QSAR of Chemical Polarizability and Nerve Toxicity. 2

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Polarizability is a property of molecules that has long been of interest to scientists from a variety of viewpoints. However, in the area of the QSAR of chemical−biological interactions, it has received little attention. Recently we have shown that one can use the simple summation of the valence electrons (H = 1, C = 4, O = 6, etc.) in a molecule as a measure of its polarizability. We have found this parameter to correlate nerve toxicity of a wide variety of chemicals acting on nerves of frogs, rabbits, cockroaches, and humans.

INTRODUCTION

Among the electronic factors that must be considered to understand how chemicals effect living systems or their parts is polarizability. Over the years, there has been much discussion of the subject;[1−5] however, taking into consideration this molecular property in attempts to formulate QSAR has been largely neglected except for the work in our laboratory. For many years we have used the Lorentz−Lorenz equation:

$$\mathrm{MR} = n^2 - 1/n^2 + 2\left(\frac{\mathrm{MW}}{d}\right) \quad (1)$$

In this expression, molar refractivity is defined by *n* (refractive index), MW (molecular weight), and *d* (density). Thus, MR is composed of two components, volume and the ability of the electrons to interact with light. It is of interest that this equation was defined in 1880 before anyone had thought of electrons. Leo developed an algorithm somewhat like what he formulated for calculating log P for octanol/water partitions.[6] We have found 1450 QSAR where calculated CMR plays an important role in chemical−biological interactions. However, we have realized that CMR is ambivalent, but that it could not be replaced by molar volume. We have now gained a deeper understanding of polarizabiliy[5] from the work of Agin et al.[4] In an unusual study of a very miscellaneous set of compounds that blocked the action of frog sartorius muscle, they showed that a plot of log 1/C vs αI_p yielded a very straight line. From their data we formulated eq 2.

$$\log 1/\mathrm{C} = 0.010(\pm 0.00)\alpha \mathrm{I_p} - 0.983(\pm 0.174) \quad (2)$$

$$n = 39,\ r^2 = 0.987,\ s = 0.240,\ q^2 = 0.984$$

The polarizability α was calculated as was the ionization potential I_p.

Deriving QSAR 2 for α alone, we obtained QSAR 3:

$$\log 1/\mathrm{C} = 0.082(\pm 0.005)\alpha - 0.664(\pm 0.23) \quad (3)$$

$$n = 39,\ r^2 = 0.973,\ s = 0.344,\ q^2 = 0.969$$

Thus we see that polarizability is the main factor in rationalizing their data. Using CMR calculated via the BioByte Clog P Program[6] we obtained QSAR 4.

$$\log 1/\mathrm{C} = 0.82(\pm 0.05)\mathrm{CMR} - 0.64(\pm 0.25) \quad (4)$$

$$n = 37,\ r^2 = 0.969,\ s = 0.375,\ q^2 = 0.964$$

outliers: antipyrine; methyl anthranilate

Next we showed that simply by adding up the number of valence electrons of the elements in the compounds (H = 1, C = 4, O = 6, N = 5, halogens = 7, S = 6, P = 5) to define NVE, we obtained QSAR 5.

$$\log 1/\mathrm{C} = 0.064(\pm 0.005)\mathrm{NVE} - 0.779(\pm 0.301) \quad (5)$$

$$n = 37,\ r^2 = 0.958,\ s = 0.458,\ q^2 = 0.953$$

outliers: antipyrine; octanol

QSAR 5 is not quite as good as QSAR 4. It does not contain the large volume component contained in the Lorentz−Lorenz equation and CMR, although volume is involved to some degree. That is the more electrons the greater the volume. We assumed that elements beyond F would be more easily polarized and hence would not fit QSAR 5 as well. However, this is not true; all of the halogens are well fit in many examples. We now have 373 QSAR based on NVE. In fact, $CHCl_3$ is not an outlier in QSAR 5.

