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A comparison between two polarizability parameters in chemical–biological interactions

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Abstract—The polarizability of a molecule, an important physical property, is currently attracting our attention particularly in the area of QSAR (quantitative structure–activity relationships) for chemical–biological interactions. Our primary focus in the present study has been upon the computational aspects by using NVE (sum of the valence electrons) as a means for estimating polarizability, we have been surprised at its utility. In this report we demonstrate how NVE can be related to the calculated polarizability from a variety of efforts to better understand the subject. A comparison between the use of two polarizability parameters, that is, NVE and CMR (calculated molar refractivity) in the formulation of QSAR for chemical–biological interactions has been also discussed.

1. Introduction

The electrons and nuclei of a molecule are mobile and free to move to a limited degree. Thus, a small charge displacement in a polar or nonpolar molecule will take place in an electric field. As a result, a dipole would be introduced in the molecule, in addition to the permanent one that may exist. Thus, the polarizability (α) of a molecule is a measure of the overall electronic charge distribution that can be distorted by an external electric field.

Molar refractivity (MR) is one of the oldest and successful additive-constitutive physicochemical properties of a compound, which has a strong correlation with the molecular polarizability. Thus, MR is known to be a measure of polarizability and is calculated by the well-documented Lorentz–Lorenz equation:

$$\mathrm{MR} = (n^2 - 1)/(n^2 + 2) \cdot \mathrm{MW}/\rho = 4\pi N\alpha/3 \qquad (1)$$

In this equation, n is the refractive index, MR is the molar refractivity, MW is the molecular weight, and ρ is the density of the compound. N is the Avogadro's number, α is the polarizability, and $\pi = 3.14$.

A relationship between molar refractivity and number of electrons has long been known, and represented by the following equation:

$$\mathrm{MR} = (4N\alpha/3)\cdot(sv_e^2/v_v^2 - v_i^2) \qquad (2)$$

In this equation, v_e, v_v, and v_i are the frequencies of vibration of the electron, the electric oscillator, and the light, respectively, and s is the number of dispersion electrons per molecule.

Charton and Charton[1] extended this work by deriving the correlation between molar refractivity of group X ($\mathrm{MR_X}$) and number of electrons, which is represented by the following Eq.:

$$\mathrm{MR_X} = a_c n_c + a_\sigma n_\sigma + a_\pi n_\pi + a_n n_n + a_o \qquad (3)$$

In this equation, n_c is the total number of core electrons, n_σ is the total number of σ-bonding electrons, n_π is the total number of π-bonding electrons, and n_n is the total number of nonbonding electrons in the group X. As the value of a_σ and a_π were 0.684 and 0.680, respectively, that is, there is no significant difference between a_σ and a_π. Thus, the authors recommended the correlation with an Eq. 4.

$$\mathrm{MR_X} = a_c n_c + a_b n_b + a_n n_n + a_o \qquad (4)$$

In this equation, n_b is the total number of bonding electrons in the group X. The term n_n in the equation was just barely significant. Thus, Eq. 4 was modified to Eq. 5.[2]

Keywords: Chemical–biological interactions; Hydrophobicity; Molar refractivity; NVE; Polarizability; QSAR.
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$$MR_X = 0.320n_c + 0.682n_b - 0.0825n_n + 0.991 \quad (5)$$

In the development of topological descriptors, electron count information is given by connectivity delta values. The simple δ value is the count of adjacent atoms (other than hydrogen) in the molecular skeleton. This definition is equivalent to describing just the σ-bond skeleton network. Thus, the simple δ value is represented by Eq. 6.[3]

$$\delta = \sigma - h \quad (6)$$

In this equation, σ is the number of electrons in σ-orbitals and h is the number of hydrogen atoms bonded to the atom. The valence delta value (δ^v) includes the total number of valence electrons (Z^v) and represented by Eq. 7.[3]

$$\delta^v = Z^v - h = \sigma + \pi + n - h \quad (7)$$

In this equation, π is the number of electrons in π-orbitals, and n is the number of electrons in lone pairs.

The valence electrons of a molecule are usually based on the valence electrons assigned to σ, π, and lone pair orbitals. Also usually included is some representation of resonance forms and/or aromaticity. Recently[4–6] we found that simply by computing (adding up) the number of valence electrons in a molecule (H = 1, C = 4, Si = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7), one could obtain a parameter (NVE) of a great importance in QSAR.

NVE has shown a strong correlation with calculated/observed polarizability. Thus, NVE is a measure of polarizability and has been represented by Eq. 8.

$$\begin{aligned} \text{NVE} &= \text{Total number of valence electrons}(Z^v) \\ &= n_\sigma + n_\pi + n_n = n_b + n_n \end{aligned} \quad (8)$$

In this equation, n_σ is the number of electrons in σ-orbitals, n_π is the number of electrons in π-orbitals, n_b is the bonding electrons, and n_n is the number of electrons in lone pairs. It is surprising that the NVE is a measure of polarizability when it includes a positive contribution for hydrogen whereas unsaturated and aromatic hydrocarbons (which have fewer H's than saturated) are more polarizable than the corresponding saturated compounds. This will be supported by comparing the correlation of polarizability with NVE and (NVE − h) by using Eqs. 8 and 10, respectively.

$$\text{NVE} - h = n_\sigma + n_\pi + n_n - h = n_b + n_n - h \quad (9)$$

From Eqs. 7 and 9, we obtained Eq. 10

$$\delta^v = \text{NVE} - h \quad (10)$$

Recently, the computer intensive methods are seeing increased usage because of the developments in the high-speed computing, as well as the accuracy and precision of the computed values. There are two different approaches: ab initio and semi-empirical. Ab initio calculations include all electrons and all one and two-electron integrals. Therefore, the computational time is high. Thus the types of the atoms and size of the molecules[7,8] limit ab initio calculations.

The second types of approach, semi-empirical MO methods (MNDO, AM1, and PM3), in which the required integral values are approximated or neglected, are applied to reduce the calculation time for polarizability by personal computers. In this method, the polarizabilities calculation is not sufficiently reliable and the results are in poor agreement with those obtained experimentally.

In the present paper, we have discussed the validity of NVE (sum of the total number of valence electrons) as the measure of polarizability and its comparison with well-known polarizability parameter, that is, CMR (calculated molar refractivity) in the formulation of QSAR for chemical–biological interactions.

2. Materials and methods

All the data have been collected from the literature (see individual equation for respective references). C is the molar concentration of a compound and $\log 1/C$ is the dependent variable that defines the biological parameter for QSAR equations. Physicochemical descriptors are auto-loaded, and multiregression analyses (MRA) used to derive the correlation were executed with the C-QSAR program.[9] The parameters used in this paper have been already discussed in detail along with their applications.[10] Briefly, Clog P is the calculated octanol/water partition coefficient. Mlog P is the experimentally obtained octanol/water partition coefficient. B1 is the calculated sterimol parameter, that is, largely the measure of steric effect of the first atom of a substituent. NVE (number of valence electrons) is a parameter[4–6] that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule, that is, H = 1, C = 4, Si = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7. CMR is the calculated molar refractivity for the whole molecule and calculated from the Lorentz–Lorenz equation, which is described as follows: $(n^2 - 1/n^2 + 2)(MW/\rho)$, where n is the refractive index, MW is the molecular weight, and ρ is the density of a substance. NVE, CMR, and Clog P are available from the C-QSAR program.[9] In QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction, and s is the standard deviation.

3. Results and discussion

From the published data of Staikova et al.[11] that contained the molecular polarizabilities of 146 chlorinated organic compounds obtained from the density functional theory, we formulated Eqs. 11, 11a, and 11b. The data used in the correlation of these equations are reported in Table 1. A comparison between polarizability and NVE of the chlorinated organic compounds used in Eq. 11 has been shown in Figure 1.

$$\begin{aligned} &\alpha = 0.34(\pm 0.01)\text{NVE} - 1.75(\pm 0.42) \\ &n = 146, \quad r^2 = 0.987, \quad s = 0.719, \quad q^2 = 0.986 \end{aligned} \quad (11)$$

$$\alpha = 3.70(\pm 0.05)\mathrm{CMR} - 0.48(\pm 0.30)$$
$$n = 146, \quad r^2 = 0.992, \quad s = 0.546, \quad q^2 = 0.992 \tag{11a}$$

$$\alpha = 0.35(\pm 0.01)\delta^{\mathrm{v}} - 0.61(\pm 0.64)$$
$$n = 146, \quad r^2 = 0.966, \quad s = 1.14, \quad q^2 = 0.965 \tag{11b}$$

In these equations α is the polarizability in Å and δ^{v} is the valence delta value ($\delta^{\mathrm{v}} = \mathrm{NVE} - h$). All these three Eqs. 11, 11a, and 11b gave good correlations between the polarizability and NVE, CMR as well as δ^{v}, respectively. The near equality between r^2 and q^2 in these equations are attributed to the accuracy of DFT. The strong correlation between polarizability and CMR (Eq. 11a) is almost the same with that of polarizability and NVE (Eq. 11). The statistics of Eq. 11 is better that that of 11b indicates that the presence of hydrogen in the calculation of NVE is favorable. Thus, we can say that the positive contribution of hydrogen in NVE is good for the measure of polarizability whereas unsaturated and aromatic hydrocarbons (which have fewer H's than saturated) are more polarizable than the corresponding saturated compounds.

It is our interest to note here that there is a high mutual correlation between NVE and CMR as shown by Eq. 11c, which suggests that a similarity between these two parameters for this data set.

$$\mathrm{NVE} = 10.79(\pm 0.13)\mathrm{CMR} + 4.06(\pm 0.74)$$
$$n = 146, \quad r^2 = 0.995, \quad s = 1.33, \quad q^2 = 0.994 \tag{11c}$$

If the chlorinated aromatic compounds are run as a group, Eqs. 12, 12a, 12b, and 12c are obtained (Table 1).

$$\alpha = 0.33(\pm 0.01)\mathrm{NVE} - 0.91(\pm 0.69)$$
$$n = 107, \quad r^2 = 0.962, \quad s = 0.732, \quad q^2 = 0.960 \tag{12}$$

$$\alpha = 3.82(\pm 0.12)\mathrm{CMR} - 1.25(\pm 0.78)$$
$$n = 107, \quad r^2 = 0.972, \quad s = 0.622, \quad q^2 = 0.971 \tag{12a}$$

$$\alpha = 0.33(\pm 0.02)\delta^{\mathrm{v}} + 0.83(\pm 1.22)$$
$$n = 107, \quad r^2 = 0.924, \quad s = 1.03, \quad q^2 = 0.921 \tag{12b}$$

$$\alpha = 1.73(\pm 0.17)n_{\pi} + 3.78(\pm 1.85)$$
$$n = 107, \quad r^2 = 0.797, \quad s = 1.68, \quad q^2 = 0.786 \tag{12c}$$

Eqs. 12, 12a, and 12b gave almost the same results as compared to that of 11, 11a, and 11b. We are concerned about the π electrons for aromatic compounds, but have not obtained a very good correlation as shown by Eq. 12c. The high correlation between NVE and CMR is shown by Eq. 12d.

$$\mathrm{NVE} = 11.57(\pm 0.12)\mathrm{CMR} - 1.20(\pm 0.72)$$
$$n = 107, \quad r^2 = 0.997, \quad s = 0.575, \quad q^2 = 0.997 \tag{12d}$$

If the chlorinated aliphatic compounds are run as a group, Eqs. 13, 13a, 13b, and 13c are obtained (Table 1).

