On the Role of Polarizability in Chemical−Biological Interactions

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This report considers the importance of electronic effects in their role in the QSAR of chemical−biological interactions. The problem of accounting for polarizability effects in ligand−substrate interactions is discussed in terms of molecular polarizability (MR) and NVE (number of valence electrons) using additive values for valence electrons. The two approaches give essentially the same result in examples of frog nerve toxicity and examples of nerve toxicity with rabbits and cockroaches. The point is made that no matter how one approaches QSAR, electronic interactions must be considered if we are to begin to develop a science of chemical−biological interactions.

I. INTRODUCTION

In these ultra modern times with the use of combichem and in silico approaches, computational scientists seem to forget about 20th century research on the role of electronic interactions between ligand and receptor. This might seem reasonable in the Las Vegas approach of synthesizing tens of thousands of more or less pure compounds in the search for new leads, but sooner or later one has to face the fact that electronic interactions between receptor and ligand can be crucial. At present, our bio database of 9000 bio QSAR contains 2022 equations that have Hammett type parameters (σ, σ^-, σ^+, σ*, σ_I) to account for specific electronic effects. These do not include polarizability, and so we have used molecular refractivity (MR) or CMR to account for this effect. This term occurs in 1940 QSAR. Sometimes both Hammett and MR terms occur in a QSAR. In addition, there are 71 examples based on HOMO, LUMO or BDE (bond dissociation energy). BDE has been shown to be useful in correlating radical reactions.[1] Such reactions are important in toxic situations such as smoking or certain environmental chemicals.

The Hammett parameters have been most useful in rationalizing a large number of radical reactions.[2,3] A huge amount of information on mechanistic organic chemistry has been rationalized via Hammett parameters. We now have in our physical chemical database, slightly more than 8900 QSAR of which 8875 are based on Hammett parameters. Thus, there is an enormous amount of information showing the importance of electronic effects in chemicals reacting with chemicals. Of course, all biological systems are composed of chemicals.

At present, there are two ways of taking into account electronic characteristics of these interactions, Hammett parameters or molecular orbital (MO) parameters. Currently, we have 137 instances where HOMO or LUMO have been used to explain electronic effects in biological QSAR. Of these 71 were better explained by Hammett parameters and 66 equations are based on MO parameters. In most of the latter examples, complex aromatic and heteroaromatic compounds, were under consideration where Hammett parameters could not be applied. In a recent study of a large number of phenols acting on *T. pyriformis* we found σ and LUMO to give essentially the same result.[4]

Using well established parameters is the only way to do comparative QSAR which is the road to a science of chemical−biological interactions by means of which one can make estimates of the biological activity of compounds not yet tested. This problem has not been generally faced by the scientific community. For example, the *great* temporary success of CoMFA was, among other things, due to the use of PLS (principle components) that covered up the possible roles of electronic and hydrophobic properties of chemicals. The terms in CoMFA equations are unique for each data set. Comparisons between sets are impossible, but we are definitely making progress in anticipating the biological properties of various functional groups[3] in terms of Hammett's ideas.

The most unfortunate aspect of the theoretical approach to understanding how chemicals effect living organisms (or their parts from DNA to protein, enzymes, etc. and organisms from bacteria to man), is that one needs all of the mechanistic chemistry *and* biology that can be stuffed into one's head, plus the expertise to do meaningful modeling with the 'proper' system. This is something that cannot be attained in a few years. This problem has led to compartmentalization in QSAR studies. One needs synthetic chemists to make the chemicals, biologists to test them and computational experts to understand the chemical−biological interactions. Often there is not close cooperation between these three groups. There are three major types of interactions that the modeler must deal with: hydrophobic, electronic and steric. Of course, the chemist making compounds must incorporate into his set of congeners a good range in these properties, otherwise their importance or lack of it cannot be established. The buzzword these days in drug research is ADME

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(absorption, distribution, metabolism and elimination). Here the experience of the biologists becomes essential and needs to be organized. QSAR can do it.

Another serious problem in computational chemistry pertains to the dependent variable in the QSAR. To make any sense at all, the left-hand term in the QSAR (dependent variable) must be uniform. Often researchers take great satisfaction in demonstrating how many molecules can be covered by a correlation equation. As we have recently demonstrated[4] with a large set of phenols, it makes no sense to lump compounds together unless it can be shown that they are all acting by the same mechanism. For example, for the compound $HOC_6H_4NH_2$ which is the substituent and which is the functional group?

