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QSPR Calculation of Normal Boiling Points of Organic Molecules Based on the Use of Correlation Weighting of Atomic Orbitals with Extended Connectivity of Zero- and First-Order Graphs of Atomic Orbitals

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Abstract: We report the results of a calculation of the normal boiling points of a representative set of 200 organic molecules through the application of QSPR theory. For this purpose we have used a particular set of flexible molecular descriptors, the so called Correlation Weighting of Atomic Orbitals with Extended Connectivity of Zero- and First-Order Graphs of Atomic Orbitals. Although in general the results show suitable behavior to predict this physical chemistry property, the existence of some deviant behaviors points to a need to complement this index with some other sort of molecular descriptors. Some possible extensions of this study are discussed.

Keywords: Boiling point – Flexible Molecular Descriptors – Correlation Weighting of Atomic Orbitals.

Introduction

One of the topics of continuing interest in structure-property studies is to arrive at simple correlations between the selected properties and the molecular structure. For such considerations the molecular structure is often represented as a simple mathematical object, such as a number, sequence,

or a set of selected invariants of matrices, generally referred to as *molecular descriptors*. Multiple regression analysis is usually used in such studies in the hope that it might point to structural factors that influence a particular property. Of course, regression analysis does not establish a causal relationship between structural components and molecular properties. Nevertheless, it may help one in model building and assist in the design of molecules with prescribed desirable properties, which is an important goal in drug research. In chemistry, anything that can be said about the magnitude of the property and its dependence upon changes in the molecular structure depends on the chemist's capability to establish valid relationships between structure and property. In many physical-chemistry, organic, biochemical and biological areas, it is increasingly necessary to translate those general relations into quantitative associations expressed in useful algebraic equations known as **Q**uantitative **S**tructure-**A**ctivity (-**P**roperty) **R**elationships (QSAR/QSPR). To obtain a significant correlation, it is crucial that appropriate descriptors be employed, whether they be theoretical, empirical or derived from readily available experimental features of the molecular structures. Many descriptors reflect simple molecular properties and thus they can provide some meaningful insights into the physical-chemistry nature of the activity/property under consideration.

Chemical graph theory [1] advocates an alternative approach to QSAR/QSPR studies based on mathematically derived molecular descriptors. Such descriptors, often referred to as *topological indices* [2], include the well-known Wiener index W [3], the Hosoya index Z [4], and the connectivity index χ [5]. The last three decades have witnessed an upsurge of interest in applications of graph theory in chemistry. Constitutional formulae of molecules are chemical graphs where vertices represent the set of atoms and edges represent chemical bonds [6]. The pattern of connectedness of atoms in a molecule is preserved by constitutional graphs. A graph G = [V,E] consists of a finite nonempty set V of points together with a prescribed set E of unordered pairs of distinct points of V [7].

The correlation and prediction of physical-chemistry properties of pure liquids and of mixtures, such as boiling point, density, viscosity, static dielectric constant, and refractive index, is of practical (process design and control) and theoretical (role of the molecular structure in determining the macroscopic properties of the solvent) relevance to both chemists and engineers. Traditionally, procedures for estimating these properties have been based either on theoretical relationships often making use of empirical parameters that have to be fitted or on empirical relationships derived from additive-constitutive schemes based on atomic groups or bonds contribution within the molecule [8-12]. More recently, the QSPR approach has been applied especially to predict boiling points (BPs), partition coefficients, chromatographic retention indexes, surface tension, critical temperatures, viscosity, refractive index, thermodynamic state functions and static dielectric constant, among other properties. The use of calculated molecular descriptors in QSPR analysis has two main advantages: (a) the descriptors can be univocally defined for any molecular structure or fragment; (b) thanks to the high and well-defined physical information content encoded in many theoretical descriptors, they can clarify the mechanism relating the studied property with the chemical structure. Furthermore, QSPR models based on calculated descriptors help understanding of the inter- and intramolecular interactions that are mainly responsible for the behavior of complex chemical systems and processes.

The normal BP (i.e. the boiling point at 1 atm) is one of the major physical-chemistry properties used to characterize and identify a compound. Besides being an indicator for the physical state (liquid or gas) of a compound, the BP also provides an indication of its volatility. In addition, the BPs can be used to predict or estimate other physical properties, such as critical temperatures, flash points,

enthalpies of vaporization, etc. [13-15]. The BP is often the first property measured for a new compound and one of the few parameters known for almost every volatile compound. Normal BPs are easy to determine, but when a chemical is unavailable, as yet unknown, or hazardous to handle, a reliable procedure for estimating its BP is required. Furthermore, the rapid and nearly explosive growth of combinatorial chemistry, where literally millions of new compounds are synthesized and tested without isolation, could render such a procedure very useful.

A large number of methods for estimating BPs have been devised and numerous QSPR correlations of normal BPs have been reported and detailed reviews have been given elsewhere [15-22]. The aim of this study is to present the results derived from the use of a particular sort of *flexible molecular descriptors* to estimate the BPs of a representative set of organic molecules, in order to seek better ways of calculating physical-chemistry properties. Some previous experience with this issue has shown the convenience of resorting to this special sort of molecular descriptor.

