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ABSTRACT

This work presents a new approach to predict thermal stability of nitroaromatic compounds based on quantum chemical calculations and on Quantitative Structure-Property Relationship (QSPR) methods. The data set consists of 22 nitroaromatic compounds of known decomposition enthalpy (taken as a macroscopic property related to explosibility) obtained from differential scanning calorimetry. Geometric, electronic and energetic descriptors have been selected and computed using Density Functional Theory (DFT) calculation to describe the 22 molecules. First approach consisted in looking at their linear correlations with the experimental decomposition enthalpy. Molecular weight, electrophilicity index, electron affinity and oxygen balance appeared as the most correlated descriptors (respectively R^2= 0.76, 0.75, 0.71 and 0.64). Then multilinear regression was computed with these descriptors. The obtained model is a six-parameter equation containing descriptors all issued from quantum chemical calculations. The prediction is satisfactory with a correlation coefficient R^2 of 0.91 and a predictivity coefficient R^2_{cv} of 0.84 using a cross validation method.

keywords: Thermal stability, explosibility, property prediction, Quantitative Structure-Property Relationship (QSPR), quantum chemistry

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1. Introduction

An important initial step for the management of industrial risks consists in identifying and determining as soon and as accurately as possible explosive abilities of molecules, whatever their final use. Moreover, the explosive intrinsic property of a substance ranks at top of physicochemical hazards that may be feared from the use of a given chemical [1]. This is a reason why, in addition to the complexity with which this hazardous property is triggered in real case, the experimental approach has remained the "golden" way to assess hazards. Keeping on this unique approach would however be a real burden for the industry with the requirements of the new regulatory framework REACH[1] and its tool the GHS[2] given the tremendous number of substances (up to 30000) that might require a new assessment of hazardous properties. Another interest for predictive methods is to address needs of screening processes of substances that are applied to search for a targeted chemical activity (e.g. phytotoxicity, medical efficiency for a given illness, reactivity…) at the R&D level.

A number of early works are worth being mentioned in the field of hazard prediction. At first, some methods of prediction based on thermodynamic concepts have been developed. Significant weaknesses in those methods lie in the chemical thermodynamic and energy release evaluation (CHETAH) [2] and the calculated adiabatic reaction temperature (CART) [3]. Grewer [4,5] proposed another way to predict the thermal stability by considering the influence of the chemical structure on the decomposition of nitro compounds. Keshavarz's works have also to be noted as the elemental

[1] REACH for "Registration, Evaluation and Authorization of Chemicals" is a new European regulation published by the European Commission in December 2006 and entered into force on 1st June 2007. All manufacturers, importers and suppliers of chemicals must identify and manage risks linked to the substances they manufacture and market. http://echa.europa.eu/

[2] GHS for "Globally Harmonized System of classification and labeling of chemicals" is a United Nations system which aims to identify hazardous chemicals and to inform users about these hazards through

composition of substances is used to predict various properties of energetic materials such as the impact sensitivity [6]. Saraf et al. [7] outlined the pertinence (in terms of way of investigation) of screening tools based on the identification of relationships between chemical structure and thermal stability for nitroaromatic compounds and we have made up our mind to explore this route.

An alternative tool for the prediction of chemical hazards is the Quantitative Structure Activity/Properties Relationship (QSAR/QSPR) methods. Nowadays, they are generally limited to the scope of toxic property screening (i.e. the nitrobenzene molecule [8]). Indeed, the first applications of these methods based on statistical analyses have mainly concerned biology [9,10], toxicology [11,12] or drug design [13-15]. However, their interest has been growing up in recent years for other physico-chemical activities [16-18]. In such methodology, computational chemistry may help to describe the molecular electronic structure and the decomposition reaction at quantum chemical level.