In our earlier report[5] we found that NVE QSAR were often associated with nerve toxicity. Examples were found for the inhibition of cockroach, rabbit, and frog nerves. It is of special interest that we concluded that the toxic effect occurs at the synapse of the nerve axon. This appears to be a polar region, because most often we find no dependence on log P. No doubt, nerves could be blocked by hydrophobic compounds, but this is not our current interest. We believe that understanding this type of toxicity will have an important role in drug development in medicinal chemistry. However, it is now abundantly clear that NVE is important for other types of chemical−biological interactions.

RESULTS

A. Barbiturates. A logical place to look for nerve toxicity would be with barbiturates. At present, we have many QSAR on all aspects of this class of drugs. However, only a few are suitable for assaying nerve toxicity. Most of these are correlated by log P. In part, this is due to the fact that NVE and log P are perfectly collinear for saturated hydrocarbons. Many studies with barbiturates have been made with varia-

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Table 1. LD_{50} of Barbiturates for Female White Mice

no.	substituents	log 1/C obsd	log 1/C pred (eq 6)	log 1/C Δ	Clog P	NVE
1	5-Me, 5-C(Me)=CHC_2H_5	2.62	2.60	0.02	1.50	82
2	5-C_2H_5, 5-CH(Me)=CHC_2H_5[a]	3.09	2.82	0.27	2.03	88
3	5-C_3H_7, 5-CH(Me)=CHC_2H_5	2.95	3.05	−0.10	2.56	94
4	5-$CHMe_2$, 5-C(Me)=CHC_2H_5[a]	3.38	3.23	0.15	2.43	94
5	5-Me, 5-C(C_2H_5)=CHMe	2.56	2.60	−0.04	1.50	82
6	5-C_2H_5, 5-C(C_2H_5)=CHMe	2.90	2.82	0.08	2.03	88
7	5-C_3H_7, 5-C(C_2H_5)=CHMe	2.95	3.05	−0.10	2.56	94
8	5-$CHMe_2$, 5-C(C_2H_5)=CHMe	3.19	3.23	−0.04	2.43	94
9	5-Me, 5-C(Me)=CHC_3H_7	2.78	2.82	−0.04	2.03	88
10	5-C_2H_5, 5-C(Me)=CHC_3H_7	3.17	3.05	0.13	2.56	94
11	5-Me, 5-C(Me)=$CHCHMe_2$	3.05	3.01	0.04	1.90	88
12	5-Me, 5-C(Me)=CHC_4H_9[a]	2.82	3.05	−0.23	2.56	94
13	5-C_2H_5, 5-C(Me)=CHC_4H_9	3.29	3.27	0.02	3.09	100
14	5-C_2H5, 5-C(C_3H_7)=CHC_2H_5	3.29	3.27	0.02	3.09	100

[a] Outliers.

Table 2. Elimination Rate Constant of Barbiturates for Rabbits[10]

no.	substituents	log k obsd	log k pred (eq 7)	log k Δ	NVE
1	hexobarbital	0.17	0.01	0.17	92
2	pentobarbital	−0.01	−0.14	0.13	90
3	cyclobarbital	−0.05	0.01	−0.06	92
4	amobarbital	−0.35	−0.14	−0.22	90
5	allobarbaital	−0.92	−0.84	−0.09	80
6	phenobarbital[a]	−1.60	−0.28	−1.33	88
7	barbital	−1.34	−1.40	0.06	72

[a] Outlier.

tion at the 5-position, using alkyl groups. There are a few illustrative examples that contain unsaturated alkyl groups. For these we can distinguish NVE from log P correlation. The SAR of barbiturates has been discussed.[7,8]

LD_{50} for Female White Mice. Data from Cope and Hancock[9] (Table 1).

$$\log 1/C = -1.44(\pm 1.07)\ \text{Clog P} + 0.16(\pm 0.095)\ \text{NVE} - 8.70(\pm 6.25) \quad (6)$$

$n = 11$, $r^2 = 0.924$, $s = 0.077$, $q^2 = 0.879$

outliers: 5-C_2H_5, 5-C(Me)=CHC_2H_5; 5-CH(Me)$_2$, 5-CH(Me)=CHC_2H_5; 5-Me, 5-C(Me)=CHC_4H_9

The negative C log P term is what we would expect if the synapse is polar in character.

