A QSPR STUDY ON SEVERAL NEW *N*-ALCOXY-DINITROANILINES

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*Opt derivați de **N**-alcoxy-dinitroanilină sintetizați şi caracterizați anterior, au fost utilizați în studii QSPR. În aceste studii, au fost implicate valori determinate experimental (δ, RMN si λ, UV-Vis) şi valori determinate prin calcul (log P, suprafața, volum, sarcina atomică). S-a observat că valorile δ (RMN) pot fi calculate utilizând sarcina atomică, în timp ce valorile λ (UV-Vis) pot fi calculate utilizând volumul şi suprafața moleculei. În acest fel s-au obținut ecuații matematice care pot fi utilizate pentru predicția unor proprietăți, cu un coeficient de corelare de 80-90%.*

Eight N-alcoxy-dinitroanilines previously synthesized and characterized have been used in a QSPR study. Experimental (NMR δ and UV-Vis λ values) and calculated (log P, surface, volume, atomic charges) properties were employed. It was noticed that NMR δ values can be calculated using atomic charges, while UV-Vis λ values can be estimated using the volume and the surface of the molecule; thus, mathematical equations were obtained, and these can be used for prediction of that properties with a correlation coefficient between 80-90%.

Keywords: *N*-Alcoxy-dinitroaniline derivatives, QSPR study

1. Introduction

N-Alcoxy-dinitroaniline derivatives (Ar-NH-OR) are organic compounds with very interesting physico-chemical properties. Thus, by oxidation, they easily generate free *N*-alkoxy-aminyl (or aminoxyl) radicals (Ar-N$^{\cdot}$-OR) [1-6], which may react with other stable radicals, such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) and its congeners, leading to the blue-colored betaines [7,8]. Another interesting property is their high acidity [9-12], which leads in a presence of a base to the corresponding anions (R-O-N^{-}-Ar), also with very intense colors, red, blue, or blue-violet [9,11]. These anions have been involved as partners in supramolecular hydrophobic complexes with alkaline cations and crown ethers [9,11,13,14], and as nucleophiles in the synthesis of *N*-methyl or *N*-aryl

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derivatives [9,11]. These properties are dependent on the chemical structure, with both the adjacent alkoxy moiety and the aromatic ring having a major influence on their physico-chemical behavior; this is currently explained by the push-pull (capto-dative or mero-stabilizing) effect [15-23] with considerable electron density on the aromatic ring. For more information about the relationship between the structure of the compounds **1**-**8** and their physical-chemical properties, we performed also some computational studies [24].

The term QSPR (quantitative structure-property relationships) is widely used for some empirical models, in order to find out some correlations between structure and properties of the molecules. Compared to group/bond contribution approaches, QSPR may employ more informative molecular descriptors and, thus, may achieve higher accuracy. Therefore, methods to assess the QSPR prediction accuracy are of major importance [25].

In this work we used eight *N*-alcoxy-dinitroanilines previously synthesized and characterized (Fig. 1) [26] in our trial to predict properties of such compounds.

