Dual Substituent Parameter Modeling of Theoretical, NMR and IR Spectral Data of 5-Substituted Indole-2,3-diones

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Abstract: Correlations of AM1 and PM3 theoretical data, ^{13}C-NMR substituent chemical shifts (^{13}C-SCS) and IR carbonyl group wave numbers [$\nu(C_3{=}O)$] were studied using dual substituent parameter (DSP) models for 5-substituted indole-2,3-diones. For the C_7 atom a reverse substituent effect attributed to extended π-polarization was observed. On the other hand, the DSP approaches for the C_3 atom showed normal substituent effects with some contribution of reverse effect supported strongly by ^{13}C-SCS correlations. In the $\nu(C_3{=}O)$ and $p(C_3{=}O)$ DSP correlations the field effect contribution predominates over the resonance effect, which justifies the using of earlier suggested vibrational coupling (V-C) model for 5- and 6-substituted indole-2,3-diones.

Keywords: 5-Substituted indole-2,3-diones, AM1 and PM3 theoretical data, IR and NMR data DSP correlations, π-polarization, reverse substituent effect.

Introduction

Indole-2,3-dione (isatin) derivatives have shown a wide scale of biological activities. Many of them are antibacterial, antifungal and anticonvulsant compounds [1-3]. Moreover, some isatin derivatives exhibit remarkable anti-HIV [4] and cytostatic activity [5]. Recently the substituent effects and the phenomenon of vibrational coupling have been studied in a series of 5- and 6-substituted indole-2,3-diones using IR, NMR and theoretical AM1 data [6]. It was shown that the two $\nu(C=O)$ absorption bands of isatins could be attributed to the symmetric and the asymmetric stretching vibrational modes in the mechanically coupled cyclic α-dicarbonyl system. Consequently a vibrational coupling (V-C) model was suggested for mono substituent parameter (MSP) correlations of IR spectral data of 5- and 6-substituted derivatives.

The aim of this work was to study and compare Reynolds' and Taft's dual substituent parameter (DSP) models [7] for correlations of theoretical (AM1 and PM3) as well as ^{13}C-NMR and IR spectral data of a series of 5-substituted indole-2,3-diones (1-8) (Scheme 2).

Results and Discussion

The correlations of carbonyl vibrational wave numbers $\nu(C_3=O)$ of the series of compounds **1 – 8** using DSP Reynolds' and Taft's models (for $\sigma_R = \sigma_R^o$) show the following results:

Reynolds' model: $\rho_F = 3.22, \rho_R = 3.37$ Taft's model: $\rho_F = 3.80, \rho_F = 3.09$

$R = 0.965$ $R = 0.982$

$F = 58.9, f = 0.289$ $F = 68.4, f = 0.221$

Generally the Taft's model approach gave statistically more significant results than the Reynolds' model for both q_C and q_M correlations. Almost identical correlations were found for the q_C and q_M property for given atom. Hence we will use the q_M value as a representative for interpretation of Taft's model correlations.

The best-chosen resonance parameters were σ_R^{BA} values for the carbon atoms and σ_R^o constants for the oxygen atom of the $C_3=O$ group. This may justify the lower quality behavior of Reynolds' model mentioned earlier for carbon atoms since this uses σ_R^o values while the best chosen resonance parameter in Taft's model is σ_R^{BA}. According to Taft's model the atoms used in correlations can be classified into two groups: i) those within the benzene ring, namely C_7 and C_{7a} and ii) those outside the benzene ring, such as C_3 and O_3'. The atoms C_7 and C_{7a} alternate in charge sign similarly to their corresponding ρ_I and ρ_R values, ρ_I and ρ_R being negative for C_7 and indicating a reverse resonance and field effects respectively. The C_7 atom represents a meta-position in 5-X-isatin series. A similar effect was observed for α-carbon atoms of the side chains in p-disubstituted benzenes on probing ^{13}C NMR substituent chemical shifts (^{13}C SCS) [14]. Craik *et al*. [14] have proposed two types of field π-polarizations, namely localized and extended π-polarization. It is believed that the localized π-

polarization accounts for non-terminal atoms, whereas both localized and extended π-polarizations contribute to electron charge density at terminal atoms. In our case the reverse substituent effect at the C_7 site can be attributed to extended π-polarization, which predominates over the localized π-polarization in analogy to [8]. This effect can be schematically drawn as structures **I** and **II**, respectively (Scheme 1).

