

# QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIPS GENERATED WITH OPTIMIZABLE EVEN/ODD WIENER POLYNOMIAL DESCRIPTORS\*

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Chemical structures of organic compounds are characterized numerically by a variety of structural descriptors, one of the earliest and most widely used being the Wiener index  $W$ , derived from the interatomic distances in a molecular graph. Extensive use of distance-based structural descriptors or topological indices has been made in QSPR and QSAR models, drug design, toxicology, virtual screening of combinatorial libraries, similarity and diversity assessment. Novel topological indices are introduced representing a partitioning of the Wiener polynomial based on counts of even and odd molecular graph distances. During the QSAR/QSPR modeling process the variables of the even and odd power functions are optimized in order to offer an improved mapping of the investigated property. These novel topological indices are tested in QSPR models for the boiling temperature, molar heat capacity, standard Gibbs energy of formation, vaporization enthalpy, refractive index, and density of alkanes. In many cases, the even/odd Wiener polynomial indices proposed here give notably improved correlations or suggest simpler QSPR models.

*Keywords:* Quantitative structure-property relationships; Topological indices; Graph distance descriptors; Even/odd Wiener polynomial indices

## INTRODUCTION

Structural descriptors are used in molecular modeling to express in a numerical form the chemical structure. The continual development of

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\* Dedicated to Professor Alexandru T. Balaban on the occasion of his 70th birthday.

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structural descriptors and statistical models has transformed quantitative structure-property relationships (QSPR) and quantitative structure-activity relationships (QSAR) into powerful and widely used methods for the prediction of physical, chemical, and biological properties. In a first approximation the chemical structure of a molecule can be represented as a molecular graph, in which vertices correspond to atoms, and edges represent covalent bonds between atoms. Using molecular graphs the chemical structure of a compound can be expressed by means of various graph matrices, polynomials, spectra, spectral moments, distance-counting sequences, paths, and walks, or yet other topological indices. A topological index (TI) is a numerical descriptor of the molecular structure based on certain topological features of the molecular graph [1–11]. Significant results have been obtained in the design of novel TIs, with improved correlational abilities [7–11]. Another direction of intense research is represented by the parametrization of vertex- and edge-weighted molecular graphs, representing organic compounds with heteroatoms and multiple bonds [8, 9]; this research direction is stimulated by the novel application of molecular graph descriptors in similarity and diversity assessment, database mining, and in the virtual screening of combinatorial libraries.

The use of modern topological indices in QSPR and QSAR begins with the Wiener index  $W$ , which was applied for establishing correlations between molecular structure and various physical properties of alkanes [12–15]. Hosoya extended the original definition to cyclic compounds with the aid of the distance matrix and gave a graph-theoretical formula for the Wiener index as “the half sum of the off-diagonal elements of a distance matrix  $\mathbf{D}$  whose element  $d_{ij}$  is a number of bonds for the shortest path between atoms  $i$  and  $j$ ” [16]. Its successful application in a large number of QSAR/QSPR models stimulated the research in the domain of structural descriptors based on graph distances [9], novel molecular matrices [10] and Wiener-type indices [11]. The relatively high degeneracy of  $W$  due to the global summation of distances can be reduced by using information theory, as shown by Bonchev and Trinajstić who used all graph distances to define indices  $I_D^E$ ,  $\bar{I}_D^E$ ,  $I_D^W$ , and  $\bar{I}_D^W$  [17], and by Balaban and Balaban who defined the  $U$ ,  $V$ ,  $X$ , and  $Y$  indices based on the vertex partitioning of graph distances [18]. Recently, the  $U$ ,  $V$ ,  $X$ , and  $Y$  information indices were extended for any symmetric molecular matrix derived from vertex- and edge-weighted molecular graphs [19, 20], giving the graph operators  $\mathbf{U}(\mathbf{M})$ ,  $\mathbf{V}(\mathbf{M})$ ,  $\mathbf{X}(\mathbf{M})$ , and  $\mathbf{Y}(\mathbf{M})$  that were applied with success in QSPR equations [21] and in modeling the retention indices of alkylphenols in gas-liquid chromatography [22]. Using a Randić-type formula and a vertex partitioning of distances,

Balaban defined the index  $J$  [23–25], which was successfully applied in QSPR [26], QSAR [27], and virtual screening of combinatorial libraries [28]. The Balaban index  $J$  was used as a basis for the definition of the **IB** operator for vertex- and edge-weighted molecular graphs [29].