An illustration of the lack of communication between the various types of workers trying to understand chemical−biological interactions comes from a recent meeting of 70 computational scientists, where the director asked: how many of you have heard of the Hammett equation. Four hands went up. He then asked one person what it meant to him. His reply was that he had only heard of it and had no idea of what it meant. Yet thousands of Hammett equations have been formulated by organic chemists who by and large have no interest in biology. At present, the Hammett parameters are the only practical way of accounting for electronic interactions of chemicals. MO parameters are too time-consuming in their formulation to be broadly useful although in certain instances they are essential.[1]

II. MOLECULAR POLARIZABILITY

Another kind of electronic effect that has been overlooked by most computational chemists is that of polarizability. Traditionally this has been defined by the Lorentz−Lorenz equation.[5]

$$MR = (n^2 - 1/n^2 + 2)MW/d$$

In this expression, n is the refractive index, MW is the molecular weight and d is the density of the substance. The refractive index is a measure of the interaction of light with the electrons in a molecule. This is a very sensitive measure of their polarizability and MW/d characterizes the volume. Since there is not a large variation in n, MR is also dependent on MW/d. In our first thinking about MR in QSAR, it was assumed that it was for practical purposes a volume related parameter (of course, volume will be related to electrons).[6] It has gradually become apparent to us that it can be much more than this.

Leo found that MR could be calculated (CMR) from fragments somewhat like the procedure he developed for octanol/water partition coefficients.[7] Many examples of MR for a variety of molecules were determined by Vogel's group.[8−10] Also it was the practice in Russia for many years to report refractive index and density for each newly synthesized liquid. Sometimes researchers went to considerable trouble to estimate MR for solid compounds by studying various concentrations in solution and then extrapolating to obtain the value for the solid. All of this information was used by Leo to develop CMR.

A more sophisticated approach can be found in the monographs by Karplus and Porter[11] and Flygare.[12] The following results are germane to our discussion. The polarizability is the conversion factor between an applied electric field and the induced dipole moment. Since most molecules are asymmetric, it is a three-dimensional tensor. However, the average of the tensor's diagonal elements, α, suffices for most purposes including ours.

$$\alpha = (1/3)(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \quad (1)$$

Several options exist for the determination of α: (1) an experimental determination, a tedious process, (2) calculation using an ab initio program such as Gaussian, (3) estimation from the molecular structure using parameters derived from small molecules,[13] and (4) estimation using a surprisingly simple method outlined here. Our method yields the static polarizability, $\alpha(0)$, which is obtained when a static or DC electric field is applied. This is often the quantity that is reported although authors are not always clear in indicating the type of polarizability.

Karplus and Porter[11] show in a semiclassical argument that $\alpha(0)$ can be expressed by the following sum over the types of electrons, e.g. 1s, 2s, 2p

$$\alpha(0) = e^2 \sum N_i/k_i \quad (2)$$

where N_i is the number of electrons of type i whose binding to the atom or molecule is described by a force constant k_i. k_i is equal to $IP_i/2r_{e,i}$[12] where IP_i and $r_{e,i}$ are the ionization potential and Bohr radius of electron i, respectively. If IP_i and $r_{e,i}$ are expressed by the Bohr formula, formula (2) simplifies to

$$\alpha(0) = 4a_0^3 \sum N_i(n_i/Z_{e,i})^4 \quad (3)$$

where a_0 is the Bohr radius of atomic hydrogen and n_i and $Z_{e,i}$ are the principal quantum number and effective nuclear charge of electron i. The sum can be truncated to include only terms from the valence electrons. n_i is large and $Z_{e,i}$ is small for valence electrons because the total nuclear charge is screened by the core electrons. As a result, eq 3 is dominated by the contributions from the valence electrons. Furthermore, although the ratio $(n/Z)^4$ varies by orders of magnitude as Z increases, the relevant ratio $(n_i/Z_{e,i})^4$ exhibits comparatively small variations for the elements present in the bulk of the substrates.

Using the effective nuclear charges calculated by Clementi and Raimondi,[14] the ratio $(n_i/Z_{e,i})^4$ for the elements C, H, N, O and F lies in the narrow range 0.61 to 2.6. As a bold simplifying first approximation, we treated all valence electrons as equal. In this case, the static polarizability is directly proportional to the total number of valence electrons in the molecule, NVE. This model was tested with 39 molecules in Agin's data set and the fit yielded an R^2 of 0.964. As a further test, we selected 37 molecules from the NIST CCCBDB database[15] whose primary mission is the evaluation of ab initio methods. Static polarizabilities are tabulated for molecules containing 0 to 6 heavy atoms; we selected values calculated using the MP2FC method with a 6-311G* basis set. This second test fully supported the first yielding the equation:

$$\alpha(0)\ [\text{Å}^3/\text{molecule}] = 0.27(\pm 0.011)\ \text{NVE} \quad (4)$$
$$s = 0.76, \qquad R^2 = 0.924$$

