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A COMPUTATIONAL STUDY ON SOME HYDRAZYL RADICALS AND CONGENERS

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A number of 11 organic stable free radicals of hydrazyl type, together with their corresponding hydrazines and their anions were investigated by quantitative structure-properties relationships (QSPR). Experimental visible absorption data, pK_a values and cyclic voltammetry oxidation potential E_{ox} were correlated with bond dissociation energies (BDE), computed spin population, atomic charges and Mulliken charges. Multiple regression equations were drawn using the leave-one-out cross-validation method. It was shown that pK_a and E_{ox} give good correlation data, while BDE values cannot be estimated using the same procedure.

Keywords: hydrazyl, QSPR, free radicals.

1. Introduction

Hydrazyl radicals are well known for their indefinite stability under normal conditions [1]. They are also used in many physico-chemical processes, such are acid-base or redox ones [2-4]. The most known hydrazyl radical, 2,2-diphenyl-1-picrylhydrazyl, discovered in 1922 by Goldschmidt and Renn and known as DPPH [5], is widely used in the determination of total antioxidant capacity of natural compounds [6]. Since then, many hydrazyl radicals were synthesized and their interesting properties studied [2-4,7-13]. In this study we drawn on 11 hydrazyl radicals, together with their corresponding hydrazines (the reduced form of the radicals) and their anion counterparts (practically the corresponding salts), Fig. 1; all these species are easily inter-convertible by the appropriate acid-base or redox processes, as shown in Scheme 1.

The term QSPR (quantitative structure-property relationships) is widely used in computational chemistry for some empirical models, with the aim to find out correlations between structure and properties of the molecules [14]. Molecular modeling is a technique widely used by the medicinal chemists and pharmaceutical companies in order to predict the best structure for medicines, and

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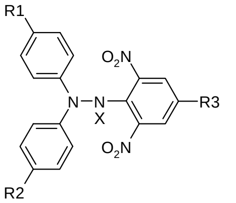
can be used also to select from a large library of chemical compounds those that are suitable to be tested *in vivo*. The QSPR technique may employ many molecular descriptors and, thus, selecting the representative ones may achieve better accuracy. In this way methods to increase the QSPR prediction accuracy are of major importance.



1 X = · (free radical)
2 X = H (hydrazine)
3 X = $^-$ (anion)

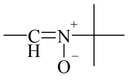
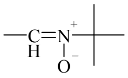
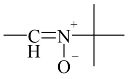
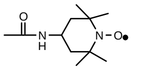
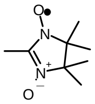
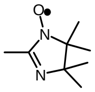
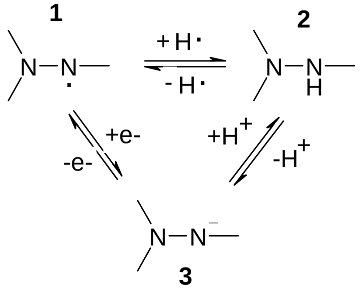
Comp.	R1	R2	R3
1-3a	H	H	NO_2
1-3b	NO_2	H	NO_2
1-3c	NO_2	NO_2	NO_2
1-3d	SO_3Na	H	NO_2
1-3e	SO_3Na	SO_3Na	NO_2
1-3f	H	H	
1-3g	NO_2	H	
1-3h	NO_2	NO_2	
1-3i	H	H	
1-3j	H	H	
1-3k	H	H	

Fig. 1. Structure of the hydrazyl radicals (compounds **1a-k**) and the corresponding hydrazines (**2a-k**) and anions (**3a-k**)



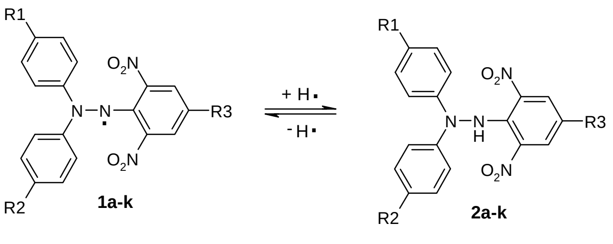
Scheme 1. Inter-conversion of the hydrazyl **1** to hydrazine **2** and anion **3** by acid-base or redox processes

Acid-base interactions are evaluated by the pK_a values, while redox reactions by the oxidation potential E_{ox}. In this study we used these experimental values, which were also employed for the experimental determination of the bond dissociation energy (BDE). The BDE value of the N-H group in these compounds is an asset of the chemical behavior of hydrazyl radicals [11] and was calculated using the equation $BDE = 1.37pKa + 23.06E_{ox} + 56$; therefore, in this work the experimental data were fitted with the computed ones.