$$\alpha = 0.30(\pm 0.002)\mathrm{NVE} - 0.48(\pm 0.10)$$
$$n = 39, \quad r^2 = 0.999, \quad s = 0.088, \quad q^2 = 0.999 \tag{13}$$

$$\alpha = 3.70(\pm 0.04)\mathrm{CMR} - 0.38(\pm 0.14)$$
$$n = 39, \quad r^2 = 0.999, \quad s = 0.124, \quad q^2 = 0.999 \tag{13a}$$

$$\alpha = 0.28(\pm 0.013)\delta^{\mathrm{v}} + 1.48(\pm 0.48)$$
$$n = 39, \quad r^2 = 0.981, \quad s = 0.516, \quad q^2 = 0.979 \tag{13b}$$

$$\alpha = 0.33(\pm 0.04)n_{\mathrm{n}} + 4.09(\pm 0.90)$$
$$n = 39, \quad r^2 = 0.899, \quad s = 1.195, \quad q^2 = 0.888 \tag{13c}$$

NVE and CMR gave exactly the same correlation with polarizability as shown by Eqs. 13 and 13a. By the comparison of Eqs. 13 and 13b, it is again clear that the presence of hydrogen in the calculation of NVE is favorable. We are concern about the nonbonding lone pair electrons for the aliphatic compounds and got a good correlation as shown by Eq. 13c. There is a high mutual correlation between NVE and CMR (Eq. 13d) for this data set.

$$\mathrm{NVE} = 12.34(\pm 0.06)\mathrm{CMR} + 0.30(\pm 0.21)$$
$$n = 39, \quad r^2 = 1.00, \quad s = 0.194, \quad q^2 = 1.00 \tag{13d}$$

A worrisome aspect of this approach is the use of seven valence electrons for all halogens regardless of their size. It has been thought that bromine and iodine are more polarizable than chlorine. Our first conformation of the fact that NVE works well for halogens came from a study by King.[12] In England, when a person dies from a drug overdose, commits suicide, or is accidentally killed, the government determines drug concentration in the blood from which we formulated QSAR 14.[13]

$$\log 1/C = 0.61(\pm 0.16)\log P + 0.02(\pm 0.004)\mathrm{NVE} + 1.45(\pm 0.36)$$
$$n = 37, \quad r^2 = 0.852, \quad s = 0.432, \quad q^2 = 0.820$$
outliers: morphine, theophylline, dichlorodifluoromethane, halothane
(14)

The following halogens containing compounds were well fit: chlorpromazine, flurazepam, diazepam, chlormethiazole, tetrachloroethylene, dichlorodifluoromethane,

Table 1. Physicochemical parameters for the derivation of Eqs. 11–13

No.	Compound	α	α (Eq. 11)		α (Eq. 12)		α (Eq. 13)		NVE	CMR	δ^v
			Pred.	Δ	Pred.	Δ	Pred.	Δ			
1	Chlorobenzene	10.48	10.52	−0.04	11.10	−0.62			36	3.18	31
2	1,2-Dichlorobenzene	12.14	12.56	−0.42	13.07	−0.93			42	3.67	38
3	1,3-Dichlorobenzene	12.30	12.56	−0.26	13.07	−0.77			42	3.67	38
4	1,4-Dichlorobenzene	12.35	12.56	−0.21	13.07	−0.72			42	3.67	38
5	1,2,3-Trichlorobenzene	13.89	14.61	−0.72	15.03	−1.14			48	4.16	45
6	1,2,4-Trichlorobenzene	14.11	14.61	−0.50	15.03	−0.92			48	4.16	45
7	1,3,5-Trichlorobenzene	14.22	14.61	−0.39	15.03	−0.81			48	4.16	45
8	1,2,3,4-Tetrachlorobenzene	15.75	16.65	−0.90	17.00	−1.25			54	4.65	52
9	1,2,3,5-Tetrachlorobenzene	15.92	16.65	−0.73	17.00	−1.08			54	4.65	52
10	1,2,4,5-Tetrachlorobenzene	15.98	16.65	−0.67	17.00	−1.02			54	4.65	52
11	Pentachlorobenzene	17.70	18.70	−1.00	18.96	−1.26			60	5.15	59
12	Hexachlorobenzene	19.48	20.74	−1.26	20.93	−1.45			66	5.64	66
13	1-Chloronaphthalene	17.45	16.65	0.80	17.00	0.45			54	4.87	47
14	2-Chloronaphthalene	17.80	16.65	1.15	17.00	0.80			54	4.87	47
15	1,2-Dichloronaphthalene	19.44	18.70	0.74	18.96	0.48			60	5.36	54
16	1,3-Dichloronaphthalene	19.59	18.70	0.89	18.96	0.63			60	5.36	54
17	1,4-Dichloronaphthalene	19.32	18.70	0.62	18.96	0.36			60	5.36	54
18	1,5-Dichloronaphthalene	19.26	18.70	0.56	18.96	0.30			60	5.36	54
19	1,6-Dichloronaphthalene	19.61	18.70	0.91	18.96	0.65			60	5.36	54
20	1,7-Dichloronaphthalene	19.56	18.70	0.86	18.96	0.60			60	5.36	54
21	1,8-Dichloronaphthalene	19.24	18.70	0.54	18.96	0.28			60	5.36	54
22	2,3-Dichloronaphthalene	19.80	18.70	1.10	18.96	0.84			60	5.36	54
23	2,6-Dichloronaphthalene	20.03	18.70	1.33	18.96	1.07			60	5.36	54
24	2,7-Dichloronaphthalene	20.00	18.70	1.30	18.96	1.04			60	5.36	54
25	1,2,3-Trichloronaphthalene	21.49	20.74	0.75	20.93	0.56			66	5.85	61
26	1,2,4-Trichloronaphthalene	21.35	20.74	0.61	20.93	0.42			66	5.85	61
27	1,2,5-Trichloronaphthalene	21.32	20.74	0.58	20.93	0.39			66	5.85	61
28	1,2,6-Trichloronaphthalene	21.75	20.74	1.01	20.93	0.82			66	5.85	61
29	1,2,7-Trichloronaphthalene	21.66	20.74	0.92	20.93	0.73			66	5.85	61
30	1,2,8-Trichloronaphthalene	21.26	20.74	0.52	20.93	0.33			66	5.85	61
31	1,3,5-Trichloronaphthalene	21.43	20.74	0.69	20.93	0.50			66	5.85	61
32	1,3,6-Trichloronaphthalene	21.87	20.74	1.13	20.93	0.94			66	5.85	61
33	1,3,7-Trichloronaphthalene	21.85	20.74	1.11	20.93	0.92			66	5.85	61
34	1,3,8-Trichloronaphthalene	21.45	20.74	0.71	20.93	0.52			66	5.85	61
35	1,4,5-Trichloronaphthalene	21.19	20.74	0.45	20.93	0.26			66	5.85	61
36	1,4,6-Trichloronaphthalene	21.49	20.74	0.75	20.93	0.56			66	5.85	61
37	1,6,7-Trichloronaphthalene	21.62	20.74	0.88	20.93	0.69			66	5.85	61
38	2,3,6-Trichloronaphthalene	22.13	20.74	1.39	20.93	1.20			66	5.85	61
39	2-Chlorobiphenyl	20.34	20.06	0.28	20.28	0.06			64	5.69	55
40	4-Chlorobiphenyl	21.26	20.06	1.20	20.28	0.98			64	5.69	55
41	2,2′-Dichlorobiphenyl	21.55	22.11	−0.56	22.24	−0.69			70	6.18	62
42	2,3-Dichlorobiphenyl	22.12	22.11	0.01	22.24	−0.12			70	6.18	62
43	2,3′-Dichlorobiphenyl	22.19	22.11	0.08	22.24	−0.05			70	6.18	62
44	2,4-Dichlorobiphenyl	22.56	22.11	0.45	22.24	0.32			70	6.18	62
45	2,4′-Dichlorobiphenyl	22.47	22.11	0.36	22.24	0.23			70	6.18	62
46	2,5-Dichlorobiphenyl	22.34	22.11	0.23	22.24	0.10			70	6.18	62
47	2,6-Dichlorobiphenyl	21.61	22.11	−0.50	22.24	−0.63			70	6.18	62
48	3,3′-Dichlorobiphenyl	22.82	22.11	0.71	22.24	0.58			70	6.18	62
49	3,4-Dichlorobiphenyl	23.06	22.11	0.95	22.24	0.82			70	6.18	62
50	3,4′-Dichlorobiphenyl	23.20	22.11	1.09	22.24	0.96			70	6.18	62
51	3,5-Dichlorobiphenyl	22.93	22.11	0.82	22.24	0.69			70	6.18	62
52	4,4′-Dichlorobiphenyl	23.56	22.11	1.45	22.24	1.32			70	6.18	62
53	2,3,2′-Trichlorobiphenyl	23.33	24.15	−0.82	24.21	−0.88			76	6.67	71
54	2,4,2′-Trichlorobiphenyl	23.64	24.15	−0.51	24.21	−0.57			76	6.67	71
55	2,6,2′-Trichlorobiphenyl	23.12	24.15	−1.03	24.21	−1.09			76	6.67	71
56	2,3,3′-Trichlorobiphenyl	23.99	24.15	−0.16	24.21	−0.22			76	6.67	71
57	2,3,4-Trichlorobiphenyl	24.19	24.15	0.04	24.21	−0.02			76	6.67	71
58	2,3,4′-Trichlorobiphenyl	24.30	24.15	0.15	24.21	0.09			76	6.67	71
59	2,3,5-Trichlorobiphenyl	24.18	24.15	0.03	24.21	−0.03			76	6.67	71
60	2,3,6-Trichlorobiphenyl	23.56	24.15	−0.59	24.21	−0.65			76	6.67	71
61	2,4,3′-Trichlorobiphenyl	24.45	24.15	0.30	24.21	0.24			76	6.67	71
62	2,5,3′-Trichlorobiphenyl	24.21	24.15	0.06	24.21	0.00			76	6.67	71
63	2,6,3′-Trichlorobiphenyl	23.47	24.15	−0.68	24.21	−0.74			76	6.67	71
64	2,4,4′-Trichlorobiphenyl	24.78	24.15	0.63	24.21	0.57			76	6.67	71
65	2,4,5-Trichlorobiphenyl	24.45	24.15	0.30	24.21	0.24			76	6.67	71

Table 1 (*continued*)