Elimination Rate Constant for Rabbits. Data from Watari et al.[10] (Table 2).

$$\log k = 0.070(\pm 0.025)\ \text{NVE} - 6.45(\pm 2.13) \quad (7)$$

$n = 6$, $r^2 = 0.940$, $s = 0.163$, $q^2 = 0.866$

outlier: phenobarbital

Possibly, nerves are involved in controlling elimination.

Inhibition of Acid Secretion from Gastric Mucosa of Frog. Data from Dinno et al.[11] (Table 3).

$$\log k = 0.028(\pm 0.003)\ \text{NVE} - 0.886(\pm 0.276) \quad (8)$$

$n = 5$, $r^2 = 0.996$, $s = 0.018$, $q^2 = 0.993$

outlier: thiamylal

Table 3. Inhibition of Acid Secretion from Gastric Mucosa of Frog by Barbiturates

no.	substituents	log k obsd	log k pred (eq 8)	log k Δ	NVE
1	barbital	1.15	1.15	0.00	72
2	diallylbarbituric acid	1.38	1.38	0.00	80
3	phenobarbital	1.58	1.60	−0.02	88
4	pentobarbital	1.68	1.66	0.02	90
5	secobarbital	1.77	1.77	0.00	94
6	thiamylal[a]	1.89	1.77	0.12	94

[a] Outlier.

Table 4. Narcosis of Mice by Barbiturates[12]

no.	substituents	log 1/C obsd	log 1/C pred (eq 9)	log 1/C Δ	NVE
1	5-Me, 5-C(C_3H_7)=CHC_2H_5				
2	5-C_2H_5, 5-C(Me)=CHC_4H_9	3.75	3.72	0.03	100
3	5-$CHMe_2$, 5-C(C_2H_5)=CHMe[a]	3.72	3.52	0.21	94
4	5-C_2H_5, 5-C(Me)=CHC_2H_5[a]	3.65	3.31	0.34	88
5	5-C_2H_5, 5-C(Me)=CHC_3H_7	3.64	3.52	0.13	94
6	5-C_3H_7, 5-C(Me)=CHC_2H_5	3.56	3.52	0.05	94
7	5-C_3H_7, 5-C(C_2H_5)=CHMe	3.42	3.52	−0.10	94
8	5-C_2H_5, 5-C(C_2H_5)=CHMe	3.40	3.31	0.09	88
9	5-Me, 5-C(Me)=CHC_4H_9	3.38	3.52	−0.14	94
10	5-Me, 5-C(Me)=CHC_3H_7	3.27	3.31	−0.04	88
11	5-Me, 5-C(Me)=CHC_2H_5	3.21	3.11	0.11	82
12	5-Me, 5-C(Me)=$CHCHMe_2$	3.20	3.31	−0.11	88
13	5-Me, 5-C(C_2H_5)=CHMe	3.06	3.11	0.05	82
14	5-$CHMe_2$, 5-C(Me)=CHC_2H_5[a]	3.98	3.52	0.47	94

[a] Outliers.

Table 5. LD_{100} of Miscellaneous Drugs for Humans[13]

no.		log 1/C obsd	log 1/C pred (eq 10)	log 1/C Δ	log P	NVE
1	chlorpromazine	5.20	5.38	−0.18	3.22	110
2	propoxyphene	5.08	4.98	0.10	2.36	134
3	amitriptyline	4.92	4.76	0.16	2.50	108
4	dothiepin	4.75	4.97	−0.22	2.76	108
5	secobarbital	4.19	4.13	0.06	1.97	94
6	phenobarbital	3.71	3.37	0.34	1.14	88
7	chloroform[a]	3.60	3.24	0.36	1.97	26
8	chlormethiazole	3.51	3.68	−0.17	2.12	50
9	paraldehyde	2.88	2.53	0.35	0.67	54
10	ether	2.17	2.42	−0.25	0.89	32
11	ethanol	1.06	1.27	−0.21	−0.31	20

[a] Outlier.

