UV and MO Study on the Deprotonation of some 2-Aryl-Δ^2-1,3,4-Oxadiazoline-5-thiones

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Substituent effects on the deprotonation processes of a series of 2-aryl-Δ^2-1,3,4-oxadiazoline-5-thione (**1**) derivatives have been studied experimentally as well as theoretically. The acid dissociation constants pK_a have been determined spectrophotometrically in ethanol-water solutions (7.5-92.5%) and vary between 3.76 and 5.80. Semiempirical molecular orbital (MO) calculations (AM1 and PM3) were used for the investigation of the existence of possible tautomeric thione and thiol forms of the studied compounds. Strong correlation between the pK_a values and the deprotonation enthalpies were evaluated.

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Introduction.

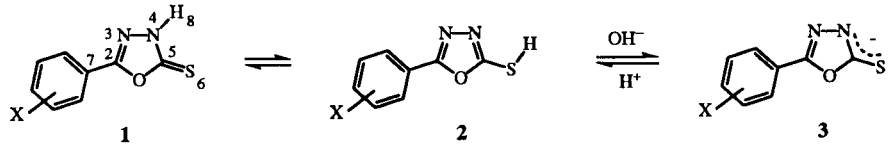
Δ^2-Oxadiazoline-5-thione derivatives **1** show a wide range of biological and pharmaceutical activities and have many other interesting applications [1]. The present investigation was undertaken as a further study on the chemistry of 1,3,4-oxadiazoline-5-thiones, to examine the relative stability of the tautomeric species as well as the correlation of experimentally determined pK_a values with the calculated deprotonation enthalpies.

Molecular orbital calculations are considered as useful tool for the investigation of a wide range of chemical problems. The semiempirical AM1 and, more recently, the PM3 methods are used for the interpretation of the experimental gas phase basicity particularly in the studies of the substituent effects on protonation of amines and other aza heterocycles as well as for the deprotonation of various classes of neutral Bronsted acids, because they give reliable results for large molecules with a reasonable CPU time. For this reason we used the above SCF-MO methods that have been previously evaluated for the proton affinities as well as the deprotonation enthalpies of a large number of bases and acids, respectively [2-5].

Results and Discussion.

Two molecular orbital calculation methods, AM1 and PM3, were used to determine the thermodynamically more stable tautomer between **1** (thione) and **2** (thiol) forms (Scheme 1). Using the AM1 method, the calculated heats of formation ΔH_f = 69.39 Kcal/mol for **1a** and ΔH_f = 64.95 Kcal/mol for **2a** were obtained, suggesting that the thiol form is slightly more stable ($\Delta\Delta H_f$ = 4.44 Kcal/mol). However, this small difference is within the averaged error of these methods [5]. It is important to note that both the AM1 and PM3 methods gave similar results for all substituted derivatives differing approximately by the same amount. Thus only the AM1 results will be presented in this paper. It is not possible to predict with certainty, which of the tautomers is more stable (in the gas phase).

Scheme 1



1 **2** **3**

	X		X		X		X		X		X		X		X
a	H	**d**	*p*-F	**g**	*p*-Cl	**j**	*p*-Br	**m**	*p*-I	**p**	*m*-OCH_3	**s**	*p*-CN	**v**	*o*-NH_2
b	*o*-F	**e**	*o*-Cl	**h**	*o*-Br	**k**	*o*-I	**n**	*m*-NO_2	**q**	*p*-OCH_3	**t**	*m*-CH_3	**w**	*m*-NH_2
c	*m*-F	**f**	*m*-Cl	**I**	*m*-Br	**l**	*m*-I	**o**	*p*-NO_2	**r**	*m*-CN	**u**	*p*-CH_3	**x**	*p*-NH_2

The infrared spectra (potassium bromide pellets) of the title compounds **1** possess a weak intensity band at 2550-2575 cm^{-1} attributed to ν(S-H) and medium to strong bands at 3280-2720 cm^{-1} due to ν(N-H) [1]. All these bands disappear in the anionic form **3**, but are becoming more intense in the protonated form suggesting that the neutral compounds exist as a mixture of the thione **1** and thiol **2** tautomers. This observation is in good agreement with the small difference in the calculated heats of formation $\Delta\Delta H_f$ between the tautomeric forms **1** and **2**.

To compare the influence of aryl substituents X on the oxadiazole ring the following electronic quantities were examined for both neutral and anionic species: the electron charge distribution between the two rings (Table 1), the atomic net charge distribution (Table 2) and the bond orders (Table 3) on the unsubstituted **1a**, the nitro- **1n** and **1o** and the amino-**1w** and **1x** derivatives.

