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Original article

Prediction of convulsant activity of gases and vapors

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Abstract

The convulsant activity of 48 compounds studied by Eger et al. has been analyzed using an Abraham solvation equation. Four compounds identified by Eger et al. as more potent than expected were similarly identified, and for the remaining 44 compounds, the equation had $R^2 = 0.978$ and a standard deviation of 0.17 log units. The structural features of compounds that lead to convulsant activity or to anesthetic activity are uncovered, and used to explain which compounds will act as convulsants and which compounds will act as anesthetics. The present equation for convulsant activity and our previous equation for inhalation anesthetic activity can be used to predict convulsant pressure and anesthetic pressure. For all 48 compounds, the predicted convulsant pressure is less than the predicted anesthetic pressure, in agreement with experiment. Although convulsants tend to have a small hydrogen bond acidity, this is not the only factor that influences the effect. The difference between the compound pressure needed to produce convulsions and that needed to produce anesthesia is quite small for many of the 48 compounds, and so minor structural features can be significant. These structural features are incorporated into our equations that successfully predict convulsant/anesthetic effects for the 48 compounds.

Keywords: Convulsant activity; Inhalation anesthesia; Linear free energy relationship; Hydrogen bonding; Abraham equation

1. Introduction

Eger et al. [1] have determined the partial pressure of inhaled compounds that do not produce anesthesia but cause convulsions and twitching in rats. They studied 45 convulsants (Eger et al. actually list 48 values but some values were for isomers, and they always refer to 45 compounds) and found that for 36 convulsants there was an excellent correlation of the solubility of the gaseous compound in olive oil and its convulsant potency, with $R^2 = 0.99$; R is the correlation coefficient. Four compounds were more potent than predicted from solubility in olive oil (perfluorodimethylcyclobutane, 1,1,1,2,2,3,3,4,5,6,6,6-dodecafluorohexane, bis(2,2,2-trifluoroethyl)ether, and perfluorotoluene) and five compounds (octane, nonane, cyclohexane, cycloheptane, and cyclooctane) were less potent than predicted, again from solubility in olive oil.

The explanation advanced [1] for these observations was that convulsants act through two mechanisms. First, there is an inherent unexplained mechanism that involves a nonpolar phase. Second, there is a variable capacity to affect $GABA_A$ receptors. It is known that bis(2,2,2-trifluoroethyl)ether is a noncompetitive antagonist of $GABA_A$ and acts to decrease the maximal effect of $GABA_A$ and it was postulated that the four unusually potent convulsants produce convulsions by their ability to block the action of GABA. The five less potent convulsants enhance the effect of GABA and hence partially oppose action via the first mechanism.

The findings and suggestions of Eger et al. [1] give rise to a number of interesting points. It has been shown that solubility of gases and vapors in olive oil is a poor predictor of inhalation anesthesia, and since olive oil is such a good predictor of convulsant activity there must be some particular structural differences in anesthetics and convulsants that lead to these observed results. As Eger et al. [1] suggested, the nonpolar phase in the unexplained mechanism could be a lipid site or the hydrophobic interior of a protein. We

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have studied the solubility of gases and vapors in a variety of biological phases, including blood [2], brain [3], muscle [4], fat [5], lung [6], and liver [7], and the only phase that can be regarded as 'nonpolar' is human fat. Most biological phases, such as those mentioned above (with the exception of fat) are composed of hydrated protein and are far from nonpolar, and so there is scope for further investigation of the unexplained mechanism. There is also a need to connect molecular structure with convulsant activity, and to attempt to explain anesthetic and convulsant effects in terms of molecular structure; this is another aim of the present work. We have recently shown that structural effects on inhalation anesthesia can be explained using our general equation for solubility of gases and vapors [8], and so it seemed useful to apply the same analysis to convulsant activity.