Elements of the distance matrix were used to define various molecular matrices and graph metrics. The idea to use reciprocal distances in computing degree-distance  $VTI$  indices [30] was adopted in the definition of the reciprocal distance **RD** [31–33] and distance-valency **Dval** [34] matrices. Another distance measure was defined as the resistance-distance matrix  **$\Omega$**  [35]; this metric is identical with that induced by the distance matrix only for acyclic compounds, while for cyclic compounds the resistance-distance matrix offers the possibility to compute an index analogous but not identical to the Wiener index. Other recently defined distance-related matrices are the detour  $\Delta$  [36], detour-distance  $\Delta$ -**D** [36], distance complement **DC** [37], complementary distance **CD** [38], reciprocal complementary distance **RCD** [38], and reverse Wiener **RW** [39] matrices. The original formula of the Wiener index was extended to afford the computation of the hyper-Wiener index  $WW$  [40, 41]. Because initially  $WW$  was defined only for acyclic graphs, an extension was proposed for cyclic graphs [42] and a related molecular matrix was defined by Diudea [43, 44]. The **HyWi** graph operator, which implements a hyper-Wiener type formula for any molecular matrix [9], was used to describe the diversity and descriptor clustering for molecules selected from the National Cancer Institute AIDS database [45, 46]. Recent developments in the area of distance descriptors include the characterization of molecular cyclicity and centrality [47], Wiener-related sequences [48, 49], a multiplicative version of the Wiener index [50], and novel graph metrics [51, 52]. The mean Wiener index for alkanes, computed as an average property of isomeric series [53–55], was introduced with the aim of characterizing mixtures of organic compounds.

Hosoya used distances between pairs of graph vertices to define the Wiener polynomial, whose first derivative gives the Wiener index  $W$  [56]; several years later, an equivalent formula was proposed by a group of mathematicians [57]. The higher derivatives of the Wiener polynomial give a sequence of Wiener-type topological indices used with success in several QSPR models [58–60]. Recently we have defined a group of novel graph descriptors based on even and odd distances which are separately summed to give two distinct graph invariants that are subsequently combined into a series of new graph descriptors, that measure the molecular size and shape [61]. In this paper we propose and study two graph descriptors obtained

from the Wiener polynomial by summing into two distinct indices the terms corresponding to even and odd graph distances. These novel topological indices computed from the Wiener polynomial are tested in QSPR models for the normal boiling temperature, molar heat capacity, standard Gibbs energy of formation, vaporization enthalpy, refractive index, and density of 134 alkanes  $C_6-C_{10}$ . During the QSPR modeling process the variables of the even and odd power functions are optimized in order to generate an improved mapping of the investigated property. The statistical results of the QSPR models demonstrate that such splitting of the Wiener polynomial into even/odd distance sums is a successful one, offering topological indices with an enhanced correlational power. In several QSPR equations the optimum value of the variable suggests efficient ways for generating more simple QSPR models.

## EVEN/ODD DISTANCE INDICES

Together with the connectivity indices [1, 2], the Wiener index is the most frequently used graph descriptor in QSAR/QSPR models. The Wiener index  $W = W(G)$  of a molecular graph  $G$  with  $N$  vertices is [9, 29]:

$$W(G) = \sum_{i=1}^N \sum_{j=i}^N [\mathbf{D}(G)]_{ij} \quad (1)$$

where  $\mathbf{D} = \mathbf{D}(G)$  is the distance matrix of  $G$ , and  $[\mathbf{D}(G)]_{ij}$  represents the topological distance between vertices  $v_i$  and  $v_j$ . This formula, which is slightly modified from the definition proposed by Hosoya [16], can be used for vertex- and edge-weighted molecular graphs representing organic compounds with heteroatoms and multiple bonds.

In a recent study we have partitioned all graph distances into two classes, *i.e.* even and odd distances, which are separately summed to give two distinct structural descriptors, *SumE* and *SumO* [61]. The sum of even graph distances *SumE* from the molecular graph  $G$  is:

$$SumE(p, G) = \sum_{i < j}^{d_{ij} \text{ even}} [\mathbf{D}(G)]_{ij}^p \quad (2)$$

where the summation goes over all even elements in the upper triangle of the distance matrix  $\mathbf{D}$ , and  $p$  is a constant that affords an increased flexibility to this graph invariant. In a similar way we define *SumO*, the sum of odd graph distances from the molecular graph  $G$ , by collecting together all odd graph

distances:

$$SumO(q, G) = \sum_{i < j}^{d_{ij} \text{ odd}} [\mathbf{D}(G)]_{ij}^q \quad (3)$$

