Toward the Toxicology of Some Nitro-Compounds

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Abstract: Nitro-compounds are widely used in medicine, agriculture and industry. Their toxicity issues attract more and more attention. There are a lot of factors influencing toxicity, and the degrees are different from one another. Some physical properties of compounds, such as the surface properties, may play crucial roles in the toxicity of these compounds. Twenty seven parameters of twenty eight nitro-compounds, including molecular size related parameters, molecular surface electrostatic potential based parameters, solubility parameters, molecular cohesive energies, surface tensions, dielectric constants and Mulliken charges of nitro groups, were considered to correlate with toxicity (semi-lethal dose, \(LD_{50}\)) of the nitro-compounds. Fourteen parameters with higher correlation coefficients were selected to join in the modelling process of heredity and variation (genetic function approximation), further screening toxicity related parameters, the screened parameters are molecular surface electrostatic potentials based \(\sigma^2\), \(\sigma^2\), \(\nu\sigma^2\), \(A^+_\), \(\bar{V}_{g}\), Log \(P_{ow}\), and nitro group’s Mulliken charges \(q_{NO}\). Building the linear relation between toxicity and these screened parameters, and quantitatively studying the toxicity of nitro-compounds, this work may help us evaluate health risks and approach the toxicology of nitro-compounds.

Keywords: Acute toxicity test; semi-lethal dose; electrostatic potentials; genetic function approximation; toxicology

1 Introduction

Nitroaromatic compounds are widely used in medicine, industry and agriculture. Nitroaromatic pesticides and explosive residues are considered as being toxic environmental pollutants [1]. Therefore, it is very important to study the toxicity of nitro containing compounds.

The toxicity studies cover a wide field, ranging from carcinogenesis, the whole body system (reproductive system, immune system, nervous system, digestive system, respiratory system, cardiovascular system, dermal system, endocrine system, the individual viscera (liver, kidney, belly, et al.), to acute toxicity test.

Acute toxicity test, also called single dose acute toxicity test, is a kind of toxic reaction of the animal subject one or many times tests per 24 hr (6-8hr interval between two tests), including the general behaviours, the changes of appearance, the changes of gross morphology and death effects, which is characterized half lethal dose \((LD_{50})\) in unit of mg/kg. The higher is the \(LD_{50}\), the lower is the toxicity.

The toxicology of nitro-compounds is not well known so far, some investigators argued that covalent addition reactions between metabolic intermediates of nitro-compounds and cell proteins is the mechanism of toxication [2~4].

The cytotoxic, mutagenic and carcinogenic properties of nitroaromatic environmental pollutants are frequently related to their electron-accepting properties [1,5]. Chung et al explored the influences of nitro group on genomic mutation and toxicity [6].

In the past few years, quantitative structure-activity relationship (QSAR) [7~9] plays more and more important role in the study of the relationship between the molecular structures of chemicals and their bioactivities, which can be used to quickly predict biotoxicities of newly found or synthesized compounds.

Hansch et al proposed Hansch-Fujita model and turned a new page of QSAR or QSPR [10,11] in the research of activities of compounds. By the beginning of twentieth century, it is commonly believed that bioactivities of compounds are mainly determined by their physical properties, including vapor pressure,
Henry's law constants, water solubility, octanol/water partition coefficients, heats of formation and ionization potentials of explosive TNT [12], acidity and basicity of hydrogen bond, solubility, surface tension, dipole moment, refractive index and dielectric constant [13], solid, liquid and gaseous enthalpies of formation in terms of molecular electrostatic potentials [14], density, vaporization enthalpy, heat capacity, surface tension, isothermal compressibility and dielectric constant [15–18], the role of polarization in the interaction between chemistry and biology [19]. Nano toxicology also begins to attract more and more attention with the fast development of nano technology in recent years [20].

In this work the correlation between toxicity of 28 kinds of nitro compounds and their properties were studied, which include molecular volume, superficial area, enthalpy of vaporization, density of cohesive energy, solubility parameter, polarizability, dipole moment, dielectric constant, surface tension, charge distribution of nitro groups, molecular surface electrostatic potential based functions, and solubility parameters, surface tension, dipole moment and molecular surface electrostatic potentials based parameters were screened to build the relationship with LD50.

2 Theory

Molecular electrostatic potential and related equations proposed by Politzer [21] were displayed in formulas (1) to (8):

\[ V(r) = \sum_{A} \frac{Z_{A}}{|r - r'|} - \int \frac{\rho(r')dr'}{|r - r'|} \]  

(1)

where \( V(r) \), \( Z_{A} \) and \( \rho(r) \) denote electrostatic potential, charge on A nucleus located at \( R_{A} \) and electron density, respectively. The relative properties are defined as \( P = f[A_{s}, A^{+}_{s}, A^{-}_{s}, V_{S}^{+}, V_{S}^{-}, V_{S}, II, \sigma_{s}^{2}, \sigma_{s}^{+}, \sigma_{s}^{-}, V, \sigma_{s}^{2}, V_{S_{min}}, V_{S_{max}}] \), where \( A_{s}, A^{+}_{s} \) and \( A^{-}_{s} \) are molecular total surface area, electropositive surface area and electronegative surface area, respectively. \( V_{S_{min}}, V_{S_{max}} \) and \( II \) are the minimum surface electrostatic potential, maximum surface electrostatic potential and average deviation of surface electrostatic potential at \( r \) point, respectively [22].