Table 1
Compound descriptors, and values of log(1/CON), observed and calculated in Eq. (2)

Compound	*E*	*S*	*A*	*B*	*L*	log(1/CON)	
						Obs.	Calc.
Dibromodifluoromethane	0.272	0.36	0.00	0.00	1.961	1.59	1.32
Chloropentafluoroethane	−0.360	−0.10	0.00	0.00	0.543	−0.32	−0.19
1,2-Dichlorotetrafluoroethane	−0.190	0.05	0.00	0.00	1.427	0.41	0.64
Bromopentafluoroethane	−0.160	−0.20	0.00	0.04	0.970	0.02	0.11
1,1,2-Trifluorotrichloroethane	0.010	0.13	0.00	0.00	2.210	1.36	1.29
1,1,1,2,2-Pentafluoropropane	−0.492	0.01	0.01	0.05	0.516	0.02	0.15
Octafluoropropane	−0.750	−0.52	0.00	0.03	−0.004	−0.88	−0.93
2-Chloroheptafluoropropane	−0.549	−0.32	0.00	0.00	0.770	−0.26	−0.23
1,2,3-Trichloropentafluoropropane	−0.072	−0.03	0.00	0.06	2.420	1.31	1.49
1-Bromoheptafluoropropane	−0.360	−0.27	0.00	0.00	1.251	0.03	0.16
2-Bromoheptafluoropropane	−0.360	−0.22	0.00	0.01	1.259	0.13	0.26
1,1,1,2,2,3,3,4,4-Nonafluorobutane	−0.886	−0.43	0.04	0.10	0.700	0.12	0.12
2,3-Dichlorooctafluorobutane	−0.507	−0.19	0.00	0.00	1.913	1.04	0.80
1,2,3,4-Tetrachlorohexafluorobutane	−0.030	0.15	0.00	0.03	3.638	2.52	2.54
1-Bromononafluorobutane	−0.558	−0.26	0.00	0.00	1.559	0.59	0.45
1,4-Dibromooctafluorobutane	−0.131	−0.03	0.00	0.04	2.982	1.86	1.87
1,1,1,2,2,3,3,4,5,6,6,6-Dodecafluorohexane[a]	−1.176	−0.05	0.10	0.19	1.433	2.31	1.71
1-Bromo-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexane	−0.727	−0.10	0.06	0.01	2.765	1.68	1.84
Pentane	0.000	0.00	0.00	0.00	2.162	1.16	1.10
Octane	0.000	0.00	0.00	0.00	3.677	2.18	2.28
Nonane	0.000	0.00	0.00	0.00	4.182	2.80	2.67
Octafluorocyclobutane	−0.510	−0.39	0.00	0.07	0.722	0.01	−0.13
Perfluorodimethylcyclobutane[a]	−0.909	−0.75	0.00	0.08	0.890	0.82	−0.31
cis-1,2-Dichlorohexafluorocyclobutane	−0.033	−0.16	0.00	0.10	2.177	1.41	1.27
trans-1,2-Dichlorohexafluorocyclobutane	−0.033	−0.16	0.00	0.10	2.169	1.19	1.26
racemic-1,2-Dichlorohexafluorocyclobutane	−0.033	−0.16	0.00	0.10	2.214	1.26	1.30
Cyclohexane	0.305	0.10	0.00	0.00	2.964	1.66	1.78
Cycloheptane	0.350	0.10	0.00	0.00	3.704	2.34	2.34
Cyclooctane	0.413	0.10	0.00	0.00	4.329	2.82	2.81
$CF_3CH_2OCF_3$	−0.472	0.03	0.00	0.06	0.700	0.66	0.31
$CF_3CH_2OCF_2Cl$	−0.270	0.11	0.02	0.06	1.615	1.63	1.14
$CHF_2OCClFCF_3$	−0.334	0.05	0.00	0.06	1.374	0.84	0.83
$CHF_2OClF_2CClF_2$	−0.334	0.10	0.00	0.03	1.434	0.77	0.84
$CClF_2OCClFCF_3$	−0.194	−0.37	0.00	0.07	1.687	0.71	0.57
$CClF_2OCF_2CClF_2$	−0.194	−0.31	0.00	0.03	1.765	0.68	0.57
$CClF_2OCCl_2CF_3$	0.044	−0.21	0.00	0.08	2.607	1.61	1.46
$CClF_2OCF_2CCl_2F$	0.044	−0.17	0.00	0.06	2.656	1.52	1.47
$CCl_2FOCF_2CClF_2$	0.044	−0.16	0.00	0.05	2.656	1.36	1.45
$CHF_2OC(F)(CHF_2)CF_3$	−0.668	0.21	0.04	0.07	1.166	1.25	1.10
$CH_2FOCF_2CH(CF_3)_2$	−0.766	0.06	0.06	0.07	1.811	1.43	1.51
$CF_3CH_2OCH_2CF_3$[a]	−0.472	0.12	0.07	0.32	1.419	2.81	2.08
$CH_3OCF_2CF_2CF_2CF_3$	−0.650	−0.27	0.00	0.13	1.501	0.67	0.85
$CH_3OCF_2CF(CF_3)_2$	−0.650	−0.27	0.00	0.13	1.501	0.67	0.85
1,3,5-Tri(trifluoromethyl)benzene	−0.293	−0.01	0.00	0.05	3.077	1.85	2.04
Perfluorotoluene[a]	−0.055	0.35	0.00	0.04	2.880	3.46	2.23
1,4-Difluorobenzene	0.384	0.60	0.00	0.06	2.766	2.22	2.41
Helium	0.000	0.00	0.00	0.00	−1.741	−1.93	−1.92
Neon	0.000	0.00	0.00	0.00	−1.575	−1.96	−1.80