Table 1

Net Charge Distribution between Aryl and Oxadiazole Rings for *m*- and *p*-Nitro and Amino Substituted Neutral, **1a,n,o,w,x**, and Anionic, **3a,n,o,w,x**, Species [a]

	Neutral **1**			Anion **3**		
Substituent	Aryl	Oxadiazole	ΔQ [b]	Aryl	Oxadiazole	ΔQ
H	1413	-1413	0	-34	-9966	0
p-NO_2	1101	-1101	312	-1006	-8994	972
p-NH_2	1594	-1594	-181	162	-10162	-196
m-NO_2	1127	-1127	286	-534	-9466	500
m-NH_2	1452	-1452	-39	1	10001	-35

[a] AM1, charge in electrons x10^4. [b] $\Delta Q = Q_{Ar-H} - Q_{Ar-X}$. Positive ΔQ means gain in electronic charge of aryl ring due to the substituent X.

In compound **1a**, the oxadiazole ring attracts 0.1413 electrons from the phenyl ring whereas in compound **1x** the *p*-NH_2 group increases the electron-donating character of aryl group resulting to the transfer of 0.1594 electrons to the oxadiazole ring (Table 1).

This charge difference of 0.0181 electrons is distributed mostly on both the N3 and on the exocyclic sulfur through the known mesomeric structures (Scheme 2). On the other hand, in the *p*-NO_2 derivative the effect of the nitro group opposes that of the oxadiazole ring resulting in a redistribution of the electronic charge between the oxadiazole ring and the nitro group. As a result, 0.0312 electrons are moved towards the nitro group. The above mentioned results are shown in detail in Tables 1 and 2. It can be seen that the substituents in the *p*-position exert a stronger influence on charge redistribution due to the combination of their conjugative and inductive effects. The net charge distrubution on the oxadiazole ring atoms and on the directly bonded atoms due to the aryl substituents (X = H, *m*-NO_2, *p*-NO_2, *m*-NH_2 and *p*-NH_2) is listed in Table 2.

The mesomeric structures in Scheme 2 are also supported by the bond order values presented in Table 3. In compound **1x** the bond orders increase for the bonds C2-C7, N4-C5 and decrease for the bonds C2-N3, N3-N4 and C5-S6. In compound **1o** the bond orders increase for the bonds N3-N4, C5-S6 and decrease for the bond N4-C5.

The deprotonation enthalpy (DPE) of an acid AH is calculated [3a] by the following expression (1) and represents the heat of reaction for the proton abstraction equilibrium

Scheme 2

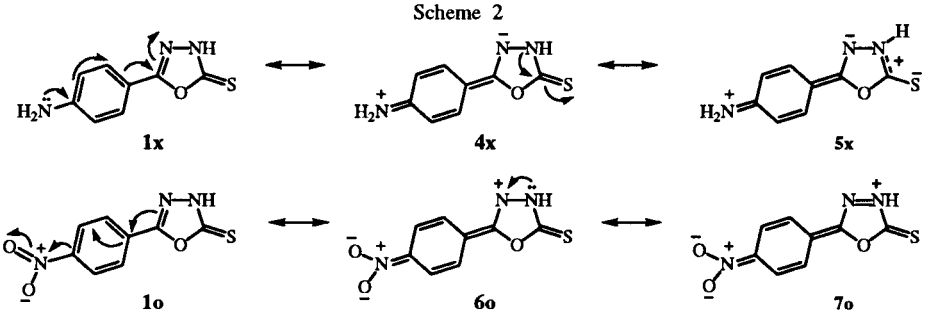


Table 2

Net Charge Distribution on Atoms 1-8 for Neutral and Anionic Species for *m*- and *p*- Nitro and Amino Oxadiazoline Derivatives [a]

A. Neutral Compounds **1a,n,o,w,x**

Atom [b]	H	*m*-NO_2	ΔQ_i [c]	*p*-NO_2	ΔQ_i	*m*-NH_2	ΔQ_i	*p*-NH_2	ΔQ_i
1	-1479	-1509	30	-1479	0	-1450	-29	-1515	36
2	474	286	188	209	265	487	-13	709	-235
3	-531	-312	-219	-282	-249	-546	15	-732	201
4	-2665	-2658	-7	-2666	1	-2674	9	-2646	-19
5	502	454	48	436	66	517	-15	552	-50

Table 2 (continued)