Narcosis of Mice. Data from Hansch et al.[12] (Table 4).

$$\log 1/C = 0.034(\pm 0.011)\ \text{NVE} + 0.303(\pm 1.00) \quad (9)$$

$n = 11$, $r^2 = 0.847$, $s = 0.095$, $q^2 = 0.782$

outliers: 5-CH(Me)$_2$, 5-C(C_2H_5)=CHMe; 5-C_2H_5, 5-C(Me)=CHC_2H_5; 5-CH(Me)$_2$, 5-CH(Me)=CHC_2H_5

B. Drug Toxicity to Humans. Of course, toxicity to humans is of greatest interest and the studies of King are surprising.

LD_{100} of Miscellaneous Drugs to Humans. Data from King[13] (Table 5).

$$\log 1/C = 0.83(\pm 0.30)\log P + 0.13(\pm 0.008)NVE + 1.26(\pm 0.44) \quad (10)$$

$n = 10$, $r^2 = 0.970$, $s = 0.270$, $q^2 = 0.922$

outlier: phenobarbital

In a previous study based only on log P, $r^2 = 0.876$. These data come from studies in England where, whenever an individual commits suicide or dies from an overdose of a drug, the drug concentration in their blood is immediately determined. From average values of many examples, King established log 1/C.

In a second, larger study[14] we were unable to formulate a QSAR, now using NVE we have derived QSAR 11 (Table 6).

$$\log 1/C = 0.61(\pm 0.17)\log P + 0.017(\pm 0.004)NVE + 1.44(\pm 0.37) \quad (11)$$

$n = 36$, $r^2 = 0.850$, $s = 0.438$, $q^2 = 0.817$

outliers: morphine; theophylline; $CF_2(Cl)_2$; halothane; paraldehyde

It is noteworthy that a number of drugs containing Cl and Br are reasonably well fit. Two of the drugs having these elements are outliers. The terms in QSAR 11 are similar to those of QSAR 10. In QSAR 10 and 11, there are log P terms that account for the movement of the drugs from the stomach to the nerves of the central nervous system.

Antiinflammatory Potency of Glucocorticoid Derivatives in Man. Data from Ahmad and Mellors[15] *(Table 7*).

$$\log AE = -0.78(\pm 0.35)\,\text{Clog P} + 0.091(\pm 0.03)\,NVE - 11.6(\pm 4.6) \quad (12)$$

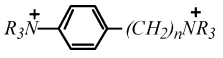
$n = 16$, $r^2 = 0.897$, $s = 0.278$, $q^2 = 0.836$

outliers: 6-Me-16-OH-prednisolone; 6,9-di-F-16-OH-prednisolone; 9-F-16-OH-prednisolone

AE is esonipenic potency of glucorticoids.

Obviously nerves are involved in inflammation so that one would anticipate that NVE would be important.

Paralysis of Rabbit Diaphragm by Injection of into Phrenic



Nerve. Data from Wein and Mason[16] *(Table 8*)

$$\log RBR = 0.034(\pm 0.005)\,NVE - 4.22(\pm 0.70) \quad (13)$$

$n = 16$, $r^2 = 0.933$, $s = 0.211$, $q^2 = 0.916$

outliers: R = Me, $n = 3$; R = Me, $n = 5$

RBR = relative biological response.

The same authors tested a similar set of congeners for which we found a similar QSAR.[5]

Inhibition of Cockroach Nerve Conduction by Miscellaneous Chemicals. Data from Uchida et al.[18] *(Table 9*).

$$\log 1/C = 0.084(\pm 0.009)\,NVE - 1.68(\pm 0.41) \quad (14)$$

$n = 11$, $r^2 = 0.981$, $s = 0.198$, $q^2 = 0.969$

outlier: L-menthol

Table 6. LD_{100} of Miscellaneous Drugs to Humans[14]