[a] Not used to obtain Eq. (2).

2. Methods

The general equation that we use for the correlation and prediction of the solubility of gases and vapors in organic solvents and biophases, and for the correlation and prediction of the bioactivity of gases and vapors is the linear free energy relationship (LFER) [9,10]:

$$\mathrm{SP} = c + eE + sS + aA + bB + lL \quad (1)$$

In Eq. (1), SP is the dependent variable. For the solubility of gases and vapors, SP is log K, where K is the gas to solvent (or biophase) equilibrium constant for a series of compounds in a given phase. For inhalation anesthesia, SP is log(1/MAC) where MAC is the alveolar concentration in atmospheres of an inhaled anesthetic agent that prevents movement in 50% of rats in response to noxious stimulation. For convulsant activity, SP is log(1/CON) where CON is the partial pressure in atmospheres at which convulsion in rats takes place. We use the reciprocals of MAC and CON in order that the larger the value of SP, the greater is the compound activity. The independent variables, or compound descriptors, in Eq. (1) are as follows. E is the compound excess molar refractivity in units of $(\mathrm{cm^3\ mol^{-1}})/10$, S is the compound dipolarity/polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, and L is the logarithm of the gas to hexadecane partition coefficient at 25 °C [9,10], a measure of the size of the compound. The compound descriptors needed for the analysis of the convulsant activity were obtained as described before [10], making use of the physical properties determined by Eger et al. [1]. In addition, it was helpful as a preliminary analysis to predict the compound descriptors using commercially available software [11]. The convulsants studied by Eger et al. [1] are in Table 1, together with values of log(1/CON) with CON in atmospheres [1], and the descriptors that we have obtained from experimental data. There are 48 compounds in Table 1.

The statistics we use are as follows. The average error is defined as $\mathrm{AE} = (1/N)\sum(\mathrm{pred.} - \mathrm{obs.})$, the absolute average error is defined as $\mathrm{AAE} = (1/N)\sum(|\mathrm{pred.} - \mathrm{obs.}|)$, the root mean square error $\mathrm{RMSE} = \sqrt{[\sum(\mathrm{pred.} - \mathrm{obs.})^2]/(N)}$ and the standard deviation $\mathrm{S.D.} = \sqrt{[\sum(\mathrm{pred.} - \mathrm{obs.})^2]/(N-1)}$. Note that the S.D. for a regression equation such as Eq. (2) is given by $\sqrt{[\sum(\mathrm{calc.} - \mathrm{obs.})^2]/(N-v-1)}$, where v is the number of independent variables.

3. Results and discussion

The experiments used to obtain convulsant partial pressures are carried out over a long time scale, some 20 min, and so it is reasonable to suppose that equilibrium exists between the vapor phase and the central nervous system. If a compound undergoes substantial metabolism during the course of the experiment, then we would not expect any LFER to account for the observed convulsant partial pressure. If a good LFER can be obtained, this must indicate that the influence of metabolism is negligible.