2. Results and discussion

*2.1 Redox couple of compounds **1** and **2***

Fig. 2 shows the experimental visible absorption data for the compounds **1a-k** (λ_1) and **2a-k** (λ_2), BDE values for the couples **1/2**, as well as the computed atomic charges (AC) for the compounds **1a-k** and spin populations (SP) for the compounds **2a-k**. N1 and N2 refer to the nitrogen atoms that make the hydrazyl moiety; previous studies showed that these atoms were mostly taken in mechanic or semi-empirical calculations [8,11].



1a-k

2a-k

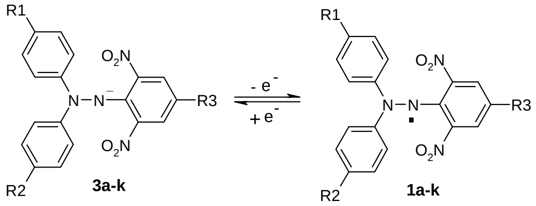
Couple	λ_1	λ_2	BDE	AC_{N1}	AC_{N2}	SP_{N1}	SP_{N2}

1a/2a	518	322	74.62	-0.206	-0.065	0.479	0.403
1b/2b	500	352	77.37	-0.214	-0.075	0.512	0.370
1c/2c	500	352	78.73	-0.223	-0.079	0.561	0.346
1d/2d	524	353	75.07	-0.233	-0.067	0.548	0.361
1e/2e	518	368	-	-0.203	-0.082	0.581	0.339
1f/2f	524	324	76.81	-0.180	-0.081	0.544	0.333
1g/2g	517	330	76.96	-0.175	-0.056	0.681	0.203
1h/2h	508	332	70.67	-0.141	-0.126	0.494	0.189
1i/2i	486	392	75.45	-0.201	-0.072	0.450	0.362
1j/2j	507	404	75.08	-0.184	-0.078	0.551	0.340
1k/2k	510	482	75.30	-0.165	-0.078	0.676	0.266

Fig. 2. Experimental visible absorption data (λ, nm) and BDE; computed AC and SP (*Hyperchem*)

*2.2 Redox couple of compounds **3** and **1***

Fig. 3 shows the experimental absorption data and E_{ox} for the couples formed by compounds **3** and **1**.

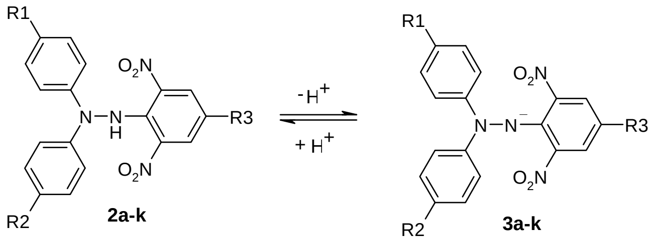


Couple	λ_3	λ_1	E_{ox}
3a/1a	424	518	0.30
3b/1b	505	500	0.49
3c/1c	485	500	0.60
3d/1d	413	524	0.34
3e/1e	409	518	-
3f/1f	655	524	0.87
3g/1g	495	517	1.17
3h/1h	492	508	1.23
3i/1i	620	486	0.173
3j/1j	645	507	0.107
3k/1k	654	510	0.130

Fig. 3. Experimental visible absorption data (λ, nm) and E_{ox} values (V)

*2.3 Acid-base couple of compounds **2** and **3***

Fig. 4 shows the experimental absorption data and pK_a values of the couple **2/3**, together with computed AC using Huckel (H) and Mulliken (M) methods.