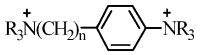
		log 1/C				
no.		obsd	pred (eq 11)	Δ	log P	NVE
1	morphine[a]	5.45	3.45	2.00	0.15	110
2	chlorpromazine	5.24	5.32	−0.08	3.22	110
3	propoxyphene	5.08	5.22	−0.14	2.36	134
4	strychnine	4.57	4.09	0.48	0.68	128
5	quinine	4.45	4.93	−0.48	2.11	126
6	maprotiline	4.74	4.19	0.55	1.42	108
7	pentazocine	4.50	4.68	−0.18	2.04	114
8	dothiepin	4.75	5.01	−0.26	2.76	108
9	flurazepam	4.86	5.35	−0.49	2.35	142
10	amitriptyline	4.92	4.85	0.07	2.50	108
11	nortriptyline	4.24	4.27	−0.03	1.71	102
12	cocaine	4.70	4.14	0.56	1.05	118
13	secobarbital	4.14	4.28	−0.14	1.97	94
14	desipramine	4.15	4.14	0.01	1.45	104
15	propranolol	4.46	3.94	0.52	1.18	102
16	diazepam	4.20	4.89	−0.69	2.80	100
17	phenobarbital	3.71	3.67	0.04	1.14	88
18	chlormethiazole	3.51	3.61	−0.10	2.12	50
19	theophylline[a]	3.51	2.62	0.89	−0.02	68
20	caffeine	3.23	2.69	0.54	−0.07	74
21	tetrachloroethylene	4.56	4.14	0.42	3.40	36
22	$CF_2(Cl)_2$[a]	4.61	3.32	1.29	2.16	32
23	toluene	4.34	3.73	0.61	2.73	36
24	$C(Cl)_4$	3.14	3.73	−0.59	2.83	32
25	$CH_3C(Cl)_3$	3.22	3.52	−0.30	2.49	32
26	trichloroethylene	3.91	3.44	0.47	2.42	30
27	$C(Cl)_3F$	4.06	3.54	0.52	2.53	32
28	nitrous oxide	2.39	1.99	0.41	0.43	16
29	benzene	3.99	3.26	0.73	2.13	30
30	$CH(F)_2Cl$	2.37	2.56	−0.19	1.08	26
31	halothane[a]	2.68	3.61	−0.93	2.30	44
32	$ClCH_2CH_2Cl$	2.49	2.80	−0.31	1.48	26
33	chloroform	3.60	3.10	0.50	1.97	26
34	CH_2BrCl	2.81	2.65	0.16	1.41	20
35	CH_2Cl_2	2.37	2.55	−0.18	1.25	20
36	CH_3CH_2Cl	2.21	2.66	−0.45	1.43	20
37	paraldehyde[a]	1.52	2.79	−1.27	0.67	54
38	EtOEt	2.17	2.54	−0.37	0.89	32
39	butanol	2.19	2.54	−0.35	0.88	32
40	2-propanol	1.26	1.93	−0.67	0.05	26
41	ethanol	1.26	1.82	−0.56	0.05	20

Table 7. Antiinflammatory Potency of Glucocorticoids in Humans[15]

		log AE			Clog	
no.		obsd	pred (eq 12)	Δ	P	NVE
1	cortisol	0.00	0.24	−0.24	1.70	144
2	coticosterone	−1.22	−0.79	−0.43	2.32	138
3	prednisolone	0.60	0.30	0.30	1.38	142
4	6-Me-11-OH−progesterone	−1.30	−1.45	0.15	3.17	138
5	6-Me-9-F-21-deoxycortisol	0.30	0.25	0.05	2.39	150
6	6-Me-prednisolone	0.70	0.60	0.10	1.70	148
7	6-Me-0-F-prednisolone	1.00	1.27	−0.27	1.55	154
8	6-Me-9-F-21-deoxyprednisolone	0.30	0.31	−0.01	2.07	148
9	9-Me-16-OH-prednisolone[a]	0.00	1.58	−1.58	1.14	154
10	6-F-cortisol	0.60	0.75	−0.15	1.74	150
11	6-F-prednisolone	0.95	0.81	0.14	1.43	148
12	6,9-di-F-16-OH-prednisolone[a]	0.70	2.46	−1.77	0.71	160
13	9-F-16-Me-prednisolone	1.08	1.11	−0.04	1.75	154
14	6,9-di-F-16-Me-prednisolone	1.48	1.63	−0.15	1.79	160
15	9-F-cortisol	0.90	0.91	−0.01	1.54	150
16	9-F-prednisolone	1.30	0.97	0.33	1.23	148
17	9-F-21-deoxy-prednisolone	−0.30	0.01	−0.32	1.75	142
18	9-F-16-OH-prednisolone[a]	0.70	1.95	−1.25	0.67	154
19	9-F-16-Me-21-deoxy-prednisolone	0.70	0.16	0.54	2.27	148

EC_{50} To Induce a Repetitive Train of Impulses and Conduction Blockage by Benzyl Chrysanthemates in Cockroach Nerves. Data from Nishimura et al.[19] *(Table 10*).