Table 1. Minimum Concentration Required for Complete Block of Excitability in Sartorious Muscle of Frog

		log1/C						
no.	compound	obsd	calcd (eq 6)	calcd (eq 7)	calcd (eq 8)	α	CMR	NVE
1	methyl alcohol	−0.09	0.01	0.02	−0.01	8.20	0.79	12.0
2	ethyl alcohol	−0.25	0.39	0.39	0.50	12.90	1.26	20.0
3	acetone	0.40	0.66	0.68	0.75	16.20	1.60	24.0
4	2-propanol	0.45	0.78	0.77	0.88	17.60	1.72	26.0
5	propanol	0.60	0.77	0.77	0.88	17.50	1.72	26.0
6	urethane	1.00	1.23	1.11	1.52	23.20	2.13	36.0
7	ethyl ether	1.07	1.18	1.15	1.90	22.50	2.19	42.0
8	butanol	1.22	1.14	1.15	1.90	22.10	2.19	42.0
9	antipyrine[a,b]	1.22	1.77	3.92	4.45	29.80	5.56	82.0
10	pyridine	1.23	1.31	1.39	1.13	24.10	2.48	30.0
11	chloroform	1.50	1.09	1.10	0.88	21.40	2.12	26.0
12	hydroquinone	1.60	1.74	1.82	1.90	29.40	3.00	42.0
13	aniline	1.70	1.92	1.87	1.52	31.60	3.06	36.0
14	benzyl alcohol	1.70	1.99	2.07	1.52	32.50	3.31	36.0
15	acetanilide	1.83	1.83	2.66	2.54	30.50	4.02	52.0
16	pentanol	1.80	1.53	1.53	1.65	26.80	2.65	38.0
17	phenol	2.00	1.61	1.69	1.52	27.80	2.84	36.0
18	toluene	2.00	1.88	1.95	1.52	31.10	3.15	36.0
19	benzimidazole	2.19	2.62	2.31	2.03	40.20	3.60	44.0
20	hexanol	2.44	1.90	1.92	2.03	31.40	3.11	44.0
21	nitrobenzene	2.53	1.99	2.07	2.73	32.50	3.30	55.0
22	quinoline	2.70	2.78	2.78	2.03	42.10	4.17	44.0
23	8-hydroxyquinoline	2.70	2.99	2.90	2.41	44.70	4.32	50.0
24	heptanol	2.80	2.28	2.30	2.41	36.00	3.58	50.0
25	2-naphthol	3.00	3.05	3.08	2.67	45.40	4.53	54.0
26	methylanthranilate[a]	3.00	3.34	6.07	2.92	48.90	8.17	58.0
27	octanol[b]	3.16	2.66	2.68	2.16	40.60	4.04	46.0
28	thymol	3.52	3.20	3.22	3.69	47.30	4.70	70.0
29	o-phenanthroline	3.80	4.06	4.10	3.69	57.80	5.78	70.0
30	ephedrine	3.80	3.44	3.52	3.43	50.20	5.07	66.0
31	procaine	4.67	4.81	4.99	5.22	67.00	6.86	94.0
32	xylocaine	4.96	5.26	5.25	5.60	72.50	7.17	100.0
33	diphenyhydramine	5.80	5.84	5.96	5.60	79.50	8.04	100.0
34	tetracaine	5.90	5.85	5.75	5.98	79.70	7.79	106.0
35	phenyltoloxamine	6.20	5.87	5.96	5.60	79.90	8.04	100.0
36	quinine	6.60	7.01	7.14	7.26	93.80	9.48	126.0
37	eserine	6.66	6.07	5.70	6.11	82.40	7.72	108.0
38	caramiphen	7.00	6.45	6.45	6.62	87.00	8.63	116.0
39	dibucaine	7.20	7.81	7.73	7.26	103.60	10.19	126.0

[a] Data points not included in deriving QSAR 7. [b] Data points not included in deriving QSAR 8.

We also considered a multivariate model in which the polarizability is linearly related to the number of valence electrons on each atom. This more sophisticated model did not yield better results, and therefore the simpler model of direct proportionality with the total number of valence electrons was adopted. That is, the easily calculated NVE can be used as a model for polarizability.

