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Research Article

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QSPR and DFT Studies on the Melting Point of Carbocyclic Nitroaromatic Compounds

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Abstract

A quantitative structure-property relationship (QSPR) study was performed to predict the melting points of 60 carbocyclic nitroaromatic compounds using the electronic and topologic descriptors computed respectively, with ACD/ChemSketch and Gaussian 03W programs. The structures of all 60 compounds were optimized using the hybrid density functional theory (DFT) at the B3LYP/6-31G(d) level of theory. In both approaches, 50 compounds were assigned as the training set and the rest as the test set. These compounds were analyzed by the principal components analysis (PCA) method, a descendant multiple linear regression (MLR) analyses and an artificial neural network (ANN). The robustness of the obtained models was assessed by leave-many-out cross-validation, and external validation through test set. This study shows that the PCA and MLR have served also to predict melting point and some other physicochemical properties, but when compared with the results given by the ANN (R=0.997), we realized that the predictions fulfilled by this latter were more effective and much better than other models.

Keywords: DFT; QSPR; Energetic compounds; Melting point; Artificial neural network; Cross validation

Introduction

Energetic materials contain metastable compounds, for many of which the experimental thermophysical property data have not been published yet. Due to their expensive and often hazardous synthesis, testing, and fielding, elimination of a poor candidate before investing in synthesis and testing is of great value [1]. Furthermore, the safety for the scientists and engineers who work with them should be considered.

The relationship between the molecular structures of energetic compounds and their various properties such as performance, sensitivity, physical and thermodynamic properties is very important [2-4]. For new energetic compounds, the calculated properties can help to decide whether it is worth attempting a new and complex synthesis [5]. Recently a number of methods have been introduced to predict the thermochemical properties of different classes of energetic compounds, such as heat of sublimation [6-8], impact sensitivity [9-12], heat of formation [13-17], and detonation temperature [16,18].

Prediction of the melting point (**Mp**) of energetic compounds has become an important subject because melting point is one of the fundamental physical properties used in chemical identification and purification as well as in the calculation of other physicochemical properties such as vapor pressure and aqueous solubility.

One approach for the calculation of melting point of energetic compounds was developed special attention has been paid on the evaluation of melting point because large numbers of experimental data exist for melting points of different classes of energetic compounds. Quantitative structure-property relationships (QSPR) [19] has been recently introduced to predict melting points, it can be used to predict physicochemical parameters based on the structure of an organic compound. They connect physical or chemical properties to a set of molecular descriptors, which have developed relationships for use in different fields [19]. However, the main aim of QSPR is the identification of the appropriate set of descriptors that allow the desired attribute of the compound to be adequately predicted. This method has a key limitation because the set of organic compounds used to develop the relationship should be similar to those compounds, for which predictions are desired.

In this study, we have modeled the melting point of energetic compounds (Mp) of a series of carbocyclic nitroaromatic compounds (Table 1), using several statistical tools, principal components analysis (PCA), multiple linear regression (MLR)and artificial neural network (ANN) calculations [20,21]. The quantitative structure-propriety relationship (QSPR) method focuses on the motto that the properties of chemical compounds are determined by their molecular structures [22]. Thus, based on accurate experimental data of only some of the chemicals in one group, the melting point (Mp) of chemicals in the whole group can be predicted using the suitable models, including compounds that have not yet been experimentally synthesized [23-27].

The objectives of this work are to develop predictive QSPR models for the melting point Mp of our studied molecules. On the other hand, several quantum chemical methods and Quantum-chemistry calculations have been performed in order to study the molecular structure and electronic properties. The more relevant molecular properties were calculated, these properties are the: highest occupied molecular orbital energy $\mathbf{E_{HOMO}}$, lowest unoccupied molecular orbital energy $\mathbf{E_{LUMO}}$, energy gap $\mathbf{\Delta E}$, dipole moment $\boldsymbol{\mu}$, total energy $\mathbf{E_T}$, activation energy $\mathbf{E_a}$, absorption maximum $\boldsymbol{\lambda_{max}}$ andfactor oscillation strengths **f.o.**

In the present work, multiple linear regression (MLR) and artificial neural network (ANN) were used to establish the quantitative relationship between molecular structure and melting point for the same data used by Keshavarz and Pouretedal [28]. We used the Gaussian 03 on the calculated electronic descriptors to generate QSPR sets, i.e., the training and test sets. Then, MLR was utilized to select the

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structural features of the molecules relevant to the melting point and to construct the linear model. Using the selected descriptors as inputs, the nonlinear model was constructed by ANN. Both models were validated by an internal validation methods including cross-validation to characterize robustness and an external validation to estimate the predictive power of the models. Final, the ultimate objective was to establish reliable QSPR models for the melting point prediction of carbocyclic nitroaromatic compounds.

Materials and Methods

Experimental data

The experimental Mp values for the 60 carbocyclic nitroaromatic compounds were taken from the literature [29]. The compounds and their corresponding Mp values are listed in Table 1.

Calculation of molecular descriptors

Calculation of descriptors using Gaussian 03W: DFT (density functional theory) methods were used in this study. These methods have become very popular in recent years because they can reach similar precision to other methods in less time and less cost from the computational point of view. In agreement with the DFT results, energy of the fundamental state of a polyelectronic system can be expressed through the total electronic density, and in fact, the use of electronic density instead of wave function for calculating the energy constitutes the fundamental base of DFT [30,31] using the B3LYP functional [32] and a 6-31G(d) basis set. The B3LYP, a version of DFT method, uses Becke's three-parameter functional (B3) and includes a mixture of HF with DFT exchange terms associated with the gradient corrected correlation functional of Lee, Yang and Parr (LYP). The geometry of all species under investigation was determined by optimizing all geometrical variables without any symmetry constraints.