Table 8. Paralysis of Rabbit Diaphragm into Phrenic Nerve by Injection of[16]



no.	substituents R	*n*	log RBR obsd	pred (eq 13)	Δ	NVE
1	Me, Me, Me	0	−1.00	−1.00	0.00	94
2	Me, Me, Me	1	−0.70	−0.79	0.06	100
3	Me, Me, Me	2	−0.70	−0.59	0.11	106
4	Et, Me, Me	2	−0.22	−0.17	−0.05	118
5	Et, Et, Me	2	0.40	0.24	0.16	130
6	Et, Et, Et	2	0.48	0.65	−0.17	142
7	Me, Me, Me	3	−0.70	−0.38	−0.32	112
8	Et, Me, Me	3	0.00	0.03	−0.03	124
9	Et, Et, Me	3	0.60	0.44	−0.16	136
10	Et, Et, Et	3	0.78	0.86	−0.08	148
11	Me, Me, Me	4[a]	0.48	−0.17	0.65	118
12	Et, Me, Me	4	0.18	0.24	−0.06	130
13	Et, Et, Me	4	0.70	0.65	0.05	142
14	Et, Et, Et	4	1.30	1.06	0.24	154
15	Me, Me, Me	5[a]	0.78	0.03	0.75	124
16	Et, Et, Et	5	1.00	1.27	−0.27	160
17	Me, Me, Me	6	0.70	0.24	0.46	130
18	Et, Et, Et	6	1.40	1.47	−0.07	166

[a] Outlier.

Table 9. Inhibition of Cockroach Nerve Conduction by Miscellaneous Chemicals[18]

no.		log 1/C	pred (eq 14)	Dev	NVE
1	C_2H_5OH	−0.01	−0.01	0.00	20
2	C_3H_7OH	0.41	0.49	−0.08	26
3	C_4H_9OH	1.05	0.99	0.06	32
4	$C_5H_{11}OH$	1.55	1.49	0.06	38
5	$C_6H_{13}OH$	2.08	2.00	0.09	44
6	$C_7H_{15}OH$	2.71	2.50	0.21	50
7	$C_8H_{17}OH$	2.92	3.00	−0.08	56
8	L-menthol[a]	2.80	3.83	−1.03	66
9	thymol	3.52	3.33	0.19	60
10	gamma benzenehexachloride	3.40	3.83	−0.43	66
11	delta-benzenehexachloride	4.00	3.83	0.17	66
12	ether	0.82	0.99	−0.17	32

[a] Outlier.

$$\log 1/C = 0.97(\pm 0.31)\ \text{Mlog P} + 0.070(\pm 0.053)\ \text{NVE} - 0.85(\pm 4.63) \quad (15)$$

$n = 15$, $r^2 = 0.829$, $s = 0.369$, $q^2 = 0.720$

outliers: X = 6-Cl-3-pyridyl, Y = $CHNO_2$, Z = NH; X = CH_2CH_2-(6-Cl-3-pyridyl), Y = $CHNO_2$, Z = NH; X = CH_2-(6-Cl-3-pyridyl), Y = NNO_2, Z = $NHCH_2$; X = CH_2-(6-Cl-3-pyridyl), Y = $CHNO_2$, Z = O

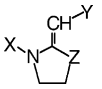
Minimum Blocking Concentration To Suppress Action Potential in Excised Central Nerve Cord of Cockroach Below 1 MV by Pyrethroids. Data from Nishimura et al.[20] *(Table 11).*

$$\log 1/C = 0.25(\pm 0.10)\ \text{Clog P} - 0.36(\pm 0.32)\ B1_3 + 0.020(\pm 0.008)\ \text{NVE} + 1.47(\pm 0.95) \quad (16)$$