III. EARLY EFFORTS TO CORRELATE BIOLOGICAL REACTIONS WITH LIGAND POLARIZABILITY

The first effort to apply molecular refractivity in terms of the Lorentz−Lorenz equation to biological processes was made by Pauling and Pressman.[16] They considered polarizability in hapten antibody interactions. It was later shown that only steric factors were involved in their example.[17] Nevertheless, their effort sparked our interest in the subject.

Agin et al.[18] made a highly interesting study of the ability of a wide variety of chemicals to block the sartorius muscle of the frog presumably by nerve inhibition. From this, they obtained the minimum blocking concentration. To correlate the data, they studied two parameters: α (polarizability) and I_P (ionization potential). Their plot of the data was very impressive. From their data we formulated the following QSAR (Table 1):

$$\text{Log } 1/C = 0.010(\pm 0.000)\ \alpha I_P - 0.996(\pm 0.17) \quad (5)$$
$$n = 39,\ r^2 = 0.987,\ s = 0.240,\ q^2 = 0.984$$

$$\text{Log } 1/C = 0.082(\pm 0.005)\ \alpha - 0.664(\pm 0.23) \quad (6)$$
$$n = 39,\ r^2 = 0.973,\ s = 0.344,\ q^2 = 0.969$$

In these equations, C is the molar concentration of chemical. It is clear that ionization potential has rather little to do with the inhibitory process. Using that as the independent variable yields an $r^2 = 0.265$. This is a remarkable result that has received essentially no attention from the computational industry.

Employing CMR we obtain the following result:

$$\text{Log } 1/C = 0.82(\pm 0.05)\ \text{CMR} - 0.64(\pm 0.25) \quad (7)$$
$$n = 37,\ r^2 = 0.969,\ s = 0.375,\ q^2 = 0.964$$
data points omitted: antipyrine, methyl anthranilate

QSAR 7 is not a bad result, considering how CMR values are obtained. All CMR were estimated via the BioByte

Table 2. Minimum Blocking Concentration for Frog Muscle

		obsd log 1/C	YPRED log 1/C	DEV	NVE
1	toluene	2.0	1.599	0.401	36.0
2	methanol	−0.090	−0.238	0.148	14.0
3	ethanol	0.250	0.263	−0.013	20.0
4	propanol	0.60	0.764	−0.164	26.0
5	2-propanol	0.450	0.764	−0.314	26.0
6	butanol	1.220	1.265	−0.045	32.0
7	pentanol	1.80	1.766	0.034	38.0
8	hexanol	2.440	2.267	0.173	44.0
9	heptanol	2.80	2.767	0.033	50.0
10	octanol	3.160	3.268	−0.108	56.0
11	acetone	0.40	0.597	−0.197	24.0
12	phenol	2.0	1.599	0.401	36.0
13	thymol	3.520	3.602	−0.082	60.0
14	benzyl-alc.	1.70	2.10	−0.40	42.0
15	ether	1.07	1.265	−0.195	32.0
16	$CHCl_3$[a]	1.50	0.764	0.736	26.0
17	aniline	1.70	1.599	0.101	36.0
18	nitrobenzene	2.530	2.433	0.097	46.0
19	2-naphthol	3.0	3.101	−0.101	54.0
20	pyridine	1.230	1.098	0.132	30.0
21	quinoline	2.70	2.60	0.10	48.0

[a] Data point not used in the derivation of QSAR 9.

Table 3. Reduction of Action Potential of Frog Nerves by 50%

		obsd log 1/C	YPRED log 1/C	DEV	NVE
1	methanol	−0.379	−0.306	−0.073	14.0
2	ethanol	0.055	0.148	−0.093	20.0
3	*n*-propanol	0.629	0.603	0.026	26.0
4	*n*-butanol	1.161	1.057	0.104	32.0
5	*n*-pentanol	1.699	1.512	0.187	38.0
6	n-hexanol	2.180	1.967	0.214	44.0
7	*n*-heptanol	2.658	2.421	0.236	50.0
8	phenol[a]	2.092	1.360	0.731	36.0
9	benzyl alcohol	1.699	1.815	−0.116	42.0
10	phenethyl alcohol	2.00	2.270	−0.270	48.0
11	3-phenyl-1-propanol	2.509	2.724	−0.216	54.0

[a] Data point not used in the derivation of QSAR 10.

algorithm,[7] while the parameters of QSAR 5 and 6 were calculated for each specific compound. CMR values can be calculated almost instantly from their SMILES formulas. We were pleased and surprised by the good correlation of QSAR 7. Steinmetz's approach for estimating polarizability can be obtained via the number of valence electrons in the ligand. From the data of Agin et al., we derived QSAR 8 (Table 1).