In this paper, we decided to explore the abilities of molecular modeling to predict the explosibility of nitroaromatic compounds (known as potentially explosive chemical substances and presenting complex decomposition channels [19]). A series of geometric, electronic and energetic descriptors were computed using quantum chemical calculations. Correlations between these data and macroscopic properties related to explosibility were determined. In particular, explosibility is related to detonation and deflagration performances and to sensitivity to mechanical (impact, shock or friction) and thermal stresses or to electric discharges. Here, we focused on the thermal stability property and more precisely on the experimental decomposition enthalpy (or heat of decomposition). Experimental characterization is well defined, particularly by calorimetric measurements [20] but, until now, only few approaches concern the

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standard symbols and phrases on the packaging labels and through safety data sheets (SDS). http://ecb.jrc.ec.europa.eu/classification-labelling/

prediction of the thermal stability properties based on QSPR models [21-23]. In most of the cases, they are dedicated to specific (and small) classes of compounds (e.g. chromophores [24] or ionic liquids [25]). In the framework of chemical hazards management, Saraf and coworkers [7] proposed, to our knowledge, the only existing model concerning the heat of decomposition with an average absolute error of about 6%:

$$-\Delta H\,(kcal/mol) = 75 \times n_{NO2} \qquad (1)$$

where n_{NO2} is the number of nitro groups in the molecule.

Our work presents the first significantly correlated model for the prediction of this experimental property using an original approach combining QSPR methodology with quantum chemical calculations.

2. QSPR methodology

The quantitative structure-property relationship methodology (QSPR) consists in correlating quantitatively an experimental property with the molecular structures of the considered compounds. Thus, the relationship has the following general form between macroscopic and microscopic properties:

$$Property = f\,(Descriptors) \qquad (2)$$

An experimental data set provides the property values. Then different descriptors can be calculated to characterize the molecular structure of the compounds of the data set. The method can be based on neural networks [26], genetic algorithms [27] or statistical analyses such as multilinear regressions. We chose the last approach in this study.

The model obtained with such a regression has the following form:

$$Y = A_0 + A_1 X_1 + A_2 X_2 + ... + A_n X_n \qquad (3)$$

where Y is the property to predict, X_i are the molecular descriptors and A_i the corresponding regression constants. The reliability of this model is estimated with the coefficient R^2, which characterize the fitting of the calculated values with the experimental ones. To ensure the validation of the models, the use of external data is recommended. Nevertheless, in this study, the set of available experimental data contained only 22 molecules making its division into training and validation sets impossible. For this reason, the coefficient R^2_{cv}, using a cross-validated method, has been considered to characterize the predictivity of the model.

The cross-validation technique [28] is based on a leave-one-out procedure. For each molecule in the data set, a new multilinear regression is recalculated without changing the descriptors for all compounds in the data set, except this one. Then, the corresponding property value is predicted from this model equation. Finally, R^2_{cv} is calculated by correlating the obtained values for each compound with the experimental ones.

Once a reliable equation is validated, this model can be used to predict the property, for other similar compounds to the selected ones, not yet measured and maybe not yet produced. The results can also help to understand the mechanisms leading to the studied property.

3. Data set selection

The choice of the training set of experimental data is a critical point in a QSPR analysis. Experimental conditions may have a strong influence on the studied properties. Therefore, all experimental values used in the fitting procedure have to be obtained in the same conditions. Differential Scanning Calorimetry (DSC) is often used to characterize the thermal stability of explosive compounds [29]. The experimental property studied in this work is the decomposition enthalpy taken from literature [30]. Our data set is composed of 22 nitroaromatic compounds, known as potentially explosive chemicals [31]. The 22 molecules and their corresponding experimental decomposition enthalpy values are presented in Figure 1 and Table 1.

4. Descriptors

Different types of descriptors (geometric, electronic and energetic) have been selected to describe the 22 molecules. In Table 2 are presented the 14 descriptors calculated among the large number and diversity of those actually used in QSPR methodology [32].

4.1. Local descriptors

In nitro compounds, the carbon-nitrogen bond dissociation is currently considered as a rate-determining step of decomposition [33]. For this reason, we decided to describe this carbon- nitrogen bond and its attached nitro group using geometric, electronic and energetic descriptors.