$n = 12$, $r^2 = 0.938$, $s = 0.120$, $q^2 = 0.892$

outliers: $CH_2C_6H_5$; NO_2

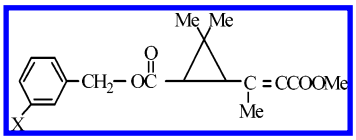
Table 10. EC50 To Induce a Repetitive Train of Impulses and Conduction Blockage by



no.	substituents X	Y	Z	log 1/C obsd	pred (eq 15)	Δ	Mlog P	NVE
1	CH_2−3-Pyridyl	$CHNO_2$	NH	4.54	4.07	0.47	−1.02	84
2	CH_2-(6-Cl-3-pyridyl)	$CHNO_2$	NH	5.65	5.30	0.35	−0.19	90
3	CH2-(6-Me-3-pyridyl)	$CHNO_2$	NH	4.94	4.91	0.03	−0.59	90
4	6-Cl-3-pyridyl	$CHNO_2$	NH[a]	6.10	4.84	1.26	−0.23	84
5	CH_2CH_2-(6-Cl-3-pyridyl)	$CHNO_2$	NH[a]	4.12	5.68	−1.56	−0.23	96
6	CH_2−2-pyridyl	$CHNO_2$	NH	3.70	4.22	−0.52	−0.87	84
7	CH_2−4-pyridyl	$CHNO_2$	NH	4.09	4.05	0.05	−1.05	84
8	benzyl	$CHNO_2$	NH	4.66	5.38	−0.72	0.33	84
9	4-Cl-benzyl	$CHNO_2$	NH	6.04	6.44	−0.40	0.99	90
10	CH_2-[5-(2-Cl)-thiazolyl]	$CHNO_2$	NH	5.35	5.16	0.19	−0.04	86
11	CH_2−3-pyridyl	NNO_2	NH	4.80	4.88	−0.08	−0.19	84
12	CH_2-(6-Cl-3-pyridyl)	NNO_2	NH	6.30	6.05	0.25	0.59	90
13	CH_2-(6-Cl-3-pyridyl)	NNO_2	NH-CH_2[a]	3.86	6.15	−2.29	0.26	96
14	CH_2-(6-Cl-3-pyridyl)	NCN	NH	5.82	5.66	0.16	0.77	82
15	CH_2-(6-Cl-3-pyridyl)	CHCN	NH	5.34	5.23	0.11	0.32	82
16	CH_2-(6-Cl-3-pyridyl)	$CHNO_2$	CH_2	6.25	6.14	0.11	0.68	90
17	CH_2-(6-Cl-3-pyridyl)	$CHNO_2$	O[a]	5.22	6.00	−0.78	0.54	90
18	CH_2-(6-Cl-3-pyridyl)	$CHNO_2$	S	6.42	5.11	0.31	0.65	90
19	CH_2-(6-Cl-3-pyridyl)	$CHNO_2$	NH	4.99	5.30	−0.31	−0.62	96

[a] Outlier.

Table 11. Minimum Blocking Concentration To Suppress Action Potential of Cockroach Nerve below 1 MV by Pyrethroids[20]



no.	substituents X	log 1/C obsd	pred (eq 16)	Δ	Clog P	B1-3	NVE
1	H	4.61	4.57	0.04	4.24	1.00	118
2	F	4.39	4.60	−0.21	4.38	1.35	124
3	Br	4.56	4.57	−0.01	5.11	1.95	124
4	Me	4.78	4.63	0.15	4.74	1.52	124
5	C_2H_5	4.80	4.89	−0.09	5.27	1.52	130
6	$CH_2C_6H_5$	5.27	5.59	−0.32	6.31	1.52	152
7	OMe	4.83	4.67	0.16	4.16	1.35	130
8	OC_2H_5	4.84	4.92	−0.08	4.69	1.35	136
9	$OCHMe_2$	5.11	5.12	−0.01	5.00	1.35	142
10	OC_6H_5	5.67	5.66	0.01	6.34	1.35	152
11	COC_6H_5	5.32	5.27	0.05	5.28	1.92	156
12	NO_2[a]	5.00	4.58	0.42	3.99	1.70	134
13	CN	4.42	4.38	0.05	3.68	1.60	126
14	SO_2Me	4.23	4.28	−0.05	2.60	2.06	142

[a] Outlier.