$$\log 1/C = 0.064(\pm 0.005)\,\mathrm{NVE} - 0.779(\pm 0.301)$$
$$n = 37,\ r^2 = 0.958,\ q^2 = 0.953,\ s = 0.435 \quad (8)$$
$$\text{outliers: antipyrene, octanol}$$

The number of valence electrons is simply added up by hand and can be calculated automatically from the molecular formula (NVE H = 1, C = 4, O = 6, N = 5, halogens = 7, S = 6, P = 5). The results with QSAR 7 and 8 when compared with QSAR 6 indicate that polarizability values can be estimated via CMR or number of valence electrons for the study of chemical−biological interactions. The collinearity between NVE and α is high $r^2 = 0.973$ as is that between α and CMR, $r^2 = 0.925$. One might have anticipated that the data of Agin et al. could have been rationalized with Clog P, but using this hydrophobic parameter, a very poor result is obtained ($r^2 = 0.588$). We have many QSAR for simple miscellaneous sets of compounds that are well correlated by Clog P. Another way of looking at the data of Agin et al. is to tie it to molar volume as such. Our C-QSAR program[7] calculates molar volume according to the method of McGowan.[7a] Using this parameter in place of α in QSAR 6, we obtain a much poorer correlation, $r^2 = 0.873$. The data obtained by Agin et al. from frog muscle appears to depend on inhibition of the nerve.

Table 4. Toxicity of Chemicals in Table 5 to Rabbit Nerves QSAR

	log RBR				
compound	obsd	calcd (eq 11)	calcd (eq 12)	NVE	CMR
1	−1.00	−1.00	−1.00	94	6.39
2	−0.70	−0.79	−0.79	100	6.85
3	−0.70	−0.59	−0.59	106	7.31
4	−0.22	−0.17	−0.17	118	8.24
5	0.40	0.24	0.24	130	9.17
6	0.48	0.65	0.65	142	10.10
7	−0.70	−0.38	−0.38	112	7.78
8	0.00	0.03	0.03	124	8.71
9	0.60	0.44	0.44	136	9.63
10	0.78	0.86	0.86	148	10.56
11[a]	0.48	−0.17	−0.17	118	8.24
12	0.18	0.24	0.24	130	9.17
13	0.70	0.65	0.65	142	10.10
14	1.30	1.06	1.06	154	11.02
15[a]	0.78	0.03	0.03	124	8.71
16	1.00	1.27	1.27	160	11.49
17	0.70	0.24	0.24	130	9.17
18	1.40	1.47	1.47	166	12.00

[a] Data points not included in deriving QSAR 9 and 10.

Another example of the minimum blocking concentration of miscellaneous drugs on frog muscle comes from a study by Kamlet et al.[20] (Table 2).

$$\log 1/C = 0.083(\pm 0.008)\,\mathrm{NVE} - 1.41(\pm 0.32)$$
$$n = 20,\ r^2 = 0.962,\ s = 0.213,\ q^2 = 0.955 \quad (9)$$
$$\text{outlier: } CHCl_3$$

Hahin et al.[21] studied the action of miscellaneous alcohols on frog nerves (Table 3) from their data we derived QSAR 10.

$$\log 1/C = 0.076(\pm 0.011)\,\mathrm{NVE} - 1.37(\pm 0.42)$$
$$n = 10,\ r^2 = 0.969,\ s = 0.192,\ q^2 = 0.952 \quad (10)$$
$$\text{outlier: phenol}$$

It is noteworthy that the slopes and intercepts of QSAR 9 and 10 are quite similar, despite the different types of end points. CMR is not quite as good as NVE. For QSAR 9, $r^2 = 0.940$ and for QSAR 10, $r^2 = 0.917$.

IV. OTHER EXAMPLES OF THE IMPORTANCE OF POLARIZABILITY

As noted above, we have numerous QSAR based on CMR terms. Of these, 575 are based on MR for substituents. We have published 1536 such values for substituents.[19] It is of interest to compare results of studies of nerve toxicity with those of Agin et al. [Paralysis of rabbit by injection of chemicals into nerve (phrenic diaphragm) (Table 4)—see

Table 5. Compounds in Table 4[a]