First, the length of the carbon-nitrogen bond d_{CN} and the charge on the NO_2 functional group were calculated.

Secondly, the mid-point potential V_{mid}, also used as a descriptor [34,35] in the field of energetic materials, was evaluated. This descriptor is an approximation of the electrostatic potential at the midpoint of the carbon-nitrogen bond [36].

$$V_{mid} = \frac{Q_C + Q_N}{0.5 d_{CN}} \qquad (4)$$

where Q_C and Q_N are respectively the atomic charges on carbon and nitrogen atoms.

The C-NO_2 dissociation bond energy (E_{diss}) has already been correlated to the impact sensitivity [37,38] and considered for the estimation of decomposition temperatures [39]. To calculate this energy, an homolytic dissociation of the R-NO_2 molecule is considered:

$$R - NO_2 \rightarrow R^{\bullet} + NO_2^{\bullet} \qquad (5)$$

Finally, the corresponding dissociation energy E_{diss} is calculated as the energy difference between products and reactants:

$$E_{diss} = E(R^{\bullet}) + E(NO_2^{\bullet}) - E(RNO_2) \qquad (6)$$

It is worth being noted that, for polynitroaromatic compounds, these descriptors were extracted for the weakest carbon-nitrogen bond in the molecules considering their dissociation energy.

4.2. Global descriptors

If the previous local descriptors as above defined are specific for nitro compounds, global descriptors present the advantage to be more suitable for extended data sets with compounds without any nitro group. Among such descriptors, the molecular weight M_w was considered. It has also been used in the calculation of the oxygen balance as defined by Shanley et al. [40].

$$OB = \frac{\left[-1600\left(2X + Y/2 - Z\right)\right]}{M_w} \qquad (7)$$

X, *Y* and *Z* are respectively the number of carbon, hydrogen and oxygen atoms in the molecule. This is a traditional empirical descriptor used in hazard prediction related to energetic materials [41].

The atomization energy is the energy needed to break all bonds in the molecule. It can be calculated from the following equation:

$$E_{atomization} = \sum_{i}^{natom} E_i(atom\ i) - E(molecule) \qquad (8)$$

The electronic structure can be described by the dipole moment (DM) and the mean polarizability (α). Dipole moment and polarizability characterize the influence of an external field on the electronic density. The dipole moment is a scalar entity whereas the polarizability is a tensor. The mean polarizability is calculated from the polarizability matrix:

$$\alpha = \frac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right) \qquad (9)$$

where α_{ii} are the diagonal components of the polarizability matrix.

4.3. Conceptual density functional theory descriptors

Global electronic descriptors can also be estimated from conceptual density functional theory [42,43]. This methodology allows to redefine classical chemical reactivity concepts, e.g. electronegativity, in the framework of the density functional theory [44]. The ionisation potential (IP) and the electron affinity (EA) are calculated from the energies of the highest occupied and the lowest unoccupied molecular orbital ε_{HOMO} and ε_{LUMO}, according to the Koopmans theorem [45].

$$IP = -\varepsilon_{HOMO} \qquad (10)$$

$$EA = -\varepsilon_{LUMO} \qquad (11)$$

The electronegativity (χ) characterizing the electron donating property of the system was identified to be the negative of the chemical potential (μ) [46] and therefore:

$$\chi = \frac{(IP + EA)}{2} = -\frac{(\varepsilon_{HOMO} + \varepsilon_{LUMO})}{2} = -\mu \qquad (12)$$

The hardness (η) [47] has been defined similarly to express the resistance of the system to the change in the number of electrons.

$$\eta = IP - EA = \varepsilon_{LUMO} - \varepsilon_{HOMO} \qquad (13)$$

These quantities (eq. 12 and 13) are already used as descriptors for different physico-chemical properties such as heats of formation or boiling points [48].

