Quantitative Structure–Activity Relationships and Dipole Moments of Anticonvulsants and CNS Depressants

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Abstract □ The anticonvulsant and CNS-depressant activities of 16 commercially available antiepileptics were subjected to regression analysis. For the maximal electroshock seizure test and pentylenetetrazol seizure threshold test, good correlations were obtained only after diazepam, clonazepam, and carbamazepam were deleted; for the median toxic dose (rotorod ataxia), all 16 compounds can be included in one single equation using log *MW*, log *P*, and dipole moment (μ) terms. For the anticonvulsant activities of 7-substituted 1,4-benzodiazepinones, a parabolic equation of π combined with the Hammett σ constant gave fair correlations for most derivatives examined in three different tests. Based upon the correlations obtained, further molecular modifications are suggested. The dipole moments of seven clinically used antiepileptic drugs were measured in 1,4-dioxane for the first time.

Keyphrases □ Anticonvulsants—quantitative structure–activity relationships and dipole moments □ CNS depressants—quantitative structure–activity relationships and dipole moments □ Structure–activity relationships—anticonvulsants and CNS depressants □ Dipole moments—anticonvulsants and CNS depressants

According to a literature survey in 1970, no more than 50% of epileptic patients were controlled by available antiepileptic drugs (1). Unfortunately, because of the limited market, relatively few pharmaceutical companies are actively pursuing antiepileptic drug research and development. To stimulate interest, a screening program was initiated in 1975 by the Antiepileptic Drug Development Program. Standardized testing methods have been used to evaluate new as well as 16 marketed antiepileptic drugs (1). This evaluation provides uniform sets of data suitable for quantitative structure–activity analysis.

The main purpose of this report is to analyze the structure–activity relationships of various anticonvulsant drugs (Tables I and II) in quantitative terms. The results obtained may be helpful to medicinal chemists in designing new antiepileptic drugs.

EXPERIMENTAL

The first set of data was from the recent publication (1) on 16 marketed antiepileptic drugs, using three anticonvulsant screening methods: the maximal electroshock seizure (MES) test, the subcutaneous pentylenetetrazol seizure threshold (MET) test, and the median toxic dose (TD_{50}) test. The biological data were all converted to log $1/C$, where C is the ED_{50} or LD_{50} value in moles per kilogram. The octanol–water partition coefficients (log *P*) were taken from the literature (2–4). The dipole moments were either from the literature (2, 5) or were experimentally determined in this study (Table III) using the published method of Halverstadt and Kumler (6, 7). The method of least squares was used in deriving the equations listed in Tables IV and V.

The second set of data, on anticonvulsant activities of 7-substituted 1,4-benzodiazepinones (Table II), was taken from the work of Sternbach *et al.* (8). The results of the regression analysis are given in Table V.

RESULTS AND DISCUSSION

Equations correlating the anticonvulsant activities of 16 clinically used antiepileptics are summarized in Table IV. For the maximal electroshock seizure test, a fair correlation with log *P* was obtained when all 16 compounds were included (Eq. 1). Addition of the nonlinear term [(log *P*)^2] or dipole moment term (μ) did not improve the correlation significantly, as judged by the correlation coefficients (r) and standard deviations (s).

A recent study (9) suggested that benzodiazepines appeared to occupy specific receptors. This led the authors to delete diazepam, clonazepam, and carbamazepine from the regression. When these structurally quite different compounds were eliminated, much better correlations were obtained (Eqs. 6–10). Not only were the correlation coefficients increased, but the standard deviations were decreased. Surprisingly, log *MW* gave the best correlation (Eq. 7). Similar dependence of biological activity on the log *MW* term and its implications were reported previously[2].

Table I—Anticonvulsant Activities and Physicochemical Constants of Various Drugs Used in the Regression Analysis