The paper is organized in the following way: the next section deals with the basic methodology, presenting some general properties of flexible molecular descriptors and some previous uses of the same. Then, we describe the calculation strategy, after which we give and discuss the results. Finally, our conclusions are presented together with some possible future further extensions of the method.

Molecular Descriptors

The basic algebraic expression of the fundamental principle governing the QSAR/QSPR, i.e. the quantitative formula representing the structure-activity/property relationship, is

$$P = f(\{d\}) \quad (1)$$

where P stands for the activity/property, {d} is a set of molecular descriptors and f is an arbitrary function. The commonest and simplest cases are those where {d} is reduced just to one variable and f is a linear function, i..e.

$$P = a + bd \quad (2)$$

with $a,b \in \Re$, and real numbers a, b are determined by a standard least squares procedure.

Since there are too many possibilities to choose the set of molecular descriptors and besides they can be highly interrelated, this leads to a nasty situation which is termed *the nightmare of the regression analysis*. Some of these drawbacks include how to make the selection of descriptors, as well as ambiguities of the criteria used to select optimal descriptors and uncertainties when choosing the order in which descriptors are to be orthogonalized. Naturally, none of these difficulties exists for simple regression based on a single molecular descriptor, particularly if the regression is linear. This is one of the major reasons why researchers are striving to find or to design novel descriptors that would produce good correlation for a single molecular property of a set of compounds. However, not many molecular properties can be sufficiently well described by a single descriptor [23].

A quite interesting alternative to surmount these difficulties was proposed long ago by Randic [24] and it consists on defining {d} as a function of one or several variables that are determined during the search for the best correlation. Thus, in contrast to the traditional topological indices, which one can calculate after selecting a set of compounds to be studied and then proceed with statistical analysis, the variable indices are initially non-numerical. Hence, they cannot be calculated in advance for the set of

compounds. Instead, one starts with an arbitrary set of values for the yet undetermined variables and, through an iterative procedure, one varies these initial values seeking optimal values that will produce the smallest standard error for the property under consideration. It is clear that the use of *variable descriptors* (also called *flexible descriptors*) can only improve correlations over the use of simple indices because if all variables take on a zero value (which is very unlikely), we would obtain the results that coincide with the results based on he traditional rigid molecular descriptors. Current literature shows that the use of variable molecular descriptors dramatically improved regression statistics [23].

Among the different alternatives of choosing flexible molecular descriptors, one of us (A.A.T.) has presented the so called **O**ptimization of **C**orrelation **W**eights of **L**ocal **G**raph **I**nvariants (OCWLGI) procedure which has proved to be a rather suitable way to apply the method to calculate several biological activities and physical-chemistry properties [25-34]. The OCWLI may be based on the labeled hydrogen filled graph (LHFG) [35] and the graph of atomic orbitals (GAO) [36]. The OCWLI based upon the LHFGs yield reasonable good models of enthalpies of formation from elements of coordination compounds [37]. Besides, OCWLI based on LHFG have been used to model the Flory-Huggins polymer-solvent interaction parameters [26]. The OCWLI based upon the GAOs give rather good results to predict stability constants of amino acids complexes [36].

Molecular descriptors DCW are calculated by means of the following relationship

$$DCW = \sum_{\text{all vertices}} CW(ao_k) + \sum_{\text{all vertices}} CW({}^1EC_k) \qquad (3)$$

where $CW(ao_k)$ and $CW({}^1EC_k)$ are correlation weights of the atomic orbitals that are image of the k-th vertex in the GAO and correlation weights of Morgan extended connectivity of first order that have a k-th vertex in the GAO. The Monte Carlo method is then applied to determine optimum correlation weight values which produce the largest possible values of the correlation coefficient between the physical property as a function of the descriptor computed via Eq. (3). Numerical data of the GAO local invariants are listed in Table 1 and an illustrative example is reproduced in Table 2.

Table 1. Correlation weights for calculating DCW^0 and DCW^1

DCW^0

1s1	-0.246
1s2	0.165
2s2	-0.556
2p2	1.780
2p3	3.738
2p4	2.722
2p5	-4.591
2p6	-0.726
3s2	-0.437
3p2	1.760
3p3	-2.030
3p4	5.491
3p5	4.532
3p6	0.093
3d10	0.551
4s2	2.873

Table 1. Cont.

4p5	0.193
0003	0.626
0004	1.648
0005	0.475
0006	0.175
0007	1.159
0008	0.623
0009	1.758
0010	0.546
0011	1.198
0012	0.463
0013	1.247
0014	3.437
0015	1.877
0016	-0.404

DCW[1]

1s1	0.939
1s2	0.155
2s2	0.104
2p2	0.704
2p3	4.943
2p4	0.748
2p5	-2.191
2p6	0.222
3s2	-0.183
3p2	0.827
3p3	4.546
3p4	5.322
3p5	0.939
3p6	8.663
3d10	9.470
4s2	8.444
4p5	8.422
0012	5.903
0015	-2.827
0018	0.150
0020	0.376
0021	1.669
0024	-0.381
0027	2.112
0030	1.574
0033	2.507
0035	0.685
0036	1.462
0038	1.577
0039	0.219
0042	0.224
0045	0.033
0048	1.204
0050	0.071
0051	1.528
0053	1.086
0054	1.323

Table 1. Cont.