\[ \sigma_{s}^{2} = \sigma_{s}^{2} + \sigma_{s}^{2} = \frac{1}{r} \sum_{i=1}^{r} \left[ V_{S}^{+}(r_{i}) - V_{S}^{-}(r_{i}) \right]^{2} + \frac{1}{s} \sum_{j=1}^{s} \left[ V_{S}^{+}(r_{j}) - V_{S}^{-}(r_{j}) \right]^{2} \]  

(2)

\[ V_{S}^{+}(r_{i}) = \frac{1}{r} \sum_{i=1}^{r} V_{S}^{+}(r_{i}) \quad V_{S}^{-} = \frac{1}{s} \sum_{j=1}^{s} V_{S}^{-}(r_{j}) \]  

(3)

where \( \sigma_{s}^{2} \) and \( \sigma_{s}^{2} \) are positive and negative standard deviation of molecular electrostatic potential respectively, \( \sigma_{s}^{2} = \sigma_{s}^{2} + \sigma_{s}^{2} \). \( V_{S}^{+}(r_{i}) \) and \( V_{S}^{-}(r_{j}) \) are positive and negative electrostatic potential located at \( r_{i} \) and \( r_{j} \), respectively. \( II \) is the average deviation of \( V(r) \) on the molecular surface, interpreted as the local polarity, or internal charge separation.

\[ \nu = \frac{\sigma_{s}^{2} \sigma_{s}^{2}}{[\sigma_{s}^{2}]^{2}} \]  

(4)

\[ II = - \frac{1}{2} \sum_{i=1}^{r} \left[ V(r_{i}) - V_{S} \right] \]  

(5)

Enthalpy of vaporization, coefficient of diffusion and water/oil partition coefficient [23–25] are derived from molecular surface electrostatic potentials, expressed as formulas (6)–(8).

\[ H^{\phi} = 1.355A_{S}^{65} + 1.176(\nu \sigma_{s})^{65} - 10.433 \]  

(6)

\[ D \times 10^{7} (\text{cm}^{2}/\text{s}) = 533.5(A_{S})^{-1} - 0.03168\sigma_{s}^{2} + 0.01425\sigma_{s}^{2} - 1.620 \]  

(7)

\[ \log P_{sat} = 0.03A_{S} - 0.00472N_{s}^{0.5} - 0.000963A_{S}^{0.5} - 0.504 \]  

(8)

The cohesive energy \( E_{coh} \) [26] of a substance in a condensed state is defined as the increase in internal energy \( U \) (in J/mol) per mole of substance if all the intermolecular forces are eliminated:
The cohesive energy \( E_{coh} = \Delta U \) (9)

Solubility parameter \( \delta = \left( \frac{E_{coh}}{V} \right)^{0.5} = \left( \frac{\Delta_{vap} H - RT}{V} \right)^{0.5} \) (10)

where \( V \) is van der Waals volume of a specific molecule.

Molecular polarizability proposed by Hansch [27] is defined as Eqn. (11):

\[
a(0)[\AA^3 / \text{molecule}] = 0.27 (\pm 0.011) NVE
\]

where \( \alpha(0) \) and \( NVE \) are volume of polarization and molecular total valence electrons, respectively. The relationship between surface tension and solubility parameter [28] of a compound can be expressed as Eqn. (12):

\[
\gamma = a\delta^2 V_m^{\alpha V} + b
\]

where empirical parameter \( a \) and \( b \) are 0.0145 and -24.283, obtained from linear fitting method.

Dielectric constants \( (\varepsilon^{at}) \) of the compounds are obtained from the fitting method in terms of electrostatic potential parameters and solubility parameters.

\[
\varepsilon^{at} = f(\delta, \delta \sigma_{tot}^{20.45})
\]

Mulliken charges of nitro groups were computed according to Eqn. (14).

\[
q_{NO} = q_{N} + q_{O(1)} + q_{O(2)}
\]

3 Computational Details

Molecular structure optimization were carried out by hybrid density function theory B3LYP/6-31G(d,p) [29,30], molecular van der Waals volumes, surface areas and surface electrostatic potentials were calculated by multifunctional wave function code Multiwfn [31]. Surface tensions and solubility parameters were fitted with the combined parameter \( \delta^2 V_m^{\alpha V} \) in terms of the literature method [28], the fitted squared-\( R \) (correlation coefficient) reaches 0.9803, which were displayed in Table 1.

Table 1. The calculated electrostatic potential based parameters \( (\sigma_{tot}^2, \sigma_e^2, \sigma_s^2, v, \Delta_{vap} H^o) \), solubility parameters \( (\delta) \), volums \( (V_m) \), molecular areas \( (A_s) \), cohesive energies \( (E_{coh}) \) and the predicted surface tensions \( (\gamma) \).