where the summation goes over all odd elements in the upper triangle of the distance matrix  $\mathbf{D}$ , and  $q$  is a constant that weights the odd distances. During the generation of the QSAR/QSPR models, the even and odd exponents  $p$  and  $q$  can be optimized to give better statistical indices. If  $p = q = 1$ , a simple relationship exists between the Wiener index  $W$  and the even/odd indices  $SumE$  and  $SumO$ :

$$W(G) = SumE(1, G) + SumO(1, G) \quad (4)$$

The individual count of graph distances according to their length was used by Hosoya in the definition of the Wiener polynomial. Let  $d(G, k)$  be the number of pairs of vertices in  $G$  that are distance  $k$  apart, and denote the largest element of  $\mathbf{D}$  by  $l$ , often called the diameter of  $G$ ; obviously,  $d(G, 1)$  is equal to the number of edges. The Wiener polynomial of a graph  $G$  is defined by the following equation [56, 57]:

$$\mathbf{H}(G, z) = \sum_{k=1}^l d(G, k) z^k = \sum_{i < j} z^{d_{ij}} \quad (5)$$

From the above definition it is obvious that the procedure of separating the Wiener index  $W$  into even and odd terms can be applied also to the Wiener polynomial. The sum of Wiener polynomial terms corresponding to even graph distances defines the topological index  $WiPolE$ :

$$WiPolE(x, G) = \sum_{i < j}^{d_{ij} \text{ even}} x^{d_{ij}} \quad (6)$$

where the summation goes over all even graph distances  $d_{ij}$ , and the variable  $x$  is an optimizable parameter. Similarly we define  $WiPolO$ , the sum of all terms in the Wiener polynomial corresponding to odd graph distances:

$$WiPolO(y, G) = \sum_{i < j}^{d_{ij} \text{ odd}} y^{d_{ij}} \quad (7)$$

where the summation goes over all odd graph distances  $d_{ij}$ , and the variable  $y$  is a parameter that can be optimized for each QSAR/QSPR property and data set of chemical compounds.

## MATERIALS AND METHODS

### Database

The QSPR models are developed for a data set consisting of 134 alkanes between  $C_6$  and  $C_{10}$ , as applied for the following six physical properties [62]:  $t_b$ , boiling temperature at normal pressure ( $^{\circ}C$ );  $C_p$ , molar heat capacity at 300 K ( $J K^{-1} mol^{-1}$ );  $\Delta_f G_{300}^{\circ}$  (g), standard Gibbs energy of formation in the gas phase at 300 K ( $kJ mol^{-1}$ );  $\Delta_{vap} H_{300}$ , vaporization enthalpy at 300 K ( $kJ mol^{-1}$ );  $n_D^{25}$ , refractive index at  $25^{\circ}C$ ;  $\rho$ , density at  $25^{\circ}C$  ( $kg m^{-3}$ ). The value of the refractive index of 2,2,3,3-tetramethylbutane is missing, while the reported density of this compound,  $821.70 kg m^{-3}$ , is seemingly too high when compared with the density of similar alkanes and it was not considered in the computation of the density QSPR models. There are 142 constitutional isomers for these alkanes, but some data for some of the six properties are missing for the following eight of them: *n*-hexane, *n*-nonane, *n*-decane, 2-methylnonane, 3-methylnonane, 4-methylnonane, 5-methylnonane, 3-ethyl-2,4-dimethylhexane.

### Structural Descriptors and QSPR Models

QSPR models for all six alkane properties are obtained with multiple linear regression (MLR) equations in which three structural descriptors are tested: *MN*, the molecular number equal to the sum of the atomic number  $Z$  for all atoms in a molecule, hydrogens included, the even and odd Wiener polynomial sums  $WiPolE(x)$  and  $WiPolO(y)$ , respectively. The  $x$  and  $y$  variables of the even and odd graph distances are optimized with a grid search algorithm in order to obtain QSPR models with highest correlation coefficient and lowest standard deviation.