More recently, Parr et al. [49] constructed the electrophilicity index (ω) to measure the loss in energy for a maximal electron flow from donor to acceptor. This index is proportional to the square of the chemical potential divided by the hardness.

$$\omega = \frac{\mu^2}{2\eta} \qquad (14)$$

This descriptor has already been applied to the prediction of biological activity [50].

5. Computational details

The molecular structures of 22 nitroaromatic compounds have been calculated. For each one, the structures of their phenyl radicals were also computed to access to the carbon-nitrogen bond dissociation energy, the NO_2 radical being of course also calculated. All calculations presented in this work were performed using the Gaussian03 package [51], employing the density functional theory (DFT) with the parameter-free PBE0 [52] hybrid functional. Geometry optimizations of stable species were performed with a 6-31+G(d,p) basis set to describe correctly the geometric structure. Vibrational frequencies were obtained at the same level of theory. The nature of the stationary points was checked by showing no imaginary frequency for our stable structures. The electronic structure of these molecules has been investigated using the natural population analysis (NPA) [53].

The Codessa software [54] has been used to obtain correlation coefficients and the QSPR model (using the integrated Best Multi Linear Regression analysis) for the

prediction of the experimental decomposition enthalpy from the computed descriptors. The significance of each descriptor in the equations was validated by performing a Student t-test validation at a 95% confidence level.

6. Results and Discussion

6.1. Linear correlations

The molecular descriptors, presented above, have been calculated for each molecule of the data set. These data, reported in Table 3, were analyzed to obtain a relationship between the molecular descriptors and the experimental explosibility.

Simple linear fittings were computed between each descriptor and the experimental enthalpy change. Correlations were appreciated from the coefficient R^2 (in Table 3) as shown for the descriptors that provide the best and lowest correlations (see Figure 2), with R^2 of 0.76 for molecular weight and less than 0.01 for mean polarizability respectively.

The local descriptors related to the C-NO_2 bond (presented in paragraph 4.1) do not exhibit any significant correlation with the decomposition enthalpy ($R^2<0.5$). Therefore, a simple and direct breaking of the carbon-nitrogen bond appears to be not sufficient for the description of the decomposition enthalpy. More complex processes might occur [19] and in particular other decomposition paths could exist as experimentally observed [55] and evidenced computationally [56]. Furthermore, major decomposition paths involving interactions between the nitro group and ortho-substituents have been calculated [57,58].

More substantial correlations are exhibited for the molecular weight ($R^2=0.76$), the electrophilicity index (0.75), the electron affinity (0.71) and the oxygen balance (0.64).

It can be noted that these descriptors are auto-correlated. Indeed, the molecular weight and the electron affinity are used in the calculation of the oxygen balance and the electrophilicity index respectively.

Even if significant correlations appear, a single-descriptor approach is not sufficient for the prediction of the experimental property. For instance, considering the molecular weight or oxygen balance, the values of these descriptors do not vary with the position of the substituent. Indeed, ortho, meta and para nitrotoluenes present the same molecular weight (137 g/mol) whereas their decomposition enthalpies are different, i.e. 329, 284 and 318 kJ/mol, respectively. The use of at least one more descriptor is needed to characterize the influence of the substituent position in this case. Therefore, in a next step, multivariable regressions are investigated.

6.2. Multilinear model

All the descriptors previously studied have been integrated in a multivariable analysis using a multilinear regression. The best QSPR model is estimated as the most predictive in term of R^2_{cv}.

The obtained model is a six-parameter equation composed with the hardness, the electrophilicity index, the mean polarizability, the ionization potential, the dipole moment and the dissociation energy.

$$-\Delta H = 33854\,\eta + 40050\,\omega - 1030.3\,\alpha - 33785\,IP + 25.1\,DM - 14.0\;E_{diss} + 973.2 \qquad (15)$$
$$R^2 = 0.91, \quad R^2_{cv} = 0.84$$

First we note that the six descriptors selected by this multilinear fitting procedure are different from the four global descriptors presenting the best linear correlations with the experimental decomposition enthalpy (see paragraph 6.1). The only exception is the

electrophilicity index. The other parameters (Eq.15) are less linearly correlated with the experimental property.