Several quantum chemical methods and quantum-chemistry calculations have been performed in order to study the molecular structure and electronic properties, from the results of the DFT calculations, the quantumchemistry descriptors were obtained for the model building as follows: the total energy **E_T(ev)**, the highest occupied molecular orbital energy **E_{HOMO}(ev**), the lowest unoccupied molecular orbital energy **E_{LUMO}(ev)**, the energy difference between the LUMO and the HOMO energy **Gap(ev)**, the total dipole moment of the molecule **μ (Debye)**, activation energy **E_a (ev)**, absorption maximum **λ_{max} (nm)**and factor of oscillation **f.o.** [33-35].

ChemSketch program (Demo version 10.0) [10] was employed to calculate the others molecular descriptors, Molar Volume (**MV** (cm^3)), Molecular Weight (**MW**), Molar Refractivity (**MR** (cm^3)), Parachor (**Pc** (cm^3)), Density (**D** (g/cm^3)), Refractive Index (**n**), Surface Tension (**γ** (dyne/cm), and Polarizability (**α** (cm^3)).

Statistical analysis

Principal Components Analysis (PCA): The energetic compounds of carbocyclic nitroaromaticderivatives (1 to 60) were studied by statistical methods based on the principal component analysis (PCA) [36] using the software XLSTAT 2009.

This is an essentially a descriptive statistical method which aims to present, in graphic form, the maximum information's contained in the data Table 1.

PCA is a statistical technique useful for summarizing all the information's encoded in the structures of compounds. It is also very helpful for understanding the distribution of the compounds.

Multiple Linear Regressions (MLR): The multiple linear regression statistic technique was used to study the relation between one dependent variable and several independent variables. It is a mathematic technique that minimizes differences between actual and predicted values. The qualities of the statistics of the MLR equation were judged by parameters such as the Rvalue (coefficient of correlation), the *F* value (Fischer statistics) and the RMSE value (the Root Mean Squared Error).

The multiple linear regression model (MLR) [37] was generated using the software XLSTAT 2009, to predict the melting point Mp. It has served also to select the descriptors used as the input parameters for a back-propagation network (ANN).

Artificial Neural Networks (ANNs): Nonlinear models were then developed by submitting the selected descriptors from MLR to a three-layer, fully connected, feedforward ANN. The number of input neurons was equal to that of the descriptors in the linear model. The number of hidden neurons was optimized by a trial and error procedure on the training process. One output neuron was used to represent the experimental Mp. To avoid overtraining, one tenth of the data from the training set was randomly selected as a separate validation set to monitor the training process; that is, during the training of the network the performance was monitored by predicting the values for the systems in the validation set. When the results for the validation set ceased to improve, the training was stopped [38].

Model evaluation and validation: In order to check the reliability and the stability of QSPR model elaborated by MLR and ANN methods, both the internal and external validations were conducted. The goodness of the fitting was firstly characterized by the coefficient of determination (R^2) between calculated and experimental values for the molecules of the training set. The formula is given by equation (1):

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - y_i')^2}{\sum_{i=1}^{n} (y_i - \bar{y})^2} \qquad (1)$$

where y_i, y'_i and $\bar{y}$ are the observed value, calculated value and mean value of the activity, respectively.

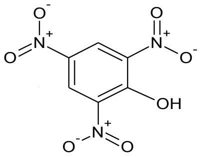
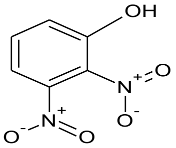
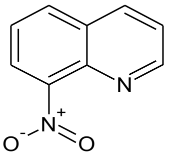
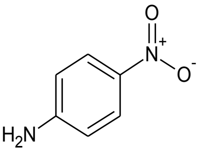
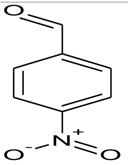
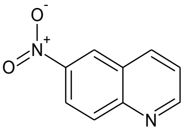
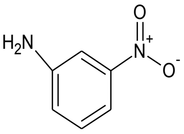
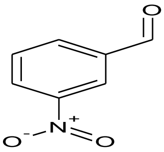
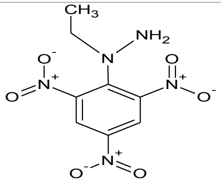
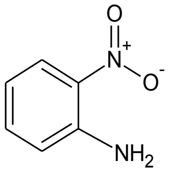
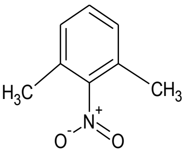
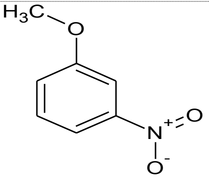
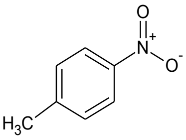
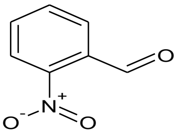
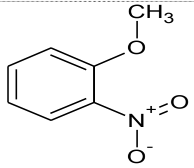
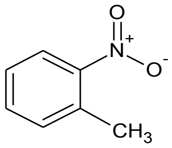
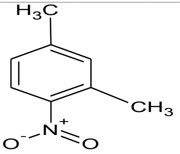
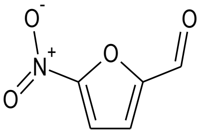
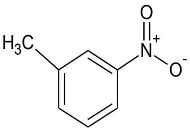
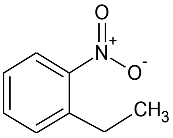
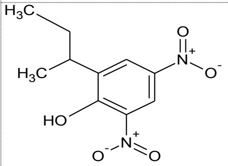
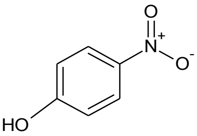
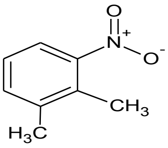
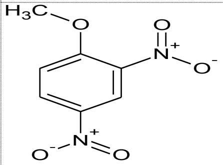
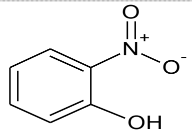
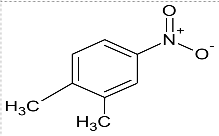
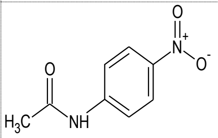
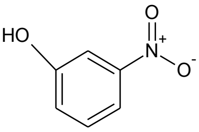
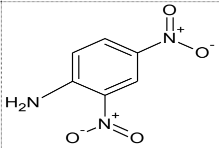
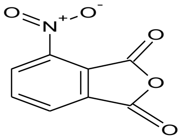
Cross-validation is one of the most popular methods of estimating the robustness of a model. In this work, the internal predictive capability of the model was evaluated by the leave-many-out (8% out) cross-validation (R^2_{CV}), following the mathematic form:

$$R^2_{CV} = 1 - \frac{\sum_{i=1}^{training\ set} (y_i - y_i')^2}{\sum_{i=1}^{training\ set} (y_i - \bar{y})^2} \qquad (2)$$