No.	Compound	α	α (Eq. 11)		α (Eq. 12)		α (Eq. 13)		NVE	CMR	δ^v
			Pred.	Δ	Pred.	Δ	Pred.	Δ			
66	2,4,6-Trichlorobiphenyl	23.80	24.15	−0.35	24.21	−0.41			76	6.67	71
67	2,5,4′-Trichlorobiphenyl	24.05	24.15	−0.10	24.21	−0.16			76	6.67	71
68	2,6,4′-Trichlorobiphenyl	23.64	24.15	−0.51	24.21	−0.57			76	6.67	71
69	3,4,2′-Trichlorobiphenyl	23.78	24.15	−0.37	24.21	−0.43			76	6.67	71
70	2,3,5′-Trichlorobiphenyl	24.02	24.15	−0.13	24.21	−0.19			76	6.67	71
71	3,4,3′-Trichlorobiphenyl	25.00	24.15	0.85	24.21	0.79			76	6.67	71
72	3,3′,5-Trichlorobiphenyl	24.84	24.15	0.69	24.21	0.63			76	6.67	71
73	3,4,4′-Trichlorobiphenyl	25.43	24.15	1.28	24.21	1.22			76	6.67	71
74	3,5,4′-Trichlorobiphenyl	25.25	24.15	1.10	24.21	1.04			76	6.67	71
75	2,3,2′,3′-Tetrachlorobiphenyl	25.18	26.20	−1.02	26.17	−0.99			82	7.17	76
76	2,3,2,4′-Tetrachlorobiphenyl	25.51	26.20	−0.69	26.17	−0.66			82	7.17	76
77	2,3,4,2′-Tetrachlorobiphenyl	25.35	26.20	−0.85	26.17	−0.82			82	7.17	76
78	2,3,5,2′-Tetrachlorobiphenyl	25.42	26.20	−0.78	26.17	−0.75			82	7.17	76
79	2,3,2′,5′-Tetrachlorobiphenyl	25.39	26.20	−0.81	26.17	−0.78			82	7.17	76
80	2,3,6,2-Tetrachlorobiphenyl	25.06	26.20	−1.14	26.17	−1.11			82	7.17	76
81	2,3,2′,6′-Tetrachlorobiphenyl	24.92	26.20	−1.28	26.17	−1.25			82	7.17	76
82	2,4,2,4′-Tetrachlorobiphenyl	25.85	26.20	−0.35	26.17	−0.32			82	7.17	76
83	2,4,5,2′-Tetrachlorobiphenyl	25.58	26.20	−0.62	26.17	−0.59			82	7.17	76
84	2,2′,4,6′-Tetrachlorobiphenyl	25.26	26.20	−0.94	26.17	−0.91			82	7.17	76
85	2,5,2′,5′-Tetrachlorobiphenyl	25.58	26.20	−0.62	26.17	−0.59			82	7.17	76
86	2,5,2′,6′-Tetrachlorobiphenyl	25.13	26.20	−1.07	26.17	−1.04			82	7.17	76
87	2,6,2,6′-Tetrachlorobiphenyl	24.74	26.20	−1.46	26.17	−1.43			82	7.17	76
88	2,3,4,3′-Tetrachlorobiphenyl	26.06	26.20	−0.14	26.17	−0.11			82	7.17	76
89	2,3,3′,4′-Tetrachlorobiphenyl	26.04	26.20	−0.16	26.17	−0.13			82	7.17	76
90	2,3,4,4′-Tetrachlorobiphenyl	26.44	26.20	0.24	26.17	0.27			82	7.17	76
91	2,3,4,5-Tetrachlorobiphenyl	26.16	26.20	−0.04	26.17	−0.01			82	7.17	76
92	2,3,4′,5-Tetrachlorobiphenyl	26.41	26.20	0.21	26.17	0.24			82	7.17	76
93	2,3,4′,6-Tetrachlorobiphenyl	25.63	26.20	−0.57	26.17	−0.54			82	7.17	76
94	2,3,5,6-Tetrachlorobiphenyl	25.56	26.20	−0.64	26.17	−0.61			82	7.17	76
95	2,4,3,4′-Tetrachlorobiphenyl	26.57	26.20	0.37	26.17	0.40			82	7.17	76
96	2,3′,4,5-Tetrachlorobiphenyl	26.38	26.20	0.18	26.17	0.21			82	7.17	76
97	2,3′,4,6-Tetrachlorobiphenyl	25.70	26.20	−0.50	26.17	−0.47			82	7.17	76
98	2,5,3′,4′-Tetrachlorobiphenyl	26.31	26.20	0.11	26.17	0.14			82	7.17	76
99	2,6,3′,4′-Tetrachlorobiphenyl	25.43	26.20	−0.77	26.17	−0.74			82	7.17	76
100	2,5,3′,5-Tetrachlorobiphenyl	26.17	26.20	−0.03	26.17	0.00			82	7.17	76
101	2,4,5,4′-Tetrachlorobiphenyl	26.72	26.20	0.52	26.17	0.55			82	7.17	76
102	2,4,6,4′-Tetrachlorobiphenyl	25.89	26.20	−0.31	26.17	−0.28			82	7.17	76
103	3,4,3′,4′-Tetrachlorobiphenyl	27.26	26.20	1.06	26.17	1.09			82	7.17	76
104	3,4,5,3′-Tetrachlorobiphenyl	26.89	26.20	0.69	26.17	0.72			82	7.17	76
105	3,4,3′,5′-Tetrachlorobiphenyl	27.05	26.20	0.85	26.17	0.88			82	7.17	76
106	3,5,3′,5′-Tetrachlorobiphenyl	26.86	26.20	0.66	26.17	0.69			82	7.17	76
107	3,4,5,4′-Tetrachlorobiphenyl	27.35	26.20	1.15	26.17	1.18			82	7.17	76
108	Monochloromethane	3.55	3.02	0.53			3.72	−0.17	14	1.13	11
109	Dichloromethane	5.30	5.07	0.23			5.52	−0.22	20	1.62	18
110	Trichloromethane	7.23	7.11	0.12			7.32	−0.09	26	2.12	25
111	Tetrachloromethane	9.13	9.16	−0.03			9.12	0.01	32	2.61	32
112	Monochloroethane	5.53	5.07	0.46			5.52	0.01	20	1.60	15
113	1,1-Dichloroethane	7.36	7.11	0.25			7.32	0.04	26	2.09	22
114	1,1,1-Trichloroethane	9.25	9.16	0.09			9.12	0.13	32	2.58	29
115	1,2-Dichloroethane	7.35	7.11	0.24			7.32	0.03	26	2.09	22
116	1,1,2-Trichloroethane	9.12	9.16	−0.04			9.12	0.00	32	2.58	29
117	1,1,1,2-Tetrachloroethane	10.96	11.20	−0.24			10.92	0.04	38	3.07	36
118	1,1,2,2-Tetrachloroethane	10.84	11.20	−0.36			10.92	−0.08	38	3.07	36
119	Pentachloroethane	12.75	13.25	−0.50			12.72	0.03	44	3.56	43
120	Hexachloroethane	14.55	15.29	−0.74			14.52	0.03	50	4.05	50
121	1-Monochloropropane	7.38	7.11	0.27			7.32	0.06	26	2.06	19
122	1,1-Dichloropropane	9.19	9.16	0.03			9.12	0.07	32	2.55	26
123	1,1,1-Trichloropropane	11.03	11.20	−0.17			10.92	0.11	38	3.04	33
124	2-Monochloropropane	7.48	7.11	0.37			7.32	0.16	26	2.06	19
125	1,2-Dichloropropane	9.11	9.16	−0.05			9.12	−0.01	32	2.55	26
126	1,1,2-Trichloropropane	10.85	11.20	−0.35			10.92	−0.07	38	3.04	33
127	1,1,1,2-Tetrachloropropane	12.77	13.25	−0.48			12.72	0.05	44	3.53	40
128	2,2-Dichloropropane	9.33	9.16	0.17			9.12	0.21	32	2.55	26
129	1,2,2-Trichloropropane	10.91	11.20	−0.29			10.92	−0.01	38	3.04	33

(*continued on next page*)

Table 1 (*continued*)

No.	Compound	α	α (Eq. 11)		α (Eq. 12)		α (Eq. 13)		NVE	CMR	δ^v
			Pred.	Δ	Pred.	Δ	Pred.	Δ			
130	1,1,2,2-Tetrachloropropane	12.75	13.25	−0.50			12.72	0.03	44	3.53	40
131	1,1,1,2,2-Pentachloropropane	14.54	15.29	−0.75			14.52	0.02	50	4.03	47
132	1,3-Dichloropropane	9.12	9.16	−0.04			9.12	0.00	32	2.55	26
133	1,1,3-Trichloropropane	10.97	11.20	−0.23			10.92	0.05	38	3.04	33
134	1,1,1,3-Tetrachloropropane	12.83	13.25	−0.42			12.72	0.11	44	3.53	40
135	1,2,3-Trichloropropane	10.79	11.20	−0.41			10.92	−0.13	38	3.04	33
136	1,1,2,3-Tetrachloropropane	12.73	13.25	−0.52			12.72	0.01	44	3.53	40
137	1,2,2,3-Tetrachloropropane	12.56	13.25	−0.69			12.72	−0.16	44	3.53	40
138	1,1,2,2,3-Pentachloropropane	14.47	15.29	−0.82			14.52	−0.05	50	4.03	47
139	1,1,1,2,2,3-Hexachloropropane	16.28	17.34	−1.06			16.32	−0.04	56	4.52	54
140	1,1,3,3-Tetrachloropropane	12.76	13.25	−0.49			12.72	0.04	44	3.53	40
141	1,1,2,3,3-Pentachloropropane	14.49	15.29	−0.80			14.52	−0.03	50	4.03	47
142	1,1,1,2,2,3,3-Heptachloropropane	18.09	19.38	−1.29			18.12	−0.03	62	5.01	61
143	1,1,3,3,3-Pentachloropropane	14.53	15.29	−0.76			14.52	0.01	50	4.03	47
144	1,1,2,3,3,3-Hexachloropropane	16.35	17.34	−0.99			16.32	0.03	56	4.52	54
145	1,1,1,2,3,3,3-Heptachloropropane	18.09	19.38	−1.29			18.12	−0.03	62	5.01	61
146	Octachloropropane	19.85	21.43	−1.58			19.92	−0.07	68	5.50	68

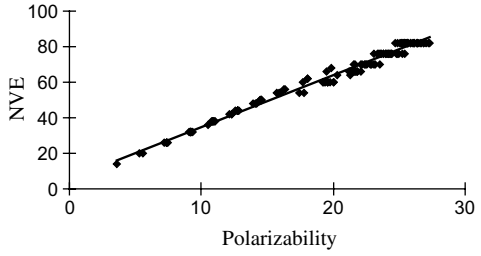


Figure 1. Comparison between polarizability and NVE of the chlorinated organic compounds used in Eq. 11.

trichloroethylene, $CFCl_3$, CHF_2Cl, $CHBrClCF_3$, CH_2ClBr, CCl_4, $CHCl_3$, CH_2CCl_3, $ClCH_2CH_2Cl$, CH_2Cl_2, C_2H_5Cl.

Thus, we see that NVE holds good for halogens regardless of size.

In the next attempt, we used a set of calculated/experimental polarizabilities for a wide range of halogen molecules.[14] From this data in Table 2, we formulated Eqs. 15 and 15a. The comparison between polarizability and NVE of the halogen containing compounds used in the derivation of Eq. 15 is shown in Figure 2.

$$\alpha = 0.30(\pm 0.02)\mathrm{NVE} + 0.90(\pm 0.89)$$
$$n = 90, \quad r^2 = 0.901, \quad s = 1.997, \quad q^2 = 0.896 \tag{15}$$

$$\alpha = 3.80(\pm 0.10)\mathrm{CMR} + 0.70(\pm 0.35)$$
$$n = 90, \quad r^2 = 0.985, \quad s = 0.785, \quad q^2 = 0.984 \tag{15a}$$

From Eq. 15, it is clear that the use of seven valence electrons for all halogens regardless of their size for the calculation of NVE is satisfactory. The correlation between NVE and CMR for this data set is shown by Eq. 15b.

$$\mathrm{NVE} = 11.67(\pm 0.82)\mathrm{CMR} + 2.97(\pm 2.83)$$
$$n = 90, \quad r^2 = 0.900, \quad s = 6.431, \quad q^2 = 0.896 \tag{15b}$$

Now we considered a set of experimentally determined polarizabilities of oxygen containing compounds.[15] From this data in Table 3, we formulated Eqs. 16 and 16a. The comparison between polarizability and NVE of the oxygen containing compounds used in the derivation of Eq. 16 is shown in Figure 3.

$$\alpha = 0.28(\pm 0.01)\mathrm{NVE} - 0.70(\pm 0.50)$$
$$n = 58, \quad r^2 = 0.967, \quad s = 0.564, \quad q^2 = 0.965 \tag{16}$$

$$\alpha = 3.87(\pm 0.05)\mathrm{CMR} + 0.16(\pm 0.11)$$
$$n = 58, \quad r^2 = 0.998, \quad s = 0.135, \quad q^2 = 0.998 \tag{16a}$$

We are concern about the nonbonding lone pair electrons for oxygen containing compounds, but a good correlation was not obtained ($r^2 = 0.338$, $q^2 = 0.291$). There is a high mutual correlation between NVE and CMR as shown by Eq. 16b.

$$\mathrm{NVE} = 13.56(\pm 0.61)\mathrm{CMR} + 4.03(\pm 1.47)$$
$$n = 58, \quad r^2 = 0.972, \quad s = 1.822, \quad q^2 = 0.971 \tag{16b}$$

In another attempt, we considered a set of experimentally determined polarizabilities of nitrogen containing compounds.[15] From this data in Table 4, we formulated Eqs. 17 and 17a. The comparison between polarizability and NVE of the nitrogen containing compounds used in Eq. 17 is shown in Figure 4.