Obviously, 22 molecules are not sufficient to obtain a robust predictive model. However, these results (with a R^2 of 0.91) are promising. For instance, when applied to the evaluation of the decomposition enthalpy of a molecule not included in the training set, as 2,4,6-trinitrotoluene (TNT), the predicted value is 920 kJ/mol which is close to its experimental value (998 kJ/mol [20]). Work is in progress in this direction, but here we stress, once again the difficulty to obtain homogenous experimental data. Moreover, the model gives interesting indications for the future exploration of larger data sets. Indeed, the presence of descriptors arising from the so-called conceptual density functional theory (i.e. η, ω, IP) has to be noticed, all being related to the molecular reactivity. Hence, the characterization of the C-NO_2 bond, through E_{diss} in Eq 15, and the molecular reactivity properties are important parameters for the prediction of decomposition properties like thermal stability.

Furthermore, contrary to classical constitutional descriptors (for instance, the oxygen balance OB), the selected descriptors in the model are able to distinguish between isomers. Hence, a model based only on the number of nitro groups (like Eq. 1) is not sufficient to completely characterize thermal stability of nitroaromatic compounds. Nevertheless this parameter is obviously fundamental. Indeed, the presence of chemical groups indicating explosive properties (e.g. nitro) in chemicals is a pre-evaluation element in chemical safety regulations for substances which may have explosive properties [59]. Besides, mono-, di- and tri-nitroaromatic compounds can be clearly distinguished on figure 3, which represents the calculated values versus the experimental ones. So our model is consistent with this empirical consideration.

7. Conclusion

Nitroaromatic compounds have been modeled using the density functional theory. The aim was to observe correlation between the molecular structure of such compounds and an experimental property of explosibility, the decomposition enthalpy. The electronic and geometric structures were characterized with 14 molecular descriptors. The molecular weight, the oxygen balance, the electron affinity and the electrophilicity index are the descriptors the most correlated with the experimental values of a data set containing 22 nitroaromatic molecules whereas the description of the direct breaking of the carbon nitrogen bond does not seem to be sufficient to describe the energy released during the thermal decomposition of these nitroaromatic compounds. A multivariable model has been established. It consists in a six-parameter equation with promising correlation (R^2=0.91) and predictivity (R^2_{cv}=0.84) coefficients. These first results on the use of descriptors calculated from quantum chemical calculation to develop QSPR models to predict decomposition enthalpy are very encouraging. In particular, parameters characterizing the C-NO_2 bond and the molecular reactivity have demonstrated their pertinence in such a study. Keeping in mind that our data set contains only 22 molecules, a robust model for the prediction of decomposition enthalpy of nitroaromatic compounds can be expected using an extended data set and associating the selected descriptors of this study with other classes of descriptors, e.g. constitutional and topological descriptors.

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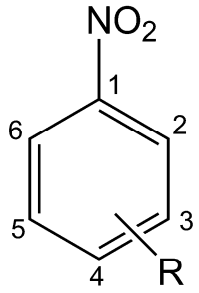
List of figure legends:

Fig. 1. Sketchs of the considered nitroaromatic molecules (see table 1 for the exact nomenclature).



R=NO_2, CH_3, NH_2, COOH, OH, Cl

Fig. 2. Plot of (a) molecular weight and (b) mean polarizability with the experimental decomposition enthalpy.