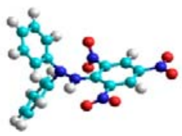
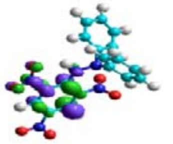
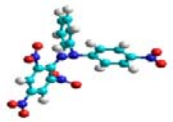
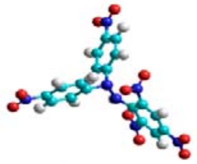
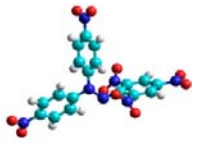
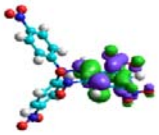
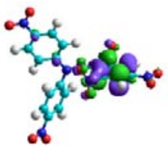
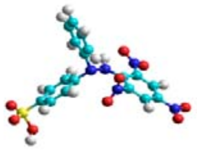
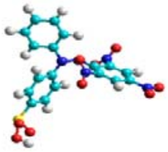
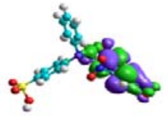
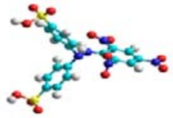
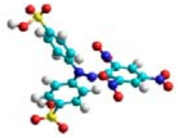
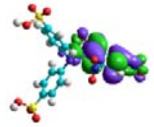
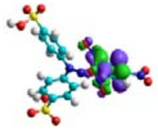
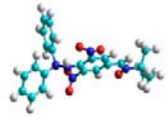
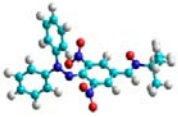
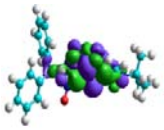
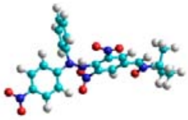
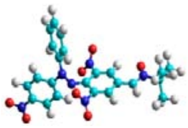
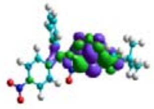
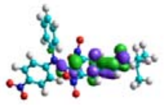


Couple	λ_2	λ_3	pK_a	$AC_{N1(H)}$	$AC(_{N2})_H$	$AC(_{N1})_M$	$AC(_{N2})_M$
2a/3a	322	424	8,54	0.276	0.265	-0.246	-0.099
2b/3b	352	505	7,35	0.287	0.361	-0.229	-0.101
2c/3c	352	485	6,49	0.286	0.366	-0.211	-0.131
2d/3d	353	413	8,20	0.349	0.283	-0.236	-0.088
2e/3e	368	409	7,10	0.356	0.276	-0.189	-0.108
2f/3f	324	655	12,5	0.176	0.313	-0.207	-0.111
2g/3g	330	495	11,6	*0.196*	*0.354*	-0.262	-0.079
2h/3h	332	492	10,9	*0.191*	*0.392*	*-0.279*	*-0.104*
2i/3i	392	620	7,82	*0.178*	*0.3*	*-0.148*	*-0.131*
2j/3j	404	645	8,07	*0.172*	*0.301*	*-0.147*	*-0.125*
2k/3k	482	654	8,33	*0.225*	*0.321*	*-0.227*	*-0.132*

Fig. 4. Experimental visible absorption data (λ, nm) and pK_a; computed AC (for neutral molecule) using Huckel (H) and Mulliken (M) methods (*ChemBio3D*)

2.4 Computing

HyperChem [15] and *ChemBio3D* [16] software packages were used to obtain some calculated data about the compounds and also to try to predict such data, comparing the experimental with calculated properties. Our previous experience on this type of compounds showed that the semi-empirical method AM1 it is one of the most suitable for this purpose [8,11]. The energy minimization was the first step in calculations for the geometry optimization of the molecules; because in the physico-chemical properties of compounds **1**-**3** the nitrogen atoms from the =N-NH- moiety play the main role in their acid-base and redox properties, we have calculated the net atomic charge (AC) on these atoms. Molecular structures of the compounds **1a-k** are shown in Fig. 1 and Fig. 5. Mathematical equations to predict such properties were employed, using the leave-one-out cross-validation method [17]. 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. Thus, using eq. 1, it was possible to calculate the pK_a values (with good statistical parameters, R^2=0.823, RCV=0.778, SD=0.921). In the same way was calculated E_{ox} (eq. 2, R^2=0.851, RCV=0.808, SD=0.183). The experimental and calculated values are compiled in Table 1.

