indicators. It is also advisable, with any series of compounds, to check the stability of the system by changing dependent substituents at various segments, solving the system of equations again, and comparing the two sets of solution values. With an unstable system of equations, there is no unique set of solution coefficients; thus, the substituent contributions are unreliable and no sound conclusion can be reached about the resulting connection between changes in structure and changes in activity.

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Structure–Activity Correlations for Anticonvulsant Drugs

ERIC J. LIEN

School of Pharmacy, University of Southern California, University Park, Los Angeles, California 90007

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The anticonvulsant activity of series of drugs in mice and in rats against electroshock and pentylenetetrazole-induced seizures has been found to be highly correlated with the log P values of the drugs, where P is the 1-octanol–water partition coefficient. From the data on hand, linear dependence on log P is found for the anti-electroshock test in mice and the pentylenetetrazole protection test in rats, where the slope of the regression line associated with log P is about 0.6 ± 0.2. Parabolic dependence on log P is found for the antielectroshock activity in rats with an optimum lipophilic character (log P_0) of 1.75.

It was estimated that more than 20,000 compounds had been screened for anticonvulsant action in the last 10 years,[1] but many of them were not active or had very low activity. The need for better anticonvulsants to cope with epileptic seizures is reflected by continuous publications in this field. Unfortunately, not only is the mechanism of anticonvulsant action unknown, but also, few guide lines are available to help medicinal chemists in searching for better and safer anticonvulsants. The "common denominator" of clinically useful anticonvulsants has been known for some time.[2,3] However, no quantitative correlation of the relative potency of these drugs with the chemical structure has been satisfactory.

Recently Andrews examined the anticonvulsant activity of a number of potent anticonvulsants and tried to correlate it with the atomic charges of the so-called "biological active center" obtained from MO calculations and with the dipole moments of the drugs.[4] No significant correlation was obtained. The H-bonding atoms, although common to all the drugs studied, were not proven responsible for variations in activity.

In view of the fact that the anticonvulsant activity was studied *in vivo* and that the availability of the drug at the biophase and the receptor site must be considered before any meaningful structure–activity correlation can be obtained,[5] the author wishes to show that the variation in the anticonvulsant activity of series of potent drugs in 4 different tests can be correlated satisfactorily with log P (P = 1-octanol–H_2O partition coefficient).

Methods

The antisupramaximal-electroshock data in mice, the atomic charge and the dipole moments were taken from Andrews' paper.[4] The antielectroshock data in rats and in mice were from the work of Chen and Ensor.[6] The data of pentylenetetrazole protection were from the report of Swinyard.[7] For the details of the biological tests the original articles should be consulted. The log P values of 4 compounds were experimentally determined by Hansch's group and the others were calculated from the log P values of the parent molecules and the π constants of the substituents[8–11] (see Table I). The following log P of π values were used in the calculation of the log P values: π of oxazolidine-2,4-dione = $\pi_{OCO} + \pi_{CH_2CON} = (-1.14) + (-0.79) = -1.93$; $\pi_{CH_2CO} = -0.55$; $\pi_{NHCONH_2} = -1.01$; $\pi_{Br(aliphatic)} = 0.60$; $\pi_{hydantoin}$ = log P of 5-ethyl-5-phenylhydantoin $- (\pi_{Et} + \pi_{Ph}) = 1.53 - (1.00 + 1.77) = -1.24$; $\pi_{succinimide}$ = log P of 2-ethyl-2-phenylglutarimide $- (\pi_{Et} + \pi_{Ph} + \pi_{1/6\ cyclohexane}) = 1.90 - (1.00 + 1.77) - 1/6(2.51) = -1.29$; $\pi_{Ph} = 1.77$ (on the heterocyclic ring); $\pi_{Ph} = 2.13$ (for terminal substituents); π_{Me} (on N) = 0.56; π_{Me} (on C) = 0.50.

The equations correlating the antielectroshock and the antipentylenetetrazole activity in mice and rats with the physicochemical constants (see Table II) were derived *via* the method of least squares using an IBM 360/65 computer.

Results and Discussion

The equations obtained from the regression analysis are summarized in Table II. The results are not presented where no better correlation coefficient than 0.85 could be obtained. From eq 1–3 it is clear that neither the dipole moment nor the charge on the "biological activity center" (EHT, CNDO/2) can account for the variations in the anticonvulsant activity ($r < 0.4$).