A. Neutral Compounds **1a,n,o,w,x**

Atom [b]	H	*m*-NO_2	ΔQ_i [c]	*p*-NO_2	ΔQ_i	*m*-NH_2	ΔQ_i	*p*-NH_2	ΔQ_i
6	-731	-443	-288	-368	-363	-788	57	-954	223
7	-420	-389	-31	100	-520	95	-515	-1182	762
8	3017	3055	-38	3048	-31	3002	15	2992	25

B. Anionic Compounds **3a,n,o,w,x**

Atom [b]	H	*m*-NO_2	ΔQ_i [c]	*p*-NO_2	ΔQ_i	*m*-NH_2	ΔQ_i	*p*-NH_2	ΔQ_i
1	-1690	-1696	6	-1607	-83	-1665	-25	-1735	45
2	-1616	-1927	311	-2081	465	-1595	-21	-1379	-237
3	-596	-324	-272	-211	-385	-618	22	-752	156
4	-2167	-2063	-104	-1958	-209	-2183	16	-2197	30
5	64	42	22	-25	89	66	-2	70	-6
6	-3961	-3498	-463	-3112	-849	-4006	45	-4169	208
7	623	688	-65	1301	-679	1020	-397	30	593

[a] AM1, charge in electrons x10^4. [b] For numbering see Figure 1. [c] $\Delta Q_i = Q_{i(Ar\text{-}H)} - Q_{i(Ar\text{-}X)}$. Positive ΔQ_i means gain in electronic charge of atom i due to the substituent X.

Table 3

Variation of Bond Orders in Neutral and Anionic Species for Some Amino and Nitro Oxadiazoline Derivatives

	Neutral					Anion				
Bond	H	*m*-NO_2	*p*-NO_2	*m*-NH_2	*p*-NH_2	H	*m*-NO_2	*p*-NO_2	*m*-NH_2	*p*-NH_2
2-7	1.000	1.000	1.001	0.996	1.013	1.038	1.060	1.105	1.035	1.027
2-3	1.700	1.702	1.699	1.701	1.690	1.500	1.457	1.401	1.503	1.523
3-4	1.060	1.071	1.075	1.059	1.050	1.342	1.389	1.446	1.338	1.312
4-5	1.107	1.094	1.088	1.108	1.122	1.334	1.288	1.237	1.337	1.364
1-5	1.032	1.023	1.024	1.035	1.034	1.026	1.029	1.044	1.027	1.017
5-6	1.602	1.625	1.631	1.598	1.583	1.339	1.380	1.416	1.336	1.320

to form the conjugate base A^- according to the typical dissociation reaction:

$$AH \leftrightarrows A^- + H^+$$

$$DPE\ (AH) = \Delta H_f(A^-) + \Delta H_f(H^+) - \Delta H_f(AH) \qquad (1)$$

where $\Delta H_f(H^+)$, $\Delta H_f(AH)$ and $\Delta H_f(A^-)$ are the heats of formation for the proton, acid and its conjugate base. According to the practice used before [2,5], the experimental value of 367.2 Kcal/mol was used for $\Delta H_f(H^+)$ instead of the calculated value (314.9 Kcal/mol by AM1 and 353.6 Kcal/mol by PM3), because the calculated deprotonation enthalpy DPE(AH) values are better. The calculated heats of formation ΔH_f for neutral compounds **1**, **2** and their anionic species as well as their DPE values are presented in Table 4 with the experimentally measured pK_a values and the σ Hammett constants of the substituents [6]. The correlations of pK_a *vs* deprotonation enthalpy for thione and thiol forms are depicted in Figures 1 and 2 and the correlation of pK_a *vs* σ Hammett constants for *meta*- and *para*- substituted derivatives is presented in Figure 3.

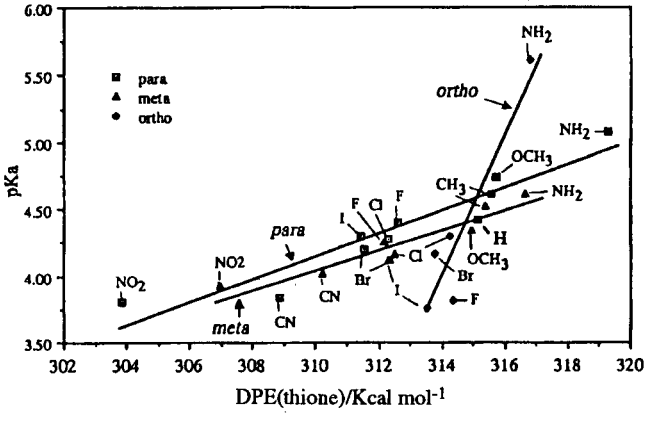


Figure 1. Plot of pK_a values *versus* the calculated (AM1) deprotonation enthalpies (DPE) for aryl substituted oxadiazoline derivatives **1** (thione form).