$$\alpha = 0.35(\pm 0.03)\mathrm{NVE} - 2.07(\pm 1.02)$$
$$n = 29, \quad r^2 = 0.969, \quad s = 0.940, \quad q^2 = 0.962 \tag{17}$$

Table 2. Physicochemical parameters for the derivation of Eq. 15

No.	Compounds	α (Eq. 15)			NVE	CMR
		Obsd.	Pred.	Δ		
1	Dibromodifluoromethane	9.00	10.35	−1.35	32	2.23
2	Dichlorodifluoromethane	7.93	10.35	−2.42	32	1.65
3	Phosgene	7.29	7.99	−0.70	24	1.66
4	Thiophosgene	10.20	7.99	2.21	24	2.52
5	Trichlorofluoromethane	9.47	10.35	−0.88	32	2.13
6	Trichloronitromethane	10.80	13.31	−2.51	42	2.73
7	Bromoform	11.80	8.58	3.22	26	2.97
8	Bromodifluoromethane	5.70	8.58	−2.88	26	1.45
9	Chlorodifluoromethane	6.38	8.58	−2.20	26	1.16
10	Dichlorofluoromethane	6.82	8.58	−1.76	26	1.64
11	Fluoroformaldehyde	1.76	6.21	-4.45	18	0.69
12	Dibromomethane	9.32	6.80	2.52	20	2.20
13	Chloronitromethane	6.90	9.76	−2.86	30	1.74
14	Bromomethane	5.87	5.03	0.84	14	1.42
15	Fluoromethane	2.97	5.03	−2.06	14	0.66
16	Iodomethane	7.97	5.03	2.94	14	1.95
17	Bromoacetylene	7.39	5.62	1.77	16	1.68
18	Chloroacetylene	6.07	5.62	0.45	16	1.39
19	*trans*-Dichloroethylene	9.28	7.99	1.29	24	2.06
20	*cis*-Dichloroethylene	9.19	7.99	1.20	24	2.06
21	Chloroacetylchloride	8.92	9.76	−0.84	30	2.12
22	1,2,2-Trichloro-1-fluoroethane	10.20	12.13	−1.93	38	2.59
23	Chloroacetonitrile	6.10	7.39	−1.29	22	1.61
24	1,1-Difluoroethylene	5.01	7.99	−2.98	24	1.11
25	Bromoethylene	7.59	6.21	1.38	18	1.86
26	Chloroethylene	6.41	6.21	0.20	18	1.57
27	1-Chloro-1,1-difluoroethane	8.05	10.35	−2.30	32	1.63
28	Acetylchloride	6.62	7.99	−1.37	24	1.63
29	Methylchloroformate	7.10	9.76	−2.66	30	1.79
30	Iodoethylene	9.30	6.21	3.09	18	2.39
31	1-Bromo-2-Chloroethane	9.50	8.58	0.92	26	2.37
32	1,2-Dibromoethane	10.70	8.58	2.12	26	2.66
33	1-Chloro-2-fluoroethane	6.50	8.58	−2.08	26	1.61
34	1-Chloro-1-nitroethane	10.90	11.53	−0.63	36	2.21
35	Bromoethane	7.28	6.80	0.48	20	1.88
36	Chloromethyl-methylether	7.10	8.58	−1.48	26	1.75
37	Fluoroethane	4.96	6.80	−1.84	20	1.12
38	Iodoethane	10.00	6.80	3.20	20	2.41
39	1,1-Dichloropropene	10.10	9.76	0.34	30	2.53
40	1-Chloropropene	8.30	7.99	0.31	24	2.03
41	Chloroacetone	8.40	9.76	−1.36	30	2.10
42	Ethylchloroformate	9.00	11.53	−2.53	36	2.25
43	1-Chloro-1-nitropropane	10.40	13.31	−2.91	42	2.67
44	1-Bromopropane	9.07	8.58	0.49	26	2.35
45	2-Bromopropane	9.60	8.58	1.02	26	2.35
46	1-Iodopropane	11.50	8.58	2.92	26	2.88
47	4-Chloro-1,2-butadiene	10.00	9.17	0.83	28	2.52
48	1-Chloro-2-methylpropene	10.80	9.76	1.04	30	2.50
49	1,4-Dichlorobutane	12.00	12.13	−0.13	38	3.02
50	1-Bromobutane	10.86	10.35	0.51	32	2.81
51	1-Chlorobutane	11.30	10.35	0.95	32	2.52
52	1-Chloro-2-methylpropane	11.10	10.35	0.75	32	2.52
53	2-Chloro-2-methylpropane	12.50	10.35	2.15	32	2.52
54	2-Chlorobutane	12.40	10.35	2.05	32	2.52
55	1-Iodobutane	12.65	10.35	2.30	32	3.34
56	1-Bromopentane	13.10	12.13	0.97	38	3.27
57	1-Chloropentane	12.00	12.13	−0.13	38	2.99
58	1-Fluoropentane	9.95	12.13	−2.18	38	2.51
59	2,5-Dichloro-1,4-benzoquinone	18.40	16.27	2.13	52	3.48
60	*p*-Bromofluorobenzene	13.40	13.31	0.09	42	3.48
61	*p*-Chloronitrobenzene	14.60	16.27	−1.67	52	3.79
62	*p*-Fluoroiodobenzene	15.50	13.31	2.19	42	4.01
63	*p*-Fluoronitrobenzene	12.80	16.27	−3.47	52	3.32
64	Bromobenzene	13.62	11.53	2.09	36	3.47

(*continued on next page*)

Table 2 (*continued*)

No.	Compounds	α (Eq. 15)			NVE	CMR
		Obsd.	Pred.	Δ		
65	*p*-Chlorophenol	13.00	13.31	−0.31	42	3.33
66	Fluorobenzene	10.30	11.53	−1.23	36	2.70
67	Iodobenzene	15.50	11.53	3.97	36	4.00
68	1-Bromohexane	14.44	13.90	0.54	44	3.74
69	1-Fluorohexane	11.80	13.90	−2.10	44	2.98
70	*p*-Bromotoluene	14.80	13.31	1.49	42	3.93
71	*p*-Chlorotoluene	13.70	13.31	0.39	42	3.64
72	*p*-Fluorotoluene	11.70	13.31	−1.61	42	3.17
73	*p*-Iodotoluene	17.10	13.31	3.79	42	4.46
74	1-Bromoheptane	16.23	15.67	0.56	50	4.20
75	1-Fluoroheptane	13.66	15.67	−2.01	50	3.44
76	1-Bromooctane	18.02	17.45	0.57	56	4.66
77	1-Fluorooctane	15.46	17.45	−1.99	56	3.90
78	1-Bromononane	19.81	19.22	0.59	62	5.13
79	1-Fluorononane	17.34	19.22	−1.88	62	4.37
80	1-Bromodecane	21.60	21.00	0.60	68	5.59
81	1-Fluorodecane	19.18	21.00	−1.82	68	4.83
82	1-Fluoroundecane	21.00	22.77	−1.77	74	5.29
83	1-Bromododecane	25.18	24.55	0.63	80	6.52
84	1-Fluorododecane	22.83	24.55	−1.72	80	5.76
85	4,4′-Dibromodiphenylether	27.80	23.36	4.44	76	6.91
86	4-Bromodiphenylether	24.20	21.59	2.61	70	6.13
87	*p*-Bromophenyl-*p*-tolylether	26.60	23.36	3.24	76	6.59
88	1-Fluorotetradecane	26.57	28.09	−1.52	92	6.69
89	1-Bromohexadecane	32.34	31.64	0.70	104	8.38
90	1-Bromooctadecane	35.92	35.19	0.73	116	9.30

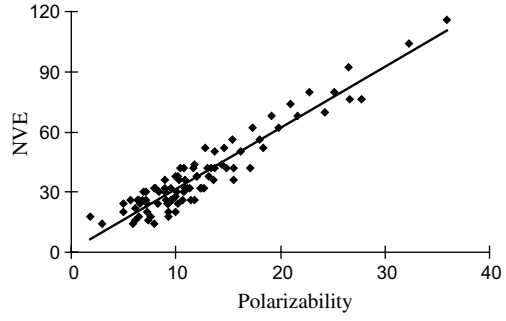


Figure 2. Comparison between polarizability and NVE of the halogen containing compounds used in Eq. 15.

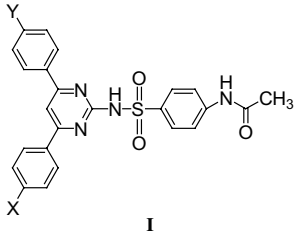
$$\alpha = 3.97(\pm 0.12)\mathrm{CMR} - 0.23(\pm 0.38)$$
$$n = 29, \quad r^2 = 0.994, \quad s = 0.400, \quad q^2 = 0.993 \tag{17a}$$

We did not get a good correlation between polarizability and the nonbonding lone pair electrons for this set of compounds. A high mutual correlation between NVE and CMR is given by Eq. 17b.

$$\mathrm{NVE} = 10.94(\pm 0.71)\mathrm{CMR} + 6.04(\pm 2.27)$$
$$n = 29, \quad r^2 = 0.974, \quad s = 2.406, \quad q^2 = 0.969 \tag{17b}$$

Finally, we consider the compounds containing sulfur, phosphorus, and silicon, and find that NVE works well. These can be demonstrated by the formulation of following QSAR:

Minimum inhibitory concentration of ***I*** *on penicillium notatum.* Data from Wasfy and Aly[16] (Table 5)



I

$$\log 1/C = 0.03(\pm 0.01)\mathrm{NVE} - 1.76(\pm 1.57)$$
$$n = 8, \quad r^2 = 0.885, \quad s = 0.09, \quad q^2 = 0.809 \tag{18}$$
outliers: X = Cl, Y = Me; X = NO_2, Y = Me

$$\log 1/C = 0.62(\pm 0.46)\mathrm{CMR} - 6.18(\pm 4.94)$$
$$n = 8, \quad r^2 = 0.639, \quad s = 0.159, \quad q^2 = 0.359 \tag{18a}$$

$$\mathrm{NVE} = 23.53(\pm 12.76)\mathrm{CMR} - 169.94(\pm 134.16)$$
$$n = 8, \quad r^2 = 0.773, \quad s = 4.369, \quad q^2 = 0.609 \tag{18b}$$

The statistics of Eq. 18 are better than that of 18a. Thus NVE parameter is favorable for this data set. A correlation between NVE and CMR has been shown by Eq. 18b.