We first applied Eq. (1) to the log(1/CON) values in Table 1 and for 44 compounds (that is, excluding the four compounds found by Eger et al. to have enhanced activity) obtained Eq. (2). The term in A was hardly statistically significant ($T = 1.40$, $P = 0.169$), but this is almost certainly due to the very small range of A-values of the convulsants, only from 0.00 to 0.10, and so we retain the term.

$$\begin{aligned}\log(1/\mathrm{CON}) = {} & -0.573(0.062) - 0.228(0.133)E \\ & + 1.198(0.160)S + 3.232(2.303)A \\ & + 3.355(0.689)B + 0.776(0.023)L \end{aligned} \quad (2)$$

$$N = 44,\ \mathrm{S.D.} = 0.167,\ R^2 = 0.978,\ F = 344.2$$

In Eq. (2), N is the number of data points (compounds), S.D. is the correlation standard deviation, R is the correlation coefficient and F is the F-statistic. The S.D. values for the coefficients are in parentheses. We include in Eq. (2) the five compounds (octane, nonane, cyclohexane, cycloheptane, and cyclooctane) rejected by Eger et al. [1] as being less potent than calculated on the basis of solubilities in olive oil. A plot of calculated log(1/CON) values in Eq. (2) against observed log(1/CON) values is shown in Fig. 1, and numerical details are in Table 1. The four compounds that are more potent than calculated and the compounds rejected by Eger et al. [1] as being less potent than calculated (from solubilities in olive oil) are shown separately in Fig. 1. As can be seen, the alkanes and cycloalkanes fit perfectly according to Eq. (2).

In order to test the predictive capability of Eq. (2), we divided the 44 convulsants into a training set of 29 compounds and a test set of 15 compounds. Since the number of compounds is rather limited for such a procedure, we carried out the division three times. For the first division we listed the 44 compounds in order of log(1/CON) and selected every third compound as the test set. For the second division, the list was in order of the descriptor B, and for the third division the list was in order of descriptor L. We chose these two particular

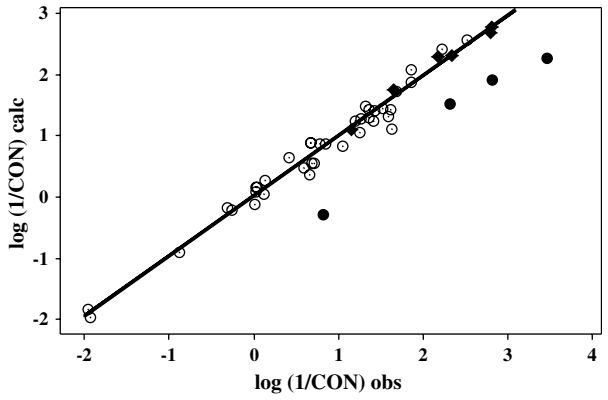

Fig. 1. A plot of log(1/CON) calculated in Eq. (2) against observed values of log(1/CON). The line is that of unit slope. The points marked ● are the four outliers that are more potent than calculated, and the points marked ◆ are for the compounds pentane, octane, nonane, cyclohexane, cycloheptane and cyclooctane.

Table 2
Details of the three training equations for 29 compounds and statistics for the three independent test sets of 15 compounds

Set[a]	*c*	*e*	*s*	*a*	*b*	*l*	S.D.	R^2	*F*
1	−0.598	−0.158	1.018	4.523	3.110	0.788	0.177	0.976	185.6
2	−0.591	−0.268	1.176	3.196	3.078	0.784	0.165	0.9825	254.9
3	−0.567	−0.233	1.110	2.835	2.749	0.776	0.161	0.980	226.5

Set[b]	AE	AAE	RMSE	S.D.
1	0.025	0.116	0.160	0.166
2	0.011	0.129	0.172	0.178
3	0.034	0.132	0.183	0.189

[a] Training sets of 29 compounds.
[b] Test sets of 15 compounds.

descriptors because the terms *bB* and *lL* make the most contributions to the overall values. Details of the three training equations and of the statistics for three independent test sets are in Table 2.