In order to assess the value of QSPR models obtained with  $WiPolE(x)$  and  $WiPolO(y)$ , we use the same molecular data base to obtain structure-property models with several widely used topological indices. This group of QSPR models is represented by biparametric equations in which one descriptor is  $N$ , the number of carbon atoms, while the second one is either a connectivity index ( ${}^0\chi, {}^1\chi, {}^2\chi$ ), the Wiener index  $W$ , or the best even/odd graph distance descriptor identified in our recent study [61]. In choosing the above set of descriptors we were guided by the following considerations: (a) the widespread use of connectivity indices in QSPR; (b) the necessary comparison with the Wiener index  $W$ , since  $WiPolE(x)$  and  $WiPolO(y)$  are proposed as Wiener-type indices; (c) our recent finding that even/odd graph

TABLE I Structural descriptors SD, coefficients and statistical indices for linear regression equations with the general form  $P = a_0 + a_1N + a_2SD$ , where  $N$  is the number of carbon atoms and  $P$  is a physical property of the set of 134  $C_6-C_{10}$  alkanes

$P$	Eq.	$a_0$	$a_1$	$a_2$	SD	$r$	$s$	$F$
$t_b$ (°C)	8	-73.99	34.07	-13.13	$0 \times$	0.9762	5.80	1329
	9	-78.52	14.49	20.48	$1 \times$	0.9800	5.32	1591
	10	-81.80	27.12	-7.277	$2 \times$	0.9841	4.75	2013
	11	-89.47	25.86	-0.07479	$W$	0.9730	6.17	1164
	12	-138.6	25.79	24.02	$W_{o,c}(-1,-1)$	0.9835	4.83	1939
	13	4.983	25.85	-3.458	$0 \times$	0.9873	4.07	2523
	14	3.771	21.20	4.292	$1 \times$	0.9873	4.06	2540
	15	3.226	23.68	-1.165	$2 \times$	0.9873	4.06	2533
	16	3.822	23.14	0.0009397	$W$	0.9870	4.11	2470
	17	-9.624	25.30	-0.06525	$W_{e \times o}(-2,0.5)$	0.9874	4.05	2545
	18	-79.66	-9.400	26.09	$0 \times$	0.8550	7.69	178
	19	-70.23	18.88	-17.45	$1 \times$	0.8218	8.45	136
	20	-69.07	9.971	2.065	$2 \times$	0.8045	8.81	120
	21	-171.3	30.09	-0.7176	$W$	0.9159	5.96	341
	22	-128.8	21.09	-0.1276	$W_{e+o}(1.5,2)$	0.9274	5.55	403
	23	7.323	10.21	-8.361	$0 \times$	0.9866	0.71	2399
	24	4.354	-0.1386	8.388	$1 \times$	0.9785	0.89	1477
25	3.378	4.621	-2.055	$2 \times$	0.9662	1.12	920	
26	20.87	0.5436	0.1180	$W$	0.9633	1.16	845	
27	-9.477	9.276	-2.719	$W_{e+o}(-1.5,-2)$	0.9796	0.87	1560	
28	1.302	-0.003034	0.01802	$0 \times$	0.9022	0.0059	284	
29	1.308	0.01559	-0.01001	$1 \times$	0.8822	0.0065	228	
30	1.308	0.01098	0.0001236	$2 \times$	0.8751	0.0067	213	
31	1.231	0.02575	-0.0005525	$W$	0.9490	0.0043	589	
32	1.387	-0.03370	0.03564	$SumO(-2)$	0.9663	0.0035	917	
33	523.9	-6.554	35.07	$0 \times$	0.8825	12.50	229	
34	536.2	28.36	-16.55	$1 \times$	0.8598	13.57	184	
35	535.4	21.39	-1.208	$2 \times$	0.8548	13.79	176	
36	370.5	52.29	-1.181	$W$	0.9459	8.62	552	
37	707.9	-76.62	77.65	$SumO(-2)$	0.9713	6.32	1084	
$C_p$ ( $J K^{-1} mol^{-1}$ )	8	-73.99	34.07	-13.13	$0 \times$	0.9762	5.80	1329
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34	536.2	28.36	-16.55	$1 \times$	0.8598	13.57	184	
35	535.4	21.39	-1.208	$2 \times$	0.8548	13.79	176	
36	370.5	52.29	-1.181	$W$	0.9459	8.62	552	
37	707.9	-76.62	77.65	$SumO(-2)$	0.9713	6.32	1084	

distance descriptors often give better correlations than connectivity and Wiener-type indices. In Table I we present all QSPR equations used for comparison purposes, together with the corresponding statistical indices.

## RESULTS AND DISCUSSION

The main objective of this investigation is to evaluate the QSPR usefulness of even/odd topological indices derived from the Wiener polynomial. Because in previous studies we found that molecular size is an important factor for QSPR modeling of the six alkane properties [61], for each property we investigate all bi- and triparametric MLR equations obtained with the three descriptors:  $MN$ ,  $WiPolE(x)$ , and  $WiPolO(y)$ .