Table 3. Physicochemical parameters for the derivation of Eq. 16

No.	Compounds	α (Eq. 16)			NVE	CMR
		Obsd.	Pred.	Δ		
1	Water	1.45	1.52	−0.07	08	0.33
2	Methanol	3.26	3.18	0.08	14	0.79
3	Ethanol	5.07	4.84	0.23	20	1.26
4	1-Propanol	6.77	6.51	0.26	26	1.72
5	Propan-2-ol	6.97	6.51	0.46	26	1.72
6	Cyclohexanol	11.56	10.94	0.62	42	2.94
7	Glycol	5.71	6.51	−0.80	26	1.41
8	Dimethylether	5.16	4.84	0.32	20	1.26
9	Diethylether	8.73	8.17	0.56	32	2.19
10	*n*-Propylmethylether	8.86	8.17	0.69	32	2.19
11	*n*-propylethylether	10.68	9.83	0.85	38	2.65
12	Di-*n*-propylether	12.53	11.50	1.03	44	3.11
13	Dioxane	8.60	9.28	−0.68	36	2.16
14	Acetone	6.40	5.95	0.45	24	1.60
15	Methylethylketone	8.19	7.62	0.57	30	2.07
16	Diethylketone	9.93	9.28	0.65	36	2.53
17	Methylpropylketone	9.93	9.28	0.65	36	2.53
18	Diisopropylketone	13.53	12.61	0.92	48	3.46
19	Formaldehyde	2.45	2.63	−0.18	12	0.68
20	Acetaldehyde	4.59	4.29	0.30	18	1.14
21	*n*-Propionaldehyde	6.35	5.95	0.40	24	1.60
22	*n*-Butylaldehyde	8.18	7.62	0.56	30	2.07
23	Formic acid	3.32	4.29	−0.97	18	0.83
24	Acetic acid	5.15	5.95	−0.80	24	1.29
25	Propionic acid	6.96	7.62	−0.66	30	1.76
26	Butyric acid	8.58	9.28	−0.70	36	2.22
27	Methylformate	5.05	5.95	−0.90	24	1.29
28	Ethylformate	6.88	7.62	−0.74	30	1.76
29	Methylacetate	6.81	7.62	−0.81	30	1.76
30	Ethylacetate	8.62	9.28	−0.66	36	2.22
31	Methylpropionate	8.97	9.28	−0.31	36	2.22
32	Ethylpropionate	10.41	10.94	−0.53	42	2.69
33	Methylbutyrate	10.41	10.94	−0.53	42	2.69
34	Ethylbutyrate	12.23	12.61	−0.38	48	3.15
35	$CH_2OHCH_2OCH_3$	7.44	8.17	−0.73	32	1.88
36	$CH_2OHCH_2OC_2H_5$	9.28	9.83	−0.55	38	2.34
37	CH_2ClCH_2OH	6.88	6.51	0.37	26	1.75
38	$CH_2ClCH_2OCH_3$	8.71	8.17	0.54	32	2.21
39	$CH_2ClCH_2OC_2H_5$	10.56	9.83	0.73	38	2.68
40	$CH_2Cl(CH_2)_2COOH$	10.45	10.94	−0.49	42	2.71
41	$CH_2Cl(CH_2)_2COOCH_3$	12.27	12.61	−0.34	48	3.18
42	$CH_2Cl(CH_2)_2COOC_2H_5$	14.11	14.27	−0.16	54	3.64
43	$CH_3CHClCH_2COOH$	10.54	10.94	−0.40	42	2.71
44	$CH_3CHClCH_2COOCH_3$	12.31	12.61	−0.30	48	3.18
45	$CH_3CHClCH_2COOC_2H_5$	14.13	14.27	−0.14	54	3.64
46	$CH_3CH_2CHClCOOH$	10.61	10.94	−0.33	42	2.71
47	$CH_3CH_2CHClCOOCH_3$	12.33	12.61	−0.28	48	3.18
48	$CH_3CH_2CHClCOOC_2H_5$	14.16	14.27	−0.11	54	3.64
49	$C_2H_5CHClCH_2OH$	10.70	9.83	0.87	38	2.68
50	$CH_3CHClCH_2CH_2OH$	10.38	9.83	0.55	38	2.68
51	$CH_3CHClCH_2OH$	8.89	8.17	0.72	32	2.21
52	$CH_2ClCH_2CH_2OH$	8.84	8.17	0.67	32	2.21
53	$CH_3CH_2CHClCOOH$	10.87	10.94	−0.07	42	2.71
54	$CH_3CHClCH_2COOH$	10.80	10.94	−0.14	42	2.71
55	$CH_2ClCH_2CH_2COOH$	10.69	10.94	−0.25	42	2.71
56	$CH_3(CH_2)_2CHClCOOH$	12.69	12.61	0.08	48	3.18
57	$CH_3CH_2CHClCH_2COOH$	12.57	12.61	−0.04	48	3.18
58	$CH_3CHClCH_2CH_2COOH$	12.53	12.61	−0.08	48	3.18

*Inhibition of protein tyrosine phosphatase (PTP) by miscellaneous compounds **IIa–e** (Fig. 5).* Data from Ibrahimi et al.[17] (Table 6)

$$\log 1/C = 0.03(\pm 0.01)\mathrm{NVE} + 0.81(\pm 0.41)$$
$$n = 5, \quad r^2 = 0.989, \quad s = 0.039, \quad q^2 = 0.932 \tag{19}$$

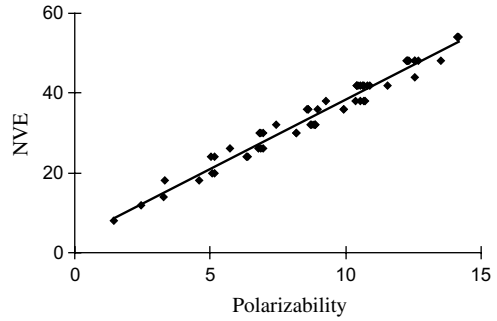


Figure 3. Comparison between polarizability and NVE of the oxygen containing compounds used in Eq. 16.

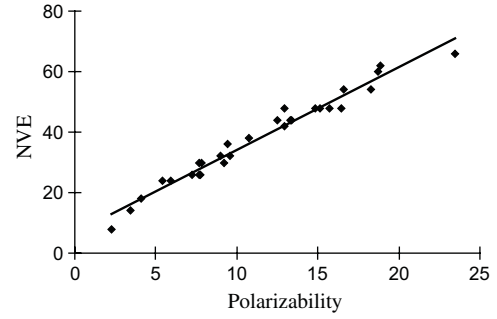
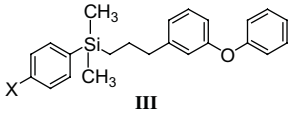


Figure 4. Comparison between polarizability and NVE of the nitrogen containing compounds used in Eq. 17.

$$\log 1/C = 0.25(\pm 0.14)\mathrm{CMR} + 1.41(\pm 0.84)$$
$$n = 5, \quad r^2 = 0.919, \quad s = 0.106, \quad q^2 = 0.840 \tag{19a}$$

$$\mathrm{NVE} = 9.89(\pm 6.64)\mathrm{CMR} + 40.36(\pm 25.70)$$
$$n = 5, \quad r^2 = 0.882, \quad s = 5.098, \quad q^2 = 0.712 \tag{19b}$$

Minimum lethal dose of ***III*** *for American cockroaches*. Data from Okimoto et al.[18] (Table 7)



III

$$\log 1/C = 0.78(\pm 0.52)\mathrm{C}\log P - 1.74(\pm 0.65) \times (\beta \times 10^{\mathrm{C}\log P} + 1) + 0.03(\pm 0.01)\mathrm{NVE} - 4.58(\pm 1.78)$$
$$n = 16, \quad r^2 = 0.932, \quad s = 0.134, \quad q^2 = 0.887$$
$$\text{optimum } \mathrm{C}\log P = 8.86$$
$$\log \beta = -8.94$$
$$\text{outliers: } \mathrm{X} = \mathrm{OC_2H_5};\ \mathrm{OCH_2CF_3};\ \mathrm{NMe_2} \tag{20}$$

Table 4. Physicochemical parameters for the derivation of Eq. 17

No.	Compounds	α (Eq. 17)			NVE	CMR
		Obsd	Pred.	Δ		
1	NH_3	2.26	0.76	1.50	08	0.55
2	*n*-Propylamine	7.70	7.12	0.58	26	1.94
3	Isopropylamine	7.77	7.12	0.65	26	1.94
4	Diethylamine	9.61	9.24	0.37	32	2.40
5	Di-*n*-propylamine	13.29	13.48	−0.19	44	3.33
6	Triethylamine	13.38	13.48	−0.10	44	3.33
7	Tri-*n*-propylamine	18.87	19.85	−0.98	62	4.72
8	Pyridine	9.18	8.54	0.64	30	2.48
9	Quinoline	15.70	14.90	0.80	48	4.17
10	Isoquinoline	16.43	14.90	1.53	48	4.17
11	1-Methylisoquinoline	18.28	17.02	1.26	54	4.63
12	Quinoxaline	15.13	14.90	0.23	48	3.95
13	2,3-Dimethylquinoxaline	18.70	19.14	−0.44	60	4.88
14	Phenazine	23.43	21.26	2.17	66	5.64
15	Hydrazine	3.46	2.88	0.58	14	0.91
16	Phenylhydrazine	12.91	12.78	0.13	42	3.43
17	1,1-Methylphnylhydrazine	14.81	14.90	−0.09	48	3.89
18	1,1-Ethylphnylhydrazine	16.62	17.02	−0.40	54	4.35
19	Pyrazole	7.23	7.12	0.11	26	1.91
20	*N*-Methylpyrazole	8.99	9.24	−0.25	32	2.37
21	1,5-Dimethylpyrazole	10.72	11.36	−0.64	38	2.83
22	1-Ethyl-5-methylpyrazole	12.50	13.48	−0.98	44	3.30
23	Formamide	4.08	4.30	−0.22	18	1.05
24	Acetamide	5.39	6.42	−1.03	24	1.51
25	*N*-Methylformamide	5.89	6.42	−0.53	24	1.51
26	*N*,*N*-Dimethylformamide	7.69	8.54	−0.85	30	1.97
27	*N*-Ethylacetamide	9.45	10.66	−1.21	36	2.44
28	*N*-Methylacetamide	7.82	8.54	−0.72	30	1.97
29	*N*,*N*-Diethylacetamide	12.96	14.90	−1.94	48	3.36

Table 5. Minimum inhibitory concentration of **I** on penicillium notatum and physicochemical parameters for the derivation of Eq. 18

No.	X	Y	log 1/*C* (Eq. 18)			NVE	CMR
			Obsd.	Pred.	Δ		
1	OMe	H	2.98	3.10	−0.12	172	12.99
2	Cl	H	2.98	2.94	0.04	166	12.86
3	NO_2	H	3.29	3.21	0.08	176	12.98
4	OMe	Me	3.29	3.27	0.03	178	13.45
5[a]	Cl	Me	3.29	3.10	0.19	172	13.33
6[a]	NO_2	Me	3.00	3.37	−0.37	182	13.45
7	Me	OMe	3.29	3.27	0.03	178	13.45
8	OMe	OMe	3.30	3.43	−0.13	184	13.61
9	NO_2	OMe	3.62	3.54	0.08	188	13.60
10	NO_2	NO_2	3.64	3.65	−0.01	192	13.60

[a] Data points not included in the derivation of Eq. 18.

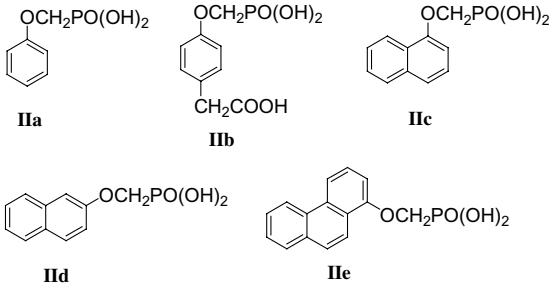


Figure 5.

Table 6. Inhibition of protein tyrosine phosphatase (PTP) by miscellaneous compounds **IIa–e** and physicochemical parameters for the derivation of Eq. 19

No.	Compound	log 1/*C* (Eq. 19)			NVE	CMR
		Obsd.	Pred.	Δ		
1	**IIa**	2.48	2.45	0.03	66	4.40
2	**IIb**	2.96	3.00	−0.04	88	5.52
3	**IIc**	2.89	2.90	−0.01	84	6.09
4	**IId**	2.89	2.90	−0.01	84	6.09
5	**IIe**	3.39	3.35	0.04	102	7.78

$$\log 1/C = 1.12(\pm 0.99)\mathrm{C}\log P - 2.19(\pm 1.23) \times (\beta \times 10^{\mathrm{C}\log P} + 1) + 0.33(\pm 0.31)\mathrm{CMR} - 9.26(\pm 4.62)$$
$$n = 16, \quad r^2 = 0.807, \quad s = 0.225, \quad q^2 = 0.690$$
$$\text{optimum } \mathrm{C}\log P = 8.86$$
$$\log \beta = -8.84 \qquad (20a)$$

$$\mathrm{NVE} = 9.03(\pm 5.73)\mathrm{CMR} + 68.65(\pm 34.43)$$
$$n = 16, \quad r^2 = 0.450, \quad s = 6.553, \quad q^2 = 0.318 \qquad (20b)$$

Thus, from the results of QSAR 18–20, we see that NVE holds well for those compounds, which also have S, P, and Si, respectively.