The AE is a measure of any bias in the predictions. From Table 2 it can be seen that any such bias is minimal, with AE = 0.025, 0.011 and 0.034 log units only. AAE, RMSE and S.D. are all measures of the predictive capability of the training equations. The average S.D. for the three test sets is 0.178 log units and this can be taken as an estimate of the predictive capability of the full Eq. (2).

The maximum cross-correlation of the descriptors in Eq. (2) is $R = 0.534$, and $R^2 = 0.285$, between *E* and *S*, which we consider to be not very significant. If cross-correlations are significant in any equation, this may lead to the equation becoming unstable. We can check this as follows. First we carry out a principal component analysis, PCA, on the five descriptors used in Eq. (2), to yield five orthogonal PCs that contain all the information of the original five descriptors. If we then carry out a regression of log(1/CON) on all five PCs, we simply obtain the statistics of Eq. (2). The first four PCs contain 96.1% of the total information in the five descriptors, which shows that there is little redundancy in the five descriptors. We then regress log(1/CON) against the first four PCs for the training set 2 (which is close to the average of the three training sets that we used, above) and then predict log(1/CON) for the relevant 15 compound test set. We find that AE = 0.039, AAE = 0.214, RMSE = 0.247, and S.D. = 0.255 log units. Hence if all cross-correlations are removed, and if five descriptors are reduced to four, the predictive statistics are still good, and are not far from those in Table 2 using all five descriptors. We conclude that Eq. (2) is quite stable, and that the predictive statistics in Table 2 are soundly based.

It is interesting to compare structural features of the convulsants with those of the inhalation anesthetics, in terms of the compound descriptors, see Table 3. The range of values of the descriptors for the convulsants and for the anesthetics is quite similar, except for the *A*-descriptor. The range of *A* in the convulsants is so small that this descriptor has very little effect on convulsant activity, in the 48 compounds studied by Eger et al. [1]. However, for the anesthetics, the range of *A* is reasonably large.

We can calculate the contribution made by each term in Eq. (2) by multiplying each coefficient by the mean value of the corresponding descriptor to give the percentage contribution. In Table 4 are given percentage contributions of the terms in Eq. (2), and for comparison the percentage contributions to inhalation anesthesia. For the convulsants in Table 1, by far the overriding structural feature is the compound size in terms of *L*; the larger the convulsant, the greater is its activity. Hydrogen bond acidity appears to have little effect on convulsant activity, but this is due to the lack of hydrogen bond acidity of the convulsants, see Tables 1 and 3. The corresponding equation for inhalation anesthetics is Eq. (3), where the *aA* term is very significant [8], but the 'size' term *lL* is less significant than is the case for the convulsants, see Table 4. It is thus no coincidence that the convulsants have no hydrogen bond acidity – if a potential anesthetic or convulsant has a significant hydrogen bond acidity it will prefer to act as an inhalation anesthetic, but if it has only a small or zero hydrogen bond acidity it will prefer to act as a convulsant. We use the word 'prefer' because there appears to be no rigorous separation into convulsants and anesthetics just on the basis of hydrogen bond acidity – some compounds such as 2-heptanone and 4-heptanone have quite good anesthetic activity even though they have zero hydrogen bond acidity.

Table 3
Statistics of descriptors for convulsants and inhalation anesthetics

	Convulsants				Inhalation anesthetics			
	Min	Max	Mean	Range	Min	Max	Mean	Range
E	−1.18	0.41	−0.26	1.59	−1.18	0.66	−0.24	1.84
S	−0.75	0.60	−0.07	1.35	−0.43	0.70	0.28	1.13
A	0.00	0.10	0.01	0.10	0.00	0.77	0.12	0.77
B	0.00	0.32	0.05	0.32	0.00	0.56	0.17	0.56
L	−1.74	4.33	1.81	6.07	−0.82	4.62	2.05	5.44

Table 4
Percentage contribution of terms in Eq. (1) to convulsant activity and inhalation anesthesia for the compounds used in Eqs. (2) and (3)

Term	Percentage contribution	
	Convulsants	Anesthetics
eE	3.4	0.6
sS	5.0	19.3
aA	1.5	30.4
bB	10.0	8.7
lL	80.1	41.0

$$\log(1/\mathrm{MAC}) = -0.752 - 0.034E + 1.559S + 3.594A + 1.411B + 0.687L \quad (3)$$

It is very important to note that the contributions listed in Table 4 are calculated only for the 44 convulsants used in Eq. (2) and for the 148 anesthetics used in Eq. (3).