0057	1.983
0059	0.574
0060	0.469
0062	0.669
0063	-0.236
0066	-0.161
0069	0.737
0070	-2.190
0075	3.355
0078	3.944
0079	0.582
0080	0.582
0081	2.970
0082	0.904
0084	0.646
0086	-0.466
0087	-0.007
0089	0.376
0090	2.254
0091	4.903
0094	-0.955
0096	2.028
0097	-1.506
0098	4.564
0099	1.506
0100	5.589
0101	3.285
0102	-5.967
0103	1.738
0105	1.969
0108	0.273
0109	4.121
0110	2.223
0111	2.796
0112	1.653
0116	4.641
0120	-2.254
0122	0.616
0124	1.832
0134	1.828

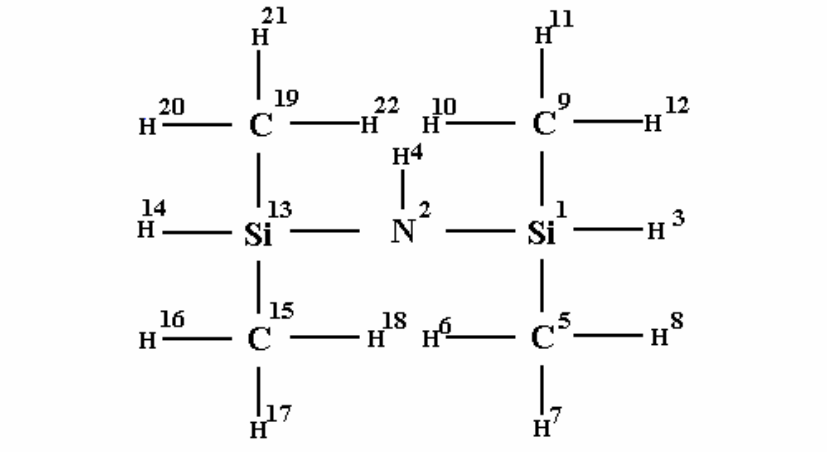


Table 2. Calculation of the DCW^1 for 1,1,3,3-tetramethyldisilazane (DCW^1 = 8.39793)

atom	Nat	EC1	ao	Nao	EC1	CW(V)	CW(LI)
Si	1	12	1s2	1	86	0.155	-0.466
			2s2	2	86	0.104	-0.466
			2p6	3	86	0.222	-0.466
			3s2	4	86	-0.183	-0.466
			3p2	5	86	0.827	-0.466
N	2	9	1s2	6	103	0.155	1.738
			2s2	7	103	0.104	1.738
			2p3	8	103	4.943	1.738
H	3	4	1s1	9	50	0.939	0.071
H	4	3	1s1	10	33	0.939	2.507
C	5	7	1s2	11	59	0.155	0.574
			2s2	12	59	0.104	0.574
			2p2	13	59	0.704	0.574
H	6	4	1s1	14	24	0.939	-0.381
H	7	4	1s1	15	24	0.939	-0.381
H	8	4	1s1	16	24	0.939	-0.381
C	9	7	1s2	17	59	0.155	0.574
			2s2	18	59	0.104	0.574
			2p2	19	59	0.704	0.574
H	10	4	1s1	20	24	0.939	-0.381
H	11	4	1s1	21	24	0.939	-0.381
H	12	4	1s1	22	24	0.939	-0.381
Si	13	12	1s2	23	86	0.155	-0.466
			2s2	24	86	0.104	-0.466
			2p6	25	86	0.222	-0.466
			3s2	26	86	-0.183	-0.466
			3p2	27	86	0.827	-0.466
H	14	4	1s1	28	50	0.939	0.071
C	15	7	1s2	29	59	0.155	0.574
			2s2	30	59	0.104	0.574
			2p2	31	59	0.704	0.574
H	16	4	1s1	32	24	0.939	-0.381
H	17	4	1s1	33	24	0.939	-0.381
H	18	4	1s1	34	24	0.939	-0.381
C	19	7	1s2	35	59	0.155	0.574
			2s2	36	59	0.104	0.574
			2p2	37	59	0.704	0.574
H	20	4	1s1	38	24	0.939	-0.381
H	21	4	1s1	39	24	0.939	-0.381
H	22	4	1s1	40	24	0.939	-0.381

Since the complete and detailed description of these flexible descriptors has been given before, we refer the reader interested in further minutiae to the specific papers where these details were largely reported [25-34].