Table 7. Minimum lethal dose of **III** for American cockroaches and physicochemical parameters for the derivation of Eq. 20

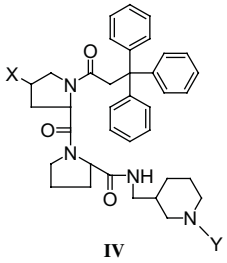
No.	X	log 1/*C* (Eq. 20)			Clog*P*	NVE	CMR
		Obsd.	Pred.	Δ			
1	H	7.97	8.11	−0.14	8.90	128	11.07
2	F	8.13	8.25	−0.12	9.04	134	11.08
3	Cl	8.02	8.00	0.02	9.61	134	11.56
4	Br	8.11	7.90	0.21	9.76	134	11.85
5	Me	8.29	8.13	0.16	9.40	134	11.53
6	C_2H_5	7.86	7.93	−0.07	9.93	140	12.00
7	CF_3	8.20	8.36	−0.16	9.78	152	11.58
8	CHO	8.22	8.21	0.01	8.25	138	11.57
9	OMe	8.53	8.43	0.10	8.82	140	11.69
10[a]	OC_2H_5	9.02	−6.79	15.81	9.35	146	12.15
11	OC_3H_7	8.34	8.29	0.05	9.87	152	12.61
12	$OCHMe_2$	8.52	8.45	0.07	9.65	152	12.61
13	$OCHF_2$	8.76	8.66	0.10	9.26	152	11.72
14	OCH_2CH_2F	8.73	8.72	0.01	9.07	152	12.17
15[a]	OCH_2CF_3	8.60	−7.03	15.63	10.10	164	12.20
16	SMe	8.16	8.25	−0.09	9.46	140	12.34
17	SC_2H_5	7.89	8.05	−0.16	9.99	146	12.80
18[a]	NMe_2	7.87	−6.52	14.39	9.06	146	12.37
19	$SiMe_3$	6.87	6.85	0.02	11.48	152	13.35

[a] Data points not included in the derivation of Eq. 20.

On comparison between the Eqs. 11, 12, 13, 15, 16, and 17 with that of 11a, 12a, 13a, 15a, 16a, and 17a, one can assume that these two polarizability parameters should be identical, which is further supported by Eqs. 11c, 12d, 13d, 15b, 16b, and 17b, but actually it is not in the chemical–biological interactions as shown by Eqs. 18b, 19b, and 20b. The results with NVE cannot be replaced with CMR or vice versa. The volume component of CMR must have something to do with changing the geometry of receptors to provide better access to the ligands. In examples where NVE is ideal, it would seem that the receptor is more flexible. These two polarizability parameters are different in nature can be supported by comparing the QSARs, which has been formulated by using NVE and CMR terms, respectively.

3.1. Comparison between the use of NVE and CMR, where NVE is ideal

*Binding affinity of cloned human muscarinic M_4 receptor by triphenylpropionamide derivatives **IV***. Data from Sagara et al.[19] (Table 8)



IV

$$\log 1/K_i = 0.07(\pm 0.01)\mathrm{NVE} - 10.70(\pm 2.70)$$
$$n = 14, \quad r^2 = 0.948, \quad s = 0.292, \quad q^2 = 0.928 \qquad (21)$$

Table 8. Binding affinity of cloned human muscarinic M_4 receptor by triphenylpropionamide derivatives **IV** and physicochemical parameters for the derivation of Eq. 21

No.	X	Y	log 1/K_i (Eq. 21)			NVE	CMR
			Obsd.	Pred.	Δ		
1	H	H	5.80	5.53	0.27	230	17.57
2	H	CH_2CH_3	6.01	6.37	−0.36	242	18.50
3	H	$CH_2CH_2CH_3$	6.66	6.80	−0.14	248	18.96
4	H	$CH_2CH_2CH_2CH_3$	7.21	7.22	−0.01	254	19.43
5	H	Cyclohexylmethyl	8.64	8.35	0.29	270	20.64
6	OH	H	6.13	5.95	0.18	236	17.73
7	OH	CH_2CH_3	6.57	6.80	−0.23	248	18.65
8	OH	$CH_2CH_2CH_3$	7.24	7.22	0.02	254	19.12
9	OH	$CH_2CH_2CH_2CH_3$	7.89	7.64	0.24	260	19.58
10	OH	$(CH_2)_5CH_3$	8.82	8.49	0.33	272	20.51
11	OH	$(CH_2)_7CH_3$	8.44	8.91	−0.47	278	21.44
12	OH	$CH_2CH(CH_2)_2$	7.14	7.50	−0.36	258	19.44
13	OH	$CH_2C_6H_{11}$	9.09	8.77	0.32	276	20.80
14	OH	$CH_2C_8H_{15}$	9.52	9.62	−0.10	288	21.62

$$\log 1/K_i = 0.92(\pm 0.18)\mathrm{CMR} - 10.41(\pm 3.58)$$
$$n = 14, \quad r^2 = 0.909, \quad s = 0.385 \quad q^2 = 0.868 \tag{21a}$$

$$\mathrm{NVE} = 13.12(\pm 1.18)\mathrm{CMR} + 23.21(\pm 1.38)$$
$$n = 14, \quad r^2 = 0.980, \quad s = 2.501, \quad q^2 = 0.970 \tag{21b}$$

It is our interest to note here that there is a high mutual correlation between NVE and CMR as shown by Eq. 21b ($r^2 = 0.980$ and $q^2 = 0.970$). Thus, the statistics of the equation with NVE or CMR should be expected to be the same, but we see that the statistics of QSAR 21 with NVE is better than that of QSAR 21a with CMR.

Inhibition of acid secretion from frog gastric mucosa by barbiturates.[6] Data from Dinno et al.[20] (Table 9)

$$\log K = 0.03(\pm 0.003)\mathrm{NVE} - 0.89(\pm 0.28)$$
$$n = 5, \quad r^2 = 0.996, \quad s = 0.018, \quad q^2 = 0.993 \tag{22}$$
outlier: Thiamylal

$$\log K = 0.33(\pm 0.16)\mathrm{CMR} - 0.93(\pm 0.38)$$
$$n = 5, \quad r^2 = 0.933, \quad s = 0.074, \quad q^2 = 0.851 \tag{22a}$$

$$\mathrm{NVE} = 11.85(\pm 4.66)\mathrm{CMR} + 26.69(\pm 17.39)$$
$$n = 5, \quad r^2 = 0.956, \quad s = 2.124 \quad q^2 = 0.879 \tag{22b}$$

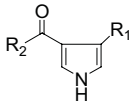
Inhibition of housefly mitochondria by salicylanilides and miscellaneous compounds.[6] Data from Williamson and Metcalf[21] (Table 10)

$$\log 1/C = 0.06(\pm 0.01)\mathrm{NVE} + 1.01(\pm 0.91)$$
$$n = 15, \quad r^2 = 0.952, \quad s = 0.342, \quad q^2 = 0.935$$
outlier: 4, 5, 6, 7-Tetrachloro-2-CF_3-benzimidizide
(23)

$$\log 1/C = 0.60(\pm 0.14)\mathrm{CMR} + 2.27(\pm 1.26)$$
$$n = 15, \quad r^2 = 0.874, \quad s = 0.554, \quad q^2 = 0.834 \tag{23a}$$

$$\mathrm{NVE} = 10.74(\pm 1.58)\mathrm{CMR} + 21.12(\pm 14.66)$$
$$n = 15, \quad r^2 = 0.943, \quad s = 6.444, \quad q^2 = 0.926 \tag{23b}$$

COX-2 inhibition by V.[6] Data from Dannhardt et al.[22] (Table 11)



V

Table 9. Inhibition of acid secretion from frog gastric mucosa by barbiturates and physicochemical parameters for the derivation of Eq. 22

No.	Compound	log 1/K (Eq. 22)			NVE	CMR
		Obsd.	Pred.	Δ		
1	Barbital	1.15	1.15	0.00	72	4.55
2	Diallylbarbituric acid	1.38	1.38	0.00	80	5.43
3	Phenobarbital	1.58	1.60	−0.02	88	6.14
4	Pentobarbital	1.68	1.66	0.02	90	5.95
5	Secobarbital	1.77	1.77	0.00	94	6.38
6[a]	Thiamylal	1.89	1.77	0.12	94	7.24

[a] Data point not included in the derivation of Eq. 22.

Table 10. Inhibition of housefly mitochondria by salicylanilides and miscellaneous compounds, and physicochemical parameters for the derivation of Eq. 23

No.	Compound	log 1/*C* (Eq. 23)			NVE	CMR
		Obsd.	Pred.	Δ		
1	Salicylanilide	4.97	5.51	−0.54	80	6.22
2	3-OH-2-Naphthylcarbanilide	6.44	6.52	−0.08	98	7.91
3	5-Cl-2′-Cl-4′-NO_2-Salicylanilide	7.59	7.09	0.50	108	7.82
4	5-Cl-3-Ph-2′,5′-Cl_2-Salicylanilide	7.91	8.10	−0.20	126	10.21
5	5-Cl-3-Ph-3′,4′-Cl_2-Salicylanilide	8.03	8.10	−0.07	126	10.21
6	5-Cl-3-(*p*-Cl-Ph)-4′-Cl-Salicylanilide	8.03	8.10	−0.07	126	10.21
7	5-Cl-3-Ph-2′,4′,5′-Cl_3-Salicylanilide	8.42	8.44	−0.02	132	10.70
8	5-Cl-3-Ph-3′-Cl-4′-NO_2-Salicylanilide	8.56	8.66	−0.10	136	10.33
9	5-Cl-3-(*p*-Cl-Ph)-2′-Cl,5′-NO_2-Salicylanilide	8.75	9.00	−0.25	142	10.82
10	5-Cl-3-(*p*-Cl-Ph)-2′,4′,5′-Cl_3-Salicylanilide	8.76	8.78	−0.02	138	11.19
11	5-Cl-3-(*p*-Cl-Ph)-2′-Cl-4-CN-Salicylanilide	8.85	8.55	0.30	134	10.68
12	5-Cl-3-(*p*-Cl-Ph)-2′-Cl-4′-CF_3-Salicylanilide	9.08	9.45	−0.37	150	10.72
13	2,4-DNP	4.72	4.83	−0.11	68	4.06
14	4,6-$(NO_2)_2$-*o*-Cresol	5.50	5.17	0.33	74	4.53
15	5-Cl-3-(*tert*-butyl)-2′-Cl-4′-NO_2-Salicylanilide	9.14	8.44	0.70	132	9.67
16[a]	4,5,6,7-Tetra-Cl, 2-CF_3-Benzimidizide	7.06	6.13	0.93	91	5.92

[a] Data point not included in the derivation of Eq. 23.