B1 is the Verloop sterimol parameter (ref 2, pp 76−78).

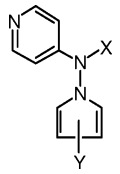
Inhibition of [^{3}H]Quinuclidinyl Benzylate Binding in Rat Forebrain Membrane by (Y-Pyrrole) Amino-pyridin-4-yls. Data from Kushwana et al.[17] *(Table 12).*

$$\log 1/C = -0.53(\pm 0.15)\ \sigma^*\text{-sum} + 0.018(\pm 0.011)\ \text{NVE} + 3.65(\pm 0.95) \quad (17)$$

$n = 12$, $r^2 = 0.912$, $s = 0.183$, $q^2 = 0.799$

outliers: X = Me, Y = 2-CHO; X = C_2H_5, Y = H; X = Me, Y = 2-CN

Table 12. IC_{50} Inhibition of [^{3}H]Quinuclidkinyl Benzilate Binding to Rate Forebrain Membrane by



	substituents		log 1/C			S′-
no.	X	Y	obsd	pred (eq 17)	Δ	sum
1	C_4H_9	H	4.90	4.60	0.30	0.85
2	Me	2-CH═CHC_6H_5	4.77	5.01	0.24	0.90
3	Me	2-CH═CH_2	4.74	4.52	0.22	0.89
4	C_3H_7	H	4.67	4.57	0.10	0.86
5	Me	2-C_2H_5	4.66	4.82	−0.16	0.39
6	Me	3-CH(OH)Me	4.62	4.63	0.01	0.95
7	CH_2CH═CH_2	H	4.57	4.41	0.16	1.10
8	Me	2-CHO[a]	4.28	3.59	0.70	2.64
9	Me	H	4.15	4.29	−0.14	0.98
10	C_2H_5	H[a]	3.92	4.45	−0.53	0.88
11	C_3H_7	3-CHO	3.86	3.87	0.01	2.52
12	H	H	3.73	3.93	−0.26	1.47
13	Me	3-CHO	3.73	3.59	0.15	2.64
14	Me	2-CN[a]	3.53	2.77	0.76	4.13
15	H	2-CHO	3.14	3.23	−0.09	3.13

[a] Outliers.

σ*-sum is the σ* for all substituents. This is Taft's definition of an inductive effect.[2] This is an interesting study in that the compounds studied possessed anti-Alzheimer activity. The most active compound was X = C_4H_9, Y = H. It would be interesting to test compounds with higher NVE and electron releasing ability such as Y = OC_4H_9, X = 2-CH═CHOMe.

SUMMARY

Polarizability is a property of chemicals that has received almost no attention, outside of our laboratory, by those studying chemical−biological interactions. This despite the fact that an algorithm for calculating molar refractivity has been available for many years on the widely used Clog P program.[6] As we have pointed out[5] there is surprisingly little interest in those developing new software for drug design in considering specific electronic interactions of any kind between simple chemicals and the more complex chemicals that make up living systems.

Our database contains 2400 biological QSAR that are based on the Hammett electronic parameters, 373 based on NVE and 2311 based on MR or CMR. Where these are a measure of polarizability based on the Lorentz−Lorenz equation. Thus, there is strong support for consideration of electronic effects in chemical biological interactions. Another surprising aspect of our findings is that good correlations can be obtained with whole animals, including humans! This highlights the unique character of the synaptic site associated with NVE. Recent studies of this region reveal a very complex mode of its operation.[21,22]

Another important observation of the present study as well as unpublished results is that our fear of elements beyond F (e.g., Cl, Br, I, S, P) would be more easily polarizable and hence would not fit QSAR based on the smaller elements is not justified. An important aspect of having a database of over 10 000 QSAR for chemical−biological interactions is that one can almost instantly retrieve long forgotten QSAR to support new ideas. Traditional QSAR is far from being a static subject.

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