The reliability and robustness of the models were further validated by using the external test set composed of data not used to develop the prediction models. The external R^2_{test} for the test set is determined with the following equation:

$$R^2_{test} = 1 - \frac{\sum_{i=1}^{test\ set} (x_i - x_i')^2}{\sum_{i=1}^{test\ set} (x_i - \bar{y}_{tr})^2} \qquad (3)$$

where x_i, x'_i, and $\bar{y}_{tr}$ are the observed value, the calculated value in the test set and the mean value of the activity in the training set, respectively.

N°	Compound	Mp	N°	Compound	Mp	N°	Compound	Mp
1		395	21		417	41		361.65
2		420	22		377.15	42		421.65
3		386	23		331.65	43		369
4		344	24		288	44		311.15
5		325	25		312.65	45		282.35
6		271	26		282.68	46		309
7		288.59	27		260.9	47		316.42
8		385	28		287.4	48		359.9
9		318	29		301.7	49		489.1
10		368	30		453.05	50		436.6

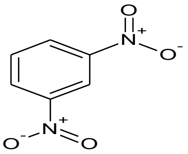
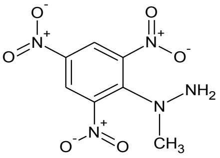
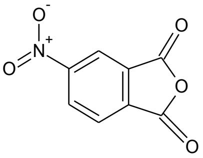
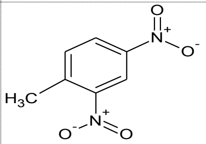
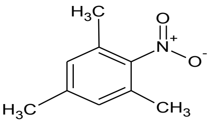
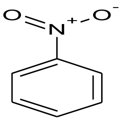
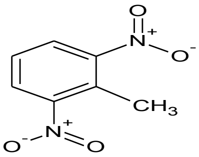
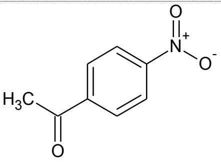
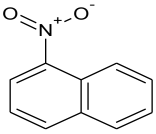
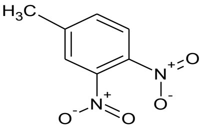
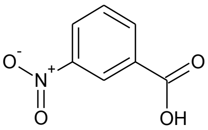
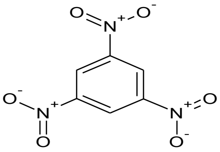
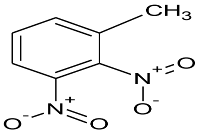
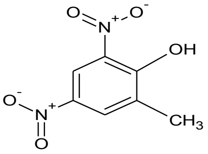
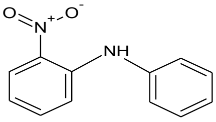
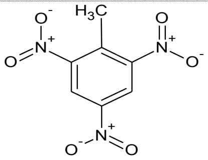
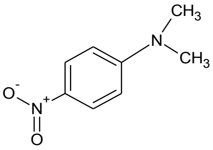
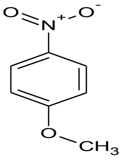
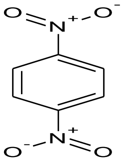
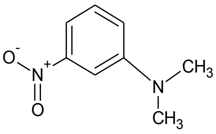
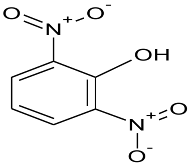
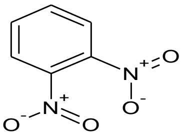
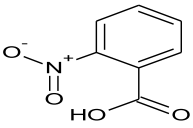
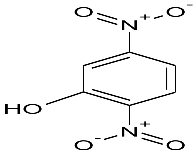
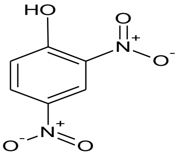
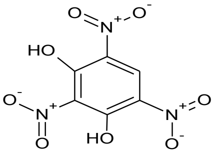
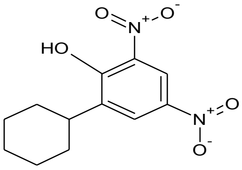
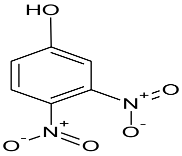
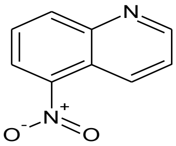
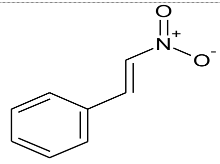
11		363	31		402.6	51		388
12		341	32		317	52		278.9
13		339	33		353.65	53		327.7
14		329	34		414.15	54		394.2
15		330	35		360.25	55		348.1
16		355.1	36		436.9	56		327.1
17		444.2	37		333.65	57		336
18		387.7	38		419	58		381
19		388	39		454.9	59		378.7
20		407	40		343	60		331

Table 1: Experimental values of melting point (Mp) of carbocyclic nitroaromatic compounds.

Results and Discussion

This study was carried for a series of 60 carbocyclic nitroaromatic compounds, in order to determine a quantitative relationship between the structural information and the Mp of the carbocyclic nitroaromatic compounds.

Table 2 shows the values of the calculated parameters obtained by DFT/B3LYP 6-31G* optimization of the studied compounds.

The set of sixteen descriptors encoding the 60 of carbocyclic nitroaromatic compounds, electronic, energetic and topologic parameters are submitted to PCA analysis [38]. The first three principal axes are sufficient to describe the information provided by the data matrix. Indeed, the percentages of variance are 42.93%, 22.33% and 9.72% for the axes F1, F2 and F3, respectively. The total information was estimated to a percentage of 74.99%. The principal component analysis (PCA) [38] was conducted to identify the link between the different variables. Bold values are different from 0 at a significance level of p=0.05.