1. $(CH_3)_3\overset{+}{N}\text{-}C_6H_4\overset{+}{N}(CH_3)_3$
2. $(CH_3)_3\overset{+}{N}CH_2C_6H_4\overset{+}{N}(CH_3)_3$
3. $(CH_3)_3\overset{+}{N}CH_2CH_2C_6H_4\overset{+}{N}(CH_3)_3$
4. $CH_3CH_2(CH_3)_2\overset{+}{N}CH_2CH_2C_6H_4\overset{+}{N}(CH_3)_2CH_2CH_3$
5. $(CH_3CH_2)_2(CH_3)\overset{+}{N}CH_2CH_2C_6H_4\overset{+}{N}(CH_3)(CH_2CH_3)_2$
6. $(CH_3CH_2)_3\overset{+}{N}CH_2CH_2C_6H_4\overset{+}{N}(CH_2CH_3)_3$
7. $(CH_3)_3\overset{+}{N}(CH_2)_3C_6H_4\overset{+}{N}(CH_3)_3$
8. $CH_3CH_2(CH_3)_2\overset{+}{N}(CH_2)_3C_6H_4\overset{+}{N}(CH_3)_2CH_2CH_3$
9. $(CH_3CH_2)_2(CH_3)\overset{+}{N}(CH_2)_3C_6H_4\overset{+}{N}(CH_3)(CH_2CH_3)_2$
10. $(CH_3CH_2)_3\overset{+}{N}(CH_2)_3C_6H_4\overset{+}{N}(CH_2CH_3)_3$
* 11. $(CH_3)_3\overset{+}{N}(CH_2)_4C_6H_4\overset{+}{N}(CH_3)_3$
12. $CH_3CH_2(CH_3)_2\overset{+}{N}(CH_2)_4C_6H_4\overset{+}{N}(CH_3)_2CH_2CH_3$
13. $(CH_3CH_2)_2(CH_3)\overset{+}{N}(CH_2)_4C_6H_4\overset{+}{N}(CH_3)(CH_2CH_3)_2$
14. $(CH_3CH_2)_3\overset{+}{N}(CH_2)_4C_6H_4\overset{+}{N}(CH_2CH_3)_3$
* 15. $(CH_3)_3\overset{+}{N}(CH_2)_5C_6H_4\overset{+}{N}(CH_3)_3$
16. $(CH_3CH_2)_3\overset{+}{N}(CH_2)_5C_6H_4\overset{+}{N}(CH_2CH_3)_3$
17. $(CH_3)_3\overset{+}{N}(CH_2)_6C_6H_4\overset{+}{N}(CH_3)_3$
18. $(CH_3)_3\overset{+}{N}(CH_2)_6C_6H_4\overset{+}{N}(CH_3)_3$

[a] The anion in all instances is I-. All substituents on phenyl ring are in 1 and 4 positions. Compounds 11 and 15 were omitted in the derivation of QSAR 11 and 12.

Table 5 for structures. Data are from ref 22. RBR = relative biological response.]

$$\log \text{RBR} = 0.034(\pm 0.005)\ \text{NVE} - 4.22(\pm 0.70) \quad (11)$$
$$n = 16,\ r^2 = 0.933,\ s = 0.201,\ q^2 = 0.916$$

$$\log \text{RBR} = 0.44(\pm 0.07)\ \text{CMR} - 3.83(\pm 0.64) \quad (12)$$
$$n = 16,\ r^2 = 0.933,\ s = 0.201,\ q^2 = 0.916$$

It is impressive that two completely different means for calculating polarizability gives exactly the same quality equations. [Minimum blocking concentration to suppress action potential in excised central nerve cord from American cockroach—data are from Nishimura et al.[23] (Table 6).]

$$\log 1/\text{C} = 0.25(\pm 0.10)\ \text{Clog P} + 0.02(\pm 0.008)\ \text{NVE} - 0.360(\pm 0.32)\ \text{B1}_3 + 1.47(\pm 0.95) \quad (13)$$
$$n = 12,\ r^2 = 0.938,\ s = 0.120,\ q^2 = 0.892$$

$$\log 1/\text{C} = 0.17(\pm 0.10)\ \text{Clog P} + 0.313(\pm 0.10)\ \text{CMR} - 0.50(\pm 0.28)\ \text{B1}_3 + 1.75(\pm 0.71) \quad (14)$$
$$n = 12,\ r^2 = 0.958,\ s = 0.099,\ q^2 = 0.923$$

QSAR 14 is a bit better than 13, which is often the case. However, they do reinforce each other in approaching polarizability from two different points of view.

V. DISCUSSION

It is amazing that the Lorentz−Lorenz equation published in 1880 grew out of the Clausius-Mossotti expression derived in 1850, long before anyone dreamed of electrons. Clearly the results presented in this study bring out the importance of polarizability in chemical−biological interactions. However, the above QSAR represent a tiny fraction of the QSAR that we have based on CMR. For instance, we have many based on parabolic and bilinear CMR, equations that would seem to involve volume, but CMR cannot be replaced by molar volume calculated by McGowan's method.