### Normal Boiling Temperature

In Table II we present the coefficients, and statistical indices for the tri- and biparametric MLR equations that model the normal boiling temperature of the 134 alkanes, *i.e.*, Eqs. (38), (44), (50), and (56). The best QSPR model, with  $r = 0.9917$ ,  $s = 3.45^\circ\text{C}$ ,  $F = 2582$ , is obtained for Eq. (38) that has three descriptors; a comparison with the best results from Table I, obtained with the connectivity index  ${}^2\chi$  ( $r = 0.9841$ ,  $s = 4.75^\circ\text{C}$ ,  $F = 2013$ ), indicate that  $WiPolE(x)$  and  $WiPolO(y)$  offer a significant improvement of the correlation. The optimum value for  $x$  and  $y$  is 0.48 and 0.01, respectively, and the correlation coefficient between  $MN$  and  $WiPolO(y)$  is almost equal to 1; another interesting observation concerning Eq. (38) is the opposite sign of the  $MN$  and  $WiPolO(y)$  coefficients, *i.e.* negative for  $MN$  and positive for  $WiPolO(y)$ . Evidently  $MN$  and  $WiPolO(y)$  (at  $y = 0.01$ ) are very nearly linearly dependent (*i.e.*, very nearly scalar multiples). But the sign and sizes of the coefficients indicate that the small difference between these two (appropriately scaled) descriptors is also relevant in obtaining a good fit. This difference between  $MN$  and  $WiPolO(y)$  becomes proportional to  $p_3$ , the number of distances of length 3 in the molecular graph. Indeed Wiener recognized the importance of  $p_3$ , and in making correlations he used  $p_3$  together with the normalized Wiener index  $W/N^2$  [12–15].

This observation prompted us to replace  $WiPolO(y)$  with  $p_3$  and to determine if only the count of paths of length 3 can offer the same high correlation. The results presented in Table III, Eq. (62) show that indeed the QSPR obtained with  $MN$ ,  $WiPolE(0.48)$ , and  $p_3$  has the same correlation coefficient and standard deviation with Eq. (38), while the Fisher test is only



TABLE II Structural descriptors, coefficients and statistical indices for linear regression equations with the general form  $P = a_0 + a_1SD_1 + a_2SD_2 + a_3SD_3$ , where  $P$  is a physical property of the set of 134  $C_6-C_{10}$  alkanes

$P$	Eq.	$a_0$	$a_1$	$SD_1$	$a_2$	$SD_2$	$a_3$	$SD_3$	$r$	$s$	$F$	Obs.
$t_b$	38	33811	-3386	MN	-15.195	WiPolE(0.48)	2711803	WiPolO(0.01)	0.9917	3.45	2582	$r(SD_1,SD_3) \cong 1$
$C_p$	39	-10.51	3.155	MN	-333.7	WiPolE(0.05)	-0.0174	WiPolO(1.84)	0.9877	4.01	1735	
$\Delta_f G_{300}^\circ$	40	2154	-215.3	MN	2.601	WiPolE(0.99)	34312	WiPolO(0.05)	0.9688	3.69	663	$r(SD_1,SD_3) \cong 1$
$\Delta_{vap} H_{300}$	41	-3.442	0.7403	MN	-9.210	WiPolE(0.32)	-0.5114	WiPolO(0.63)	0.9814	0.84	1133	
$n_D^{25}$	42	2.903	-0.1564	MN	0.1004	WiPolE(0.05)	25.12	WiPolO(0.05)	0.9813	0.0027	1115	$r(SD_1,SD_3) \cong 1$
$\rho$	43	4052	-345.7	MN	-0.3548	WiPolE(0.96)	55490	WiPolO(0.05)	0.9877	4.17	1714	$r(SD_1,SD_3) \cong 1$
$t_b$	44	-13.99			0.00817	WiPolE(2.65)	26.23	WiPolO(0.52)	0.9849	4.63	2116	
$C_p$	45	105.7			2.502	WiPolE(1.04)	3.385	WiPolO(0.95)	0.9839	4.58	1982	
$\Delta_f G_{300}^\circ$	46	-56.38			-0.000224	WiPolE(4.83)	18.63	WiPolO(0.47)	0.9236	5.69	380	
$\Delta_{vap} H_{300}$	47	22.44			0.0830	WiPolE(1.47)	0.3998	WiPolO(1.10)	0.9630	1.17	835	
$n_D^{25}$	48	1.322			-0.000183	WiPolE(1.46)	0.01916	WiPolO(0.49)	0.9655	0.0036	893	
$\rho$	49	554.6			-0.5607	WiPolE(1.41)	39.35	WiPolO(0.49)	0.9684	6.63	980	
$t_b$	50	-132.5	4.256	MN	-3.389	WiPolE(0.93)			0.9806	5.25	1635	
$C_p$	51	-3.769	2.975	MN	-168.6	WiPolE(0.05)			0.9873	4.07	2523	
$\Delta_f G_{300}^\circ$	52	-90.20	1.673	MN	-0.000337	WiPolE(4.83)			0.8878	6.83	244	
$\Delta_{vap} H_{300}$	53	-1.381	0.6631	MN	-13.40	WiPolE(0.27)			0.9807	0.85	1645	
$n_D^{25}$	54	1.274	0.002041	MN	-0.000213	WiPolE(1.61)			0.9269	0.0052	396	
$\rho$	55	461.2	4.087	MN	-0.4917	WiPolE(1.60)			0.9232	10.21	375	
$t_b$	56	-44.81	1.544	MN			6.749	WiPolO(0.73)	0.9805	5.26	1628	
$C_p$	57	-2.939	2.909	MN			-0.000011	WiPolO(4.83)	0.9871	4.09	2497	
$\Delta_f G_{300}^\circ$	58	1947	-198.2	MN			31787	WiPolO(0.05)	0.9478	4.73	579	$r(SD_1,SD_3) \cong 1$
$\Delta_{vap} H_{300}$	59	9.291	0.3357	MN			0.0385	WiPolO(1.62)	0.9546	1.29	672	
$n_D^{25}$	60	2.943	-0.1605	MN			25.78	WiPolO(0.05)	0.9810	0.0027	1663	$r(SD_1,SD_3) \cong 1$
$\rho$	61	4069	-346.9	MN			55669	WiPolO(0.05)	0.9876	4.17	2569	$r(SD_1,SD_3) \cong 1$