The Pearson correlation coefficients were summarized in the following Tables 3 and 4. The obtained matrix provides information on the negative or positive correlation between variables.

*The Polarizability **α** is perfectly correlated with the Molar Refractivity **MR** (r=1), strongly correlated with the Parachor **Pc** (r=0.982) and highly correlated with the Molar Volume (r=0.911).

*The Parachor **Pc** is strongly correlated with the Molar Refractivity **MR** (r=0.982), highly correlated with the Molar Volume **MV** (r=0.911) and the Molar Weight **MW** (r=0.906).

*The Molar Weight **MW** is strongly negatively correlated with the total Energy $\mathbf{E_t}$ (r=-0.968).

*The absorption maximum $\boldsymbol{\lambda}_{\mathbf{max}}$ is highly negatively correlated with the activation Energy $\mathbf{E_a}$ (r=-0.943).

Analysis of projections according to the planes F1-F2 and F1-F3 (65.27% and 52.65% of the total variance respectively) of the studied molecules (Figure 1) shows that the molecules are dispersed in three regions: Region 1 contains compounds having a values of density **D** between 1.10 (g/cm^3) and 1.28 (g/cm^3), Region 2 contains compounds having a values of density **D** between 1.33 (g/cm^3) and 1.47 (g/cm^3) and Region 3 contains compounds having a values of density **D** between 1.49 (g/cm^3) and 2.01 (g/cm^3).

Multiple Linear Regressions (MLR)

To establish quantitative relationships between the melting point **Mp** and selected descriptors, our array data were subjected to a multiple linear regression. Only variables whose coefficients are significant were retained.

Multiple linear regression of the melting point Mp (MLR)

Modeling the melting point **Mp** value of all training compounds (50 carbocyclic nitroaromatic derivatives) led to the best value corresponding to the linear combination of the following descriptors: the absorption maximum $\boldsymbol{\lambda}_{\mathbf{max}}$, factor of oscillation **f.o**, themolar volume **MV**, the molar refractivity **MR** and the density **D**.

The most significant QSAR model was obtained, as shown in the following equation:

$$\mathbf{Mp} = -141{,}187 + 0{,}108 \times \lambda_{\max} - 258{,}706 \times \mathbf{f.o} - 2{,}298 \times \mathbf{MW} + 10{,}199 \times \mathbf{MR} + 385{,}206 \times \mathbf{D} \qquad (4)$$

For our 50 compounds, the correlation between experimental and calculated **Mp**one based on this model are quite significant (Figure 2) as indicated by statistical values:

N=50 R=0.773R^2=0.597R$_{CV}$=0.651R$^2_{CV}$=0.424 F=13.069 RMSE=36.573

In the above regression equation, R is correlation coefficient, R_{CV} is cross-validationcoefficient, RMSE is root mean square error, F is Fisher's test and N is data points (compounds). Generally, the higher the correlation coefficient and the lower the standard error, the more reliable is the model. High values of *F* indicate the significance of Eq. (4), which reflects the ratio of variance explained by the model and the variance due to the error in the model. Based on Eq. (4), the positive correlation coefficient for **λmax, MR** and **D** indicates that a compound with a larger value for these descriptors would have a larger **Mp**value (increase **Mp**), the negative correlation for **f.o** and **MW D** indicates that a compound with a larger value for these descriptors would have a smaller **Mp** value (decrease **Mp**)**.**

The Figure 2 shows a very regular distribution of Mp values depending on the experimental values. As part of this conclusion, we can say that the melting point **Mp** values obtained from MLR are highly correlated to that of the observed melting point. 'Leave-many-out (8% out)' is an approach particularly well adapted for estimating the melting point ability of these models. In this paper, the 'leave-many-out' procedure was used to evaluate the predictive ability of the MLR. The correlations between the observed properties (Melting point) and the cross-validation (CV) calculated values are illustrated in Figure 3 and Table 5.

True predictive power of a QSPR model is to test their ability to predict accurately the melting point of compounds from an external test set (compounds which were not used for the model development), the melting point of the remained set of 10 compounds (51-60) are deducedfrom the quantitative model proposed with the 50 molecules (training set) by MLR, their observed and calculated **Mp** values are given in Table 6.

N=10R$_{test}$ (MLR)=0.642R$^2_{test}$ (MLR)=0.412

Artificial Neural Networks (ANN)

The ANN has become an important and widely used nonlinear modeling technique for QSPR studies, it can be used to generate predictive models of quantitative structure-property relationships (QSPR) between a set of molecular descriptors obtained from the MLR and observed melting point.

The correlations coefficients and Standard Error of Estimate, obtained with the ANN, show that the selected descriptors by MLR are pertinent and that the model proposed to predict melting point is relevant.

The statistic of the three steps of the calculation by the ANN: training, validation and test are illustrated in Table 4.

It can be found that the ANN model performs better than the MLR model, which further confirms the nonlinear relationship between the structural information and the Mp of the carbocyclic nitroaromatic compounds.

The values of predicted **Mp** calculated using ANN and the observed values are illustrated in Figure 4.