Table 6. Suppression Action Potential in Cockroach Nerves by Pyrethroids

		log 1/C						
	X	obsd	calcd (eq 11)	calcd (eq 12)	NVE	CMR	ClogP	$B1_3$
1	H	4.61	4.57	4.66	118	8.55	4.24	1.00
2	F	4.39	4.60	4.51	124	8.56	4.39	1.35
3	Br	4.56	4.57	4.57	124	9.32	5.11	1.95
4	Me	4.78	4.63	4.63	124	9.01	4.74	1.52
5	C_2H_5	4.80	4.89	4.86	130	9.47	5.27	1.52
6	$CH_2C_6H_5$[a]	5.27	5.59	5.69	152	11.52	6.31	1.52
7	OMe	4.83	4.67	4.66	130	9.16	4.16	1.35
8	OC_2H_5	4.84	4.92	4.90	136	9.63	4.69	1.35
9	$OCH(Me)_2$	5.11	5.12	5.10	142	10.09	5.00	1.35
10	OC_6H_5	5.67	5.66	5.68	152	11.21	6.34	1.35
11	COC_6H_5	5.32	5.27	5.32	156	11.56	5.28	1.92
12	NO_2[a]	5.00	4.58	4.54	134	9.16	3.99	1.70
13	CN	4.42	4.38	4.41	126	9.02	3.68	1.60
14	SO_2Me	4.23	4.28	4.27	142	9.88	2.60	2.03

[a] Data points not included in deriving QSAR 11 and 12.

A surprising aspect of our studies is the heterogeneity of the sets of chemicals studied. The questions arises, how are the above compounds effecting nerve response. For example, we have many QSAR (78) for the action of barbiturates on all sorts of systems, but only 8 of these are correlated by NVE; the rest are correlated by Clog P. There are two ways in which chemicals might affect the nerve axon. One is at the synapse, the other is the membrane between the synapses. Inhibitors correlated by Clog P could be perturbing the membrane, while those correlated by NVE might be interacting with the more polar synapses.

Although our simple model works well for C, H, N, O and F, where s and p orbitals are occupied, it can be expected to break down for elements of higher atomic number for two reasons. First, d orbitals can play an important role in bonding and their contribution to the polarizability has not been considered explicitly. Second, because of less than 100% shielding, $(n_i/Z_{e,i})^4$ becomes significantly greater than one as Z increases. Sulfur is a borderline case where $(n_i/Z_{e,i})^4$ for 3s and 3p electrons is 4.00 and 7.65, respectively. Similarly results are also obtained for chlorine. We note that the two sulfur compounds in the data sets examined in this paper contain one sulfur per molecule and are not outliers. However, we would hesitate in assuming that NVE would be a proxy for the polarizability of compounds with elements of higher atomic number than chlorine or even those with large numbers of chlorine or sulfur atoms.

VI. CONCLUSIONS

We have been astonished how NVE can replace CMR in correlation analysis. There would seem to be quite different ways of looking at the problem of polarizability, a problem that has been of long standing interest to chemists as outlined in our introduction. It is amazing that starting with the

Lorentz−Lorenz equation or with simple addition of the number of valence electrons yield the same answer for complex sets of chemicals. However, we have found CMR to be very valuable in the correlation of allosteric effects in enzyme−ligand interactions.[24] Here one needs − CMR + CMR^2. NVE does not work for this problem. The volume component of the Lorentz−Lorenz equation may account for this. So far in all of the studies of allosteric and apoptosis reactions, most of the data sets were made up with little or no thought of incorporating good variation in hydrophobic, steric and electronic properties of the chemicals. What is needed are more studies based on carefully designed sets of congeners. Substituents with lone pair electrons (e.g. OCH_3; NH_2) provide the potential for polarizability.

However, what is abundantly clear is that electronic effects due to polarizability must be considered along with Hammett parameters in developing software for QSAR. We have made a start[24] on a general system for QSAR that forms the basis for a science of chemical−biological interactions, but we have a long way to go.

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REFERENCES AND NOTES

(1) Selassie, C. D.; Shusterman, A. J.; Kapur, S.; Verma, R. P.; Zhang, L.; Hansch, C. On the Toxicity of Phenols to Fast Growing Cells: A QSAR Model for a Radical Based Toxicity. *Perkin Trans. 2* **1999**, 2729−2733.

(2) Hansch, C.; Gao, H. Comparative QSAR: Radical Reactions of Benzene Derivatives in Chemistry and Biology. *Chem. Rev.* **1997**, *97*, 2995−3059.