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Table I
Biological Data and Physicochemical Constants Used in Deriving the Equations in Table II

Antielectroshock activity in mice: ED_{50} (mmoles/kg)[a]	Antielectroshock activity in mice: log 1/C (moles/kg) obsd	Antielectroshock activity in mice: log 1/C (moles/kg) calcd[d]	Dipole moment[a] (μ)	Charge on BAC[a]: EHT[b]	Charge on BAC[a]: CNDO/2[c]	log P	Drug
6.85	2.16	2.19	1.74	0.618	0.122	−0.37[e]	3,5,5-Trimethyloxazolidine-2,4-dione
2.55	2.59	2.57	1.69	0.602	0.118	0.13[e]	3,5-Dimethyl-5-ethyloxazolidin-2,4-dione
0.19	3.72	3.56	(1.74)[f]	0.330	0.085	1.53[g]	5-Ethyl-5-phenylhydantoin
0.04	4.40	4.23	(1.74)[f]	0.329		2.47[g]	5,5-Diphenylhydantoin
0.90	3.05	2.96	(1.74)[f]	0.206	0.061	0.70[e]	5-Phenylhydantoin
0.53	3.28	3.21	(1.61)[f]	0.065	−0.022	0.98[e]	3-Methyl-3-phenylsuccinimide
0.10	4.00	3.82	0.87	0.050		1.42[h]	5-Ethyl-5-phenylbarbituric acid
1.01	3.00	3.16	1.13	0.048	−0.068	0.65[h]	5,5-Diethylbarbituric acid
0.29	3.54	3.57	(1.61)[f]	0.047		1.48[e]	3-Ethyl-3-phenylsuccinimide
0.18	3.74	4.13	(1.61)[f]	0.044		2.25[e]	3,3-Diphenylsuccinimide
1.70	2.77	2.85	1.61	−0.080	−0.043	0.48[e]	3-Phenylsuccinimide

Antielectroshock activity in rats: PD_{50} (mg/kg)[i]	Antielectroshock activity in rats: log 1/C (moles/kg) obsd	Antielectroshock activity in rats: log 1/C (moles/kg) calcd[j]	Antielectroshock activity in mice: PD_{50} (mg/kg)[a]	Antielectroshock activity in mice: log 1/C (moles/kg) obsd	Antielectroshock activity in mice: log 1/C (moles/kg) calcd[k]	log P	Drug
24	4.06	4.07	11.4	4.38	4.28	2.47[g,l]	Diphenylhydantoin sodium
7.1	4.49	4.23	4.5	3.69	4.01	2.09[e]	3-Methyl-5-phenyl-5-ethylhydantoin
14.2	4.16	4.26	37.5	3.74	3.61	1.53[e]	5-Phenyl-5-ethylhydantoin
8.6	4.43	4.23	23.6	3.99	3.53	1.42[h,l]	Phenobarbital sodium
24	4.01	4.26	35.5	3.84	3.93	1.98[e]	*N*-Methyl-5-phenyl-5-ethylbarbituric acid
20	3.95	3.71	150	3.07	2.92	0.57[e]	Phenylacetylurea
40	3.79	4.07	288	2.92	3.26	1.04[e]	Carbromal (bromodiethylacetylurea)
452	2.75[m]		660	2.16[n]		1.61[e]	5,5-Diphenyl-2,4-dioxazolidinedione
560	2.41	2.46	980	2.16	2.25	−0.37[e]	3,5,5-Trimethyloxazolidine-2,4-dione

Metrazole seizure protection test in rats: ED_{50} (mg/kg)	Metrazole seizure protection test in rats: log 1/C (moles/kg) obsd[o]	Metrazole seizure protection test in rats: log 1/C (moles/kg) calcd[p]	log P	Drug
54.9	3.60	4.00	2.09[e]	3-Methyl-5-ethyl-5-phenylhydantoin
25.9	3.95	3.65	1.42[h,l]	Phenobarbital
15.1	4.21	3.94	1.98[e]	1-Methyl-5-ethyl-5-phenylbarbituric acid
300.7	2.68	2.70	−0.37[e]	3,5,5-Trimethyloxazolidine-2,4-dione
136.9	3.06	2.96	0.13[e]	3,5-Dimethyl-5-ethyloxazolidine-2,4-dione
200.0	2.95	3.20	0.57[e]	Phenylacetylurea

[a] From ref 4. [b] Calcd from the extended Hückel theory. [c] Calcd from complete neglect of differential overlap. [d] Calcd from eq 7. [e] Calcd from the log *P* of the parent molecule and the π values of the substituents. [f] Estimated value. [g] Private communication from Professor Corwin Hansch. [h] From ref 11. [i] From ref 6. [j] Calcd from eq 13. [k] Calcd from eq 15. [l] The log *P* of the undissociated form is used. [m] This point was not included in eq 12 and 13. [n] This point was not included in eq 15. [o] From ref 7. [p] Calcd from eq 16.

Equations 4 and 6 indicate that log *P* alone gives very good correlation (r = 0.997; 0.952). Addition of the dipole moment (μ) term gives eq 7, which "explains" more than 93% (r^2 = 0.935) of the variance in the data. The μ term is barely significant at the 90 percentile level ($F_{1,8}$ = 3.59; $F_{1,8}$ = 3.46). Inclusion of the charge term into eq 4 does not significantly improve the correlation (eq 5). Addition of $(\log P)^2$ term to eq 6 or 7 does not further improve the correlation significantly (eq 8 and 9).