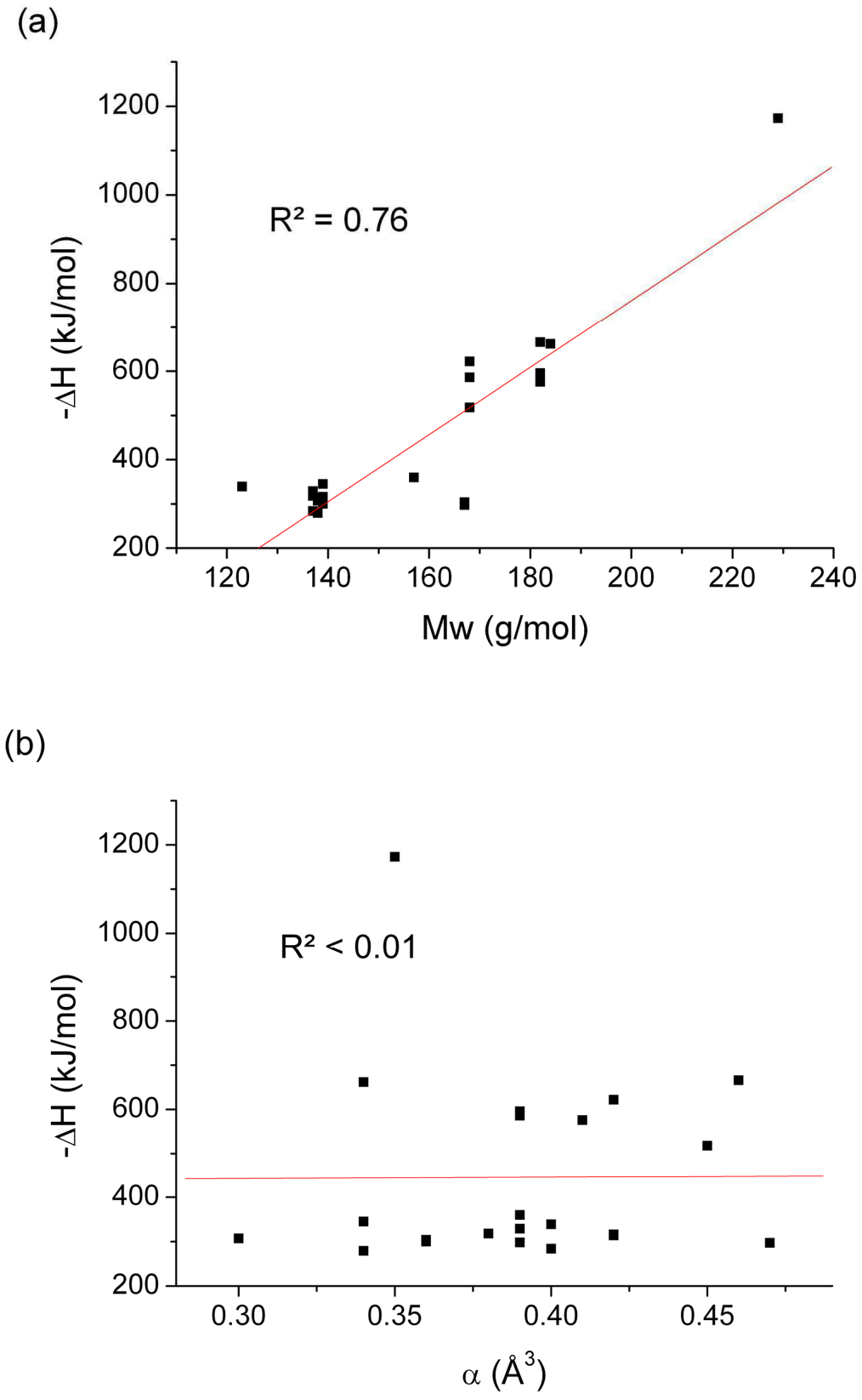


Fig. 3. Calculated vs experimental decomposition enthalpies (kJ/mol).