Scheme 1.

I   **II**
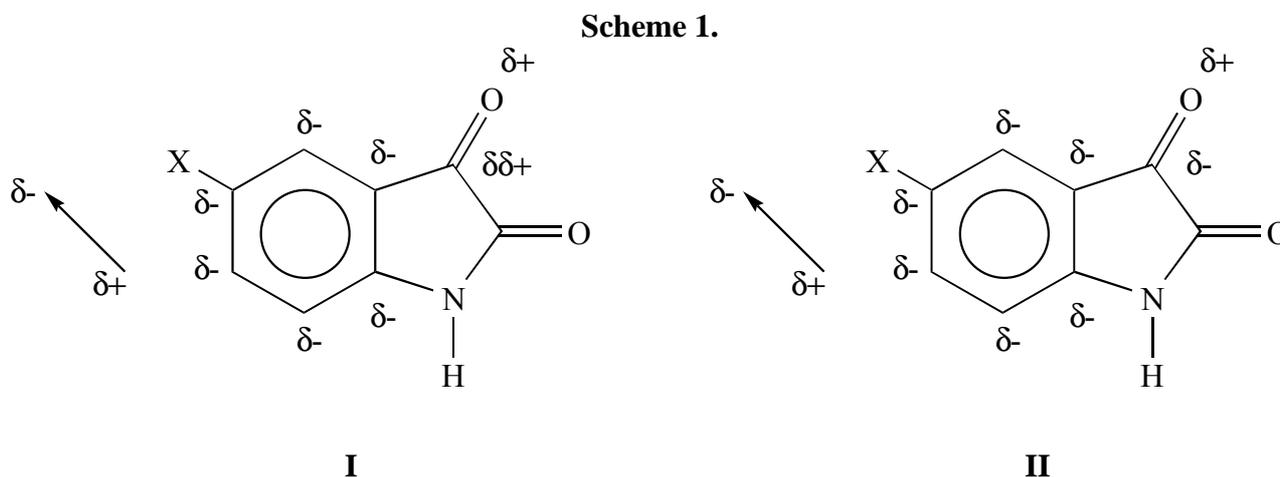
It should be noted that it is not necessary to have equal π-polarization at the benzene ring in 5-X-isatins, since the benzene ring is not symmetrically substituted. The data in Table 3 show that the reverse resonance effect in position 7 is larger than the reverse field effect. AM1 charge densities and Mulliken charges seem to overestimate the importance of reverse resonance effect, which is similar to the results published for p-substituted nitrobenzenes [8]. The ρ_I and ρ_R values at the C_7 atom are for both quantities q_M and q_C smaller in absolute values than the corresponding ρ_I and ρ_R at the C_{7a} atom. This resembles the results obtained in similar correlations at non-conjugative sites in aromatic compounds (meta-position) [9] or at α-carbon atoms of side chains in p-disubstituted benzenes [10]. The C_7 atom in compounds **1 – 8** is a non-conjugative site with the substituent on the C_5 atom and represents a meta-position.

Taft's DSP correlation for $q_M(C_{7a})$ is similar to those for ^{13}C SCS in p-disubstituted benzenes for several reasons: i) the best chosen resonance parameter is σ_R^{BA}, ii) the field and resonance effects are normal and iii) the ρ_R/ρ_I ratio is twice [11].