N°	Mp	Et	E_{HOMO}	E_{LUMO}	Gap	μ	Ea	$λ_{max}$	f.o	MW	MR	MV	Pc	n	γ	D	α
1	395	-25077.60	-8.242	-3.900	4.342	1.768	4.810	257.79	0.0004	229.104	47.77	123.3	388.7	1.701	98.5	1.86	18.93
2	420	-17461.12	-8.343	-3.508	4.834	0.113	2.115	586.35	0.0026	138.124	37.03	103.5	288.5	1.634	60.3	1.33	14.68
3	386	-13400.02	-6.140	-2.246	3.894	5.653	5.007	247.60	0.0009	128.124	37.03	103.5	288.5	1.634	60.3	1.33	14.68
4	344	-13399.41	-7.043	-1.632	5.411	5.068	5.329	232.66	0.0038	138.124	37.03	103.5	288.5	1.634	60.3	1.33	14.68
5	325	-12963.38	-7.369	-2.317	5.051	5.207	5.923	209.34	0.1054	137.136	37.62	117.5	300.4	1.553	42.6	1.17	14.91
6	271	-12963.06	-7.060	-1.965	5.096	3.713	5.951	208.35	0.0456	137.136	37.62	117.5	300.4	1.553	42.6	1.17	14.91
7	289	-12963.36	-7.273	-2.357	4.916	4.886	5.958	208.11	0.0343	137.136	37.62	117.5	300.4	1.553	42.6	1.17	14.91
8	385	-13940.34	-7.042	-1.982	5.060	4.033	5.920	209.42	0.0995	139.108	34.67	99.7	277.7	1.612	60.2	1.40	13.74
9	318	-13940.44	-6.666	-1.807	4.858	5.114	5.123	242.00	0.0346	139.108	34.67	99.7	277.7	1.612	60.2	1.40	13.74
10	368	-13940.83	-6.784	-2.398	4.386	5.826	5.852	211.87	0.0318	139.108	34.67	99.7	277.7	1.612	60.2	1.40	13.74
11	363	-17461.14	-8.419	-3.137	5.281	4.220	4.806	257.96	0.0003	168.107	39.34	113.1	318.2	1.612	62.6	1.49	15.59
12	341	-18531.49	-7.813	-2.880	4.934	4.495	4.796	258.52	0.0004	182.133	44.16	129.3	355.8	1.598	57.2	1.41	17.50
13	339	-18531.47	-7.912	-2.864	5.048	2.988	4.781	259.34	0.0003	182.133	44.16	129.3	355.8	1.598	57.2	1.41	17.50
14	329	-18531.35	-7.735	-2.924	4.811	7.304	4.742	261.46	0.0005	182.133	44.16	129.3	355.8	1.598	57.2	1.41	17.50
15	330	-18531.31	-7.678	-2.879	4.799	6.608	4.725	262.38	0.0004	182.133	44.16	129.3	355.8	1.598	57.2	1.41	17.50
16	355	-24099.79	-8.465	-3.495	4.970	1.478	4.778	259.51	0.0002	227.131	50.71	141.2	411.3	1.637	71.9	1.61	20.10
17	444	-17461.12	-8.343	-3.508	4.834	0.113	2.115	586.35	0.0026	168.107	39.34	113.1	318.2	1.612	62.6	1.49	15.59
18	388	-17460.68	-7.941	-3.036	4.904	6.672	2.054	603.76	0.0009	168.107	39.34	113.1	318.2	1.612	62.6	1.49	15.59
19	388	-19509.04	-7.642	-2.824	4.818	6.017	4.779	259.42	0.0012	184.106	41.22	111.5	333.2	1.660	79.6	1.65	16.34
20	407	-19508.85	-7.442	-2.874	4.568	7.903	4.749	261.06	0.0007	184.106	41.22	111.5	333.2	1.660	79.6	1.65	16.34
21	417	-19508.40	-7.267	-2.403	4.863	7.655	4.751	260.98	0.0006	184.106	41.22	111.5	333.2	1.660	79.6	1.65	16.34
22	377	-14978.44	-7.580	-3.121	4.459	2.506	5.048	245.61	0.0003	151.119	39.55	112.9	307.8	1.617	55.1	1.34	15.67
23	332	-14978.47	-7.519	-2.841	4.678	2.205	4.788	258.95	0.0113	151.119	39.55	112.9	307.8	1.617	55.1	1.34	15.67
24	288	-14033.73	-6.957	-1.963	4.994	3.376	5.926	209.21	0.029	151.162	42.44	133.8	338.0	1.547	40.7	1.13	16.82
25	313	-14978.05	-7.391	-2.600	4.791	6.520	4.592	269.98	0.0225	151.119	39.55	112.9	307.8	1.617	55.1	1.34	15.67
26	283	-14033.70	-6.831	-1.897	4.934	4.184	5.904	210.01	0.0744	151.162	42.44	133.8	338.0	1.547	40.7	1.13	16.82
27	261	-14033.73	-7.237	-2.288	4.949	4.233	5.942	208.65	0.0345	151.162	42.34	134	339.3	1.544	41	1.13	16.78
28	287	-14033.80	-7.030	-2.171	4.859	4.565	3.957	313.36	0.0394	151.162	42.44	133.8	338.0	1.547	40.7	1.13	16.82
29	302	-14034.00	-7.136	-2.253	4.883	5.456	5.915	209.62	0.0587	151.162	42.44	133.8	338.0	1.547	40.7	1.13	16.82
30	453	-18968.71	-6.889	-2.804	4.085	6.699	4.793	258.66	0.0003	182.121	43.58	115.3	344.0	1.679	79	1.59	17.27
31	403	-27112.96	-7.040	-3.068	3.972	5.368	3.283	377.63	0.0082	257.16	59.1	150.1	464.9	1.717	92	1.71	23.43
32	317	-15104.43	-6.911	-2.049	4.862	4.345	3.970	312.34	0.0378	165.189	47.27	150.1	375.6	1.542	39.2	1.10	18.74
33	354	-16049.23	-7.327	-2.937	4.390	3.651	5.212	237.91	0.0053	165.146	42.82	132.8	347.9	1.558	47.1	1.24	16.97
34	414	-17027.49	-7.887	-2.654	5.234	5.277	5.247	236.28	0.0056	167.119	39.72	113.8	324.8	1.615	66.4	1.47	15.74
35	360	-20579.73	-7.478	-2.724	4.754	6.721	4.814	257.53	0.0008	198.133	46.05	127.8	370.8	1.639	70.8	1.55	18.25
36	437	-15540.80	-5.828	-1.829	3.999	8.068	4.792	258.74	0.0002	166.177	47.11	139.2	364.7	1.591	47	1.19	18.67
37	334	-15540.69	-5.662	-2.130	3.532	6.166	4.194	295.63	0.0009	166.177	47.11	139.2	364.7	1.591	47	1.19	18.67
38	419	-17027.10	-7.571	-2.488	5.083	5.395	5.158	240.37	0.0066	167.119	39.72	113.8	324.8	1.615	66.4	1.47	15.74
39	455	-27125.80	-8.015	-3.716	4.299	1.646	4.818	257.35	0.0003	245.103	49.65	121.8	403.7	1.750	121	2.01	19.68
40	343	-16512.77	-6.845	-2.158	4.687	1.943	4.281	289.63	0.0629	174.156	48.73	128.6	360.7	1.682	61.8	1.35	19.31
41	362	-16512.75	-6.787	-2.010	4.776	5.905	4.211	294.44	0.0681	174.156	48.73	128.6	360.7	1.682	61.8	1.35	19.31
42	422	-16512.80	-6.915	-2.067	4.848	3.758	4.354	284.76	0.0427	174.156	48.73	128.6	360.7	1.682	61.8	1.35	19.31
43	369	-28183.51	-7.004	-3.096	3.907	5.249	3.331	372.26	0.0098	271.187	63.73	166.6	504.7	1.690	84.2	1.63	25.26
44	311	-15011.16	-6.630	-2.325	4.305	6.041	5.767	215.00	0.0273	153.135	39.47	125.2	319.4	1.542	42.2	1.22	15.64
45	282	-15010.78	-6.514	-1.747	4.766	4.889	5.780	214.51	0.0512	153.135	39.47	125.2	319.4	1.542	42.2	1.22	15.64
46	309	-14917.21	-7.404	-2.798	4.605	5.124	4.758	260.60	0.2417	141.082	31.85	95.7	261.7	1.579	55.9	1.47	12.62
47	316	-23791.17	-7.363	-2.652	4.711	7.238	4.810	257.75	0.0014	240.213	60.04	178.1	488.0	1.589	56.3	1.35	23.80
48	360	-20579.40	-7.441	-2.731	4.710	6.681	4.779	259.45	0.0014	198.133	46.02	137.1	374.9	1.586	55.8	1.44	18.24
49	489	-17556.88	-6.852	-2.500	4.352	2.466	5.135	241.46	0.0091	180.161	47.07	134.3	366.4	1.617	55.3	1.34	18.66
50	437	-20080.35	-8.174	-3.327	4.847	6.121	3.963	312.84	0.0589	193.113	42.22	114.4	340.1	1.659	78.1	1.69	16.74
51	388	-20080.35	-8.249	-3.179	5.070	2.833	3.552	349.06	0.0757	193.113	42.22	114.4	340.1	1.659	78.1	1.69	16.74
52	279	-11892.39	-7.232	-1.967	5.265	4.016	5.963	207.91	0.0699	123.109	32.79	101.2	262.7	1.561	45.3	1.22	13.00
53	328	-16076.09	-6.357	-1.971	4.386	4.013	4.388	282.56	0.0792	173.168	50.64	135.3	366.5	1.671	53.7	1.28	20.07
54	394	-23028.48	-8.368	-2.954	5.413	0.007	4.796	258.52	0.0001	213.104	45.88	124.9	373.7	1.655	80	1.71	18.19
55	348	-19691.60	-5.728	-2.310	3.417	4.440	4.834	256.47	0.0297	214.22	62.17	167.3	456.1	1.665	55.2	1.28	24.64