We can also compare Eq. (2) with the corresponding equation for the solubility of gases and vapors in olive oil [12], Eq. (4).

$$\log K_{\mathrm{olive}} = -0.156 - 0.254E + 0.859S + 1.656A + 0.873L \quad (4)$$

The *bB* term is not significant as regards solubility in olive oil. In addition, since the 48 convulsants have almost zero hydrogen bond acidity, the *aA* term in Eq. (4) will be redundant and Eq. (4) will reduce to Eq. (5). For compounds with zero hydrogen bond basicity the *bB* term in Eq. (2) is redundant, and the equation will reduce to Eq. (6). Thus Eq. (4) reduces to Eq. (5) for compounds that have $A = 0$, and Eq. (2) reduces to Eq. (6) for compounds that have $B = 0$.

$$\log K_{\mathrm{olive}} = -0.156 - 0.254E + 0.859S + 0.873L \quad (5)$$

$$\log(1/\mathrm{CON}) = -0.573 - 0.228E + 1.198S + 0.776L \quad (6)$$

Eqs. (5) and (6) show that for compounds with small or zero hydrogen bond acidity, there will be a good connection with solubilities in a solvent for which hydrogen bond basicity is not important. Hence the observation of Eger et al. [1] is that convulsant activity can be fitted very well to solubility in olive oil. This observation does not necessarily imply that the mechanism of convulsant activity involves a nonpolar phase. In our analysis, it is simply a result of the lack of hydrogen bond acidity in the convulsants and the lack of a term in *bB* for solubility in olive oil.

There are 19 compounds in Table 1 for which the corresponding anesthetic pressures are available [8]. A plot of the experimental values of log *P*/atm (CON) against the experimental values of log *P*/atm (MAC) for these 19 compounds is shown in Fig. 2. The experimental convulsant pressure is always less than the experimental anesthetic pressure – this must be the case, otherwise the convulsants would be anesthetics. We can extend the comparison by calculating anesthetic pressures through Eq. (3) for all 48 convulsants. The corresponding plot is shown as Fig. 3; once again the convulsant pressure is less than the anesthetic pressure for all 48 compounds. We can go further and calculate convulsant pressure through Eq. (2) as well as calculating anesthetic pressure through Eq. (3), see Fig. 4. For every compound in Table 1, the calculated convulsant pressure is less than the calculated anesthetic pressure, as shown in Fig. 4. This is the first time that any equations have been used to calculate convulsant and anesthetic pressures. It is now possible, again for the first time, to predict whether a compound will act as a convulsant [log *P*(CON) less than log *P*(MAC)] or will act as an anesthetic [log *P*(MAC) less than log *P*(CON)]. Note that in Figs. 2–4 we use log *P* and not log(1/*P*).

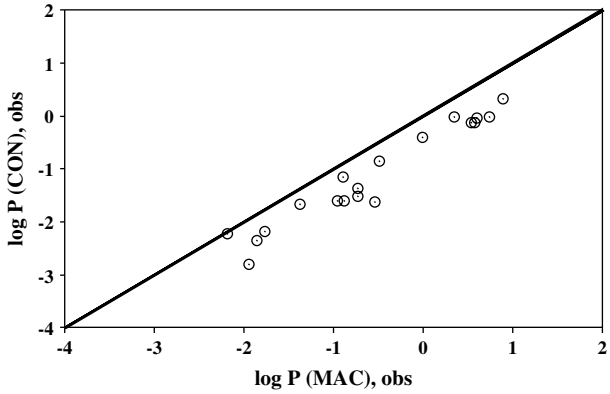

Fig. 2. A plot of observed log *P*/atm values for convulsant activity, CON, against observed log *P*/atm values for inhalation anesthesia, MAC. The line is that of unit slope.