Results and Discussion

We have chosen a representative set of 200 organic molecules of varied composition to study their normal boiling points (NBPs). These molecules, with both linear and cyclic structures, comprise ketones, acids, esters, aldehydes, nitriles, amines, alcohols, and hydrocarbons and a wide variety of atoms, such as C, H, O, N, Si, Cl, Br, F, P, S. The list of molecules is given in Table 3, together with their NBPs and the extended connectivity of zero- and first-order descriptors in the GAOs (DCW^0 and DCW^1, respectively).

Table 3. Organic molecules, experimental NBPs (Celsius degrees) and DCWs.

n	CAS	Molecule	DCW^0	DCW^1	NBP_{exp}
1	15933-59-2	1,1,3,3-Tetramethyldisilalazane	5.460	8.398	99.000
2	105-54-4	Butanoic acid, ethyl ester	5.543	11.949	120.000
3	623-27-8	1,4-Benzenedicarboxaldehyde	16.537	18.618	245.000
4	7212-44-4	1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl	14.389	17.084	68.000
5	705-86-2	5-Hydroxydecanoic acid lactone	8.596	13.405	117.000
6	620-22-4	Benzonitrile, 3-methyl-	12.826	16.075	99.000
7	621-33-0	3-Ethoxyaniline	12.735	25.122	248.000
8	150-76-5	Mequinol	14.584	23.498	243.000
9	109-52-4	Pentanoic acid	9.042	14.320	185.000
10	75-55-8	Aziridine, 2-methyl-	1.529	9.325	66.000
11	586-39-0	3-Nitrosostyrene	21.317	14.385	56.000
12	224-41-9	Dibenz[a,j]anthracene	39.917	53.421	531.000
13	105-05-5	Benzene, 1,4-diethyl-	11.384	19.030	184.000
14	110-42-9	Decanoic acid, methyl ester	8.330	13.914	108.000
15	111-69-3	Hexanedinitrile	6.906	8.394	295.000
16	1112-55-6	Silane , tetraethyl-	10.654	11.853	130.000
17	1719-57-9	Silane, chloro(chloromethyl)dimethyl-	5.129	10.177	115.000
18	123-31-9	Hydroquinoline	18.082	28.959	285.000
19	100-02-7	Phenol, 4-nitro-	23.197	25.692	279.000
20	2548-87-0	2-Octenal, (*E*)-	7.837	15.141	84.000
21	6166-86-5	2,4,6,8,10-Pentamethylcyclopentasiloxane	10.191	15.986	168.000
22	2031-79-0	1,1,3,3,5,5-Hexaethylcyclotrisiloxane	5.493	10.852	117.000
23	3862-73-5	Trifluoroaniline	4.605	2.796	92.000
24	15980-15-1	1,4-Oxathiane	3.112	11.780	147.000
25	108-41-8	Benzene, 1-chloro-3-methyl-	11.575	16.747	160.000
26	78-81-9	1-Propanamine, 2-methyl	2.006	6.152	64.000
27	7087-68-5	Diisopropylethylamine	6.556	12.133	127.000
28	17477-29-1	Propyldimethylchlorosilane	3.718	9.954	113.000
29	75-35-4	Ethylene, 1,1-dichloro-	5.812	-4.704	30.000
30	91-64-5	Coumarin	17.928	20.526	298.000
31	328-87-0	4-Chloro-3-cyanobenzotrifluoride	6.405	11.573	210.000
32	616-25-1	1-Penten-3-ol	6.438	12.844	114.000
33	75-85-4	2-Butanol, 2-methyl-	4.231	9.165	102.000
34	138-86-3	Limonene	10.367	10.009	170.000
35	333-41-5	Diazinon	4.486	6.708	83.000
36	15570-12-4	*meta*-Methoxybenzenethiol	16.490	22.256	223.000
37	198-55-0	Perylene	37.005	50.768	495.000
38	192-97-2	Benzo[e]pyrene	37.005	50.768	492.000
39	205-99-2	Benzo[b]fluoranthene	37.005	52.659	481.000
40	218-01-9	Chrysene	32.121	45.048	448.000
41	217-59-4	Triphenylene	32.121	47.211	425.000
42	611-32-5	Quinoline, 8-methyl-	16.427	22.665	143.000
43	76783-59-0	Ethyl-3-trifluoromethylbenzoate	6.641	15.738	101.000
44	76-86-8	Triphenylchlorosilane	28.953	39.379	378.000
45	1241-94-7	Phosphoric acid, 2-ethylhexyldiphenylester	26.200	33.929	375.000
46	2943-75-1	*N*-octyltriethoxysilane	9.043	15.458	98.000
47	594-72-9	Ethane,1,1-dichloro-1-nitro-	11.751	11.958	124.000
48	62-73-7	Dimethyl-2,2-dichlorovinyl phosphate	10.283	20.471	140.000
49	123-15-9	Pentanol, 2-methyl-	4.196	8.437	119.000
50	6640-27-3	Phenol, 2-chloro-4- methyl-	16.248	19.546	195.000
51	537-92-8	*N*-(3-tolyl)acetic acid amide	17.896	30.207	303.000
52	105-99-7	Hexanedioic acid, dibutyl ester	13.754	22.346	305.000
53	77-35-2	Phenanthrene, 9,10-dihydro-	22.529	27.241	168.000
54	2713-33-9	3,4-Difluorophenol	9.143	13.615	85.000
55	111-83-1	Octane, 1-bromo-	5.899	14.924	201.000
56	101-68-8	Benzene, 1,1'-methylene bis(4-isocyanato)-	26.548	29.352	200.000
57	597-49-9	3-Ethyl-3-pentanol	5.346	14.104	141.000
58	18395-90-9	di-tert-Butyldichlorosilane	10.980	18.381	190.000