	Compound **2**	Compound **1**	LUMO Compound **2**	LUMO Compound **1**
a				
b				
c				
d				
e				
f				
g				

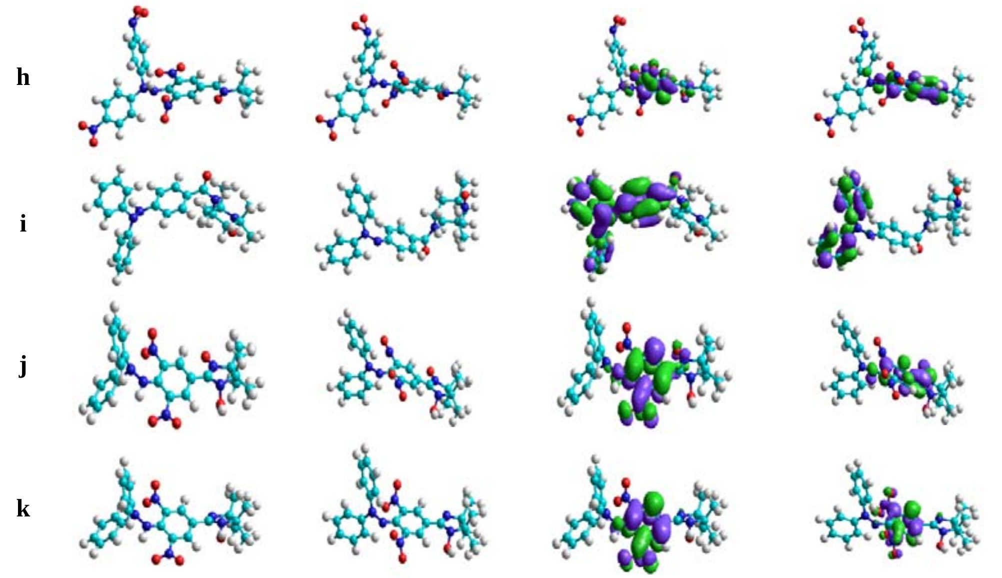


Fig. 5. Molecular structure of the compounds 1a-k and 2a-k, together with the contour plots of LUMO orbitals

$$pK_{a(calc)}=0.019*\ \Delta\lambda_{\mathbf{3\text{-}2}}+2.26*(AC_{MN1}/\ AC_{MN2})+1 \qquad (1)$$

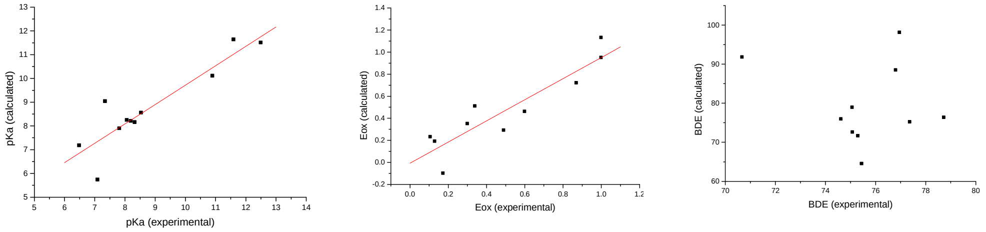
$$E_{ox(calc)}= -1.516*(SP(_{N2})/SP_{N1})+0.005*\Delta_{\mathbf{1\text{-}2}}+0.65 \qquad (2)$$

Table 1

Experimental and calculated values of pK_a, E_{ox} and BDE, and the residual values

$pK_{a(exp)}$	$pK_{a(calc)}$	ΔpK_a	$E_{ox(exp)}$	$E_{ox(calc)}$	ΔE_{ox}	$BDE_{(exp)}$	$BDE_{(calc)}$	ΔBDE
8.54	8.55	-0.01	0.30	0.35	-0.05	74.62	75.90	-1.28
7.35	9.03	-1.68	0.49	0.29	0.20	77.37	75.17	2.20
6.49	7.17	-0.68	0.60	0.46	0.14	78.73	76.32	2.41
8.20	8.20	0.00	0.34	0.51	-0.17	75.07	78.92	-3.85
7.10	5.73	1.37	-	0.52		-	75.75	
12.5	11.50	1.00	0.87	0.72	0.15	76.81	88.42	-11.61
11.6	11.63	-0.03	1.17	1.13	0.04	76.96	98.07	-21.11
10.9	10.10	0.80	1.23	0.95	0.28	70.67	91.75	-21.08
7.82	7.89	-0.07	0.173	0.10	0.07	75.45	64.51	10.94
8.07	8.24	-0.17	0.107	0.23	-0.12	75.08	72.58	2.50
8.33	8.15	0.18	0.130	0.19	-0.06	75.3	71.64	3.66

In order to see the accuracy of the calculated values, linear correlations were made; Fig. 6 shows these results. It is easily noticed that pKa and Eox values can be correlated with a good fit (R>0.9), while for BDE no correlation is possible (R=0.15).