TABLE III Structural descriptors, coefficients and statistical indices for linear regression equations with the general form  $P = a_0 + a_1SD_1 + a_2SD_2 + a_3SD_3 + a_4SD_4$ , where  $P$  is a physical property of the set of 134  $C_6-C_{10}$  alkanes

$P$	Eq.	$a_0$	$a_1$	$SD_1$	$a_2$	$SD_2$	$a_3$	$SD_3$	$r$	$s$	$F$
$t_b$	62	-86.02	3.219	MN	-15.20	WiPolE(0.48)	2.712	$p_3$	0.9917	3.45	2583
$C_p$	63	-3.285	2.965	MN	-189.8	WiPolE(0.05)	0.08461	$p_3$	0.9873	4.08	1671
$\Delta_f G_{300}^o$	64	9.054	-0.8209	MN	2.593	WiPolE(0.99)	4.281	$p_3$	0.9689	3.69	664
$\Delta_{vap} H_{300}$	65	-2.209	0.6798	MN	-9.008	WiPolE(0.32)	-0.09342	$p_3$	0.9813	0.84	1126
$n_D^{25}$	66	1.333	0.000609	MN	0.09897	WiPolE(0.05)	0.003136	$p_3$	0.9813	0.0027	1117
$\rho$	67	582.9	1.164	MN	-0.3697	WiPolE(0.96)	6.923	$p_3$	0.9877	4.17	1720
$t_b$	68	-71.57	2.612	MN			1.620	$p_3$	0.9794	5.40	1542
$C_p$	69	-2.726	2.913	MN			-0.07615	$p_3$	0.9870	4.11	2473
$\Delta_f G_{300}^o$	70	-40.05	0.4557	MN			3.968	$p_3$	0.9480	4.72	581
$\Delta_{vap} H_{300}$	71	-0.01811	0.5540	MN			-0.4005	$p_3$	0.9467	1.40	566
$n_D^{25}$	72	1.332	0.000638	MN			0.003217	$p_3$	0.9810	0.0027	1666
$\rho$	73	589	1.004	MN			6.946	$p_3$	0.9876	4.17	2577
$t_b$	74	-75.26	2.968	MN	-3.210	$p_2$	2.708	$p_3$	0.9906	3.67	2276
$C_p$	75	-3.274	2.965	MN	-0.4762	$p_2$	0.08515	$p_3$	0.9873	4.08	1671
$\Delta_f G_{300}^o$	76	-39.04	0.3589	MN	0.8746	$p_2$	3.672	$p_3$	0.9508	4.61	408
$\Delta_{vap} H_{300}$	77	-1.057	0.6540	MN	-0.9030	$p_2$	-0.09468	$p_3$	0.9811	0.84	1116
$n_D^{25}$	78	1.333	0.000610	MN	0.000248	$p_2$	0.003136	$p_3$	0.9813	0.0027	1117
$\rho$	79	588.9	1.013	MN	-0.07863	$p_2$	6.972	$p_3$	0.9876	4.18	1706
$t_b$	80	-90.82	3.267	MN	-1.513	$p_2$			0.9758	5.84	1307
$C_p$	81	-3.763	2.975	MN	-0.4228	$p_2$			0.9873	4.07	2523
$\Delta_f G_{300}^o$	82	-60.14	0.7647	MN	3.176	$p_2$			0.8546	7.70	177
$\Delta_{vap} H_{300}$	83	-0.5128	0.6436	MN	-0.9623	$p_2$			0.9804	0.85	1625
$n_D^{25}$	84	1.315	0.000955	MN	0.002216	$p_2$			0.9024	0.0059	285
$\rho$	85	548.9	1.782	MN	4.297	$p_2$			0.8825	12.50	229
$t_b$	86	33769	-3381	MN	-3.210	$p_2$	2707525	WiPolO(0.01)	0.9906	3.67	2276
$C_p$	87	-10.48	3.155	MN	-0.8343	$p_2$	-0.01737	WiPolO(1.84)	0.9877	4.01	1735
$\Delta_f G_{300}^o$	88	1799	-183.4	MN	0.8801	$p_2$	29401	WiPolO(0.05)	0.9507	4.62	407
$\Delta_{vap} H_{300}$	89	-2.074	0.7064	MN	-0.9262	$p_2$	-0.4597	WiPolO(0.63)	0.9811	0.84	1112
$n_D^{25}$	90	2.903	-0.1564	MN	0.000252	$p_2$	25.12	WiPolO(0.05)	0.9813	0.0027	1115
$\rho$	91	4080	-348.1	MN	-0.07057	$p_2$	55853	WiPolO(0.05)	0.9876	4.19	1700