Table 3. Cont.

n	CAS	Molecule	DCW^0	DCW^1	NBP_{exp}
59	107-12-0	Propanenitrile	2.677	5.531	97.000
60	1825-62-3	Silane, ethoxytrimethyl	3.096	5.122	75.000
61	56-55-3	Benz[a]anthracene	32.121	40.882	438.000
62	243-17-4	2,3-Benzofluorene	30.666	38.282	402.000
63	57-11-4	Octadecanoic acid	16.287	21.581	183.000
64	98-03-3	Thiophenecarboxaldehyde	10.468	15.608	198.000
65	605-39-0	2,2'-Dimethylbiphenyl	20.976	28.363	258.000
66	831-91-4	Benzene, [(phenylmethyl)thio]	19.804	23.867	197.000
67	761-65-9	Formamide, N,N-dibutyl-	11.705	17.359	120.000
68	348-54-9	Benzeneamine, 2-fluoro-	8.870	14.610	182.000
69	136-77-6	Hexylresorcinol	21.636	31.606	333.000
70	100-53-8	Benzenemethanethiol	16.543	18.999	194.000
71	191-30-0	1,2,9,10-Dibenzopyrene	44.801	59.414	595.000
72	109-73-9	1-Butanamine	3.292	6.593	78.000
73	100-69-6	Pyridine, 2-ethenyl-	10.659	13.058	79.000
74	1712-70-5	1-Chloro-4-isopropenylbenzene	14.368	18.139	214.500
75	95-56-7	Phenol, 2-bromo-	18.076	25.834	195.000
76	2984-50-1	Oxirane, hexyl-	4.137	8.771	63.000
77	100-43-6	Pyridine, 4-ethenyl-	10.659	8.905	62.000
78	919-31-3	Propanenitrile, 3-(triethoxysilyl)-	8.813	13.961	224.000
79	874-60-2	4-Methylbenzoic acid chloride	15.476	24.765	225.000
80	80-62-6	2-Propenoic acid, 2-methyl-, methyl ester	6.665	5.278	100.000
81	645-49-8	(*Z*)-Stilbene	22.354	27.371	307.000
82	103-84-4	Acetamide, N-phenyl-	17.128	27.646	304.000
83	106-49-0	*para*-Toluidine	11.770	24.079	200.000
84	90-90-4	Methanone, (4-bromophenyl)phenyl-	28.011	30.846	350.000
85	519-73-3	Triphenylmethane	29.768	34.483	359.000
86	832-69-9	Phenanthrene, 1-methyl-	25.093	35.107	359.000
87	60-29-7	Ethoxyethane	1.085	5.886	35.000
88	539-74-2	Propanoic acid, 3-bromo-ethyl ester	7.978	16.094	135.000
89	598-31-2	2-Propanone, 1-bromo-	6.456	13.853	137.000
90	571-61-9	Naphthalene, 1,5-dimethyl-	18.065	25.165	265.000
91	1885-14-9	Carbonochloridic acid, phenyl ester	15.117	17.640	74.000
92	754-05-2	Silane, ethenyltrimethyl-	3.945	3.490	55.000
93	238-84-6	1,2-Benzofluorene	30.666	42.448	407.000
94	99-08-1	Benzene, 1-methyl-3-nitro-	11.770	23.077	230.000
95	7209-38-3	1,4-bis(3-Aminopropyl)piperazine	19.905	11.808	150.000
96	1558-33-4	Silane, dichloro(chloromethyl)methyl-	5.349	10.947	121.000
97	65-85-0	Benzoic acid	17.310	21.998	249.000
98	132-64-9	Dibenzofuran	21.822	26.034	154.000
99	213-46-7	Picene (benzo[a]chrysene)	39.917	57.587	525.000
100	191-07-1	Coronene	46.773	57.883	525.000
101	287-92-3	Cyclopentane	2.787	2.793	50.000
102	2782-91-4	Thiourea, tetramethyl-	15.021	29.789	245.000
103	109-07-9	Piperazine, 2-methyl-	5.612	11.565	155.000
104	7005-72-3	Benzene, 1-chloro-4-phenoxy-	21.923	31.152	284.000
105	532-27-4	Ethanone, 2-chloro-1-phenyl-	15.937	19.618	244.000
106	91-57-6	Naphthalene, 2-methyl-	17.298	22.531	241.000
107	109-01-3	Piperazine, 1-methyl-	5.461	12.701	138.000
108	591-35-5	Phenol, 3,5-dichloro-	17.553	23.380	233.000
109	454-89-7	Benzaldehyde, 3-(trifluoromethyl)-	4.909	10.983	83.000
110	99-04-7	Benzoic acid, 3-methyl-	18.077	24.559	263.000
111	120-72-9	Indole	14.205	20.915	253.000
112	109-86-4	Ethanol, 2-methoxy-	4.991	10.296	125.000
113	617-84-5	*N*,*N*-Diethylformamide	9.476	14.478	176.000
114	129-00-0	Pyrene	29.210	36.066	360.000
115	86-74-8	Carbazole	22.000	31.584	355.000
116	79-06-1	Acrylamide	6.990	8.215	125.000
117	589-18-4	Benzene methanol, 4-methyl-	14.733	21.268	217.000