Compound	log $1/C$ MES Obs.[a]	log $1/C$ MES Calc.[b]	log $1/C$ MET Obs.[a]	log $1/C$ MET Calc.[c]	log $1/C$ TD_{50} Obs.[a]	log $1/C$ TD_{50} Calc.[d]	log *MW*	log P^e, Octanol–Water	μ^e, debeyes
Phenytoin	4.42	4.22	—	—	3.58	3.62	2.40	2.47	1.74
Ethotoin	3.38	3.52	3.63	3.64	3.08	3.10	2.31	1.53	1.74
Mephenytoin	3.56	3.76	3.86	3.51	3.15	3.03	2.34	2.09	1.74
Phenobarbital	4.03	3.99	4.25	4.20	3.44	3.69	2.37	1.42	0.87
Metharbital	3.19	3.45	4.30	4.02	3.47	2.92	2.30	1.21	1.13
Mephobarbital	3.86	4.15	4.02	4.10	3.10	3.46	2.39	1.98	0.87
Primidone	4.28	3.76	3.57	3.76	<2.56[f]	2.80	2.34	2.10	1.35[g]
Trimethadione	2.36	2.36	2.68	2.69	2.24	2.56	2.16	−0.37	1.74
Paramethadione	2.82	2.67	3.40	3.18	2.73	2.68	2.20	0.13	1.69
Ethosuximide	<2.15[f]	2.28	3.04	3.22	2.50	1.88	2.15	0.01	1.47
Methsuximide	3.43	3.52	3.48	3.73	3.03	3.02	2.31	1.54	1.61
Phensuximide	3.23	3.29	3.58	3.73	2.91	2.68	2.28	1.40	1.61
Phenacemide	3.31	3.06	3.19	3.23	2.63	3.25	2.25	0.57	2.06[g]
Diazepam	(4.17)[h]	(4.61)	(6.24)[h]	(1.94)	4.59	4.58	2.45	2.82	2.65[g]
Clonazepam	(3.56)[h]	(5.08)	(7.55)[h]	(2.98)	6.24	5.76	2.51	2.41[i]	2.33[g]
Carbamazepine	(4.40)[h]	(3.99)	—	—	3.52	3.79	2.37	2.18[j]	2.41[g]

[a] From Ref. 1. [b] Calculated from Eq. 7. [c] Calculated from Eq. 19. [d] Calculated from Eq. 23. [e] From Refs. 2 and 5 unless stated otherwise. [f] Exclusion of this data point does not affect the correlation significantly. [g] From this study. [h] Not included in the regression. [i] From Ref. 3. [j] Calculated from log $P_{(C_6H_5)_2NCONH_2} + \frac{1}{2}\pi(C_6H_5) = 1.53 + 0.65 = 2.18$.

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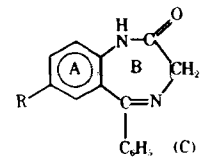

Table II—Anticonvulsant Activities and Physicochemical Constants of 7-Substituted 1,4-Benzodiazepinones

R	log 1/C: MET Obs.[a]	MET Calc.[b]	Maximum Obs.[a]	Maximum Calc.[c]	Minimum Obs.[a]	Minimum Calc.[d]	log *MW*	$\pi_{(R)}$[e]	$\sigma_{(R)}$[e]
H	<2.47[f]	(4.56)[f]	3.89	3.66	3.49	3.26	2.37	0.00	0.00
F	<2.50[f]	(4.65)[f]	2.92[f]	(3.76)[f]	3.40	3.33	2.40	0.14	0.06
Cl	4.65	4.80	4.03	4.01	3.32	3.43	2.43	0.71	0.23
Br	5.20	4.81	4.90[f]	(4.00)[f]	3.20	3.39	2.50	0.86	0.23
CN	5.31	5.23	3.89	4.00	2.59[f]	(3.79)	2.42	−0.57	0.66
NO_2	5.60	5.50	3.97	4.28	2.90[f]	(3.99)	2.45	−0.28	0.78
CF_3	5.48	5.14	4.78	4.29	4.16	3.69	2.48	0.88	0.54
CH_3	3.16[f]	(4.32)	3.22	3.66	<2.54[f]	(3.07)	2.40	0.56	−0.17
$N(CH_3)_2$	3.85	3.50	2.88	2.93	2.62	2.45	2.45	0.18	−0.83
SCH_3	4.15	4.53	3.93	3.78	2.97	3.23	2.45	0.61	0.00
SC_2H_5	3.57	4.40	3.07[f]	(3.78)	2.69	3.13	2.47	1.07	0.03
SC_4H_9	3.81	3.58	3.21	3.33	2.66	2.52	2.51	2.07	0.03
$SOCH_3$	4.07	4.20	3.52	2.91	2.99	3.07	2.47	−1.58	0.49
SO_2CH_3	2.72[f]	(4.44)	2.60	3.07	<2.60[f]	(3.25)	2.50	−1.63	0.72
C_6H_5	<2.60[f]	(3.65)	<2.59[f]	(3.27)	<2.59[f]	(2.57)	2.49	1.96	−0.01

[a] From Ref. 8. [b] Calculated from Eq. 25. [c] Calculated from Eq. 27. [d] Calculated from Eq. 29. [e] From Ref. 14. [f] Not included in the regression.

