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New method for assessment of melting points of organic azides using their molecular structures

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ABSTRACT

Organic azides are unstable chemical compounds, which can be easily decomposed or exploded. This work introduces three novel correlations for the prediction of melting point of different types of organic azides containing alkyl azides, alkenyl azides, aryl azides, acyl azides and heteroazide compounds. These models are based on the elemental composition as additive parameter and the contribution of some specific polar groups/structural moieties as non-additive functions. The new correlations have been used for 259 different organic azide compounds including complex molecular structures. The new models were validated by internal and external validation tests where their applicability domains were defined and analyzed. Third correlation, in which the contribution of Specific Polar Groups (SPG) and Inefficient Packing Factor (IPF) beside the number of carbon, hydrogen and nitrogen atoms and the number of azide groups are considered, gives the best predictions. It shows good performances in robustness and predictive power through different validation techniques. It also provides good statistical results and more reliable predictions as compared with two complex methods of the best available computer codes.

1. Introduction

Melting point is an important physical property of a chemical compound, which can be easily measured after its synthesis. It is often used routinely for determination of identity and purity of a newly synthesized compound. The other physicochemical properties of an organic compound such as solubility [1-3], boiling point [4], enthalpy and entropy of melting [5-7] are closely related to its melting point. Melting point of an organic compound can be related to its toxicity because it affects solubility. For slightly soluble compounds, their concentrations in the aqueous environment may be too low to exert toxic effects. Thus, their aqueous solubility are essential be transported to the active site within an organism [8].

Melting point of an organic drug is very important in the pharmaceutical industry for prediction of the bioavailability of drugs [9-12] because it can be used for environmental purposes [13]. The possibility of threats associated with the research investigations of hazardous materials can be decreased by improvement of novel predictive methods. Some new predictive methods have recently been developed for estimations of various thermophysical properties of hazardous compound [7,14-19].

Organic azides are widely used in chemical industries because many of their derivatives have been synthesized. They have a significant position at the interface between chemistry, biology, medicine and materials science [20]. They can be easily transformed into amines, isocyanates and other functional molecules [21,22]. Beside their enormous utility in organic synthesis, the potential hazardous properties of organic azides should be cautiously taken into account. Since organic azides contain high energy molecules, they have been used as energetic polymers or energetic compounds [23,24].

Since reliable prediction of melting point of hazardous compounds is important, different approaches have been developed. Group Contribution (GC) methods can be used to predict the physical and thermodynamic properties of a pure organic compound. They are based on the sum of contributions of small groups. Since melting points of organic hazardous materials depend heavily on the nonadditive structural features such as intermolecular

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List of symbols

AD	Applicability Domain
GC	Group Contribution
APE	Absolute Percent Error
MAPE	Mean Absolut Percent Error
RMSE	Root Mean Square Error
MAE	Mean Absolute Error
LOO	Leave-One-Out
LMO	Leave-Many-Out
CV	Cross-Validation
MLR	Multiple Linear Regression
$T_{m,core}$	The core melting point of an azide compound
$T_{m,core,SPG}$	The melting point of an azide compound by the SPG effects
$T_{m,core,SPG,IPF}$	The melting point of an azide compound by the SPG and *IPF* effects
n_C	The number of carbon atoms
n_H	The number of hydrogen atoms
n_N	The number of nitrogen atoms
n_{azide}	The number of azide groups
SPG	The contribution of Specific Polar Groups that depends on intermolecular interactions
IPF	Inefficient Packing Factor
NNA	Nearest Neighbor Approach
FDA	Food and Drug Administration

interactions and molecular symmetry, the GC methods generally have difficulty in providing reliable estimates of their melting points [25]. Joback–Reid [26] and Jain–Yalkowsky [27] methods are two of well-known group contribution methods. The GC methods cannot be used to predict melting points of organic azides because the contribution of N_3 group has not been defined in these methods. Quantitative structure property relationship (QSPR) and some empirical models have been developed for organic molecules including a number of drugs and/or homologous series [27-30]. Quantum mechanical estimations are the other approaches, which have been applied for simulating solid to liquid phase transitions in energetic compounds [31-34]. These methods have been considered by causing difficulty through simulation because they can form a liquid–solid interface in the presence of the free energy barrier.