DSP correlation of $q_M(C_3)$ reveals normal substituent effect (see Table 3). The $q_M(O_3')$ correlation using Taft's DSP approach shows more contribution of field than resonance effect at the oxygen atom. This agrees with the proposed structure of π-polarization giving more weight to field effect at the oxygen atom of C_3=O group. However, due to the existing of some reverse effect at C_3 atom the total ρ_I and ρ_R values for $q_M(C_3)$ are decreased when compared with ρ_I and ρ_R for $q_M(O_3')$ (see **I** in Scheme 2). The reverse substituent effect at C_3 site is very typical and obvious for α-carbon atom of side chains in p-disubstituted benzenes and is indicated by correlation results for ^{13}C SCS of C_3 atom in series of compounds **1 – 8**:

$$^{13}\text{C SCS} = -3\,\sigma_I - 0.89\,\sigma_R{}^o$$

$$R = 0.990$$

$$F = 80.2, f = 0.087$$

Also reverse substituent effect of ^{13}C SCS was observed when Hammett $\sigma_p{}^-$ constants were used for the same set of compounds:

$$^{13}\text{C SCS} = -1.72\,\sigma_p{}^- - 0.2$$

$$R = -0.950$$

$$F = 38.8, f = 0.211$$

The later results are in a good agreement with those obtained for p-disubstituted benzenes [10-12]. For Taft's DSP correlations the wave numbers of the stretching vibration of C_3=O group calculated using AM1 method, were employed:

$$\nu_c(C_3\text{=}O) = 3.8\,\sigma_I + 3.09\,\sigma_R{}^o$$

$$R = 0.982$$

$$F = 88.4, f = 0.221$$

The above results give more weight to the field effect than resonance effect contribution of the substituent to the $\nu(C_3$=O$)$ values. The increase of the field effect is even more for the correlation of bond orders (calculated by PM3 method) and is twice of than the resonance effect contribution:

$$p(C_3\text{=}O) = 0.0173\,\sigma_I + 0.0092\,\sigma_R{}^o$$

$$R = 0.970$$

$$F = 55.3, f = 0.117$$

These observations partly justify the use of the vibrational coupling (V-C) model suggested recently [6] for Hammet type correlations of the IR stretching vibrational wave numbers of 5- and 6-substituted isatins.

Conclusions

The following conclusions may be drawn on the basis of the above discussed results for 5-substituted indole-2,3-diones:

1) Application of the Taft's model provides always better correlation results for both Coulson charge densities and Mulliken charges than the use of Reynolds model.

2) For the C_7 site a reverse substituent effects was observed and is believed to be connected with the extended π-polarization.

3) The DSP correlation analysis for the C_3 atom of the investigated molecules shows a normal substituent effect.

4) The Taft's model DSP correlations for C_3=O bond vibrational wave numbers and bond orders show that the contribution of the field effect to this bond is roughly twice the contribution of the resonance effect.

5) The previously reported vibrational-coupling model proposed on the basis of MSP correlations was confirmed using the results of DSP correlations studied in this work.

Acknowledgements

Experimental

The ^{13}C NMR data (in DMSO-d_6) and IR data (in CHCl$_3$) of 5-substituted indole-2,3-diones (1-8, Scheme 2) were reported previously [6] and their selection for requirements of this study is listed in Table 1.

Scheme 2.
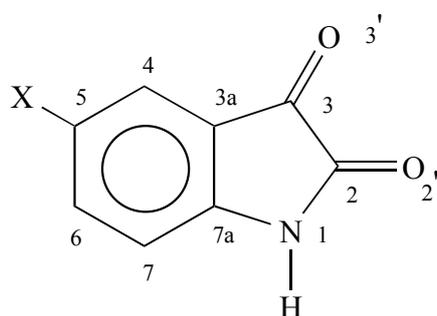
X = **1** - H, **2** - CH$_3$, **3** - OCH$_3$, **4** – F, **5** - Cl, **6** - Br, **7** - NO$_2$,

8 - COCH$_3$

Semiempirical molecular orbital calculations for Coulson atomic charge densities (q_C), Mulliken charges (q_M) and bond orders (p) were done by AM1 Hamiltonian [13] using the AMPAC program package [14]. Geometries were completely optimized without any restrictions using the keyword PRECISE. The selected AM1 and PM3 theoretical data for 5-substituted indole-2,3-diones (**1-8**) are given in Table 2.