Table III—Dipole Moments (Debyes ● *SE*) of Some CNS Acting Drugs

Compound	In Dioxane	In Benzene
Chlordiazepoxide	2.15 ± 0.02	1.99 ± 0.01
Diazepam	2.65 ± 0.02	2.62 ± 0.01
Clonazepam	2.33 ± 0.02	—
Flurazepam	3.75 ± 0.02	3.11 ± 0.01
Phenacemide	2.06 ± 0.02	(Insoluble)
Primidone	1.34 ± 0.02	(Insoluble)
Carbamazepine	2.41 ± 0.01	(Insoluble)

Although the dependence on the dipole moment (μ) was not statistically significant, the negative sign of the coefficient was in agreement with previous findings (2, 10). The fact that diazepam and clonazepam had relatively high dipole moments (2.82 and 2.41 debyes, respectively) and were still active as antiepileptics, together with the finding that much better correlations were obtained when they were excluded, appears to support the contention that benzodiazepines probably occupy different receptors (9).

Improvements in correlation after deletion of diazepam and clonazepam were even more striking in the pentylenetetrazol seizure threshold test (Eqs. 11–19). Equation 19 was the best. The optimum lipophilicity (log P_0) for maximum activity was 1.42 with a 95% confidence interval of 1.06–9.61[3]. The dependence on μ was negative. The dipole moment term is statistically significant at the 97.5 percentile level as indicated by an F-test ($F_{1,8} = 9.83$, $F_{1,8_{0.975}} = 7.57$).

[3] The 95% confidence interval is skewed toward the upper limit as dictated by the equation used. For more details, see C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.* **11**, 1 (1968).

Table IV—Equations Correlating Anticonvulsant Activities with Physicochemical Constants

Equation	*n*	*r*	*s*
Maximal Electroshock Seizure Test (MES)			
1. $\log 1/C = 0.627 \log P + 2.588$	16	0.874	0.342
2. $\log 1/C = 5.554 \log MW - 9.379$	16	0.806	0.417
3. $\log 1/C = -0.064 (\log P)^2 + 0.781 \log P + 2.554$	16	0.877	0.351
4. $\log 1/C = 0.647 \log P - 0.133\mu + 2.785$	16	0.879	0.348
5. $\log 1/C = -0.030 (\log P)^2 + 0.714 \log P - 0.105\mu + 2.727$	16	0.880	0.362
(Without Diazepam, Clonazepam, and Carbamazepine)			
6. $\log 1/C = 0.681 \log P + 2.544$	13	0.896	0.314
7. $\log 1/C = 7.776 \log MW - 14.438$	13	0.941	0.241
8. $\log 1/C = 0.028 (\log P)^2 + 0.624 \log P + 2.551$	13	0.897	0.328
9. $\log 1/C = 0.669 \log P - 0.112\mu + 2.727$	13	0.898	0.326
10. $\log 1/C = 0.043 (\log P)^2 + 0.580 \log P - 0.130\mu + 2.768$	13	0.899	0.342
Subcutaneous Pentylenetetrazol Seizure Threshold Test (MET)			
11. $\log 1/C = 0.967 \log P + 2.755$	14	0.704	0.967
12. $\log 1/C = 6.105 \log MW - 10.185$	14	0.654	1.029
13. $\log 1/C = 0.502 (\log P)^2 - 0.206 \log P + 3.002$	14	0.779	0.890
14. $\log 1/C = 4.925 \log MW + 0.335 \log P + 1.257\mu - 9.934$	14	0.864	0.750
15. $\log 1/C = 4.817 \log MW + 0.256 (\log P)^2 - 0.222 \log P + 0.971\mu - 9.145$	14	0.875	0.762
16. $\log 1/C = 0.408 \log P + 3.121$	12	0.719	0.350
17. $\log 1/C = 2.676 \log MW - 2.594$	12	0.756	0.330
18. $\log 1/C = -0.302 (\log P)^2 + 0.960 \log P + 3.082$	12	0.799	0.319
19. $\log 1/C = -0.301 (\log P)^2 + 0.852 \log P - 0.629\mu + 4.139$; $\log P_0 = 1.42$ (1.06–9.61)	12	0.915	0.227
Median Toxic Dose (Rotorod Ataxia) TD_{50}			
20. $\log 1/C = 0.647 \log P + 2.348$	16	0.637	0.769
21. $\log 1/C = 8.030 \log MW - 15.336$	16	0.823	0.566
22. $\log 1/C = 0.265 (\log P)^2 + 0.010 \log P + 2.490$	16	0.677	0.761
23. $\log 1/C = 15.939 \log MW - 0.972 \log P + 0.549\mu - 33.187$; $F_{2,12} = 8.88$, $F_{2,12_{0.995}} = 8.51$	16	0.933	0.388