Table 3. Cont.

n	CAS	Molecule	DCW^0	DCW^1	NBP_{exp}
118	123-07-9	Phenol, 4-ethyl-	14.733	23.994	218.000
119	75-78-5	Silane, dichlorodimethyl-	3.553	5.152	70.000
120	120-80-9	1,2-Benzenediol	18.082	24.434	245.000
121	123-92-2	1-Butanol, 3-methyl-, acetate	5.371	8.225	142.000
122	626-39-1	Benzene, 1,3,5-tribromo-	22.739	27.936	271.000
123	89-99-6	Benzenemethanamine, 2-fluoro-	9.428	10.347	73.000
124	366-18-7	2,2'-Dipyridine	17.702	28.255	273.000
125	75-05-8	Acetonitrile	2.119	5.271	81.000
126	77-81-6	Tabun	7.771	24.781	246.000
127	7691-02-3	CH2CHOS(CH3)(CH3)NS(CH3)(CH3)CHCH2	12.366	14.725	160.000
128	615-67-8	1,4-Benzenediol, 2-chloro-	20.155	25.666	263.000
129	591-93-5	1,4-Pentadiene	4.173	-2.541	26.000
130	350-46-9	Benzene, 1-fluoro-4-nitro-	16.391	14.681	205.000
131	108-90-7	Benzene, chloro-	10.807	16.761	132.000
132	95-78-3	Benzenamine, 2,5-dimethyl-	12.537	21.017	218.000
133	557-11-9	Urea, allyl-	8.105	11.476	163.000
134	557-17-5	Methyl propyl ether	1.085	6.407	39.000
135	110-06-5	di-tert-Butyldisulfide	13.140	19.686	200.000
136	594-70-7	Propane, 2-methyl-2-nitro-	8.789	15.359	127.000
137	5582-62-7	(Propargyloxy)trimethylsilane	5.693	10.843	110.000
138	1072-43-1	Thiirane, methyl-	1.410	6.658	72.000
139	124-07-2	Octanoic acid	10.714	15.996	237.000
140	919-30-2	1-Propanamine, 3-(triethoxysilyl)-	8.314	12.139	122.000
141	623-00-7	4-Bromobenzoic acid nitrile	16.727	19.293	235.000
142	100-44-7	Benzyl chloride	12.036	16.857	177.000
143	109-55-7	1,3-Propanediamine, N,N-dimethyl-	8.400	10.048	133.000
144	598-72-1	2-Bromopropanoic acid	11.173	11.912	203.000
145	822-86-6	Cyclohexane, 1,2-dichloro-(trans)	6.936	13.335	193.000
146	67-71-0	Dimethylsulfone	4.844	22.383	238.000
147	56-33-7	1,1,3,3-Tetramethyl-1,3-diphenyldisiloxane	20.964	14.576	155.000
148	112-57-2	Tetraethylenepentamine	18.198	37.473	340.000
149	4333-56-6	Cyclopropyl bromide	4.918	9.457	69.000
150	80-10-4	Diphenyldichlorosilane	20.633	31.348	305.000
151	96-23-1	2-Propanol, 1,3-dichloro-	8.921	25.525	174.000
152	110-89-4	Piperidine	3.373	8.827	106.000
153	95-77-2	Phenol, 3,4-dichloro-	17.553	23.879	145.000
154	123-54-6	Acetylacetone	7.922	10.594	140.000
155	91-01-0	Benzenemethanol, α-phenyl-	23.734	31.844	297.000
156	115-19-5	3-Butyn-2-ol, 2-methyl-	6.271	14.827	104.000
157	78-84-2	Propanal, 2-methyl-	3.082	6.660	63.000
158	104-54-1	2-Propen-1-ol, 3-phenyl-	16.878	23.577	250.000
159	420-56-4	Silane, fluorothiomethyl-	-1.061	-2.005	57.000
160	98-02-2	2-Furanmethanethiol	14.039	16.547	155.000
161	3970-62-5	3-Pentanol, 2,2-dimethyl-	4.617	18.157	132.000
162	92-84-2	Phenothiazine	21.133	32.840	371.000
163	93-99-2	Benzoic acid, phenyl ester	23.751	27.643	298.000
164	109-67-1	1-Pentene	2.703	3.244	30.000
165	451-40-1	Ethanone, 1,2-diphenyl-	23.901	24.618	320.000
166	625-30-9	2-Pentanamine	2.563	7.876	91.000
167	2051-60-7	1,1'-Biphenyl, 2-chloro-	21.515	27.031	274.000
168	2425-79-8	Oxirane,2,2'[1,4-butanediylbis(oximethylene)]bis-	7.299	13.704	155.000
169	623-73-4	Ethyldiazoacetate	8.784	18.857	140.000
170	103-11-7	2-Propenoic acid, 2-ethylhexyl ester	9.070	15.387	215.000
171	107-05-1	1-Propene, 3-chloro-	4.122	4.570	44.000
172	108-31-6	2,5-Furandione	11.122	13.982	200.000
173	57-06-7	Allylisothiocyanate	6.281	4.360	150.000
174	77-75-8	Meparfynol (1-pentyne-3-ol, 3-methyl)	6.828	17.020	121.000
175	229-87-8	Phenanthridine	23.456	34.557	349.000
176	5510-99-6	Phenol, 2,6-bis(1-methylpropyl)-	16.829	33.099	255.000
177	3544-25-0	4-Aminophenylacetic acid nitrile	14.885	25.592	312.000