56	327	-15011.24	-6.765	-2.161	4.604	6.000	5.311	233.45	0.0056	153.136	39.47	125.2	319.4	1.542	42.2	1.22	15.64
57	336	-19509.25	-7.536	-3.363	4.173	4.044	6.071	204.24	0.0203	184.106	41.22	111.5	333.2	1.660	79.6	1.65	16.34
58	381	-19509.49	-7.491	-3.636	3.855	1.168	4.813	257.60	0.0003	184.106	41.22	111.5	333.2	1.660	79.6	1.65	16.34
59	379	-25899.67	-7.273	-3.185	4.089	4.576	4.086	303.42	0.0039	266.25	67.08	192.7	539.6	1.612	61.4	1.38	26.59
60	331	-14000.35	-6.950	-2.634	4.316	5.867	5.691	217.86	0.0009	149.147	43.53	126.6	328.9	1.603	45.4	1.18	17.25

Table 2: Values of the calculated parameters obtained by DFT/B3LYP 6-31G* optimization of the studied compounds.

Variables	**Mp**	**E_t**	**E_{HOMO}**	**E_{LUMO}**	**Gap**	**μ**	**E_a**	**λ_{max}**	**f.o**	**MW**	**MR**	**MV**	**Pc**	**n**	**γ**	**D**	**α**
Mp	**1**																
E_t	-0.471	**1**															
E_{HOMO}	-0.250	0.385	**1**														
E_{LUMO}	-0.467	0.686	0.741	**1**													
Gap	-0.219	0.296	-0.538	0.167	**1**												
μ	-0.122	0.122	0.409	0.373	-0.132	**1**											
E_a	-0.454	0.423	0.289	0.440	0.127	0.167	**1**										
λ_{max}	0.381	-0.262	-0.323	-0.404	-0.033	-0.225	**-0.934**	**1**									
f.o	-0.343	0.364	0.149	0.316	0.178	-0.013	0.179	-0.155	**1**								
MW	0.381	**-0.968**	-0.237	-0.556	-0.350	-0.056	-0.369	0.183	-0.339	**1**							
MR	0.171	-0.721	0.153	-0.202	-0.478	0.017	-0.308	0.124	-0.281	0.852	**1**						
MV	-0.101	-0.493	0.245	-0.011	-0.374	0.098	-0.153	0.021	-0.225	0.666	0.911	**1**					
Pc	0.177	-0.792	0.046	-0.288	-0.429	0.024	-0.298	0.120	-0.319	**0.906**	**0.982**	**0.911**	**1**				
n	0.659	-0.655	-0.195	-0.478	-0.313	-0.180	-0.405	0.248	-0.211	0.586	0.392	-0.020	0.352	**1**			
γ	0.655	-0.775	-0.445	-0.669	-0.186	-0.180	-0.329	0.207	-0.261	0.654	0.270	-0.095	0.318	0.882	**1**		
D	0.629	-0.766	-0.554	-0.727	-0.100	-0.165	-0.329	0.213	-0.220	0.631	0.185	-0.153	0.255	0.801	**0.970**	**1**	
α	0.171	-0.721	0.152	-0.202	-0.478	0.017	-0.308	0.124	-0.281	0.853	**1.000**	**0.911**	**0.982**	0.392	0.270	0.185	**1**

Table 3: Correlation matrix (Pearson (n)) between different obtained descriptors.