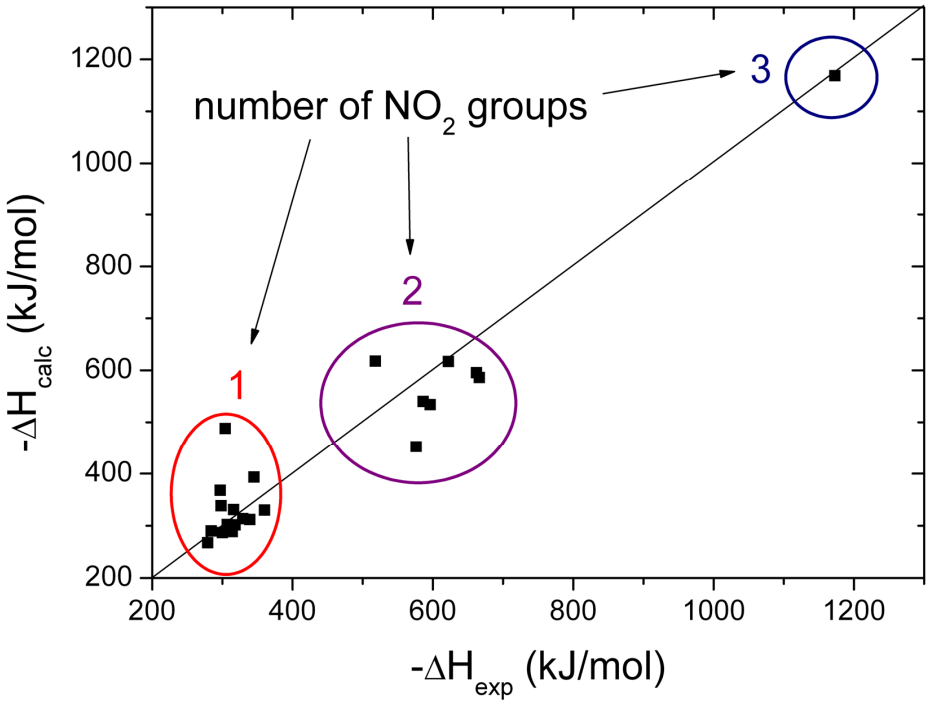


Table 1: Experimental decomposition enthalpies ($-\Delta H_{exp}$/kJ/mol) of the 22 substituted nitrobenzene molecules from [30].

		$-\Delta H_{exp}$
1	nitrobenzene	339
2	1,2-dinitrobenzene	518
3	1,3-dinitrobenzene	586
4	1,4-dinitrobenzene	622
5	2-nitrotoluene	329
6	3-nitrotoluene	284
7	4-nitrotoluene	318
8	2,6-dinitrotoluene	576
9	3,4-dinitrotoluene	666
10	2,4-dinitrotoluene	596
11	2-nitroaniline	307
12	3-nitroaniline	314
13	4-nitroaniline	279
14	2-nitrobenzoic acid	297
15	3-nitrobenzoic acid	298
16	4-nitrobenzoic acid	304
17	2-nitrophenol	345
18	3-nitrophenol	316
19	4-nitrophenol	300
20	1-chloro-4-nitrobenzene	360
21	2,4-dinitrophenol	662
22	2,4,6-trinitrophenol	1173

Table 2: Descriptors.

d_{CN}	carbon nitrogen distance in Å
Q_{NO2}	charge on the nitro group
V_{mid}	mid-point potential in $Å^{-1}$
E_{diss}	carbon nitrogen dissociation energy in a.u.
M_w	molecular weight in g/mol
OB	oxygen balance in percents
E_{atom}	atomization energy in a.u.
DM	dipole moment in D
α	mean polarizability in $Å^3$
IP	ionization potential in a.u.
EA	electron affinity in a.u.
χ	electronegativity in a.u.
η	hardness in a.u.
ω	electrophilicity index in a.u.