(3) Selassie, C. D.; Garg, R.; Kapur, S.; Kurup, A.; Verma, R. P.; Mekapati, S. B.; Hansch, C. Comparative QSAR and the Radical Toxicity of Various Functional Groups. *Chem. Rev.* **2002**, *102*, 2585−2605.

(4) Mekapati, S. B.; Hansch, C. On the Parametrization of the Toxicity of Organic Chemicals to *Tetrahymena Pyriformis.* The Problem of Establishing a Uniform Activity. *J. Chem. Inf. Comput. Sci.* **2002**, In Press.

(5) Pauling, L. *The Nature of the Chemical Bond*; Cornell University Press: 3rd Edition, 1960; p 607.

(6) Hansch, C.; Leo, A. *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology*; American Chemical Society, 1995; p 78.

(7) Biobyte Corporation, 201 West 4th St. Suite 204; Claremont, CA 91711. (a) Abraham, M. H.; Mcgowan, J. C. *Chromatographia* **1987**, *23*, 243−246.

(8) Vogel, A. I. Physical Properties and Chemical Constitution. Part XXIII. *J. Chem. Soc.* **1948**, 1833−1855.

(9) Jeffery, G. H.; Parker, R.; Vogel, A. L. Physical Properties and Chemical Constitution. Part XXXII. Thiophen Compounds. *J. Chem. Soc.* **1961**, 570−575.

(10) Vogel, W. T.; Cresswell, W. T.; Jeffery, G. J.; Leicester, J. Bond Refractions and Bond Parachors. *Chem. Ind.* **1950**, 358.

(11) Karplus, I. M.; Porter, R. H. *Atoms and Molecules*; W. A. Benjamin, Inc.: Menlo Park, CA, 1971; pp 250−262.

(12) Flygare, W. H. *Molecular Structure and Dynamics*; Prentice Hall Inc.: Englewood Cliffs, NJ, 1978; pp 402−412.

(13) Denbigh, K. G. The Polarizability of Bonds-I. *Trans. Faraday Soc.* **1940**, *36*, 936−948.

(14) Clementi, E.; Raimondi, K. L. Atomic Screening Constants from SCF Functions. *J. Chem. Phys.* **1963**, 2686−2689.

(15) Computational Chemistry Comparative and Benchmark Database, National Institute of Standards and Technology, Bethesda, MD. Http://Srdata.Nist.Gov/Cccbdb.

(16) Pauling, L.; Pressman, D. The Serological Properties of Simple Substances. IX. Hapten Inhibition of Precipitation of Antisera Homologous to the O-, M-, and P-Azophenylarsonic Acid Groups. *J. Am. Chem. Soc.* **1945**, *67*, 1003−1012.

(17) Kutter, E.; Hansch, C. The Use of Substituent Constants in the Quantitative Treatment of Hapten-Antibody Interaction. *Arch. Biochem. Biophys.* **1969**, *135*, 126−135.

(18) Agin, D.; Hersh, L.; Holtzman, D. The Action of Anesthetics on Excitable Membranes; A Quantum-Chemical Analysis. *Proc. Natl. Acad. Sci. U.S.A.* **1965**, *53*, 952−958.

(19) Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR. Hydrophobic, Electronic and Steric Constants*; American Chemical Society: Washington, DC, 1995.

(20) Kamlet, m. J.; Doherty, R. M.; Abraham, M. H.; Taft, R. W. Solubility Properties in Biological Media. 12. Regarding the Mechanism of Nonspecific Toxicity or Narcosis of Organic Nonelectrolytes. *Quant. Struct.-Act. Relat.* **1988**, *7*, 71−78.

(21) Hahin, R.; Kondratiev, A. J. ED_{50} AP Block Predictions for Phenyl Substituted and Unsaturated *n*-Alkanols. *J. Membrane Biol.* **2001**, *180*, 137−145.

(22) Wien, R.; Mason, D. F. J. The Pharmacological Actions of a Series of Phenyl Alkane P−W−Bis(Trialkylammonium) Compounds. *Brit. J. Pharmacol.* **1953**, *8*, 306−314.

(23) Nishimura, K.; Ohoka, M.; Fujita, T. Quantitative Structure−Activity Studies of Pyrethroids. *Pest. Biochem. Physiol* **1987**, *28*, 257−270.

(24) Hansch, C.; Hoekman, D.; Leo, A.; Weininger, D.; Selassie, C. D. *Chem. Rev.* **2002**, *102*, 783−812.

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