Table 1. Selected IR and ^{13}C NMR spectral data[a] for 5-substituted indole-2,3-diones (**1-8**)

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
^{13}C SCS C$_3$)[b] ppm	184.33	184.56	-[d]	184.92	183.29	183.12	182.31	-[d]
ν(C$_3$=O)[c] cm^{-1}	1744.0	1740.1	1744.0	1744.8	1750.8	1750.4	1749.0	1753.6

[a]Taken from[6]. [b]Measured in DMSO-d_6. [c]Measured in CHCl$_3$. [d]Not measured.

Table 2. Selected AM1 and PM3 theoretical data for 5-substituted indole-2,3-diones **1-8**

Comp.	AM1									PM3
	$q_C(C_3)$	$q_M(C_3)$	$q_C(C_7)$	$q_M(C_7)$	$q_C(C_{7a})$	$q_M(C_{7a})$	$q_O(C_{3'})$	$q_M(C_{3'})$	$v_c(C_3=O)^a$	$p(C_3=O)$
1	0.2710	0.3065	-0.1857	-0.2398	0.1110	0.1261	-0.2674	-0.2963	2134	1.9538
2	0.2686	0.3036	-0.1488	-0.1991	0.0727	0.0883	-0.2714	-0.2999	2135	1.9578
3	0.2708	0.3059	-0.1811	-0.2342	0.1045	0.1195	-0.2690	-0.2978	2134	1.9535
4	0.2692	0.050	-0.1611	-0.2139	0.0976	0.1128	-0.2619	-0.2906	2135	1.9611
5	0.2781	0.3080	-0.1880	-0.2416	0.1245	0.1392	-0.2591	-0.2881	2135	1.9589
6	0.2709	0.3069	-0.1785	-0.2321	0.1126	0.1276	-0.2612	-0.2901	2135	1.9589
7	0.2731	0.3111	-0.2016	-0.2510	0.1558	0.1703	-0.2420	-0.2712	2137	1.9678
8	0.2732	0.3099	-0.2042	-0.2579	0.1389	0.1535	-0.2572	-0.2863	2136	1.9598

[a]Calculated wave numbers (cm^{-1})

The statistical result for DSP modeling of AM1 charge densities and Mulliken charges for 5-substituted isatins (**1-8**) according to both Reynolds' and Taft's models [7] using equation $q(A) = \rho_F \sigma_I + \rho_R \sigma_R + q(A)^H$ and σ_I and σ_R values taken from [15-18] are given in Table 3.

Table 3. DSP correlations for AM1 charge densities and Mulliken charges of compounds **1-8**

q(A)	Reynolds' Model					Taft's Model				
	ρ_F	ρ_R	R	F^a	f^b	ρ_F	ρ_R	R	F^a	f^b
$q_C(C_3)^c$	0.0012	0.0070	0.950	78.7	0.3302	0.0010	0.0051	0.965	87.1	0.2186
$q_M(C_3)^c$	0.0041	0.0111	0.982	69.3	0.2119	0.0046	0.0084	0.966	95.3	0.2097
$q_C(C_7)^c$	-0.0058	-0.0866	0.960	66.0	0.2521	-0.0104	-0.0665	0.979	67.0	0.2122
$q_M(C_7)^c$	-0.0071	-0.0890	0.964	69.3	0.2481	-0.0107	-0.0686	0.982	70.5	0.1117
$q_C(C_{7a})^c$	-0.0425	0.1070	0.985	85.3	0.1083	0.0461	0.0815	0.990	98.4	0.1002
$q_M(C_{7a})^c$	0.0415	0.1065	0.985	86.7	0.1073	0.0452	0.0802	0.991	113.7	0.1013
$q_C(O_{3'})^d$	0.0249	0.0166	0.975	68.0	0.2613	0.0241	0.0153	0.984	83.5	0.2411
$q_M(O_{3'})^d$	0.0250	0.0175	0.976	67.9	0.2791	0.0253	0.0160	0.983	82.3	0.2489

[a]Fisher – Snedecor test for parameters significant at the 95 % level. [b]f-Test i.e. standard deviation/root mean square error of data (sd/rmse) [c]$\sigma_R = \sigma_R^{BA}$. [d]$\sigma_R = \sigma_R^o$.

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Sample Availability: Available from the authors.