| \( V_m \) | \( A_s \) | \( \sigma_{tot}^2 \) | \( \sigma_e^2 \) | \( \sigma_s^2 \) | \( v \) | \( \Delta_{vap} H^o \) | \( E_{coh} \times 10^4 \) | \( \delta \) | \( \delta^2 V_m^{\alpha V} \) | \( \gamma \) |
|---|---|---|---|---|---|---|---|---|---|---|
| Et | 39.300 | 83.755 | 3.592 | 3.156 | 0.441 | 0.1079 | 2.700 | 1.378 | 18.722 | 1828.863 | 1.034 |
| Propane | 53.669 | 105.309 | 3.409 | 2.844 | 0.565 | 0.1383 | 4.279 | 2.038 | 19.488 | 2279.870 | 7.571 |
| Butane | 67.601 | 126.571 | 3.146 | 2.589 | 0.558 | 0.1460 | 5.608 | 2.594 | 19.590 | 2555.923 | 12.530 |
| Benzene | 69.486 | 125.463 | 36.835 | 10.041 | 26.794 | 0.1983 | 7.923 | 3.563 | 22.644 | 3457.483 | 28.800 |
| BA | 78.725 | 139.236 | 147.932 | 101.752 | 46.180 | 0.2147 | 12.183 | 5.345 | 26.057 | 4842.833 | 44.880 |
| BP | 75.077 | 134.099 | 151.855 | 112.261 | 39.594 | 0.1928 | 11.621 | 5.110 | 26.089 | 4752.181 | 40.900 |
| MeB | 83.468 | 146.282 | 38.282 | 8.291 | 29.991 | 0.1697 | 8.953 | 3.994 | 21.874 | 3503.809 | 28.540 |
| PD | 65.709 | 120.416 | 127.074 | 24.746 | 102.328 | 0.1568 | 9.685 | 4.300 | 25.582 | 4303.286 | 37.120 |
| NB | 86.985 | 150.292 | 155.002 | 48.976 | 106.026 | 0.2161 | 12.985 | 5.185 | 24.542 | 4472.365 | 43.900 |

Note: Parameters \( V_m, A_s, \sigma_{tot}^2, \sigma_e^2, \sigma_s^2, \Delta_{vap} H^o, E_{coh}, \delta, \gamma \) are in unit of \( \text{cm}^3/\text{mol}, \AA^2, (\text{kcal/mol})^2, (\text{kcal/mol})^2, (\text{kcal/mol})^2, \text{kcal/mol, J/mol, J/cm}^3/\text{V}^{1/2}, \text{mN/m, respectively.} \)

The experimental surface tensions in Table 1 were taken from the data of 20°C [32]. Dielectric constants of these compounds were calculated according to the fitted genetic function approximation method, and the fitted equation was expressed as follows:

\[
\varepsilon^{at} = -3.861 X1 + 14.859 R (23.757-X1) + 33.657 R (23.316-X2) + 163.068, X1=\delta, X2=\delta^2 \sigma_{tot}^{20.45}.
\]

The experimental dielectric constants [32] were listed in Table 2, and the square of the fitted linear correlation coefficient reaches 0.9979.
\[ \varepsilon^{od} = -3.861 \times 10^{-4} \hat{R} (23.757 - X_1) + 33.657 \hat{R} (23.316 - X_1) - 0.034 \hat{R} (5492.795 - X_2) + 163.068, \]

\[ X_1 = \delta, \quad X_2 = \sigma_{\text{tot}}. \]

**Table 2.** The calculated electrostatic potential based parameters, solubility parameters, molecular volumes, cohesive energies, the number of valence electrons, dipole moments, Mulliken charges of nitro groups and the predicted dielectric constants.

|     | m-DNB | m-NTul | NB | NEt | NMe | o-NTul | p-NBA | p-NTul | TNT |
|-----|-------|--------|----|-----|-----|--------|-------|--------|-----|
| \( V_m \) | 102.942 | 99.791 | 86.085 | 56.530 | 42.563 | 99.085 | 95.339 | 99.864 | 132.754 |
| \( A_e \) | 175.830 | 171.182 | 150.292 | 110.544 | 98.912 | 167.152 | 163.927 | 171.128 | 216.994 |
| \( \sigma_{\text{tot}} \) | 96.386 | 158.003 | 155.002 | 101.578 | 107.300 | 158.479 | 361.630 | 165.486 | 91.350 |
| \( \sigma_+^2 \) | 49.823 | 33.540 | 48.976 | 35.642 | 47.327 | 35.360 | 188.916 | 35.673 | 61.362 |
| \( \sigma_-^2 \) | 46.563 | 124.463 | 106.026 | 65.936 | 59.973 | 103.119 | 172.714 | 129.813 | 29.989 |
| \( \nu \) | 0.2497 | 0.1672 | 0.2161 | 0.2278 | 0.2465 | 0.1452 | 0.2495 | 0.1691 | 0.2205 |
| \( \Delta_{\text{vap}} H^o \) | 53.18 | 53.34 | 5.185 | 3.714 | 3.290 | 5.077 | 7.319 | 5.406 | 5.946 |
| \( \sigma_+^2 \) | 22.730 | 23.119 | 24.542 | 25.633 | 27.803 | 22.636 | 27.708 | 23.267 | 21.164 |
| \( \alpha(0) \) | 16.74 | 14.04 | 12.42 | 8.10 | 6.48 | 14.04 | 14.04 | 14.04 | 22.68 |
| \( \mu \) | 4.198 | 4.889 | 4.557 | 3.599 | 3.488 | 4.304 | 7.577 | 5.237 | 1.546 |
| \( \varepsilon \) | 3.82 | 3.84 | 3.67 | 3.48 | 3.40 | 3.26 | 5.00 | 3.78 | 2.20 |
| \( q_{\text{NO}_2} \) | -0.372 | -0.410 | -0.406 | -0.310 | -0.303 | -0.425 | -0.462 | -0.417 | -0.355 |

Note: \( V_m, A_e, \sigma_{\text{tot}}, \sigma_+^2, \sigma_-^2, \Delta_{\text{vap}} H^o, E_{\text{diss}}, \delta, \sigma_2, \nu, q_{\text{NO}_2} \) are in unit of cm³/mol, Å², (kcal/mol)², (kcal/mol)², kcal/mol, J/mol, (J/cm³)¹/², Å, Debye, a.u., respectively.

The molecular electrostatic potential related parameters derived from Equations (1)–(8) were carried out by *Multiwfn* code [31]. The correlation between \( LD_{50}^\text{exp} \) and these parameters was computed by Equation (15).

**Table 2.** The calculated electrostatic potential based parameters, solubility parameters, molecular volumes, cohesive energies, the number of valence electrons, dipole moments, Mulliken charges of nitro groups and the predicted dielectric constants.

**4 Results and Discussion**

A series of physical parameters in terms of formula in theoretical and computational part of 28 nitro-compounds were obtained and displayed in Table 3, and the correlation coefficients between \( LD_{50}^\text{exp} \) and the calculated parameters were listed at the end of Table 3 to Table 6.
Table 3. The correlation prediction between $LD_{50}^{exp}$ [34] and 6 parameters.

| Compound | $LD_{50}^{exp}$ | $V_m$ | $\sigma_{ Benton}^2$ | $\sigma_{ total}^2$ | $\sigma_{+}^2$ | $\sigma_{-}^2$ | $\Delta^\circ_v$H | Corr. |
|----------|----------------|------|----------------|----------------|----------------|----------------|----------------|-------|
| 1-Cl-2-NB | 0.27 | 98.169 | 150.470 | 56.752 | 93.718 | 0.2349 | 14.009 | 0.998 |
| 1-Cl-4-NB | 0.81 | 98.723 | 138.575 | 44.362 | 94.213 | 0.2176 | 13.636 | 0.996 |
| 23-DNTul | 1.12 | 116.538 | 103.441 | 49.110 | 54.330 | 0.2494 | 14.324 | 0.995 |
| 24-DNBP | 0.035 | 107.659 | 101.031 | 49.080 | 51.951 | 0.2498 | 13.750 | 0.994 |
| 24-DNTul | 0.27 | 115.928 | 90.376 | 58.714 | 51.874 | 0.2445 | 14.911 | 0.993 |
| 25-DNTul | 0.71 | 115.882 | 75.370 | 29.208 | 46.162 | 0.2374 | 13.356 | 0.992 |
| 26-DNTul | 0.18 | 115.462 | 94.799 | 49.013 | 45.786 | 0.2497 | 13.980 | 0.991 |
| 2-NI | 0.08 | 70.698 | 271.968 | 169.513 | 102.456 | 0.2348 | 14.466 | 0.990 |
| 34-DNTul | 1.07 | 116.849 | 108.690 | 49.041 | 59.649 | 0.2476 | 14.649 | 0.989 |
| TNBP | 0.6 | 124.621 | 134.646 | 96.680 | 37.966 | 0.2025 | 15.205 | 0.988 |
| m-DNB | 0.01 | 102.942 | 96.386 | 49.823 | 46.563 | 0.2497 | 13.304 | 0.987 |
| m-NBA | 0.54 | 95.209 | 278.126 | 150.506 | 127.620 | 0.2483 | 16.693 | 0.986 |
| m-NTul | 1.07 | 99.791 | 158.003 | 33.540 | 124.463 | 0.1672 | 13.340 | 0.985 |
| NB | 0.75-1.0 | 86.085 | 155.002 | 48.976 | 106.026 | 0.2161 | 12.985 | 0.984 |
| NBu | 0.50-0.75 | 84.602 | 95.743 | 26.386 | 69.357 | 0.1996 | 11.507 | 0.983 |
| NEt | 1.10 | 56.530 | 101.578 | 35.642 | 65.936 | 0.2278 | 9.470 | 0.982 |
| NMe | 1.44 | 42.563 | 93.627 | 25.681 | 67.945 | 0.1990 | 10.231 | 0.981 |
| o-NBA | 3.56 | 94.144 | 235.101 | 105.549 | 129.552 | 0.2474 | 15.711 | 0.980 |
| o-NB | 2.828 | 91.571 | 297.564 | 182.109 | 115.455 | 0.2374 | 16.536 | 0.979 |
| o-NTul | 2.14 | 99.864 | 165.486 | 35.673 | 129.813 | 0.1691 | 13.514 | 0.978 |
| Tetryl | 0.5 | 159.537 | 144.080 | 105.549 | 34.668 | 0.1452 | 12.727 | 0.977 |
| TNT | 0.48 | 132.754 | 91.350 | 61.362 | 29.989 | 0.2205 | 14.805 | 0.976 |
| LLM-105 | 2.000 | 118.130 | 187.285 | 109.731 | 77.554 | 0.2426 | 16.186 | 0.975 |

Note: $LD_{50}^{exp}$, $V_m$, $\sigma_{ Benton}^2$, $\sigma_{ total}^2$, $\sigma_{+}^2$, $\sigma_{-}^2$, $\Delta^\circ_v$H are in unit of g/kg, cm$^3$/mol, Å$^2$, (kcal/mol)$^2$, (kcal/mol)$^2$, (kcal/mol)$^2$, kcal/mol, respectively. a, b, c, d denote, mouse, rabbit, dog and cat, respectively.

Table 4. 8 parameters in relation to $LD_{50}^{exp}$.

| Compound | $E_{coh} \times 10^{-4}$ | $\delta$ | NVE | $\alpha(0)$ | $\mu$ | $\epsilon$ | $\delta^2 V_m^{1/34}$ | $\gamma$ |
|----------|----------------|------|-----|-----------|-----|------|----------------|-----|
| 1-Cl-2-NB | 5.613 | 23.913 | 52 | 14.04 | 5.032 | 39.29 | 4504.604 | 41.034 |
| 1-Cl-4-NB | 5.457 | 23.512 | 52 | 14.04 | 2.922 | 17.45 | 4365.836 | 39.022 |
| 23-DNTul | 5.745 | 22.204 | 68 | 18.36 | 6.586 | 12.82 | 4195.395 | 36.550 |
| 24-DNBP | 5.505 | 22.613 | 68 | 18.36 | 3.378 | 6.47 | 4198.934 | 36.602 |
| 24-DNTul | 5.572 | 21.924 | 68 | 18.36 | 4.843 | 11.05 | 4080.603 | 34.886 |
| 25-DNTul | 5.340 | 21.467 | 68 | 18.36 | 0.885 | 10.76 | 3911.559 | 32.435 |
| 26-DNTul | 5.601 | 22.026 | 68 | 18.36 | 2.956 | 11.57 | 4111.202 | 35.329 |
| 2-NI | 5.805 | 28.654 | 42 | 11.34 | 5.544 | 52.42 | 5579.608 | 56.621 |
| 34-DNTul | 5.881 | 22.435 | 68 | 18.36 | 7.308 | 11.98 | 4288.283 | 37.897 |
| TNBP | 6.114 | 22.149 | 84 | 22.68 | 1.786 | 25.30 | 4302.534 | 38.104 |
| m-DNB | 5.318 | 22.730 | 62 | 16.74 | 4.198 | 2.80 | 4157.819 | 36.005 |
| m-NBA | 6.736 | 26.600 | 52 | 14.04 | 5.996 | 60.35 | 5497.54 | 55.431 |
| m-NTul | 5.334 | 23.119 | 52 | 14.04 | 4.899 | 23.80 | 4241.595 | 37.220 |
| NB | 5.185 | 24.542 | 46 | 12.42 | 4.557 | 35.70 | 4472.365 | 43.900 |
| Compound | LD | Vs,min | Vs,max | As | As* | Vs | Vs* | Corr |
|----------|----|--------|--------|----|-----|-----|-----|-----|
| 1-Cl-2-NB | 0.27 | -32.190 | 26.761 | 165.851 | 103.118 | 62.733 | 1.809 | 0.2912 |
| 1-Cl-4-NB | 0.81 | -30.247 | 25.312 | 168.939 | 111.084 | 57.256 | 2.936 | 0.4566 |
| 23-DNTul | 1.12 | -30.132 | 30.378 | 192.176 | 116.302 | 75.874 | 3.801 | -0.2346 |
| 24-DNBP | 0.035 | -28.017 | 35.737 | 198.190 | 109.672 | 72.235 | 1.563 | 0.4411 |
| 24-DNTul | 0.27 | -27.936 | 30.561 | 192.820 | 120.242 | 72.578 | 1.752 | 0.5473 |
| 25-DNTul | 0.71 | -26.020 | 26.231 | 192.792 | 122.262 | 70.530 | 1.921 | 0.5100 |
| 26-DNTul | 0.18 | -25.924 | 29.404 | 190.292 | 117.035 | 79.192 | 1.678 | 0.5060 |
| 2-NI | 0.08 | -39.949 | 56.771 | 130.884 | 72.305 | 58.580 | 1.752 | 0.5100 |
| 34-DNTul | 1.07 | -31.012 | 30.539 | 196.228 | 117.035 | 79.192 | 2.811 | 0.4411 |
| TNBP | 0.6 | -23.403 | 41.362 | 207.047 | 116.117 | 90.930 | 5.942 | 0.4411 |
| m-DNB | 0.01 | -26.105 | 31.540 | 175.830 | 103.652 | 72.178 | 3.952 | 0.4411 |
| m-NBA | 0.54 | -36.170 | 47.384 | 164.022 | 81.670 | 82.351 | 1.101 | 0.4411 |
| m-NTul | 1.07 | -33.993 | 22.297 | 171.182 | 114.510 | 56.672 | 2.034 | 0.4411 |
| NB | 0.85 | -32.983 | 25.334 | 150.292 | 100.930 | 49.362 | 1.785 | 0.4411 |
| NBu | 0.65 | -32.828 | 24.942 | 153.706 | 110.197 | 43.508 | 3.325 | 0.4411 |
| NEt | 1.10 | -31.882 | 30.561 | 192.176 | 116.302 | 75.874 | 2.034 | 0.4411 |
| NMe | 1.44 | -30.789 | 29.713 | 89.812 | 67.801 | 42.734 | 2.412 | 0.4411 |
| NPr | 0.65 | -32.983 | 25.334 | 150.292 | 100.930 | 49.362 | 1.785 | 0.4411 |
| o-NBA | 3.56 | -36.470 | 46.908 | 160.667 | 86.739 | 74.288 | 1.535 | 0.4411 |
| o-NBP | 2.828 | -38.030 | 61.879 | 157.862 | 93.308 | 64.584 | 1.169 | 0.4411 |
| o-NTul | 0.89 | -33.789 | 22.057 | 167.152 | 110.826 | 56.325 | 1.563 | 0.4411 |
| p-DNB | 0.0294 | -24.801 | 28.378 | 175.599 | 105.341 | 70.256 | 4.312 | 0.4411 |
| p-NBP | 3.25 | -40.397 | 50.522 | 163.927 | 85.016 | 78.911 | 1.151 | 0.4411 |
| p-NTul | 0.616 | -35.396 | 64.590 | 158.990 | 99.666 | 59.324 | 1.938 | 0.4411 |
| Tetryl | 2.14 | -34.575 | 21.802 | 171.128 | 114.284 | 56.844 | 2.176 | 0.4411 |
| TNT | 0.48 | -21.892 | 35.556 | 216.994 | 125.037 | 91.956 | 5.674 | 0.4411 |
| LLM-105 | 2.00 | -38.313 | 44.554 | 196.467 | 108.710 | 87.756 | 3.206 | 0.4411 |

Note: \( V_{s,\text{min}}, V_{s,\text{max}}, A_s, A_s^*, V_{s}, V_{s}^*, \sigma_{\text{tot}}, \Pi \) are in unit of kcal/mol, kcal/mol, Å^2, Å^2, kcal/mol, kcal/mol, kcal/mol, (kcal/mol)^2, kcal/mol, respectively.
Table 6. 3 electrostatic potential parameters and 4 other parameters in relation to $LD_{50}^{exp}$.

|       | $\vec{V}_s$ | $\nu \sigma_{mol}^2$ | $\Pi$ | $D \times 10^7$ | $N$ | Log $P_{OW}$ | $q_{SO_2}$ |
|-------|-------------|-----------------------|-------|-----------------|-----|--------------|-------------|
| 1-Cl-2-NB | -14.974     | 35.347                | 12.735| 1.134           | 5   | 0.226        | -0.391      |
| 1-Cl-4-NB | -12.733     | 30.160                | 10.796| 1.475           | 5   | 0.584        | -0.402      |
| 23-DNTul | -18.402     | 25.794                | 16.183| 0.374           | 10  | -0.298       | -0.350      |
| 24-DNBP  | -12.995     | 25.237                | 14.551| 0.666           | 10  | 0.130        | -0.384      |
| 25-DNTul | -14.189     | 17.889                | 13.460| 0.880           | 10  | 0.602        | -0.379      |
| 26-DNTul | -14.499     | 23.672                | 13.716| 0.283           | 10  | 0.530        | -0.392      |
| 2-NI     | -19.704     | 63.859                | 19.243| -1.454          | 7   | -2.388       | -0.425      |
| 34-DNTul | -18.674     | 26.914                | 17.382| 0.395           | 10  | -0.717       | -0.359      |
| TNBP     | -11.414     | 27.494                | 15.731| -1.565          | 17  | -0.476       | -0.344      |
| m-DNB    | -14.498     | 21.069                | 15.276| 0.499           | 5   | 1.085        | -0.372      |
| m-NB     | -13.632     | 69.061                | 14.822| -1.317          | 6   | -1.539       | -0.417      |
| m-NTul   | -15.638     | 26.420                | 11.830| 2.202           | 10  | -0.256       | -0.410      |
| NB       | -16.774     | 33.501                | 12.331| 1.889           | 5   | -0.282       | -0.406      |
| NBu      | -19.138     | 19.114                | 12.773| 2.003           | 5   | 0.580        | -0.325      |
| NEt      | -18.782     | 23.136                | 16.429| 3.016           | 5   | -0.493       | -0.310      |
| NMe      | -18.386     | 26.452                | 19.293| 3.675           | 5   | -0.894       | -0.303      |
| NPr      | -19.006     | 18.637                | 14.470| 2.566           | 5   | 0.018        | -0.324      |
| o-NBA    | -12.927     | 58.162                | 13.068| 0.203           | 6   | -1.375       | -0.496      |
| o-NBP    | -18.853     | 77.844                | 16.421| -1.172          | 7   | -3.258       | -0.418      |
| o-NTul   | -14.646     | 27.471                | 10.999| 1.921           | 5   | 0.306        | -0.425      |
| p-DNB    | -13.594     | 20.708                | 14.486| 0.781           | 10  | 0.267        | -0.374      |
| p-NB     | -16.135     | 90.226                | 16.680| -1.889          | 6   | -3.110       | -0.462      |
| p-NTul   | -16.009     | 27.983                | 12.228| 2.217           | 5   | -0.449       | -0.417      |
| Tetryl   | -10.672     | 26.326                | 15.636| -2.476          | 21  | -0.172       | -0.131      |
| TNT      | -10.793     | 20.144                | 14.33 | -0.678          | 15  | 0.888        | -0.355      |
| LLM-105  | -16.906     | 45.439                | 18.068| -1.276          | 16  | -3.885       | -0.3925     |
| Corr.    | -0.1735     | 0.5444                | 0.0630 | -0.03381        | -0.6047 | -0.3860       |

Note: $D$ is in unit of cm$^2$/s.

