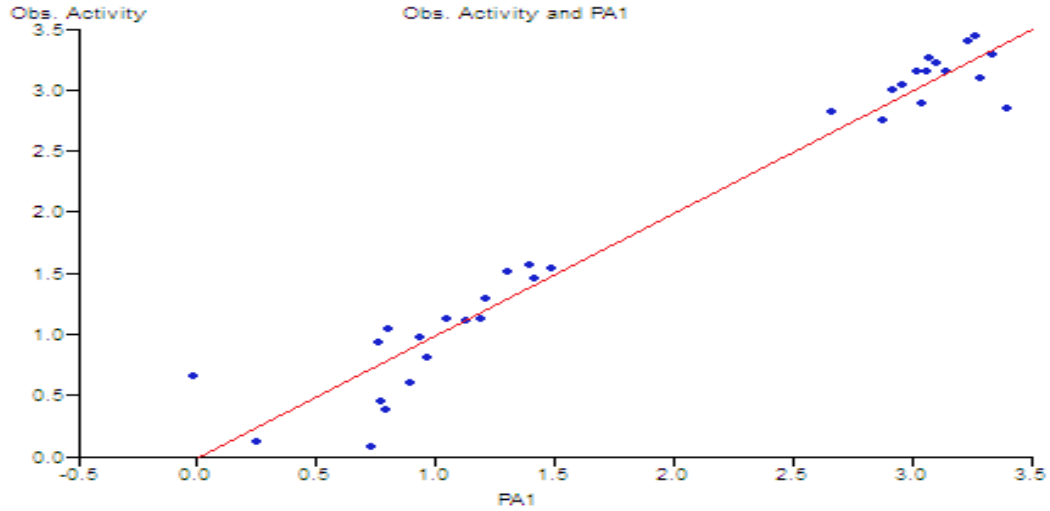
Where, MW = Molecular Weight, E_T = Energy Total (Hartree), E_{HOMO} = HOMO Energy (eV), η = Hardness, S = Softness, χ = Electronegativity, ω = Electrophilicity Index.

First best QSAR Model: The first best QSAR model is obtained by following regression equation-

$PA1 = - 0.339645*MW - 0.12401*E_T - 3.37502*\chi - 3.49989*\omega - 5.69249$

$r^2 = 0.953192$, $rCV^2 = 0.913064$, Std. Error = 0.0398, SEE = 0.2542, t-value = 25.1250, p-value = 0, DOF = 0.9517.

In the above regression equations, r^2 is correlation coefficient, rCV^2 is cross-validation coefficient, Std. Error is standard error, SEE is standard error of estimate and DOF is degrees of freedom. Descriptors used in this model are molecular weight, total energy, electronegativity and electrophilicity index. Values of correlation coefficient, cross-validation coefficient and other statistical parameters indicate that this model has excellent predictive power. The predicted activities obtained from above regression equation are given in Table-3. The trend of observed activity and predicted activity obtained fromPA1 is shown in Graph-1.



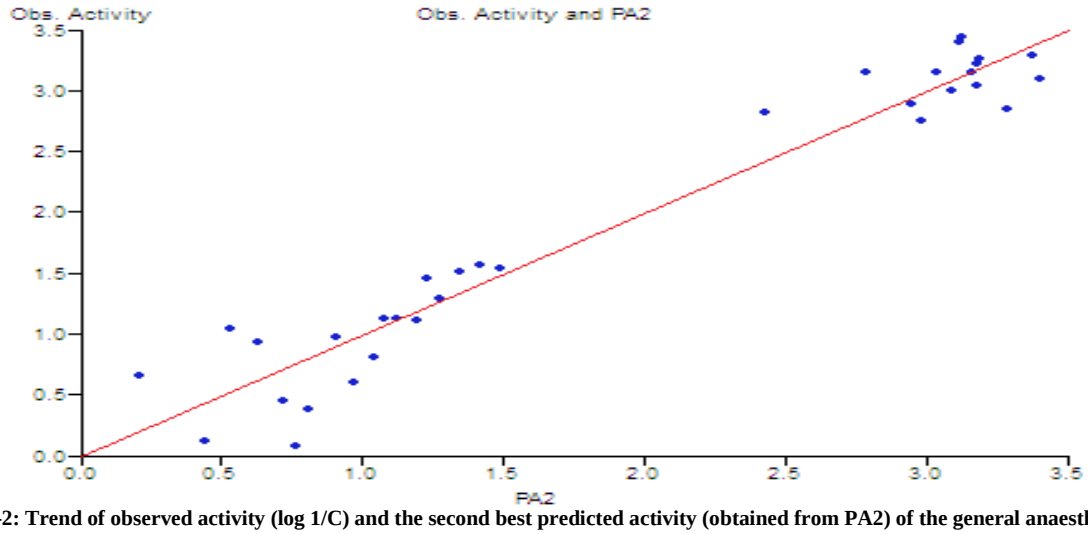
Graph-1: Trend of observed activity (log 1/C) and the best predicted activity (obtained from PA1) of the general anaesthetics