This work introduces a new reliable approach for prediction of melting points of organic azides containing alkyl azides, alkenyl azides, aryl azides, acyl azides and heteroazide compounds. The estimated results of the new method are compared with Toxicity Estimation Software Tool (T.E.S.T.) [35] and a variety of Quantitative Structure Activity Relationship (QSAR) methodologies [36], which are based on the method of Food and Drug Administration (FDA) [37] and the Nearest Neighbor Approach (NNA) [36].

2. Materials and method

Melting point of an organic compound depends on the arrangement of atoms and the pairwise group interactions [13,38]. Effective parameters for strength of the crystal lattice contain intermolecular forces, molecular symmetry, and conformational degrees of freedom of a molecule [8]. Moreover, molecular movement in crystals can influence on melting point because it depends on the shape, size of the molecules, orientation of molecules in the crystal and temperature [39]. Many compounds have different melting points because they crystallize in more than one form. They may exhibit the phenomenon of polymorphism, which can be confused with phase transitions. Since molecules containing different crystal forms have distinct heat capacity and melting point, measurements of melting points are affected by the purity of the compound and experimental errors [40].

The study of different organic azides has shown that the elemental composition and number of azide groups have an important contribution for prediction of their melting points. The measured data for 259 of different organic azides containing complex molecular structures and various polar groups were collected from 90 different sources (Supplementary Information). Among these data, 207 and 52 organic azides with different chemical structures and molecular moieties were randomly selected as training set (80%) and test set (20%), respectively, using the Kennard-Stone algorithm technique (Supplementary Information) [41]. Thus, experimental data of organic azides given in training set were used to correlate their elemental composition and the number of azide groups with their melting points through Multiple Linear Regression (MLR) method [42]. Suitable correlation can be given as follows:

$$T_{m,core} = 302.28(\pm 10.27) + 7.51(\pm 1.22)n_C - 2.61(\pm -0.80)\, n_H + 19.37(\pm 2.84)n_N - 65.44(\pm 11.78)n_{azide} \quad (1)$$

where $T_{m,core}$ is the core melting point of an azide compound in K; n_C, n_H and n_N are the number of carbon, hydrogen and nitrogen atoms, respectively; and n_{azide} is the number of azide groups. The number of oxygen, halogen and silicon atoms has insignificant contribution in Eq. (1) because their existences do not change the coefficient of determination or r^2 values of Eq. (1).

The existence of some specific polar groups can increase melting point of organic energetic compounds [14,43-45]. It was found that the existence of some specific molecular moieties may enhance intermolecular attractions, which can increase melting points of these compounds. The effects of the specific polar groups can be considered through the following re-optimized correlation using MLR method [42] as:

$$Tm,core,SPG = 265.00(\pm 7.85) + 10.34(\pm 0.89)nC - 4.11(\pm 0.59)\, nH + 19.39(\pm 2.04)nN - 57.44(\pm 8.48)nazide + 49.46(\pm 3.58)SPG \quad (2)$$

where *SPG* is the contribution of Specific Polar Groups that depends on intermolecular interactions for increasing melting point on the basis of elemental composition; $T_{m,core,SPG}$ is also the melting point of an azide compound in K by considering the effects of *SPG*. Table 1 shows different values of *SPG* containing a list of polar functional groups and molecular fragments. Since the coefficient of *SPG* in Eq. (1) has positive sign, inclusion of desired *SPG* can enhance melting point of an organic azide compound.

Another correcting function can be considered for those organic azide compounds that do not have any polar groups. Since the attachment of azide group to nonpolar carbocyclic aromatic compound can reduce planarity of molecule, inclusion of this factor can reduce melting point of this category of organic azide compounds. This factor can be added to Eq. (2) as Inefficient Packing Factor (*IPF*) through the following re-optimized correlation using MLR method [42] as: