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Research Article

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Formation enthalpy and number of conformers as suitable QSAR descriptors: a quantum chemical study involving nitrogen mustards

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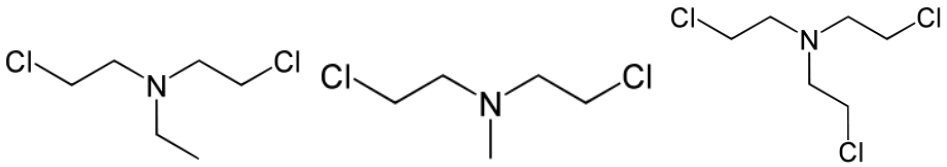
Abstract In the present work, a quantum chemical study (Semi-empirical,PM6 method) is performed using nitrogen mustards (HN1, HN2 and HN3) as subjects in order to demonstrate that there is a close relationship between pharmacological activity and parameters such as formation enthalpy and number of conformers, which could, consequently, be employed as reliable QSAR descriptors. To the studied nitrogen mustards, a very simple equation relating log P, ΔH^{o}_{f} and the number of conformers (N_c) was found: log P = [(log -ΔH^{o}_{f} + logN_c)/2]-0.28.

Keywords QSAR, Descriptors, Formation enthalpy, Conformers, Semi-empirical, Nitrogen mustards, Log P

Introduction

It is well known that lipophilicity is a very important molecular descriptor that often correlates well with the bioactivity of chemicals [1]. Hence, lipophilicity, measured as log P, is a key property in quantitative structure activity relationship (QSAR) studies. In this connection, in the pharmaceutical sciences it is a common practice to use log P (the partition coefficient between water and octanol), as a reliable indicator of the hydrophobicity or lipophilicity of (drug) molecules [1-2]. For example, relying primarily on the log P is a sensible strategy in preparing future 18-crown-6 analogs with optimized biological activity [3].

Nitrogen mustards are tertiary bis(2-chloroethyl)amines with vesicant activity. This class of compounds include HN1 [bis(2-chloroethyl) ethylamine], HN2 (2,2′-dichloro-N-methyldiethylamine), and HN3 [tris(2-chloroethyl)amine hydrochloride]. Some of these were used in therapeutic arenas rather than in warfare (4). Like sulphur mustard, exposure to nitrogen mustards may cause skin blistering, as well as respiratory tract injury and ocular damage [4].



HN1 HN2 HN3

Figure 1: Structural formulas to HN1, HN2 and (c) HN3.

Due to their toxicity and various physical–chemical properties, initial interest in these chemicals as warfare agents developed shortly before and during World War II. Although HN2and HN3 were specifically developed as military agents, HN1 was originally developed as a pharmaceutical. However, HN2was later found use as an antineoplastic agent. Nitrogen mustards and derivatives such as melphalan, chlorambucil, and cyclophosphamide are alkylating agents used as cancer therapeutic agents [4]. In the present work, a quantum chemical study is performed using nitrogen mustards as subjects in order to demonstrate that there is a close relationship between pharmacological

activity and parameters such as formation enthalpy and number of isomers, which could be employed as reliable QSAR descriptors, besides the traditional ones (log P, dipole moment, etc.).

Methodology

The quantum chemical calculations were performed usingSpartan´14 (version 1.1.8) [5] by a Semi-Empirical (PM6) method. To each molecule, the minimum energy structure was employed. The calculated physicochemical parameters are compared with experimental data [4,6].

Results and Discussion

The calculated physicochemical parameters are summarized in Table 1.

Table 1: Calculated physicochemical parameters (Semi-empirical PM6 method) to HN1, HN2 and HN3.

Parameter	HN1	HN2	HN3
E_{HOMO}/eV	-9.10	-9.35	-8.96
E_{LUMO}/eV	0.55	0.55	0.24
$E_{LUMO + 1}$/eV	0.80	0.80	0.60
logP	2.00	1.66	2.37
Dipole moment/D	2.33	2.24	0.18
Polarizability	52.71	51.18	54.02
Topological polar surface area/A^2	1.87	2.05	0.44
Ovality	1.35	1.33	1.39
$-\Delta H^o_f$/kJ mol^{-1}	149.55	123.99	165.29
Number of conformers	243	81	729

Response data from tests with informed human volunteers suggested a relative potency of HN3>HN1>HN2 forvesicant effects, although the differences were minor (4). As can be verified in Table 1, this is the same sequence for log P and E_{HOMO} values, as well as for formation enthalpy values and the number of conformers. So, can be verified that, for this series of analogous compounds, ΔH^o_f and the number of conformers acts as reliable QSAR descriptors, as well as log P. Furthermore, the calculated values to the most traditional descriptors such as E_{LUMO} and dipole moment, are not in agreement with the previous mentioned experimental data sequence.

Some interesting numerical relationships can be pointed out: the number of conformers to HN1 is the number of conformers to HN2 x 3 (81 x 3 = 243). The same "3" factor it is observed from HN1 to HN3 (243 x 3 = 729). Furthermore, the obtained sequence to log P values are 2.37 (HN3), 2.00 (HN1) and 1.66 (HN2). So, a difference of ~0.3 units it is observed form one value to another. Since the chemical formulas to the three compounds are: $N(CH_2CH_2Cl)_3$ –HN3; $(ClCH_2CH_2)_2NC_2H_5$– HN1 and $(ClCH_2CH_2)_2NCH_3$ – HN2, could be concluded that from the point of view of "group addition", a CH_2 group exerts the same effect of a Cl atom. On the other hand, such structural modifications exert a remarkable effect on the dipole moments (from HN2 to HN3).

It is worth noting that the sequence HN3>HN1>HN2 it is also observed for properties as boiling point/ °C (6): 138 > 85 > 75. It is possible to conclude that the intermolecular forces exhibits also the sequence HN3>HN1>HN2, since this is the inverse sequence measured to the vapour pressure values [6].

To the studied nitrogen mustards, a very simple equation relating log P, ΔH^o_f and the number of conformers (N_c) was found:

$$\text{Log P} = [(\log -\Delta H^o_f + \log N_c)/2]-0.28$$

Using this equation, the log P values are: 2.0, 1.7 and 2.3, in very good agreement with the previous calculated values shown in Table 1. So, the very close relationship between log P, ΔH^o_f and N_c is demonstrated.

References

1. R. Mannhold, R.F. Rekker, K. Dross, G. Bijloo, G. De Vries, *Quant.Struct-Act Rel.*,**17** (1998) 517-536.
2. A.J. Leo, D. Hoekman, *Perspect. Drug Discov.*, 18 (2000) 19–38.

3. F. Supek, T.S. Ramljak, M. Marjanovi, M. Buljuba, G. Kragol, N. Ilic, T. Smuc, D. Zahradka, K. Mlinaric-Majerski, M. Kralj, *Eur. J. Med. Chem*. 46 (2011) 3444-3454.
4. M.C. Gupta (Ed.), *Handbook of toxicology of chemical warfare agents*, 2nd ed., Academic Press, London, 2015.
5. Wavefunction Inc., Irvine, California, USA, 2014.
6. T. C. Marrs, R.L. Maynard, F.R. Sidell, *Chemical warfare agents – toxicology and treatment*, Wiley, Chichester, 2007.