Second best QSAR Model: The second best QSAR model is obtained by following regression equation-

PA2 = 0.947461*LogP - 0.368818*MW - 0.123839*E_T - 1.53324*ω + 1.46257

r^2 = 0.940561, rCV^2 = 0.893627, Std. Error = 0.0452, SEE = 0.2865, t-value = 22.1423, p-value = 0, DOF = 0.9386.

This QSAR model involves LogP as first descriptor, molecular weight as second descriptor, total energy as third descriptor and electrophilicity index as fourth descriptor respectively. The values of regression coefficient, cross validation coefficient and statistical parameters are high which indicate that this regression model has good predictive power. The predicted activities obtained from above regression equation are given in Table-3. The trend of observed activity and predicted activity obtained from PA2 is shown in Graph-2.



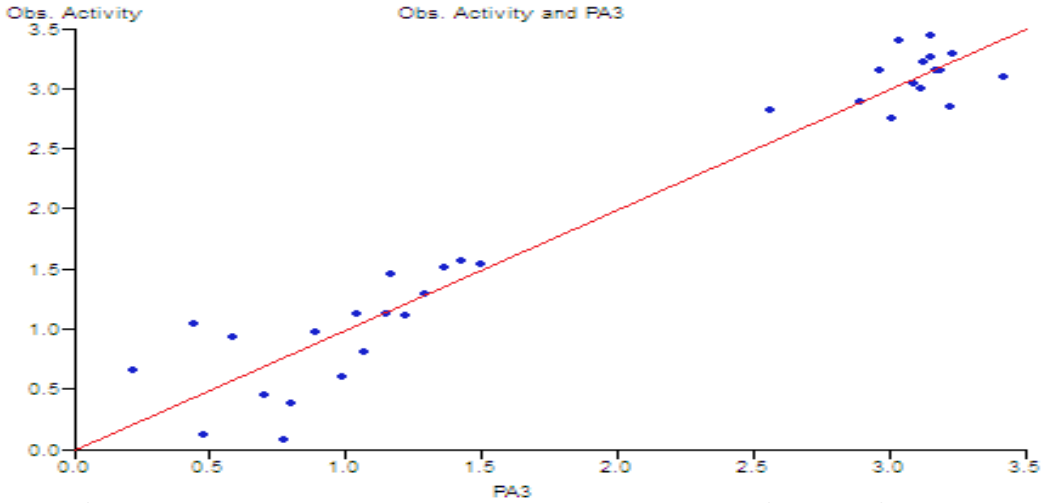
Graph-2: Trend of observed activity (log 1/C) and the second best predicted activity (obtained from PA2) of the general anaesthetics

Third best QSAR Model: The third best QSAR model is obtained by following regression equation-

PA3 = - 0.131259*MW - 0.0482813*E_T + 18.891*S - 2.01019*ω - 0.0666228

r^2 = 0.940003, rCV^2 = 0.873937, Std. Error = 0.0454, SEE = 0.2877, t-value = 22.0421, p-value = 0, DOF = 0.9381.

This QSAR model involves molecular weight as first descriptor, total energy as second descriptor, softness as third descriptor and electrophilicity index as fourth descriptor respectively. The values of regression coefficient, cross validation coefficient and statistical parameters are high which indicate that this regression model has good predictive power. The predicted activities obtained from above regression equation are given in Table-3. The trend of observed activity and predicted activity obtained from PA3 is shown in Graph-3.



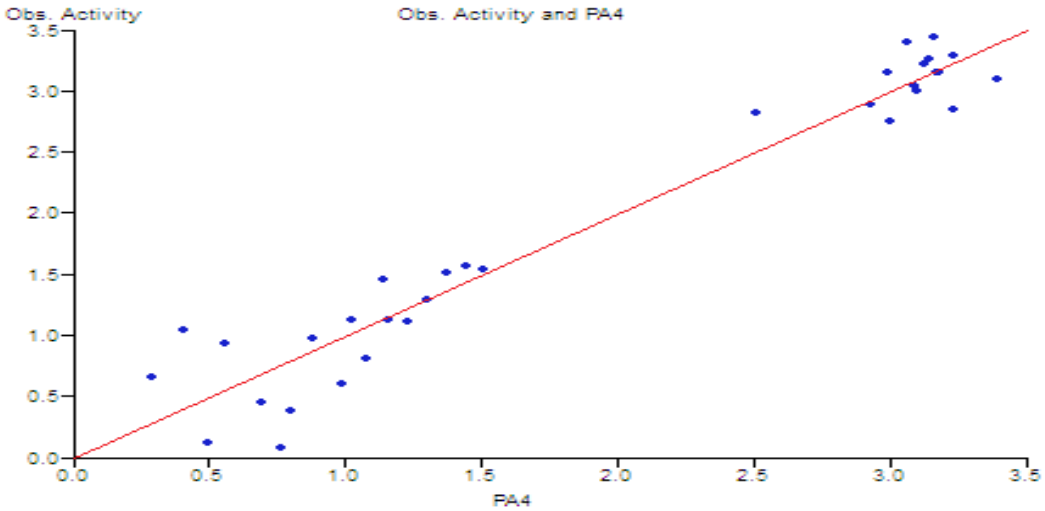
Graph-3: Trend of observed activity (log 1/C) and the third best predicted activity (obtained from PA3) of the general anaesthetics

Fourth best QSAR Model: The fourth best QSAR model is obtained by following regression equation-

$PA4 = - 0.133234*MW - 0.0489564*E_T - 0.646628*\eta - 1.59581*\omega + 4.66079$

$r^2 = 0.939744$, $rCV^2 = 0.898265$, Std. Error = 0.0455, SEE = 0.2884, t-value = 21.9875, p-value = 0, DOF = 0.9378.

This QSAR model involves descriptors molecular weight, total energy, hardness and electrophilicity index. The values of regression coefficient, cross validation coefficient and statistical parameters are high which indicate that this regression model has good predictive power. The predicted activities obtained from above regression equation are given in Table-3. The trend of observed activity and predicted activity obtained from PA4 is shown in Graph-4.



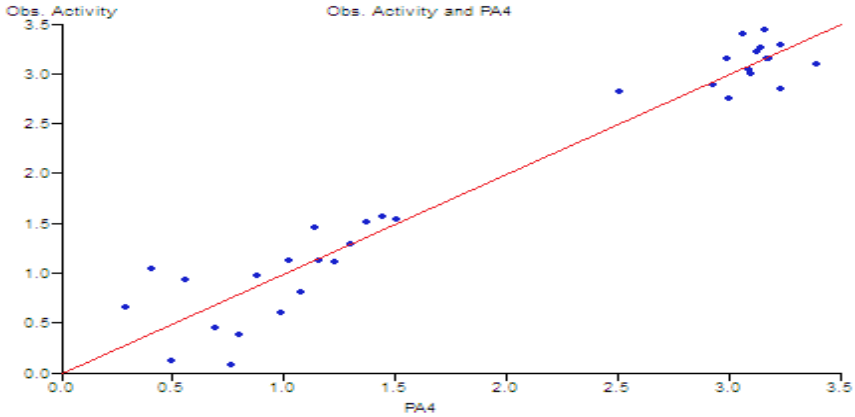
Graph-4: Trend of observed activity (log 1/C) and the fourth best predicted activity (obtained from PA4) of the general anaesthetics