Table 7. The arrangement of correlation coefficients in descending order.

| Para. $\sigma$ $\nu$ $\sigma_{mol}$ $\Pi$ $\sigma^2_{tot}$ $\nu \sigma^2_{tot}$ $\vec{V}_s$ $\delta^2 \nu_\sigma^{1.45}$ $\gamma$ |
|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| $\sigma^2$ | 0.6814 | 0.6047 | 0.5745 | 0.5623 | 0.5473 | 0.5444 | 0.5374 | 0.5100 | 0.5060 |
| $\mu$ $q_{SO_2}$ $\sigma^2$ $A^+_S$ $E_{sa}$ $A_{sp} H^0$ $V_{S,max}$ NVE |
| $\sigma^2$ | 0.4566 | 0.4411 | 0.3860 | 0.3569 | 0.3005 | 0.2912 | 0.2911 | 0.2846 | 0.2346 |
| $\nu \sigma^2_{mol}$ $\Pi$ $A^+_S$ $\nu$ $D$ |
| $\sigma^2$ | 0.2346 | 0.2131 | 0.1852 | 0.1735 | 0.1135 | 0.0630 | 0.0576 | 0.0439 | 0.03381 |

The first columns in Table 3 and Table 5 are experimental values of $LD_{50}^{exp}$, derived from the samples of rats (majority), mouses, rabbits, cats and dogs. The correlations between $LD_{50}^{exp}$ and the parameters in Table 3 and Table 5 according to Equ. (15) were displayed in the last column in Table 3 to Table 6, which were expressed in Table 7 in descending order, some electrostatic potentials based parameters, dielectric constants, surface tensions, solubility parameters, dipole moment make more contribution to the toxicity. The 9 parameters ranked high (correlation coefficient $\geq 0.3$) in Table 7 were considered in the screening process of genetic function approximation, $\sigma^2$, $\sigma^2$, $q_{SO_2}$, $A^+_S$, $\vec{V}_s$, $\nu \sigma^2_{tot}$, Log $P_{OW}$ were selected to build the relationship (Equ. (16)) with $LD_{50}^{exp}$.
\[ \text{LD}_{50} = -0.012X_1 + 0.024X_2 + 38.855X_3 + 0.164X_4 + 0.028X_5 - 0.227X_6 + 1.017\hat{R}(0.068 - X) - 74.386(\hat{R}(X3 + 0.494))^{1/2} + 346.992(\hat{R}(-0.364 - X3))^{1/2} + 0.0002(\hat{R}(117.057 - X5))^{1/2} + 17.241 \]  

where \( X_1, X_2, X_3, X_4, X_5, X_6 \) and \( X_7 \) represent \( \sigma^2_+ \), \( \sigma^2_- \), \( q_{30x} \), \( A' \), \( \nabla \), \( \nu \sigma^2_\text{tot} \), \( \text{Log P} \), respectively, \( \hat{R} \) is ramp function \([35]\), the square of correlation coefficient is 0.9724. The experimental and predicted results were displayed in Table 8 and Figure 1.

**Table 8.** The comparison of predicted semi-lethal doses (\( \text{LD}_{50}^{\text{cal}} \), g/kg) and experimental ones (\( \text{LD}_{50}^{\text{exp}} \), g/kg).

| order | name          | \( \text{LD}_{50}^{\text{exp}} \) | \( \text{LD}_{50}^{\text{cal}} \) | residual | order | name          | \( \text{LD}_{50}^{\text{exp}} \) | \( \text{LD}_{50}^{\text{cal}} \) | residual |
|-------|---------------|-------------------------------|-------------------------------|----------|-------|---------------|-------------------------------|-------------------------------|----------|
| 1     | 1-Cl-2-NB     | 0.27                          | 0.261                         | -0.009   | 15    | NBu          | 0.50-0.75                     | 0.850                         | 0         |
| 2     | 1-Cl-4-NB     | 0.81                          | 0.667                         | -0.143   | 16    | NEt          | 1.10                         | 1.040                         | -0.06    |
| 3     | 23-DNTul      | 1.12                          | 0.992                         | -0.128   | 17    | NMe          | 1.44                         | 1.480                         | 0.04     |
| 4     | 24-DNB        | 0.035                         | 0.129                         | 0.094    | 18    | NPr          | 0.50-0.75                    | 0.558                         | -0.092   |
| 5     | 24-DNTul      | 0.27                          | 0.223                         | -0.047   | 19    | o-NBA        | 3.56                         | 3.589                         | 0.029    |
| 6     | 25-DNTul      | 0.71                          | 0.573                         | -0.137   | 20    | o-NBP        | 2.828                       | 2.769                         | -0.059   |
| 7     | 26-DNTul      | 0.18                          | 0.258                         | 0.078    | 21    | o-NTul       | 0.89                         | 0.867                         | -0.023   |
| 8     | 2-NI          | 0.08                          | 0.012                         | -0.068   | 22    | p-DNB        | 0.0924                       | 0.135                         | 0.1056   |
| 9     | 34-DNTul      | 1.07                          | 1.088                         | 0.018    | 23    | p-NBA        | 3.25                         | 3.216                         | -0.034   |
| 10    | TNBP          | 0.6                           | 0.507                         | -0.093   | 24    | p-NBP        | 0.616                        | 0.630                         | 0.014    |
| 11    | m-DNB         | 0.01                          | 0.056                         | 0.046    | 25    | p-NTul       | 2.14                         | 1.755                         | -0.385   |
| 12    | m-NBA         | 0.54                          | 0.729                         | 0.189    | 26    | Tetryl       | 0.5                          | 0.498                         | -0.002   |
| 13    | m-NTul        | 1.07                          | 1.542                         | 0.472    | 27    | TNT          | 0.48                         | 0.572                         | 0.092    |
| 14    | NB            | 0.75-1.0                      | 0.820                         | -0.03    | 28    | LLM105       | 2.00                         | 2.064                         | 0.064    |

**Figure 1.** The relationship between experimental semi-lethal doses (\( \text{LD}_{50}^{\text{exp}} \)) and predicted ones (\( \text{LD}_{50}^{\text{cal}} \)).