one unit larger out of 2582. The even distance term is important for a good correlation, since both its omission, Eq. (68), or its substitution with  $p_2$ , Eqs. (74) and (80), provide MLR equations with lower statistics.

### Molar Heat Capacity

The results reported in Table II show that the best model for the alkane molar heat capacity is Eq. (39), computed with  $MN$ ,  $WiPolE(0.05)$ , and  $WiPolO(1.84)$ . This equation has good statistical indices ( $r = 0.9877$ ,  $s = 4.01 \text{ J K}^{-1} \text{ mol}^{-1}$ ,  $F = 1735$ ), slightly superior to those from Eq. (17) that was obtained with  $N$  and the product of the even and odd distances  $W_{e \times o}(-2, 0.5)$ . The optimum value for  $x$  is 0.05, and if the optimization continues, it has the tendency to converge toward 0, when  $WiPolE$  is proportional to the path count of length 2,  $p_2$ . This behavior suggests a more simple QSPR model, in which  $WiPolE(0.05)$  is substituted with  $p_2$ . A comparison of the  $C_p$  QSPR equations from Table III reveals that Eq. (87) obtained with  $MN$ ,  $p_2$ , and  $WiPolO(1.84)$  has identical statistical indices with Eq. (39), demonstrating that the substitution of  $WiPolE(0.05)$  with  $p_2$  is an effective simplification of the QSPR model. However, by deleting the odd distance term  $WiPolO(1.84)$  one obtains Eq. (81) that has only two parameters, *i.e.*  $MN$  and  $p_2$ , but with statistics very close to those from Eqs. (39) and (87):  $r = 0.9873$ ,  $s = 4.07 \text{ J K}^{-1} \text{ mol}^{-1}$ ,  $F = 2523$ .

### Standard Gibbs Energy of Formation

The use of even/odd Wiener polynomial descriptors greatly improve the QSPR model of the alkane standard Gibbs energy of formation, as revealed by a comparison of Eqs. (22) and (40). Computed with three topological indices,  $MN$ ,  $WiPolE(0.99)$ , and  $WiPolO(0.05)$ , Eq. (40) has good statistical indices ( $r = 0.9688$ ,  $s = 3.69 \text{ kJ mol}^{-1}$ ,  $F = 663$ ), with a significant decrease in the standard deviation in comparison with Eq. (22) computed with  $N$  and the sum of the even and odd distances  $W_{e+o}(1.5, 2)$ . The optimum variable for the odd distances is 0.05, suggesting again a replacement of  $WiPolO(y)$  with  $p_3$ ; indeed, Eq. (64) from Table III, computed with  $MN$ ,  $WiPolE(0.99)$ , and  $p_3$ , has almost identical statistical indices, demonstrating the importance of this simple graph descriptor in modeling  $\Delta_f G_{300}^\circ$ . Other tests intended to further simplify this QSPR models, reported in Eqs. (70), (76), (82), and (88), produced equations of lower statistical quality, indicating that the even distance term  $WiPolE(0.99)$  is important in order to obtain a  $\Delta_f G_{300}^\circ$  QSPR with a small standard deviation.