R=0.906 SD=0.783
$pK_{a(exp)} = 1.22*pK_{a(calc)} - 1.9$

R=0.908 SD=0.164
$E_{ox(exp)} = 1.042*E_{ox(calc)} - 0.01$

R=0.15

Fig. 6. Linear correlation between the experimental and calculated values (left-for pK_a, middle-for E_{ox}, right-for BDE)

The calculated energy to extract the hydrogen atom from the -NH- group is given by the equation (3). The practical meaning is the difference between the heat of formation of the native substrate (ΔH_1) and that of the corresponding free radical (ΔH_2). Henceforth, the ΔH_{abs} will be called 'hydrogen abstraction energy' [18].

$$\Delta H_{abs} = \Delta H_2 - \Delta H_1 \qquad (3)$$

We have noticed that all LUMO orbitals are located on the picril ring (Fig. 5), on both **1a-k** and **2a-k** compounds (except for **i** compound, which not contain a picril ring in molecule), with homogeneous energies, between -2.471 and -1.236 eV (except for **i** -0.086 eV), and respectively between -5.403 and -3.747 eV. The hydrogen abstraction energy is relatively constant, between 187.489 and 253.566, with a minimum (81.222) and a maximum (307.689) out of the median values, for **e** and **h**.

Table 2

The energies of the LUMO orbitals for compounds 2a-k (ε_{LUMO2}), 1a-k (ε_{LUMO1}), the differences between LUMO orbitals in 1a-k and 2a-k compounds, heats of formation for compounds 2a-k and 1a-k, and ΔH_{abs}.

Letter	ε_{LUMO2} (eV)	ε_{LUMO1}(eV)	$\Delta\varepsilon$ (eV)	ΔH_{f1}	ΔH_{f2}	ΔH_{abs}
a	-1.916	-4.963	-3.047	148.128	381.367	233.239
b	-2.225	-5.130	-2.905	153.445	349.912	241.467
c	-2.471	-5.403	-2.932	160.494	414.060	253.566
d	-2.192	-4.91	-2.718	94.729	333.808	239.079
e	-2.403	-5.29	-2.887	85.119	166.341	**81.222**
f	-1.383	-4.119	-2.736	149.540	357.007	207.467
g	-2.225	-4.432	-2.207	152.986	340.475	187.489
h	-1.862	-4.597	-2.735	167.558	475.247	**307.689**
i	**-0.083**	-3.747	-3.664	76.136	280.669	204.533
j	-1.236	-4.055	-2.819	162.71	367.918	205.208
k	-1.352	-4.070	-2.718	160.711	380.264	219.553

3. Experimental and method

Experimental data for the compounds **1-3** were taken from literature [2-4,7-13]. Two modeling packages were used*: HyperChem* (version 8 [15]) *and ChemBio3D* Ultra with Gamess [19, 20] interface (version 12 [16]). As a general rule, the geometry optimization of the molecules was done first with a molecular mechanic method, followed by a semi-empirical one. Thus, for *HyperChem*, MM+ (electrostatic bond dipoles) method was used first for the geometry optimization, followed by the semi-empirical AM1 method (RHF and using Polak-Ribiere conjugate gradient algorithm), thus obtaining the values for the atomic charge and spin population (in this case UHF was used, as the system contain unpaired electrons). In the same way, for *ChemBio3D* Ultra the energy of the molecule was minimized first using MMFF94, and using the extended Huckel atomic charges were obtained; Mulliken charges were obtained using the Gamess interface and AM1. By geometry optimization, 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 atomic charges and spin populations. For mathematical correlations, Origin 4 software program has been used. The multiple regression equations used were of type $Y=a*X_1+b*X_2+c$, where X was used as independent parameter.

4. Conclusions

This work dealt with some QSPR analysis performed on a 11 hydrazyl free stable radicals and their parent hydrazines or anions. The analysis showed that pK_a values and oxidation potential can be estimated using QSPR techniques, but bond dissociation energies cannot.

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