For many compounds, there is very little difference in the two pressures. For example, log *P* for convulsant activity is −0.41 atm for 1,2-dichlorotetrafluoroethane and our calculated log *P* for anesthetic activity is −0.31 atm. Such small differences in pressure are very difficult to relate to compound structure just by inspection (other than our observation that the 48 convulsants tend to have small hydrogen bond acidities). However, since our calculations on convulsant and anesthetic pressures through Eqs. (2) and (3) have given rise to correct predictions on relative convulsant and anesthetic pressures

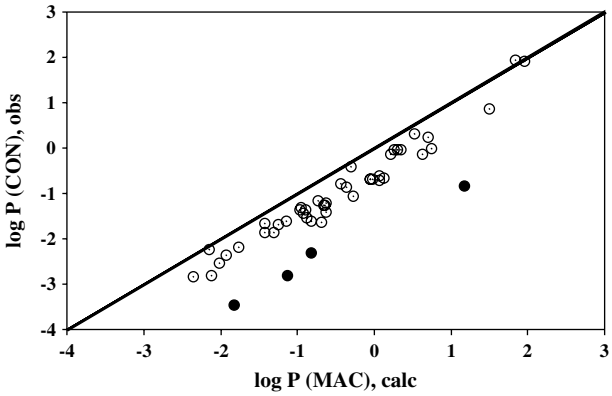

Fig. 3. A plot of observed log *P*/atm values for convulsant activity, CON, against calculated log *P*/atm values for inhalation anesthesia, MAC, in Eq. (3). The line is that of unit slope. The points marked ● are the four outliers that are more potent as convulsants than calculated.

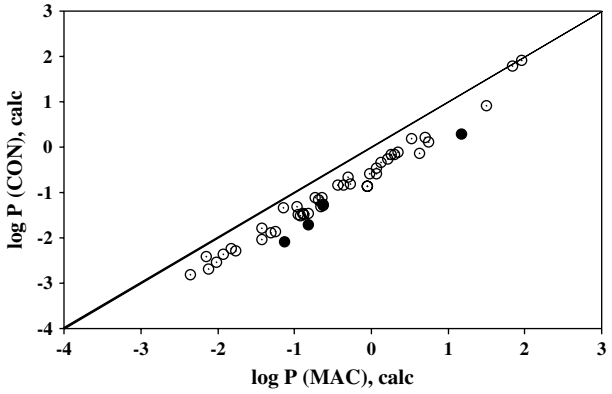

Fig. 4. A plot of calculated log *P*/atm values for convulsant activity, CON, in Eq. (2) against calculated log *P*/atm values for inhalation anesthesia, MAC, in Eq. (3). The line is that of unit slope. The points marked ● are the four outliers that are more potent as convulsants than calculated.

for every one of the 48 compounds studied by Eger et al. [1], we suggest that Eqs. (2) and (3) that incorporate the structural features that lead to convulsant or anesthetic activity, can be used to predict whether a compound will act as a convulsant or as an anesthetic. Of course, there is bound to be an area of uncertainty if the two calculated pressures are very close. In addition, the accurate calculation of compound descriptors is vital, especially for cases where the two calculated pressures are close. For the 48 convulsants, we have been fortunate that Eger et al. [1] determined by experiment solubilities in olive oil and solubilities in saline, both of which are valuable physicochemical parameters for the experimental determination of descriptors.

Not only can we make predictions about convulsant and anesthetic activity, but also our general equation is more economic than the suggestions of Eger et al. [1]. There is no need to postulate an unexplained mechanism, and no need to offer explanations for the five compounds that Eger et al. [1] regarded as less potent than calculated (on the basis of solubility in olive oil). Within the statistical limits of Eq. (2), octane, nonane, cyclohexane, cycloheptane, and cyclooctane are not outliers. There is still a need to explain the increased potency of perfluorodimethylcyclobutane, 1,1,1,2,2,3,3,4,5,6,6,6-dodecafluorohexane, bis(2,2,2-trifluoroethyl)ether, and perfluorotoluene, all of which are outliers in Eq. (2), see Fig. 2, and we can do no better than the suggestion of Eger et al. [1] that these compounds block the action of GABA.

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