## Vaporization Enthalpy

The QSPR model from Eq. (23) from Table I for the alkane vaporization enthalpy obtained with  $N$  and the first connectivity index  ${}^0\chi$ , with  $r = 0.9866$ ,  $s = 0.71 \text{ kJ mol}^{-1}$ ,  $F = 2399$ , cannot be improved with the use of the *WiPolE* and *WiPolO* indices: Eq. (53) from Table II that contains two parameters,  $MN$  and *WiPolE*(0.27) and statistical indices very close to those of Eq. (41) ( $r = 0.9807$ ,  $s = 0.85 \text{ kJ mol}^{-1}$ ,  $F = 1645$ ), suggests that only a size descriptor and the even distance term is important for the  $\Delta_{\text{vap}}H_{300}$  QSPR. An even simpler model, but with almost identical statistics, is obtained when *WiPolE* is replaced by  $p_2$  in Eq. (83). Similarly with the  $C_p$  QSPR Eq. (81), this vaporization enthalpy QSPR has two simple descriptors, a size parameter  $MN$  and a branching parameter  $p_2$ .

## Refractive Index

The results reported in Table II show that Eq. (60) obtained with  $MN$  and *WiPolO*(0.05), with  $r = 0.9810$ ,  $s = 0.0027$ ,  $F = 1663$ , is a better  $n_D^{25}$  QSPR than Eq. (32) from Table I, obtained with  $N$  and the sum of odd distances *SumO*(-2). The small value of the variable for the odd distances in the Wiener polynomial prompted us to investigate several QSPR models in which *WiPolO* is replaced with  $p_3$ ; these equations are presented in Table III. Using only two simple graph descriptors, namely  $MN$  and  $p_3$ , Eq. (72) has statistics almost identical with those of Eq. (60); this finding is a clear indication that the refractive index of alkanes can be modeled with a size descriptor and the count of distances 3, and that several more complex Wiener-type descriptors are not able to improve significantly the statistical indices.

## Density

Similarly with the refractive index QSPR, the best model for the alkane density, Eq. (61), is obtained with  $MN$  and *WiPolO*(0.05) ( $r = 0.9876$ ,  $s = 4.17 \text{ kg m}^{-3}$ ,  $F = 2569$ ), showing a significant improvement over the previously reported  $\rho$  QSPR model, Eq. (37), computed with  $N$  and the sum of odd distances *SumO*(-2). The correlation coefficient between  $MN$  and *WiPolO*(0.05) is almost equal to 1, exhibiting the same tendency identified for boiling temperature, standard Gibbs energy of formation, and refractive index. In Table III we present several  $\rho$  QSPR equations obtained when *WiPolO*(0.05) is substituted with  $p_3$ . Obviously, Eq. (73) obtained with  $MN$

and  $p_3$  has statistical indices as good as those of Eq. (61), demonstrating that odd graph distances larger than 3 have little importance for the QSPR model of alkane density.

## CONCLUDING REMARKS

Topological indices cast the structure of organic compounds represented as molecular graphs into a numerical form, and thereby provide an important class of structural descriptors for QSPR and QSAR models. The use of molecular graph descriptors in QSAR/QSPR models may generally be used to complement other classes of structural descriptors, such as fingerprints, hydrophobicity, geometrical, electrostatic, and quantum descriptors. Three classes of topological indices are extensively used in QSAR/QSPR models, namely: local-structure counts (as in group additivity schemes); second, connectivity indices; and third, distance-related descriptors, mainly represented by the Wiener index and other Wiener-type descriptors. In this paper we have developed novel graph descriptors by separating the terms of the Wiener polynomial into even and odd graph distances. The even and odd Wiener polynomial sums  $WiPolE(x)$  and  $WiPolO(y)$  are used as descriptors in QSAR/QSPR models, when the even and odd variables  $x$  and  $y$ , respectively, can be optimized in order to minimize the standard deviation of the model. Structural descriptors computed with these novel even/odd distance indices were used to develop QSPR models for six alkane properties: normal boiling temperature, molar heat capacity, standard Gibbs energy of formation, vaporization enthalpy, refractive index, and density. In many cases, the even/odd Wiener polynomial indices proposed here give notably improved correlations or suggest simpler QSPR models.

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