Table 3: Descriptors calculated for 22 nitro compounds under study. See table 1 for acronyms and figure 1 for molecules nomenclature.

	d_{CN}[a]	Q_{NO2}[b]	V_{mid}[a]	E_{diss}[a (‡)]	M_w	OB	E_{atom}[a (‡)]	DM[a]	α[a]	IP[a(#)]	EA[a(#)]	χ[a(#)]	η[a(#)]	ω[a(#)]
1	1.467	-0.26	1.64	71.2	123	-163	1497.3	4.832	0.40	0.299	0.097	0.198	0.202	0.097
2	1.467	-0.20	1.74	60.4	168	-95	1666.5	7.000	0.45	0.314	0.117	0.216	0.197	0.118
3	1.470	-0.23	1.65	68.5	168	-95	1676.5	4.458	0.39	0.329	0.122	0.226	0.207	0.123
4	1.472	-0.23	1.71	68.2	168	-95	1676.4	0.000	0.42	0.327	0.136	0.231	0.191	0.140
5	1.446	-0.26	1.65	68.7	137	-181	1778.5	4.542	0.39	0.286	0.091	0.188	0.195	0.091
6	1.467	-0.26	1.66	71.4	137	-181	1778.0	5.196	0.40	0.285	0.094	0.190	0.191	0.094
7	1.462	-0.26	1.61	72.4	137	-181	1778.5	5.567	0.38	0.289	0.092	0.190	0.197	0.092
8	1.468	-0.23	1.68	63.8	182	-114	1950.6	3.071	0.41	0.311	0.110	0.211	0.201	0.111
9	1.468	-0.20	1.78	60.5	182	-114	1948.1	7.722	0.46	0.304	0.112	0.208	0.192	0.113
10	1.469	-0.24	1.68	65.9	182	-114	1955.5	5.177	0.39	0.317	0.115	0.216	0.201	0.116
11	1.441	-0.33	1.45	75.6	138	-151	1663.2	5.026	0.30	0.243	0.087	0.165	0.155	0.088
12	1.468	-0.26	1.71	71.6	138	-151	1660.1	5.904	0.42	0.244	0.090	0.167	0.154	0.091
13	1.448	-0.30	1.49	75.7	138	-151	1662.6	7.472	0.34	0.248	0.080	0.164	0.169	0.080
14	1.466	-0.22	1.77	62.7	167	-120	1862.3	4.259	0.47	0.302	0.101	0.201	0.201	0.101
15	1.468	-0.24	1.63	70.1	167	-120	1870.3	2.815	0.39	0.312	0.106	0.209	0.206	0.106
16	1.470	-0.24	1.57	69.5	167	-120	1869.9	3.762	0.36	0.310	0.115	0.212	0.195	0.116
17	1.460	-0.25	1.49	67.4	139	-132	1589.4	6.091	0.34	0.271	0.086	0.179	0.185	0.086
18	1.469	-0.25	1.70	70.5	139	-132	1594.9	6.066	0.42	0.270	0.096	0.183	0.174	0.096
19	1.455	-0.28	1.54	73.8	139	-132	1596.8	5.504	0.36	0.275	0.090	0.182	0.185	0.090

20	1.464	-0.25	1.62	71.1	157	-122	1480.4	3.299	0.39	0.295	0.104	0.200	0.191	0.104
21	1.463	-0.22	1.53	64.6	184	-78	1769.9	6.289	0.34	0.302	0.110	0.206	0.192	0.111
22	1.466	-0.19	1.56	62.3	229	-45	1951.0	1.757	0.35	0.323	0.149	0.236	0.174	0.160
R^{2} [c]	**0.10**	**0.46**	**0.01**	**0.42**	**0.76**	**0.64**	**0.21**	**0.10**	**0.00**	**0.35**	**0.71**	**0.52**	**0.00**	**0.75**

Distances in Å, dipole moments in D, oxygen balance in %, molecular weight in g/mol, polarizability in $Å^3$, Energies [(‡)] in kcal/mol or [(#)] in u.a.

[a]*at PBE0/6-31+G(d,p) level*

[b]*at PBE0/6-31+G(d,p) level from NPA*

[c]*correlation coefficient for the linear regression with the experimental decomposition enthalpies in table 1*