Good correlations of pK_a *vs* deprotonation enthalpy (thione) or deprotonation enthalpy (thiol) are obtained expressed by the equations 2(a-c) and 3(a-c) as follows:

$pK_{a(ortho)}$ = -163.77+ 0.534 DPE(thione) (R = 0.93) (2a)
$pK_{a(meta)}$ = -18.34 + 0.072 DPE(thione) (R = 0.94) (2b)
$pK_{a(para)}$ = -22.54 + 0.086 DPE(thione) (R = 0.94) (2c)
$pK_{a(ortho)}$ = -119.34 + 0.379 DPE(thiol) (R = 0.95) (3a)
$pK_{a(meta)}$ = -17.86 + 0.070 DPE(thiol) (R = 0.91) (3b)
$pK_{a(para)}$ = -23.82 + 0.089 DPE(thiol) (R = 0.95) (3c)

The increases in the electron withdrawing character of the substituent in the benzene ring and the corresponding decreases in the deprotonation enthalpy values are in good correlation with the increase of the acidity expressed by the pK_a values. The similarity of the coefficients in equations (2b) and (3b) and equations (2c) and (3c) demonstrates that

Table 4

Calculated Heats of Formation for Neutral and Anionic Species as well as Deprotonation Enthalpies of Oxadiazoline Derivatives **1** and **2** along with their pK_a and σ Hammett Constants [a]

Compound	Substituent X	ΔH_f AH thione **1**	ΔH_f AH thiol **2**	ΔH_f A^- **3**	DPE thione	DPE thiol	pK_a	σ_{Ham}
a	H	69.39	64.95	17.34	315.15	319.59	4.42	0.00
b	*o*-F	26.99	23.03	-25.86	314.35	318.31	3.82	-
c	*m*-F	25.37	20.87	-29.65	312.18	316.68	4.26	0.34
d	*p*-F	24.56	20.00	-30.02	312.62	317.18	4.40	0.06
e	*o*-Cl	65.37	61.36	12.44	314.27	318.28	4.30	-
f	*m*-Cl	63.20	58.72	8.52	312.52	316.99	4.16	0.37
g	*p*-Cl	62.83	58.27	7.97	312.33	316.90	4.28	0.23
h	*o*-Br	78.41	74.34	25.00	313.79	317.86	4.16	-
i	*m*-Br	75.15	70.69	20.27	312.32	316.78	4.12	0.39
j	*p*-Br	75.06	70.45	19.41	311.55	316.16	4.20	0.23
k	*o*-I	90.50	86.46	36.83	313.54	317.57	3.76	-
l	*m*-I	86.40	81.92	31.55	312.35	316.83	4.12	0.35
m	*p*-I	86.47	81.86	30.70	311.43	316.04	4.30	0.18
n	*m*-NO_2	75.22	70.71	14.97	306.94	311.45	3.93	0.71
o	*p*-NO_2	75.34	70.38	11.97	303.83	308.79	3.80	0.78
p	*m*-OCH_3	32.98	27.40	-19.29	314.93	320.51	4.35	0.12
q	*p*-OCH_3	31.58	26.47	-19.89	315.73	320.84	4.74	-0.27
r	*m*-CN	102.19	97.66	45.22	310.22	315.26	4.02	0.56
s	*p*-CN	102.24	97.51	43.88	308.84	313.57	3.84	0.66
t	*m*-CH_3	61.81	57.34	10.02	315.40	319.88	4.52	-0.07
u	*p*-CH_3	61.55	57.10	9.93	315.58	320.03	4.62	-0.17
v	*o*-NH_2	67.87	62.64	17.45	316.78	322.01	5.62	-
w	*m*-NH_2	68.97	64.50	18.43	316.66	321.12	4.61	-0.16
x	*p*-NH_2	66.69	62.31	18.75	319.26	323.64	5.08	-0.66

[a] AM1, ΔH_f and DPE in Kcal/mol.