Table 3. Cont.

n	CAS	Molecule	DCW^0	DCW^1	NBP_{exp}
178	501-65-5	Diphenylethylene	19.928	22.715	170.000
179	994-49-0	Hexaethyldisiloxane	2.852	17.928	129.000
180	189-64-0	Dibenzo[a,h]pyrene	44.801	59.141	596.000
181	127-19-5	Acetamide, N,N-dimethyl-	9.128	7.664	165.000
182	14548-46-0	Phenyl, 4-pyridyl ketone	22.473	25.002	315.000
183	1897-45-6	Tetrachloroisophthalonitrile	23.673	28.057	350.000
184	135-01-3	Benzene, 1,2-diethyl-	11.384	16.301	183.000
185	109-77-3	Malononitrile	5.234	5.889	220.000
186	1008-88-4	Pyridine, 3-phenyl-	18.572	22.606	269.000
187	3741-00-2	Cyclopentane, pentyl-	4.844	9.432	181.000
188	109-92-2	Ethene, ethoxy-	2.554	2.070	33.000
189	636-30-6	Benzenamine, 2,4,5-trichloro-	17.220	22.555	270.000
190	2916-68-9	Trimethyl-2-hydroxyethylsilane	6.001	5.437	90.000
191	126-73-8	Tri-n-butylphosphate	8.164	15.583	180.000
192	69-72-7	Benzoic acid, 2-hydroxy-	21.983	30.500	211.000
193	771-51-7	1H-indole-3-acetonitrile	21.226	29.641	157.000
194	624-83-9	Methane, isocyanato-	2.312	13.655	37.000
195	191-24-2	Benzo[ghi]perylene	41.889	54.326	542.000
196	107-02-8	2-Propenal	3.253	6.809	53.000
197	622-97-9	Benzene, 1-ethenyl-4-methyl-	12.296	12.533	175.000
198	762-49-2	Ethane, 1-bromo-2-fluoro-	0.212	10.710	71.000
199	5263-87-6	Quinoline, 6-methoxy-	16.835	25.734	193.000
200	108-01-0	Ethanol, 2-(dimethylamino)-	10.248	14.465	133.000

First we have calculated the complete set via zero- and first-order descriptors, thus obtaining the following linear relationships:

$$NBP = 50.24 + 10.91\ DCW^0 \quad (4)$$

n = 200, r = 0.8910, S = 53.7, F = 763

$$NBP = 25.83 + 8.87\ DCW^1 \quad (5)$$

n = 200, r = 0.892, S = 56.0, F = 783

where the statistical parameters have the usual meanings.

The statistical data is moderately satisfactory and when Eqs.(4) and (5) are used to predict NBPs there are relatively large deviations for a significant number of molecules.

We then proceed to a more usual calculation procedure when dealing with a large number of molecules, which consists of defining two disjoint sets: a training set to determine the regression equation and a test set to perform true predictions. Results are as follows:

$$NBP = 49.16 + 10.89\ DCW^0 \quad (6)$$

n = 150, r = 0.8841, S = 55.1, F = 530 (training set)

n = 50, r = 0.9120, S = 49.3, F = 237 (test set)

$$NBP = 23.72 + 8.96\ DCW^1 \quad (7)$$

n = 150, r = 0.9328, S = 42.5, F = 530 (training set)

n = 50, r = 0.8766, S = 57.6, F = 237 (test set)

These results are somewhat better than the previous ones and large deviations occur for a smaller number of molecules. Since the choice of the molecules comprising the training and test sets are somewhat arbitrary, we have tested several partitions of the compounds, but final results are not markedly dependent on the way used to choose the molecules in both sets.