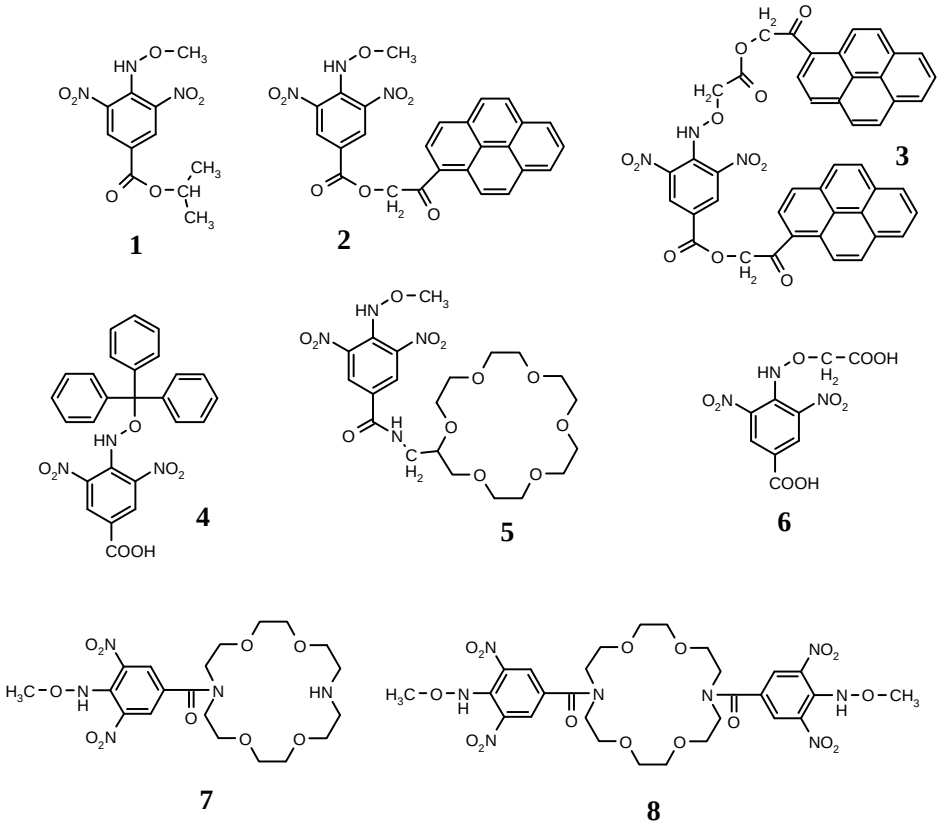


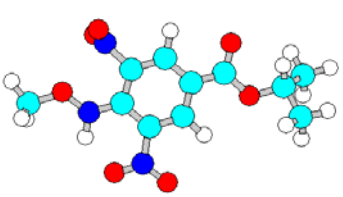
Fig. 1. Chemical structure of the employed compounds

This procedure may have importance in the design of future congeners with specific applications (such are complexation of cations, interphasic transport, pH and redox indicators) [9-11].

2. Results and Discussion

Molecular modeling [27] is a technique widely used by the pharmaceutical companies in order to predict the best structure of possible medicines, and, moreover, can be used to select from a large library of chemical compounds those that are suitable to be experimentally tested.

In our work we used the well known HyperChem [24] software package to obtain some calculated data about our compounds and to try to predict such data, comparing the experimental with calculated properties. The first step in our calculations was the geometry optimization of the molecules, using the semi-empirical method AM1 (energy minimization), because our previous experience on this type of compounds showed that it is one of the most suitable for this purpose. Thus, the optimized structures are shown in Fig. 2.



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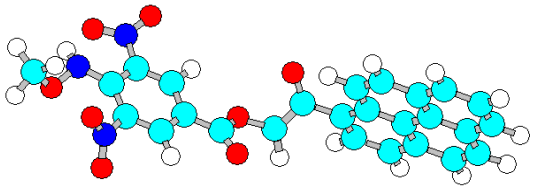

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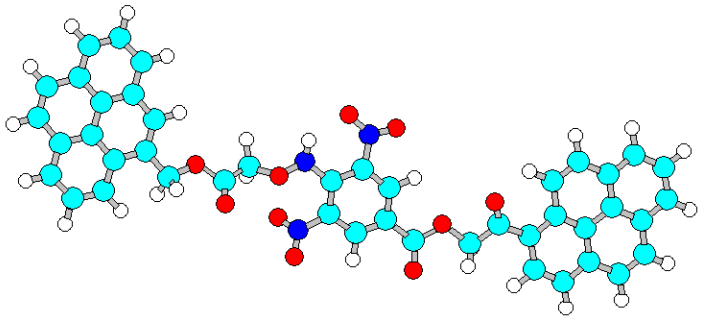

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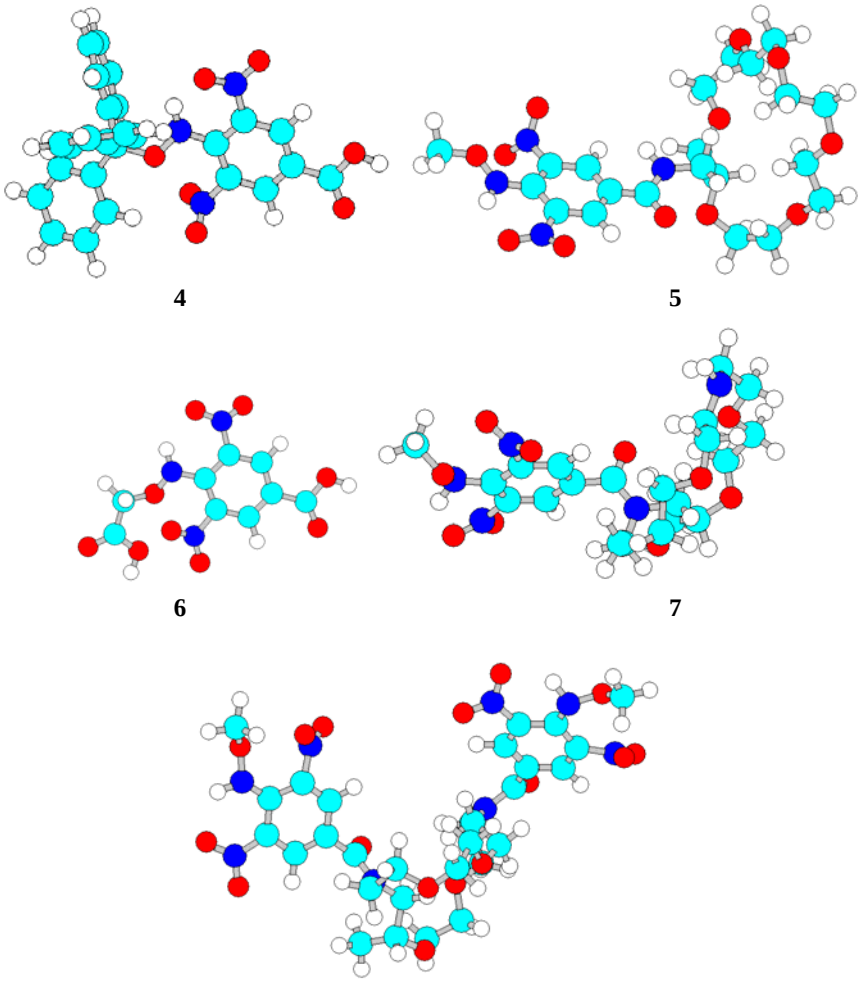


Fig. 2. Optimized structures of the compounds **1-8**

As a general observation, compounds adopt the most stable structure, based on energy minimization of the steric interaction. This step is necessarily to be performed in the aim to obtain accurate data about the surface and volume of the molecule. Besides these values, calculated and compiled in Table 1, we also calculated the log P values for compounds **1-8**, being well known that these data are important in the evaluation of the biological activity of molecules [26], and associated with the capacity of the molecule to pass the membrane cell. Because in the physico-chemical properties of compounds **1-8**, the nitrogen and the oxygen atoms from the –O-NH- moiety play the main role in their acido-basic and redox

properties, we have calculated the net atomic charge (AC) on these atoms (Table 1), [24].

Table 1

Calculated and experimental values of the compounds 1-8

Comp.	Log P	δ_{exp} ppm	$\lambda_{1(HA)}$ nm	$\lambda_{2(anion)}$ nm	AC (O)	AC (N)	Surface A^2	Volume A^3
1	2.19	11.25	391	567	-0.216	-0.136	465	777
2	4.82	10.05	394	561	-0.205	-0.137	587	1240
3	8.49	10.16	396	555	-0.21	-0.129	811	1782
4	6.53	-	405	530	-0.212	-0.105	532	1211
5	-0.32	11.48	374	572	-0.228	-0.135	660	1326
6	0.94	8.70	378	564	-0.188	-0.131	397	700
7	0.22	9.98	395	600	-0.21	-0.134	689	1320
8	1.45	10.80	395	605	-0.209	-0.133	916	1788

In order to study the properties of *N*-Alcoxy-dinitroaniline derivatives, we used mathematical equation to predict such properties, using the "leave-one-out" cross-validation method [28]. This method means that many variants were tested in order to obtain the best fit, and only the parameters that fulfill this request were kept for future examination [29].