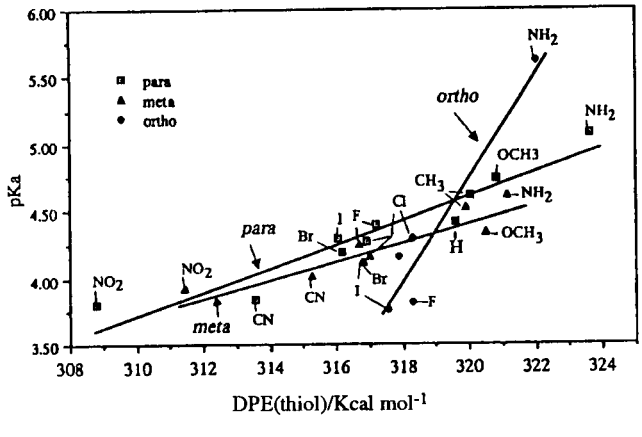


Figure 2. Plot of pK_a values *versus* the calculated (AM1) deprotonation enthalpies (DPE) for aryl substituted oxadiazoline derivatives **2** (thiol form).

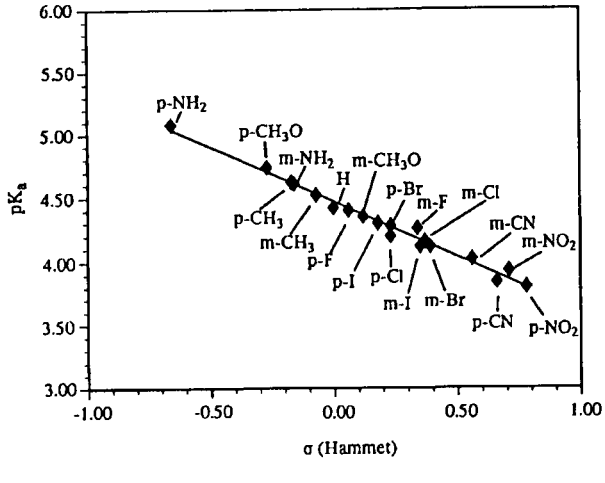


Figure 3. Plot of pK_a values *versus* σ Hammett constants for aryl substituted oxadiazoline derivatives **1**.

in the solution both the thione and thiol forms may be present. The slightly larger slope for the *para*-substituted compounds compared to the *meta* ones predict a little stronger influence of the *para*-substitution on the electron distribution of the oxadiazole ring attributed to the conjugation effect. Despite the small difference in the slope between *meta* and *para* compounds, the K_a of the compounds with extremely strong electron-withdrawing or donating effects (substituents NO_2 and NH_2) is 4.8 times larger in the case of the *meta* and 19 times in the case of the *para* compounds. The above results are in agreement with those extracted from Tables 1 and 2. The larger slope in the *ortho* compounds is due mainly to steric effects.

Furthermore, a plot of pK_a against the σ Hammett constants in Figure 3 resulted in an excellent correlation

$$pK_a = 4.472 - 0.872\,\sigma \quad (R = 0.99) \quad (4)$$

indicating a significant influence of the aryl substituent on the proton-donating ability of the oxadiazole ring.

EXPERIMENTAL

The synthesis, the electronic and infrared spectra of the title compounds are described in a previous publication [1]. The p*H* measurements were performed using an E516 Titriscop Metrohm Herisau p*H*-meter. All pK_a values have been determined spectrophotometrically [7] using ethanol-water solutions (7.5-92.5%), by determining the relative proportion of ions to molecules. This was achieved by dissolving known quantities of compounds **1** in a series of solutions containing 0.01 *M* potassium chloride as the ionic modulator. The desired p*H* values were achieved by the addition of hydrochloric acid or potassium hydroxide. All the optical density measurements have been performed with a Perkin-Elmer Hitachi 200 spectrophotometer at the analytical wavelength at which the greatest difference in optical densities between anion A^- and neutral molecule AH has been observed.

All computations were carried out on a DEC 9000 computer at the Aristotle University Computer Center and on a VAX Station 2000 using the AM1 and PM3 semiempirical methods of the MOPAC package version 6 [8]. The geometries of the molecules were fully optimized by minimizing the energy with respect to all internal coordinates except for the substituents CH_3, NH_2, OCH_3, NO_2 where some symmetry was taken into account (equal bond lengths for C-H, N-H and N-O bonds).

Conclusions.

The semiempirical molecular orbital calculations AM1 (and PM3) as well as the experimental determination of the proton donor ability of twenty four oxadiazoline-5-thiones showed that substituents on the aryl group, especially in the *para* position, can influence significantly the dissociation constant K_a of the proton in oxadiazole ring. The excellent correlation of pK_a of nineteen compounds with σ Hammett constants is a further demonstration of the influence of the aryl substituents on the charge distribution in oxadiazole ring. Based on the deprotonation enthalpy values and on the correlations of pK_a with the deprotonation enthalpy values of both the thione and thiol forms, it can be assumed that in solution both forms are present and an equilibrium is established.

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