Table 11. COX-2 inhibition by **V** and physicochemical parameters for the derivation of Eq. 24

No.	R_1	R_2	log 1/*C* (Eq. 24)			NVE	CMR
			Obsd.	Pred.	Δ		
1[a]	C_6H_5	C_6H_5	5.22	5.76	−0.54	92	7.64
2	Thiophene-2-yl	C_6H_5	5.30	5.34	−0.04	88	7.45
3	Thiophene-2-yl	4-Cl-C_6H_4	6.00	5.97	0.03	94	7.94
4	4-Cl-C_6H_4	Thiophene-2-yl	6.02	5.97	0.05	94	7.94
5	4-Cl-C_6H_4	5-Cl-Thiophene-2-yl	6.57	6.60	−0.03	100	8.43
6	5-Br-Thiophene-2-yl	5-Cl-Thiophene-2-yl	6.15	6.18	−0.02	96	8.53

[a] Data point not included in the derivation of Eq. 24.

$$\log 1/C = 0.11(\pm 0.02)\mathrm{NVE} - 3.90(\pm 1.64)$$
$$n = 5, \quad r^2 = 0.992, \quad s = 0.047, \quad q^2 = 0.960 \qquad (24)$$
$$\text{outlier: } R_1 = R_2 = C_6H_5$$

$$\log 1/K_i = 0.06(\pm 0.01)\mathrm{NVE} - 3.52(\pm 1.21)$$
$$n = 7, \quad r^2 = 0.987, \quad s = 0.043, \quad q^2 = 0.975 \qquad (25)$$
$$\text{outlier: } X = C_6H_5, \ Y = H, \ Z = H$$

$$\log 1/C = 0.94(\pm 0.88)\mathrm{CMR} - 1.52(\pm 7.10)$$
$$n = 5, \quad r^2 = 0.792, \quad s = 0.241, \quad q^2 = 0.178 \qquad (24a)$$

$$\log 1/K_i = 0.43(\pm 0.74)\mathrm{CMR} + 0.70(\pm 8.75)$$
$$n = 7, \quad r^2 = 0.306, \quad s = 0.315, \quad q^2 = -0.081 \qquad (25a)$$

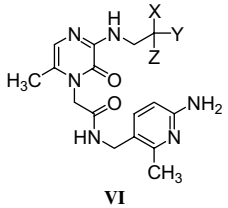
$$\mathrm{NVE} = 9.02(\pm 7.77)\mathrm{CMR} + 62.68(\pm 21.72)$$
$$n = 5, \quad r^2 = 0.820, \quad s = 2.126, \quad q^2 = 0.340 \qquad (24b)$$

$$\mathrm{NVE} = 7.12(\pm 13.15)\mathrm{CMR} + 78.22(\pm 154.86)$$
$$n = 7, \quad r^2 = 0.279, \quad s = 5.580, \quad q^2 = -0.117 \qquad (25b)$$

There is no correlation between NVE and CMR for this data set as shown by Eq. 25b.

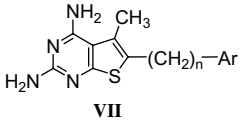
It is our interest to note here that QSAR 24 and 25 have an excellent correlation but on the other hand QSAR 24a and 25a have no significance.

*Inhibition of trypsin by **VI***. Data from Burgey et al.[23] (Table 12)



VI

*Inhibition of dihydrofolate reductase from rat liver by pyrimidine derivatives **VII**, trimethoprim and trimetrexate*. Data from Donkor et al.[24] (Table 13)



VII

Table 12. Inhibition of trypsin by **VI** and physicochemical parameters for the derivation of Eq. 25

No.	X	Y	Z	log 1/K_i (Eq. 25)			NVE	CMR
				Obsd.	Pred.	Δ		
1[a]	C6H5	H	H	5.74	5.41	0.33	156	11.68
2	C_6H_5	H	Me	5.80	5.75	0.05	162	12.14
3	C_6H_5	Me	Me	6.10	6.09	0.01	168	12.61
4	C_6H_5	F	F	6.07	6.09	−0.02	168	11.71
5	2-Pyridyl	H	H	5.44	5.41	0.03	156	11.47
6	3-Pyridyl	H	H	5.42	5.41	0.01	156	11.47
7	4-Pyridyl	H	H	5.34	5.41	−0.07	156	11.47
8	2-Pyridyl	F	F	6.10	6.09	0.00	168	11.50

[a] Data point not included in the derivation of Eq. 25.

$$\log 1/C = 0.16(\pm 0.05)\mathrm{NVE} - 14.62(\pm 5.84)$$
$$n = 7, \quad r^2 = 0.940, \quad s = 0.419, \quad q^2 = 0.865$$
$$\text{outlier: Ar = phenyl, } n = 2;\ \text{Ar = phenyl, } n = 3 \tag{26}$$

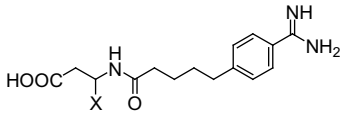
$$\log 1/C = 0.87(\pm 1.60)\mathrm{CMR} - 3.21(\pm 15.87)$$
$$n = 7, \quad r^2 = 0.282, \quad s = 1.448, \quad q^2 = -1.037 \tag{26a}$$

$$\mathrm{NVE} = 6.34(\pm 8.62)\mathrm{CMR} + 60.97(\pm 85.59)$$
$$n = 7, \quad r^2 = 0.417, \quad s = 7.810, \quad q^2 = -0.570 \tag{26b}$$

Again we see that QSAR 26 with NVE is an excellent correlation but QSAR 26a with CMR has no significance.

Now we consider the QSARs where one or more terms are needed in addition to NVE.

*Inhibition of platelet aggregation to dog platelet rich plasma by **VIII***. Data from Zablocki et al.[25] (Table 14)



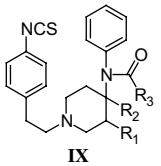
VIII

$$\log 1/C = -1.16(\pm 0.22)\mathrm{C}\log P + 0.07(\pm 0.02)\mathrm{NVE} - 3.22(\pm 2.91)$$
$$n = 9, \quad r^2 = 0.968, \quad s = 0.155, \quad q^2 = 0.930 \tag{27}$$

$$\log 1/C = -1.20(\pm 0.46)\mathrm{C}\log P + 0.99(\pm 0.69)\mathrm{CMR} - 7.20(\pm 2.48)$$
$$n = 9, \quad r^2 = 0.871, \quad s = 0.309, \quad q^2 = 0.697 \tag{27a}$$

$$\mathrm{NVE} = 13.48(\pm 5.60)\mathrm{CMR} + 61.82(\pm 3.57)$$
$$n = 9, \quad r^2 = 0.822, \quad s = 2.936, \quad q^2 = 0.743 \tag{27b}$$

*Binding to μ opioid receptors in mouse brain membrane by **IX***. Data from Chen et al.[26] (Table 15)



IX

$$\log K_i = -2.13(\pm 0.67)\mathrm{C}\log P - 0.06(\pm 0.02)\mathrm{NVE} + 28.28(\pm 5.46)$$
$$n = 9, \quad r^2 = 0.936, \quad s = 0.191, \quad q^2 = 0.886$$
$$\text{outliers: } R_1 = H,\ R_2 = COOCH_3,\ R_3 = C_4H_3S;\ R_1 = CH_3,\ R_2 = H,\ R_3 = C_4H_3S \tag{28}$$

$$\log K_i = -1.35(\pm 0.85)\mathrm{C}\log P - 0.80(\pm 0.37)\mathrm{CMR} + 25.10(\pm 6.42)$$
$$n = 9, \quad r^2 = 0.885, \quad s = 0.256, \quad q^2 = 0.792 \tag{28a}$$

Table 13. Inhibition of dihydrofolate reductase from rat liver by pyrimidine derivatives **VII**, trimethoprim and trimetrexate, and physicochemical parameters for the derivation of Eq. 26

No.	Ar	n	log 1/C (Eq. 26)			NVE	CMR
			Obsd.	Pred.	Δ		
1[a]	Phenyl	2	4.10	1.89	2.21	102	8.40
2[a]	Phenyl	3	5.89	2.86	3.03	108	8.87
3	Phenyl	5	4.82	4.80	0.02	120	9.79
4	1-Naphthyl	2	5.05	4.80	0.25	120	10.09
5	1-Naphthyl	3	6.0	5.77	0.23	126	10.56
6	2-Naphthyl	2	4.10	4.80	−0.70	120	10.09
7	2-Naphthyl	3	5.44	5.77	−0.33	126	10.56
8	Trimethoprim		3.88	3.51	0.37	112	7.83
9	Trimetrexate		8.52	8.36	0.16	142	10.35

[a] Data points not included in the derivation of Eq. 26.

Table 14. Inhibition of platelet aggregation to dog platelet rich plasma by **VIII** and physicochemical parameters for the derivation of Eq. 27

No.	X	log 1/*C* (Eq. 27)			C log *P*	NVE	CMR
		Obsd.	Pred.	Δ			
1	Cyclohexyl	4.74	4.62	0.12	2.95	148	10.62
2	Cyclohex-3-enyl	4.94	5.04	−0.10	2.47	146	10.60
3	$CH_2C_6H_5$	5.33	5.27	0.06	2.40	148	10.99
4	$CH_2CH_2C_6H_5$	5.30	5.27	0.03	2.78	154	11.45
5	4-OCH_2CH_3-C_6H_4	5.76	5.86	−0.09	2.66	160	11.61
6	3-Pyridyl	6.82	6.79	0.03	0.72	142	10.32
7	2-OCH_2CH_3-Pyridin-5-yl	6.65	6.55	0.10	2.07	160	11.40
8	3-OCH_3-C_6H_4	5.75	6.03	−0.28	2.13	154	11.14
9	1,3-Benzodioxol-5-yl	6.41	6.27	0.14	2.18	158	11.12

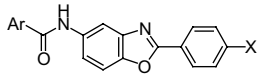
Table 15. Binding to μ opioid receptors in mouse brain membrane by **IX** and physicochemical parameters for the derivation of Eq. 28

No.	R_1	R_2	R_3	log 1/K_i (Eq. 28)			Clog *P*	NVE	CMR
				Obsd.	Pred.	Δ			
1	CH_3	H	C_2H_5	8.12	8.02	0.09	5.30	152	12.44
2	H	$COOCH_3$	C_2H_5	7.92	8.05	−0.12	4.85	168	13.10
3	H	CH_2OCH_3	C_2H_5	7.62	7.73	−0.11	5.11	164	13.06
4	H	$COOCH_3$	Furan-2-yl	7.59	7.67	−0.08	4.69	180	13.89
5	H	CH_2OCH_3	Furan-2-yl	7.66	7.33	0.33	4.96	176	13.86
6[a]	H	$COOCH_3$	Thiophene-2-yl	7.27	6.39	0.88	5.29	180	14.49
7[a]	CH_3	H	Thiophene-2-yl	8.06	6.22	1.84	5.82	164	13.84
8	H	CH_2OCH_3	Thiophene-2-yl	6.02	6.05	−0.03	5.57	176	14.45
9	CH_3	H	Furan-2-yl	7.63	7.49	0.13	5.22	164	13.24
10	CH_3	H	Tetrahydrofuran-2-yl	6.91	7.13	−0.22	5.28	168	13.25
11	H	CH_2OCH_3	Tetrahydrofuran-2-yl	6.85	6.84	0.01	5.08	180	13.96

[a] Data points not included in the derivation of Eq. 28.

$$\mathrm{NVE} = 13.73(\pm 5.60)\mathrm{CMR} - 75.59(\pm 15.32)$$
$$n = 9, \quad r^2 = 0.828, \quad s = 4.079, \quad q^2 = 0.592 \tag{28b}$$

*Minimum inhibitory concentration of **X** against Staphylococcus aureus*. Data from Temiz-Arpaci et al.[27] (Table 16)



X

$$\log 1/C = 0.03(\pm 0.007)\mathrm{NVE} - 0.60(\pm 0.29)\mathrm{B1_X} + 0.94(\pm 0.55)$$
$$n = 11, \quad r^2 = 0.955, \quad s = 0.043, \quad q^2 = 0.920$$
outliers: Ar = 2-Furyl, X = C_2H_5; Ar = 4-methoxyphenyl, X = C_2H_5 (29)

$$\log 1/C = 0.18(\pm 0.19)\mathrm{CMR} + 0.03(\pm 0.77)\mathrm{B1_X} + 2.29(\pm 1.33) \tag{29a}$$
$$n = 11, \quad r^2 = 0.538, \quad s = 0.138, \quad q^2 = 0.262$$

Table 16. Minimum inhibitory concentration of **X** against *Staphylococcus aureus* and physicochemical parameters for the derivation of Eq. 29

No.	Ar	X	log 1/*C* (Eq. 29)			NVE	$B1_X$	CMR
			Obsd.	Pred.	Δ			
1	2-Thienyl	F	3.83	3.80	0.03	118	1.35	9.09
2	2-Thienyl	H	3.81	3.82	−0.01	112	1.00	9.08
3	2-Furyl	F	3.81	3.80	0.01	118	1.35	8.50
4	2-Furyl	H	3.79	3.82	−0.03	112	1.00	8.48
5	2-Thienyl	C_2H_5	3.84	3.88	−0.04	124	1.52	10.01
6[a]	2-Furyl	C_2H_5	4.12	3.88	0.24	124	1.52	9.41
7	2-Thienyl	NMe_2	4.16	4.17	−0.01	130	1.35	10.38
8	2-Furyl	NMe_2	4.14	4.17	−0.03	130	1.35	9.78
9	4-Chlorophenyl	F	4.17	4.11	0.06	128	1.35	9.78
10	4-Chlorophenyl	C_2H_5	4.18	4.19	−0.01	134	1.52	10.69
11[a]	4-Methoxyphenyl	C_2H_5	4.16	4.38	−0.22	140	1.52	10.81
12	4-Fluorophenyl	F	4.17	4.11	0.07	128	1.35	9.30
13	4-Fluorophenyl	C_2H_5	4.15	4.19	−0.04	134	1.52	10.21

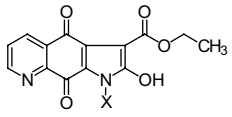
[a] Data points not included in the derivation of Eq. 29.

$$\mathrm{NVE} = 9.46(\pm 4.25)\mathrm{CMR} + 40.82(\pm 33.83)$$
$$n = 11, \quad r^2 = 0.738, \quad s = 4.394, \quad q^2 = 0.633 \tag{29b}$$

Here also we see that QSAR 29 with NVE has an excellent correlation but on the other hand QSAR 29a with CMR has no significance.