Samples	**R**	**R^2**	**RMSE**
Training	500.997	0.994	1.295×10^{-5}
Validation	7 0.9890.978	2.364×10^{-5}	
Test30.988	0.986	4.465×10^{-5}	

Table 4: Correlation coefficient (R) and root mean square error (RMSE).

N°	**Mp**						
	Obs.	**RML**		**CV**		**ANN**	
		Pred.	**Resid.**	**Pred.**	**Resid.**	**Pred.**	**Resid.**
1	395.00	424.97	-29.97	437.47	-42.47	394.99	0.01
2	420.00	412.36	7.64	383.79	36.21	420.00	0.00
3	386.00	405.26	-19.26	417.83	-31.83	386.01	-0.01
4	344.00	373.93	-29.93	383.37	-39.37	344.00	0.00
5	325.00	289.68	35.32	285.12	39.88	324.99	0.01
6	271.00	305.05	-34.05	314.13	-43.13	271.01	-0.01
7	288.59	307.95	-19.36	317.83	-29.24	288.59	0.00
8	385.00	343.63	41.37	350.11	34.89	385.01	-0.01
9	318.00	363.93	-45.93	371.37	-53.37	318.00	0.00
10	368.00	361.41	6.59	372.29	-4.29	368.01	-0.01
11	363.00	373.20	-10.20	380.21	-17.21	363.01	-0.01
12	341.00	351.34	-10.34	357.62	-16.62	341.00	0.00
13	339.00	351.45	-12.45	357.66	-18.66	339.00	0.00
14	329.00	351.63	-22.63	357.59	-28.59	328.99	0.01
15	330.00	351.75	-21.75	357.62	-27.62	329.99	0.01
16	355.10	365.37	-10.27	368.18	-13.08	355.10	0.00
17	444.20	408.00	36.20	373.13	71.07	444.20	0.00
18	387.70	410.32	-22.62	373.59	14.11	387.70	0.00
19	388.00	409.13	-21.13	412.39	-24.39	388.00	0.00
20	407.00	409.44	-2.44	412.52	-5.52	407.00	0.00
21	417.00	409.45	7.55	416.05	0.95	417.00	0.00
22	377.15	366.22	10.93	374.47	2.68	377.16	-0.01
23	331.65	364.81	-33.16	371.02	-39.37	331.64	0.01
24	288.00	303.71	-15.71	311.74	-23.74	287.99	0.01

Citation: Elidrissi B, Ousaa A, Ghamali M, Chtita S, Ajana MA, et al. (2017) QSPR and DFT Studies on the Melting Point of Carbocyclic Nitroaromatic Compounds. J Phys Chem Biophys 7: 245. doi: 10.4172/2161-0398.1000245

25	312.65	363.10	-50.45	367.51	-54.86	312.63	0.02
26	282.68	292.05	-9.37	309.07	-26.39	282.68	0.00
27	260.90	300.44	-39.54	307.26	-46.36	260.92	-0.02
28	287.40	312.24	-24.84	322.23	-34.83	287.40	0.00
29	301.70	296.07	5.63	309.02	-7.32	301.69	0.01
30	453.05	414.45	38.60	403.89	49.16	453.04	0.01
31	402.60	415.06	-12.46	427.45	-24.85	402.61	-0.01
32	317.00	310.01	6.99	312.62	4.38	317.01	-0.01
33	353.65	320.22	33.43	310.00	43.65	353.66	-0.01
34	414.15	369.30	44.85	359.91	54.24	414.16	-0.01
35	360.25	379.14	-18.89	374.56	-14.31	360.25	0.00
36	436.90	345.29	91.61	337.28	99.62	436.94	-0.04
37	333.65	349.08	-15.43	342.07	-8.42	333.64	0.01
38	419.00	369.48	49.52	361.00	58.00	419.01	-0.01
39	454.90	457.86	-2.96	461.78	-6.88	454.83	0.07
40	343.00	387.82	-44.82	402.88	-59.88	342.99	0.01
41	361.65	386.99	-25.34	407.70	-46.05	361.64	0.01
42	421.65	392.52	29.13	406.44	15.21	421.65	0.00
43	369.00	387.53	-18.53	408.08	-39.08	369.00	0.00
44	311.15	304.59	6.56	299.42	11.73	311.14	0.01
45	282.35	298.36	-16.01	299.36	-17.01	282.35	0.00
46	309.00	307.93	1.07	366.38	-57.38	309.00	0.00
47	316.42	321.98	-5.56	306.68	9.74	316.42	0.00
48	359.90	338.05	21.85	329.82	30.08	359.91	-0.01
49	489.10	356.83	132.27	345.74	143.36	489.06	0.04
50	436.60	398.32	38.28	409.87	26.73	436.62	-0.02

Table 5: Observed. predicted Mp and residue according to different methods.