The multiple regression equations used were of type $Y=a*X_1+b*X_2+c$, where X was used as independent parameter. Thus, we noticed that in this way the values can be calculated using the equation (1), see data also in Table 2 (a good correlation coefficient has been obtained, ~90%).

$$\delta \text{ (ppm)} = -68.9*AC(O)-40.5*AC(N)-9.5 \quad (1)$$

$R^2=0.882$; SD 0.394

Table 2

Calculated and experimental values using mathematical equations

Comp.	δ_{exp} ppm	δ_{calc} ppm	δ residual	$\Delta\lambda_{exp}$ nm	$\Delta\lambda_{calc}$ nm	$\Delta\lambda$ rezidual
1	11.25	10.89	0.36	176	191	-15
2	10.05	10.17	-0.12	167	154	13
3	10.16	10.19	-0.03	159	131	28
4	-	9.36	-	125	131	-6
5	11.48	11.68	-0.20	198	174	24
6	8.70	8.76	-0.06	186	172	14
7	9.98	10.40	-0.42	205	190	15
8	10.80	10.29	0.51	210	208	2

Also, in the same way, for the wavelength difference $\Delta\lambda$ (difference between λ of the anion and λ of the HA acid), the equation obtained is (2), as well with a good correlation coefficient (S means the surface and V means the volume of the molecule) [29].

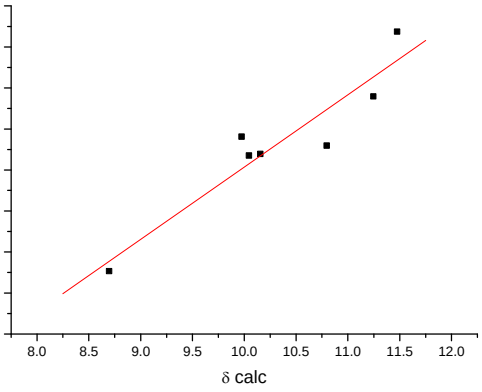
$$\Delta\lambda = 0.53*S-0.22*V+115.5 \quad (2)$$

R^2=0.801; SD 14.82

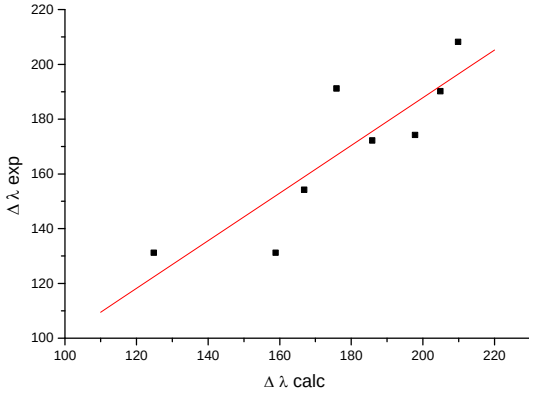
The graphical representation of these correlations is shows in the next figures (Fig. 3 and 4). Thus, as an equation of first order, of type Y=a+bX, the representation of experimental values against calculated ones lead to very well correlation coefficients, 86-93%.

4. Experimental

Compounds were synthesized and characterized as literature data showed [26,27]. For geometry optimization, HyperChem 8 Evaluation software package has been used, with the following settings: first, for a preliminary optimization (that reduce the time of calculations and increase the accuracy), molecular mechanics has been run, using MM+ force field (electrostatic bond dipoles); after successfully optimization, the geometry was re-optimized using the semi-empirical method AM1 (restricted Hartree-Fock) using Polak-Ribiere conjugate gradient algorithm. In the same way all other values were calculated. For mathematical correlations, Origin 4 software program has been used.



δ exp=1.22 + 0.88*δ calc
R=0.939; SD=0.332



Δ λ exp=13.75 +0.87* Δ λ calc
R=0.864; SD=15.37

5. Conclusion

In conclusion, using simple computational techniques, it is possible to generate equations that can be used to provide data about the structure of the compounds, such are NMR values and λ UV-Vis values, with a good accuracy (R^2=0.882 for δ values and R^2=0.801 for λ values).

R E F E R E N C E S

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