3.2. Comparison between the use of NVE and CMR, where CMR is ideal

*Inhibition of SK-MEL-2 (Human melanoma tumor cells) by **XI** and doxorubicin.* Data from Suh et al.[28] (Table 17)



XI

$$\log 1/C = 0.47(\pm 0.11)\mathrm{CMR} + 4.12(\pm 1.02)$$
$$n = 10, \quad r^2 = 0.922, \quad s = 0.247, \quad q^2 = 0.900 \tag{30}$$

$$\log 1/C = 0.03(\pm 0.01)\mathrm{NVE} + 4.50(\pm 1.13)$$
$$n = 10, \quad r^2 = 0.889, \quad s = 0.296, \quad q^2 = 0.741 \tag{30a}$$

$$\mathrm{NVE} = 15.98(\pm 1.99)\mathrm{CMR} - 18.00(\pm 8.99)$$
$$n = 10, \quad r^2 = 0.977, \quad s = 4.379, \quad q^2 = 0.845 \tag{30b}$$

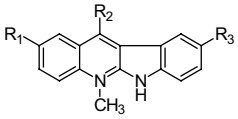
Inhibition of Tetrahymena pyriformis by miscellaneous compounds. Data from Schultz et al.[29] (Table 18)

$$\log 1/C = 1.41(\pm 0.52)\mathrm{CMR} - 2.59(\pm 1.72)$$
$$n = 8, \quad r^2 = 0.882, \quad s = 0.267, \quad q^2 = 0.821 \tag{31}$$
$$\text{outliers}: \ 2,6\text{-Dimethylpyridine; benzene}$$

$$\log 1/C = 0.12(\pm 0.06)\mathrm{NVE} - 2.49(\pm 2.21)$$
$$n = 8, \quad r^2 = 0.812, \quad s = 0.337, \quad q^2 = 0.697 \tag{31a}$$

$$\mathrm{NVE} = 11.46(\pm 1.85)\mathrm{CMR} + 6.14(\pm 1.24)$$
$$n = 8, \quad r^2 = 0.975, \quad s = 0.955, \quad q^2 = 0.952 \tag{31b}$$

*Cytotoxicity of indolo[2,3-b]quinoline derivatives **XII** to CCRF/CEM cells.* Data from Humeniuk et al.[30] (Table 19)



XII

$$\log 1/C = 0.88(\pm 0.11)\mathrm{CMR} - 1.97(\pm 0.95)$$
$$n = 6, \quad r^2 = 0.992, \quad s = 0.062, \quad q^2 = 0.968 \tag{32}$$

Table 17. Inhibition of SK-MEL-2 (Human melanoma tumor cells) by **XI** and doxorubicin, and physicochemical parameters for the derivation of Eq. 30

No.	X	$\log 1/C$ (Eq. 30)			CMR	NVE
		Obsd.	Pred.	Δ		
1	CH_3	7.71	7.65	0.07	7.44	112
2	C_2H_5	7.95	7.87	0.09	7.90	118
3	C_3H_7	8.19	8.09	0.10	8.36	124
4	C_4H_9	8.37	8.31	0.07	8.83	130
5	$CH(CH_3)_2$	7.79	8.09	−0.30	8.36	124
6	CH_2CH_2OH	8.28	7.94	0.34	8.05	124
7	$CH_2CH_2OCH_3$	7.69	8.16	−0.47	8.52	130
8	Cyclopropyl	7.96	8.02	−0.06	8.23	122
9	$CH_2C_6H_5$	9.01	8.84	0.17	9.95	140
10	Doxorubicin	10.43	10.44	−0.01	13.33	208

Table 18. Inhibition of Tetrahymena pyriformis by miscellaneous compounds and physicochemical parameters for the derivation of Eq. 31

No.	Compound	$\log 1/C$ (Eq. 31)			CMR	NVE
		Obsd.	Pred.	Δ		
1	Pyridine	0.94	0.91	0.03	2.48	30
2	2-Methylpyridine	1.19	1.56	−0.37	2.94	36
3[a]	2,6-Dimethylpyridine	1.49	2.22	−0.73	3.41	42
4	Aniline	1.67	1.73	−0.06	3.06	36
5	2-Methylaniline	2.73	2.38	0.35	3.52	42
6	2,6-Dimethylaniline	2.91	3.03	−0.12	3.98	48
7[a]	Benzene	1.89	1.21	0.68	2.69	30
8	Methylbenzene	2.22	1.86	0.36	3.15	36
9	1,4-Dimethylbenzene	2.42	2.51	−0.09	3.62	42
10	1,3-Dimethylbenzene	2.42	2.51	−0.09	3.62	42

[a] Data points not included in the derivation of Eq. 31.

Table 19. Cytotoxicity of indolo[2,3-*b*]quinoline derivatives **XII** to CCRF/CEM cells and physicochemical parameters for the derivation of Eq. 32

No.	R_1	R_2	R_3	log 1/*C* (Eq. 32)			CMR	NVE
				Obsd.	Pred.	Δ		
1	H	H	H	4.52	4.58	−0.06	7.43	86
2	H	CH_3	H	5.08	4.99	0.09	7.90	92
3	CH_3	CH_3	CH_3	5.77	5.81	−0.04	8.83	104
4	CH_3	CH_3	OCH_3	5.96	5.94	0.02	8.98	110
5	OCH_3	CH_3	CH_3	5.96	5.94	0.02	8.98	110
6	OCH_3	CH_3	OCH_3	6.05	6.08	−0.03	9.13	116

Table 20. Inhibition of *Leishmania major* by triazine derivatives **XIII** and physicochemical parameters for the derivation of Eq. 33

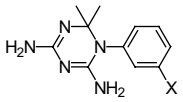
No.	X	log 1/*C* (Eq. 33)			π	CMR	NVE
		Obsd.	Pred.	Δ			
1[a]	$(CH_2)_8CH_3$	5.07	4.47	0.60	4.79	10.65	138
2	$(CH_2)_{11}CH_3$	5.10	5.26	−0.16	6.41	12.04	156
3	$O(CH_2)_2OC_6H_5$-3′-CF_3	3.90	3.97	−0.07	2.56	10.73	160
4	$CH_2NHC_6H_3$-3′,5′-$(CONH_2)_2$	3.30	3.31	−0.01	−1.34	11.55	156
5	$CH_2OC_6H_4$-3′-OCH_3	3.51	3.61	−0.10	1.64	10.22	136
6	$CH_2OC_6H_4$-3′-CH_3	3.66	3.70	−0.04	2.22	10.06	130
7	$CH_2OC_6H_4$-3′-$CH(CH_3)_2$	4.24	4.20	0.04	3.19	10.99	142
8	$CH_2OC_6H_4$-3′-C_6H_5	4.64	4.65	−0.01	3.69	12.11	152
9	CH_2O-1-Naphthyl	4.29	4.24	0.05	2.98	11.29	142
10	$SCH_2C_6H_4$-4′-Cl	4.22	4.08	0.14	3.01	10.74	130
11	$CH_2OC_6H_2$-2′,4′,6′-Cl_3	4.60	4.36	0.24	3.79	11.07	142
12	$CH_2NHC_6H_4$-4-Cl	3.58	3.65	−0.07	1.71	10.31	130

[a] Data point not included in the derivation of Eq. 33.

$$\log 1/C = 0.05(\pm 0.02)\mathrm{NVE} + 1.72(\pm 0.22)$$
$$n = 6, \quad r^2 = 0.949, \quad s = 0.156, \quad q^2 = 0.836 \tag{32a}$$

$$\mathrm{NVE} = 16.31(\pm 4.52)\mathrm{CMR} - 38.71(\pm 36.30)$$
$$n = 6, \quad r^2 = 0.962, \quad s = 2.549, \quad q^2 = 0.919 \tag{32b}$$

Inhibition of Leishmania major by triazine derivatives ***XIII***. Data from Booth et al.[31] (Table 20)



XIII

$$\log 1/C = 0.30(\pm 0.14)\mathrm{CMR} + 0.23(\pm 0.05)\pi + 1.52(\pm 0.19)$$
$$n = 11, \quad r^2 = 0.959, \quad s = 0.126, \quad q^2 = 0.914$$
$$\text{outlier: } \mathrm{X} = (\mathrm{CH_2})_8\mathrm{CH_3} \tag{33}$$

$$\log 1/C = 0.01(\pm 0.014)\mathrm{NVE} + 0.27(\pm 0.09)\pi + 1.99(\pm 2.02)$$
$$n = 11, \quad r^2 = 0.879, \quad s = 0.217, \quad q^2 = 0.661 \tag{33a}$$

$$\mathrm{NVE} = 11.56(\pm 8.58)\mathrm{CMR} + 94.64(\pm 16.03)$$
$$n = 11, \quad r^2 = 0.508, \quad s = 8.322, \quad q^2 = 0.354 \tag{33b}$$

It is our interest to note here that QSAR 33 is an excellent correlation but on the other hand QSAR 33a is not. π is the hydrophobicity of X substituents.

4. Conclusion

Polarizability has long been a subject of great interest to chemists. We have found two important ways to deal with it: the molar refractivity (MR) and the sum of the valence electrons (NVE). The strong correlation as shown by Eqs. 11–13, 15–20 are the confirmation that the term polarizability may be represented by NVE. This is further supported by Figures 1–4. By comparing the correlation of polarizability with NVE and δ^v (NVE − h), it is clear that the positive contribution of hydrogen in NVE is favorable for the measure of polarizability whereas unsaturated and aromatic hydrocarbons (which have fewer H's than saturated) are more polarizable than the corresponding saturated compounds. It has been thought that the polarizability of halogen will be increasing in the order of fluorine to iodine. This is actually a worrisome aspect for NVE approach in which we are using seven valence electrons for all halogens. NVE works well for halogens regardless of size has been supported by the strong correlation as shown by Eqs. 14 and 15 as well as Figure 2.

The results with NVE cannot be replaced with CMR (calculated MR) or vice versa. The volume component of CMR must have something to do with changing the geometry of receptors to provide better access to the ligands. In examples where NVE is ideal, it would seem that the receptor is more flexible. These two polarizability parameters NVE and CMR are different in nature have been confirmed by comparing QSARs 21–29 with that of 21a–29a, where NVE is ideal, and on the other hand the confirmation by comparing QSARs 30–33 with that of 30a–33a, where CMR is ideal.

In conclusion, we can say that CMR and NVE are the volume dependent and volume independent polarizability parameters, respectively, for the chemical–biological interactions.

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