N°	Mp		
	Obs.	RML	
		Pred.	Resid.
51.00	388.00	397.88	-9.88
52.00	278.90	308.96	-30.06
53.00	327.70	376.29	-48.59
54.00	394.20	394.03	0.17
55.00	348.10	385.35	-37.25
56.00	327.10	312.19	14.91
57.00	336.00	398.24	-62.24
58.00	381.00	409.17	-28.17
59.00	378.70	335.34	43.36
60.00	331.00	347.36	-16.36
51.00	388.00	397.88	-9.88
52.00	278.90	308.96	-30.06
53.00	327.70	376.29	-48.59
54.00	394.20	394.03	0.17
55.00	348.10	385.35	-37.25
56.00	327.10	312.19	14.91
57.00	336.00	398.24	-62.24
58.00	381.00	409.17	-28.17
59.00	378.70	335.34	43.36
60.00	331.00	347.36	-16.36

Table 6: The observed. the predicted **Mp**. and residue according to MLR for the 10 tested compounds (test set).

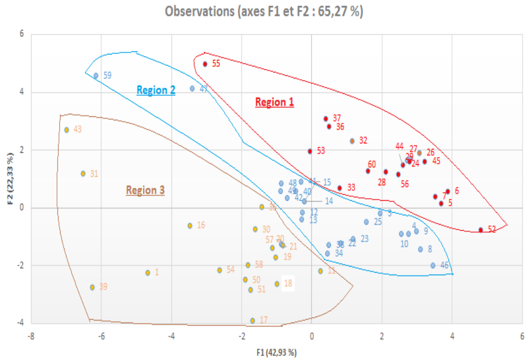


Figure 1: Cartesian diagram according to F1-F2.

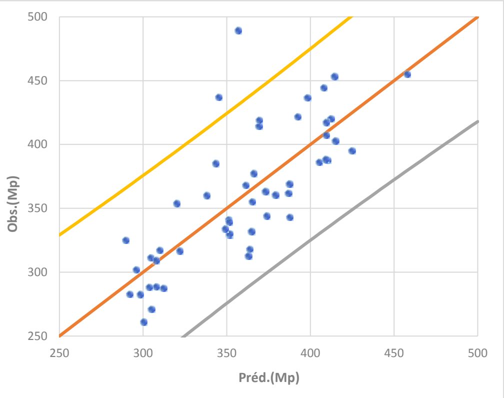


Figure 2: Graphical representation of calculated and observed melting point Mp by MLR.

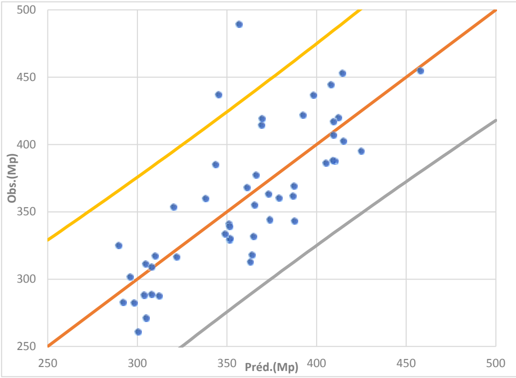


Figure 3: Correlations of observed and predicted Mp values calculated using CV.

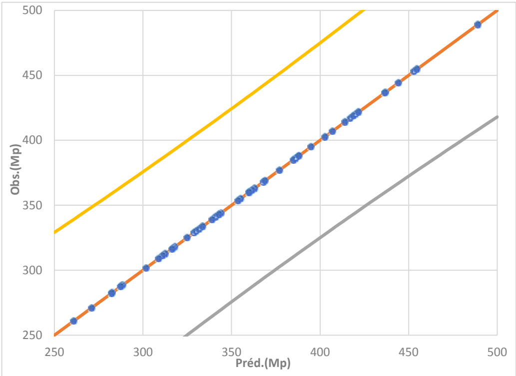


Figure 4: Correlations of observed and predicted Mp calculated using ANN.

Model validation

In order to check the reliability and the stability of the QSPR model elaborated by the MLR and ANN methods, we have used the internal and external validations. The leave-many-out (8% out) cross-validation (**R_{CV}=0.651**) of MLR, showing the good robustness of the model. Moreover, predictions realized on the test set (**R_{test} (MLR)=0.642**) were in good agreement with the experimental values.

A comparison of the quality of ACP, MLR and ANN models shows that the ANN (**R=0.954, $R_{(test)}$=0.989, $R_{(validation)}$=0.988**) is the best models that indicate the effects of these descriptors on the melting point of the studied compounds.

All the results discussed above showed that the presented MLR and ANN models could be effectively used to predict the **M_p** of carbocyclic nitroaromatic compounds, they were able to establish a satisfactory relationship between the molecular descriptors and the melting point of the studied compounds.

From the values of correlation coefficient of the ten compounds (test set) (R_{test}), the Cross-Validated coefficient (R_{CV}) and other statistical parameters of these methods (MLR and ANN), it is clear that the predictive power of our model is high and stable, it can be efficiently used for estimating the melting point of other carbocyclic nitrobenzene compounds for which no experimental data are available.

The predicted activity values of carbocyclic nitrobenzene compounds of training set, obtained by different methods are listed in Table 5 along with their observed activity.

Conclusion

In present work, we have carried out a comparative analysis of the melting point of carbocyclic nitrobenzene compounds by two QSAR approaches, MLR and ANN. Both approaches have showed good predictive power (R=0.773 and 0.997, respectively). Comparison of the qualities of MLR and ANN models shown that the ANN has a good predictive ability and strong robustness than the MLR, yields a regression model with improved predictive power, we have established a relationship between several descriptors and the melting point **Mp**. The predictive ability and robustness of the obtained models were assessed by cross-validation, and external validation through test set. Thus, the model could be efficiently employed for estimating the **Mp** and for select the descriptors which have an impact on this property and which are sufficiently rich in chemical, electronic and topological information to encode the structural feature.

The present study shows that molecular descriptors, namely the absorption maximum **λ_{max}**, factor of oscillation **f.o**, molar volume **MV**, molar refractivity **MR** and the density **D**, are useful for the prediction of the melting point of carbocyclic nitroaromatic compounds, which the experimental data are unavailable.

The QSAR model is statistically significant, robust and can be used for prediction the property more accurately, it may be helpful for a better understanding of the Mp of this class of compounds and useful as guidance to estimate the melting point as physical property of new energetic compounds.

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