Since there are some large deviant behaviors, we have resorted to removing these molecules (just five, from the total 200 molecules: numbers 11, 15, 56, 98 and 146 according to the identification number n from Table 3). Results are the following ones:

$$NBP = 43.25 + 11.41\ DCW^0 \quad (8)$$

n = 145, r = 0.9199, S = 46.8, F = 787 (training set)

n = 50, r = 0.9120, S = 46.6, F = 237 (test set)

If molecules 4, 15, 53, 91 and 98 are removed, statistical results are

$$NBP = 22.50 + 9.10\ DCW^1 \quad (9)$$

n = 145, r = 0.9530, S = 36.1, F = 1414 (training set)

n = 50, r = 0.8765, S = 53.9, F = 159 (test set)

These results show that by taking out some deviant molecules, the results improve remarkably and somewhat better predictions can be obtained.

A final numerical test was made to define training and test sets based on the clustering approach [38]. The k-**M**eans **C**luster **A**nalysis (k-MCA) may be used in training and testing (or predictive) series design [39,40]. The idea consists of carrying out a partition of the series of compounds into several statistically representative classes of chemicals. Thence, one may select from the number of all these classes of training and predicting series. This procedure ensures that any chemical classes (as determined by the clusters derived form the k-MCA will be represented in both series of compounds (i.e. training and test sets). It permits the design of both training and predicting series, which are representative of the entire experimental universe.

$$NBP = 53.09 + 11.39DCW^0 \quad (10)$$

n = 158, r = 0.9586, S = 34.8, F = 1770 (complete set)

$$NBP = 54.28 + 11.45\ DCW^0 \quad (11)$$

n = 126, r = 0.9633, S = 33.3, F = 1599 (training set)

n = 32, r = 0.9391, S = 39.1, F = 224 (test set)

$$NBP = 23.50 + 9.119\ DCW^1 \quad (12)$$

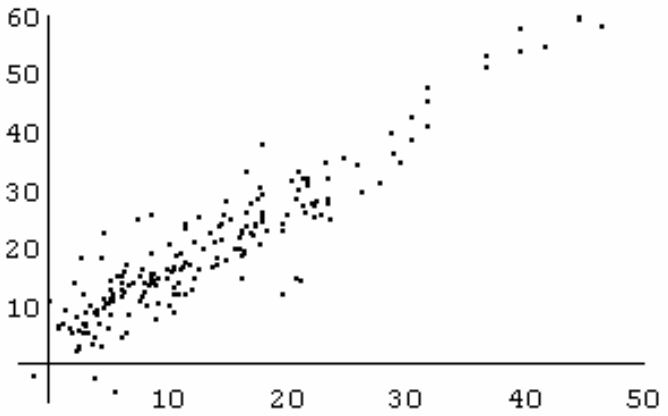
n = 144, r = 0.9592, S = 33.9, F = 1633 (training set)

n = 37, r = 0.9564, S = 34.8, F = 376 (test set)

These last results are the best ones among the different equations presented before and they represent a suitable improvement with respect to the first ones defined by Equations (4-9). An additional possibility for doing these calculations would be to employ both descriptors together, but this is not possible since they are strongly correlated, as shown in Figure 1.

We cannot make any direct comparison with other theoretical results since, to the best of our knowledge, the standard literature does not register any calculation for this particular molecular set. This is quite sensible, since the molecules are quite diverse and it is well known that working with molecular sets comprising similar molecules gives results that are better than those derived from a quite dissimilar set of molecules, as it is the present case. However, our aim has been precisely this: to make a regression approach for quite different molecules via quite simple linear equations based on a single molecular descriptor to predict NBPs. A complete listing of NBP results derived from using Eqs. (4-12) is available upon request from the corresponding author.

Figure 1. DCW^1 (vertical axis) versus DCW^0 (horizontal axis). Regression equation: $DCW^1 = 2.978 + 1.222\ DCW^0$.



Conclusions

We have presented results on NBPs for a quite diverse molecular set based upon simple linear regression equations depending on a single molecular descriptor in order to test the capability of a special kind of such parameter: a flexible molecular descriptor. Results are very encouraging and they show the power of such types of topological variables. In fact, although there are some large deviations when employing the complete initial molecular set comprising very diverse organic molecules, the average deviations are quite sensible ones. In order to judge the relative merits of the present approach one must take into consideration that a single figure is representing a physical-chemistry property (i.e. NBPs), which evidently depends on many molecular features which cannot be encoded in a single topological descriptor. In order to reproduce a given property, it is necessary to resort to a many variables regression equation, each of them taking into account a different molecular feature. Furthermore, usually one employs a set comprising similar molecules, but our main purpose has not been to make exact numerical predictions, but rather to show the real possibilities of a particular kind of flexible topological descriptor. We consider this objective has been fully met. The next step is to complement these calculations using a several variables approach, based on choosing other molecular descriptors in order to add other physical molecular features which are not included into the OCWLI. Work along this line of research is under way and results will be presented elsewhere very soon.

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