Table V—Equations Correlating Anticonvulsant and CNS-Depressant Activities of 1,4-Benzodiazepinones with Their Physicochemical Properties

Equation	n	r	s
Pentylenetetrazol Test			
24. $\log 1/C = -0.257\pi^2 - 0.082\pi + 4.869$	10	0.489	0.764
25. $\log 1/C = -0.307\pi^2 + 0.144\pi + 1.291\sigma + 4.558$	10	0.867	0.470
$\pi_0 = 0.23$ (−2.86–3.75)[a]			
Maximal Electroshock Test			
26. $\log 1/C = -0.188\pi^2 + 0.171\pi + 3.816$	11	0.513	0.592
27. $\log 1/C = -0.258\pi^2 + 0.361\pi + 0.954\sigma + 3.660$	11	0.824	0.418
$\pi_0 = 0.70$ (0.08–5.35)[a]			
Minimal Electroshock Test			
28. $\log 1/C = -0.132\pi^2 + 0.002\pi + 3.286$	10	0.379	0.497
29. $\log 1/C = -0.220\pi^2 + 0.081\pi + 0.984\sigma + 3.262$	10	0.827	0.326
$\pi_0 = 0.18$ (−2.82–2.37)[a]			

[a] For the derivation of these 95% confidence intervals, see C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.*, **11**, 1 (1968).

For the more nonspecific toxic dose (rotorod ataxia), all 16 compounds were well correlated with a three-parameter equation (Eq. 23). Furthermore, the dependence on the dipole moment was positive, in contrast with the anticonvulsant tests. Log *MW* gave better correlation than log *P*, with or without the quadratic term (compare Eq. 20 with 22). The positive dependence on log *MW* in Eqs. 21 and 23 suggests that van der Waals forces with nonspecific receptor sites are more important than hydrophobic interactions in the rotorod ataxia test.

The negative coefficient associated with the log *P* term in Eq. 23 is intriguing. Whether or not it represents interaction with somewhat hydrophilic sites remains to be studied. In any event, it is *not* parabolically dependent on log *P* as seen in many other cases of central nervous system (CNS) acting drugs (2, 10, 11).

The squared correlation matrix of the four parameters used for the 16 compounds in Eqs. 20–23 is shown here:

	log *MW*	$(\log P)^2$	log *P*	μ
log *MW*	1	0.785	0.861	0.071
$(\log P)^2$		1	0.882	0.193
log *P*			1	0.073
μ				1

It is apparent that log *MW* and log *P* are not independent while μ is practically independent of either log *MW* or log *P*. Therefore, the exact physical meaning of the log *MW* term can not be ascertained. A better selection of compounds with a wider range of log *MW* independent of log *P* is needed to delineate its contribution to the activity.

For the anticonvulsant activities of 1,4-benzodiazepinones with substitution at the 7-position of ring A, a parabolic equation of π_R combined with the Hammett σ constant appeared to give fair correlations for the results of all three tests (Table V). The ideal lipophilicity of the substituent (π_0) for the maximal electroshock test appears to be higher than those for the pentylenetetrazol test and the minimal electroshock test, although the 95% confidence intervals do overlap. Two or three compounds had to be excluded to obtain a correlation coefficient (r) of 0.82 or higher. Whether this result was due to experimental error or solubility problems (*e.g.*, the C_6H_5-derivative) could not be ascertained.

The importance of the electronic character was clearly reflected by the high coefficient associated with σ (0.95–1.29). In addition to the lipophilic and electronic characters, steric and directional factors also appear to be quite critical since substitutions at position 6, 8, or 9 of ring A reduced activity (12). Steinman *et al.* (13) reported that 7-Cl-9-NO_2- and 7,9-$(NO_2)_2$-derivatives of 1,4-benzodiazepine had weak activity (>100 mg/kg) as compared to diazepam (1 mg/kg) in pentylenetetrazol tests. Whether or not the same trend exists in the 1,4-benzodiazepinone series remains to be studied.

Clonazepam, one of the most potent compounds against pentylenetetrazol seizures, has a nitro group in ring A and a chloro atom in ring C. With regard to substitutions in ring C, Sternbach (12) showed that only the *ortho*-positions can be substituted and still maintain high activity. The 2′,6′-difluoro and dichloro derivatives had "high activity," while *meta*- and *para*-substituents decreased the activity almost to zero. It would be interesting to investigate combinations of Cl and NO_2, Br and NO_2, and CF_3 and NO_2 in the 2′,6′-positions of ring C.

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