It is found from Figure 1 and Table 5 that the calculated semi-lethal doses (\( \text{LD}_{50}^{\text{cal}} \)) according to Equ. (12) is in good agreement with experimental ones (\( \text{LD}_{50}^{\text{exp}} \)), and the squared-correlation coefficient reaches 0.9282.

The screened parameters, the positive, negative and total variances, \( \sigma^2_+ \) and \( \sigma^2_- \) are effective index to extract the information contained in the electrostatic potential pattern over an entire molecular surface. These quantities indicate the molecule’s capacity for noncovalent interactions through the regions of positive and negative potential on its surface. A variety of liquid, solid and solution phase
properties that depend upon molecular interactions can be represented analytically in terms of these quantities plus the surface area. The product $\nu_{\sigma^2_{\text{tot}}}$, is especially important for representing properties that are related to the interactions of a molecule with others of its own kind [36]. $A_0^+$ represents the positive superficial area of a molecular, which reflects the size of the molecule, and $V_s$ represents the average molecular surface electrostatic potential.

At one time Mulliken charge of nitro group was applied to measure the sensitivity of nitro containing explosives, which reflects the detonation ability of self-oxidation reduction reactions [37], and was considered to evaluate the ability of self-oxidation reduction reactions in the organism, the more negative the $q_{\text{NO}}$ is, the more difficultly the self-oxidation reduction reactions initiate. Solubility parameter $\delta_2$ reflects the extent of the similarity of the same type or different type molecules, the smaller the change ($\Delta \delta$), the more similar the molecules, abiding by the rule of “like dissolves like” or “like seeks like” [38]. Log $P_{\text{OW}}$ is the logarithm of oil/water partition coefficient for a compound, which reflects the relative size of water-solubility and fat-solubility. These multidimensional knowledges will help us to further understand the toxicity of the nitro containing compounds and reveal the toxicology and provide scientific basis for the design, the toxicity reduction and control of novel nitro-compounds.

## 5 Conclusion

Twenty seven parameters of twenty eight nitro-compounds were computed, which covered the areas of molecular surface properties, solubility, dielectric properties, polarizability and diffusibility. The correlation coefficients between the acute toxicity (semi-lethal doses) of 28 kinds nitro-compounds and these parameters were computed and sequenced in descending order. The results indicate that molecular surface electrostatic potentials based $\sigma_+^2$, $\sigma_-^2$, $\sigma_{\text{int}}^2$, $\nu\sigma_{\text{int}}^2$, $V_{s\text{min}}$, $V_s$, $A_0^+$, solubility related Log $P_{\text{OW}}$, $\delta_2^{19.45}$, $\delta_2$, dielectric constant $\varepsilon$, surface tension $\gamma$, dipole moment $\mu$, Mulliken charges related $q_{\text{NO}}$, were arranged in front. Genetic function approximations, which model heridity, variation, natural selection and survival of the fittest, were performed to screen these parameters, $\sigma_+^2$, $\sigma_-^2$, $\nu\sigma_{\text{int}}^2$, $A_0^+$, $V_s$, $q_{\text{NO}}$, Log $P_{\text{OW}}$ seven parameters were preserved to build the linear relation with toxicity ($LD_{50}$). This work will not only lay a foundation for the toxicity of nitro-compounds, but also for other compounds, and it will provide basic references for the toxicology studies of compounds.

## Acknowledgement

We will acknowledge the financial support of National Natural Science Foundation of China (11372289); Development Fund of CAEP: 2014-1-075. Some computations were carried out in Institute of Computational Science, CAEP.

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Appendix

| Abbreviated name | Systematic nomenclature |
|------------------|-------------------------|
| 1-Cl-2-NB        | 1-chloro-2-nitrobenzene |
| 1-Cl-4-NB        | 1-chloro-4-nitrobenzene |
| 23-DNTul         | 2,3-dinitrotoluene      |
| 24-DNBP          | 2,4-dinitrophenol       |
| 24-DNTul         | 2,4-dinitrotoluene      |
| 25-DNTul         | 2,5-dinitrotoluene      |
| 26-DNTul         | 2,6-dinitrotoluene      |
| 2-NI             | 2-nitroimidazole        |
| 34-DNTul         | 3,4-dinitrotoluene      |
| TNBP             | 2,4,6-trinitrophenol    |
| m-DNB            | 1,3-dinitrobenzene      |
| m-NBA            | 3-nitrobenzenamine      |
| m-NTul           | 1-methyl-3-nitrobenzene |
| NB               | nitrobenzene            |
| NBu              | 1-nitrobutane           |
| NEt              | nitroethane             |
| NMe              | nitromethane            |
| NPr              | 1-nitropropane          |
| o-NBA            | 2-nitrobenzenamine      |
| o-NBP            | 2-nitrophenol           |
| o-NTul           | 1-methyl-2-nitrobenzene |
| p-DNB            | 1,4-dinitrobenzene      |
| p-NBA            | 4-nitrobenzenamine      |
| p-NBP            | 4-nitrophenol           |
| p-NTul           | 1-methyl-4-nitrobenzene |
| Tetryl           | N-2,4,6-Tetranitro-N-methylaniline |
| TNT              | 2,4,6-trinitrotoluene   |
| LLM-105          | 2,6-diamino-3,5-dinitropyrazine-1-oxide |