Fifth best QSAR Model: The fifth best QSAR model is obtained by following regression equation-

$PA5 = - 0.168969*MW + 0.167153*E_{HOMO} - 0.0619127*E_T - 1.20369*\omega + 2.62212$

$r^2 = 0.93542$, $rCV^2 = 0.898174$, Std. Error = 0.0472, SEE = 0.2986, t-value = 21.1860, p-value = 0, DOF = 0.9333.

This QSAR model involves descriptors molecular weight, HOMO energy, total energy and electrophilicity index. The values of regression coefficient, cross validation coefficient and statistical parameters are high which indicate that this regression model has good predictive power. The predicted activities obtained from above regression equation are given in Table-3. The trend of observed activity and predicted activity obtained from PA5 is shown in Graph-5.



Graph-5: Trend of observed activity (log 1/C) and the fifth best predicted activity (obtained from PA5) of the general anaesthetics

Table-3: Predicted activities PA1 to PA6 of the 33 General Anaesthetics

C. No.	PA1	PA2	PA3	PA4	PA5	PA6
1	2.665	2.43	2.557	2.507	2.221	2.156
2	3.396	3.281	3.226	3.229	3.288	3.313
3	2.877	2.985	3.007	3.003	3.031	3.03
4	3.044	2.948	2.892	2.926	2.905	2.906
5	3.282	3.406	3.42	3.394	3.457	3.467
6	2.921	3.09	3.111	3.1	3.121	3.115
7	2.958	3.175	3.091	3.088	3.094	3.088
8	3.137	3.035	2.965	2.993	2.983	2.989
9	3.016	3.157	3.187	3.178	3.179	3.169
10	3.059	2.78	3.166	3.168	3.136	3.121
11	3.105	3.178	3.122	3.121	3.146	3.151
12	3.074	3.189	3.147	3.144	3.154	3.153
13	3.234	3.118	3.033	3.057	3.057	3.068
14	3.262	3.127	3.152	3.161	3.17	3.179
15	3.337	3.372	3.233	3.234	3.26	3.273
16	0.8	0.526	0.44	0.402	0.498	0.548
17	0.76	0.629	0.583	0.559	0.616	0.644
18	0.766	0.718	0.698	0.685	0.715	0.728
19	0.794	0.802	0.801	0.796	0.805	0.808
20	0.896	0.963	0.984	0.988	0.972	0.963
21	0.962	1.042	1.068	1.074	1.052	1.039
22	1.042	1.116	1.142	1.151	1.125	1.111
23	1.124	1.191	1.216	1.226	1.198	1.184
24	1.204	1.268	1.292	1.302	1.273	1.258
25	1.296	1.341	1.36	1.371	1.342	1.33
26	1.391	1.414	1.426	1.437	1.411	1.401
27	1.482	1.49	1.497	1.507	1.483	1.475
28	-0.022	0.209	0.219	0.284	0.278	0.257
29	0.247	0.437	0.478	0.494	0.483	0.464
30	0.725	0.762	0.769	0.764	0.776	0.776
31	0.936	0.901	0.888	0.876	0.903	0.914
32	1.192	1.073	1.039	1.018	1.056	1.077
33	1.416	1.222	1.167	1.139	1.191	1.222

CONCLUSION

It is clear from the above study that the best combination of quantum chemical descriptors is molecular weight, total energy, electronegativity and electrophilicity index for the QSAR study of general anaesthetics. However all the top five QSAR models discussed above are reliable because of having high predictive power. The descriptor electrophilicity index (ω) is present in all best five regression equations thus electrophilicity index (ω) appears an important descriptor for the study of general anaesthetics.

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