For the antielectroshock in rats, among the 9 compounds examined, 5,5-diphenyloxazolidine-2,4-dione was very poorly predicted from eq 11 with a deviation greater than 2*s*. When this compound was eliminated, eq 12 and 13 were obtained. The $(\log P)^2$ term in eq 13 is significant at 97.5 percentile level ($F_{1,5}$ = 12.3; $F_{1,5\ 0.975}$ = 10.0). For the same group of compounds tested in mice against electroshock eq 14 and 15 were obtained. Again, 5,5-diphenyloxazolidine-2,4-dione was poorly predicted from eq 14.

For the pentylenetetrazole seizure protection test in rats eq 16 is obtained. Addition of $(\log P)^2$ term does not give a significant improvement in the correlation. The slopes of the regression lines associated with the log *P* term in eq 4–7, 12, 14–16 are about 0.6 ± 0.2.

From eq 4, 6, 7, 13–16 it is clear that the variation in anticonvulsant activity of the compounds examined is mainly due to the difference in lipophilic character (log *P*). The dipole moment term in eq 7 is barely significant. The dependence on log *P* is understandable since it has been shown that hydrophobic character is very important in governing drug absorption,[12] metabolism,[13] enzyme inhibition[14] as well as other types of nonspecific biological activities.[15,16] The optimum hydrophobic character ($\log P_0$) for maximum antielectroshock activity in rats is 1.75 (eq 13), very close to what has been reported for the hypnotic activity of barbiturates and other compounds in rats and mice ($\log P_0$ = 2).[11] This suggests that the optimum log *P* for the anticonvulsant activity is not too different from the optimum value for hypnotic effect. Therefore, by changing the lipophilic character alone one can not separate the CNS depression side effect from the anti-

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TABLE II
EQUATIONS CORRELATING THE ANTICONVULSANT ACTIVITY WITH THE PHYSICOCHEMICAL CONSTANTS

Eq		n[a]	r[b]	s[c]	log P_0 (95% c.l.)
	Antisupramaximal-electroshock in mice				
1	$\log 1/C = -0.51\,\mu + 4.088$	11	0.221	0.679	
2	$\log 1/C = -1.037$ (EHT) $+ 3.508$	11	0.371	0.647	
3	$\log 1/C = -1.792$ (CNDO/2) $+ 3.003$	7	0.284	0.525	
4	$\log 1/C = 0.824 \log P + 2.456$	7	0.997	0.040	
5	$\log 1/C = 0.834 \log P + 0.242$ (CNDO/2) $+ 2.441$	7	0.998	0.039	
6	$\log 1/C = 0.727 \log P + 2.521$	11	0.952	0.214	
7[d]	$\log 1/C = 0.720 \log P - 0.396\,\mu + 3.144$	11	0.967	0.189	
8	$\log 1/C = -0.099 (\log P)^2 + 0.946 \log P + 2.468$	11	0.959	0.210	4.76 ($\pm\infty$)
9	$\log 1/C = -0.465\,\mu + 0.654$ (EHT) $-0.153 (\log P)^2 + 1.126 \log P + 2.961$	11	0.980	0.169	3.68 ($\pm\infty$)
	Antielectroshock in rats				
10	$\log 1/C = 0.324 \log P + 3.311$	9	0.417	0.702	
11	$\log 1/C = -0.589 (\log P)^2 + 1.647 \log P + 3.086$	9	0.795	0.505	1.40 (0.98–4.02)
12	$\log 1/C = 0.564 \log P + 3.156$	8	0.795	0.426	
13[d]	$\log 1/C = -0.403 (\log P)^2 + 1.416 \log P + 3.037$	8	0.946	0.251	1.75 (1.36–3.77)
	Antielectroshock in mice				
14	$\log 1/C = 0.675 \log P + 2.449$	9	0.800	0.468	
15[d]	$\log 1/C = 0.718 \log P + 2.511$	8	0.928	0.287	
	Pentylenetetrazole seizure protection in rats				
16[d]	$\log 1/C = 0.529 \log P + 2.895$	6	0.886	0.314	

[a] The number of data points used in the analysis. [b] The correlation coefficient. [c] The standard deviation. [d] The statistically most significant equation.

convulsant activity. In order to get better separation of these two effects other molecular modifications involving electronic and steric characters must be explored. The importance of the π constant, the steric constant (E_s), the polar substituent constant (σ^*), and Hammett's σ constant in determining the anticonvulsant activities of alkyl esters of 2-sulfamoylbenzoic acids has been reported previously.[17]

Although the lipophilic character is highly important in governing the relative potency of congeneric drugs, it should not be used as the only parameter in predicting the biological activity. For example, by increasing the log P of glutarimide with increasing length of side chain at the β position one can change it from inactive to convulsant and finally to anticonvulsant.[4] On the other hand it has been reported that by methylating both nitrogens of barbiturates or by extending the side chain beyond 6 C atoms one can convert the hypnotics into convulsants.[18] It has also been reported by Lien and Kumler[19] that N,N'-dimethylation of cyclic ureas and thioureas increases their CNS stimulation activity. Thus, the connection between convulsants and anticonvulsants still remains as one of the most interesting and unsolved problems in medicinal chemistry.

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