Substituent Effects and Vibrational Coupling in Indole-2,3-diones:

An IR , NMR and Theoretical Study

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Abstract. The IR C=O stretching vibrational wave numbers, ^{1}H, ^{13}C and ^{15}N NMR chemical shifts are reported for 5- and 6- substituted indole-2,3-diones and correlated with Hammett substituent constants and semiempirical AM1 data. As an alternative to the previous assignment of the C=O stretching vibrational wave numbers the two ν(C=O) absorption bands can also be interpreted as the symmetric and asymmetric stretching vibrational modes in the mechanically coupled cyclic α-dicarbonyl system. The use of 2D NMR techniques enabled to make correct assignments of the ^{13}C NMR chemical shifts, which are substantially different from those reported earlier.

Introduction

Indole-2,3-dione (isatin), its derivatives and the products of their further reactions represent an important class of biologically active organic compounds. Many isatin derivatives exhibit antibacterial and antifungal activities, (1,2). Moreover, anti-HIV (3) and cytostatic activity (4) as well as inhibition of the cell proliferation (5) has been found. Finally, several new isatin - based spiroazetidinones have been proved as efficient anticonvulsants (6).

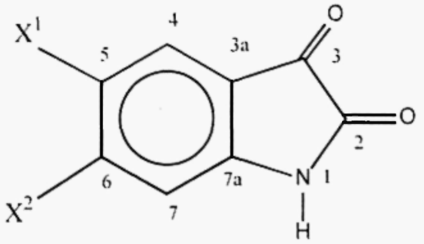
O'Sullivan and Sadler (7 - 10) proposed for the infrared spectra of 5- and 6- substituted isatins a model in which the higher wave numbers absorption band in the region of 1775 -1760 cm $^{-1}$ (in $CHCl_3$) belongs to the stretching vibration of the C_2=O carbonyl group (i.e. the adjacent one to the benzene ring). The substituent effects on the wave numbers of these bands have been also investigated.

The ^{13}C NMR chemical shifts were reported for a few 5- substituted isatins (11), however the substituent effect on the NMR data of the 5- and 6- substituted isatin derivatives have not been studied systematically and the assignment of chemical shifts was found to be incorrect.

The aim of this work was therefore a detailed study of substituent effects in the series of 5- and 6- substituted isatins (**1-12**) (**Scheme 1**) using IR and NMR spectroscopy as well as semiempirical AM1 theoretical data.

Results and Discusion

The characteristic infrared spectral data of a series of 5- and 6- substituted indole-2,3-diones (isatins) (**1**-**12**) measured in dilute solutions in trichloromethane and partly also in tetrachlormethane are listed in Table 1.



X_1,X_2 = **1** - H, H; **2** - CH_3, H; **3** - OCH_3, H; **4** - F, H;
5 - Cl, H; **6** - Br, H; **7** - NO_2, H; **8** - $COCH_3$, H; **9** - H,CH_3;
10 - H, OCH_3; **11** - H, Cl; **12** - H, Br

Scheme 1

The two absorption bands observed in the region of 1770 - 1730 cm^{-1} partially overlap and therefore their exact positions were determined after curve deconvolution and separation. Differences between the values determined in this work and those reported earlier (7,8) (see Table 1) probably can be attributed to this fact. The lower wave number bands were found to be always more intensive than those at higher wave numbers. This feature is very typical for several kinds of five membered cyclic 1,3- or 1,2- dicarbonyl compounds (12,13) and can be regarded as a result of the mechanical coupling between the stretching vibration of two C=O groups. Consequently, the higher wave number band can be assigned to the symmetric and the lower wave number one to the asymmetric vibrational mode of the cyclic α-dicarbonyl system. The wave numbers of the asymmetric vibration are considerably more sensitive to the substituent effects than those of the asymmetric one, which is in harmony with earlier results (12 - 15).

If we consider the vibrational coupling (V-C) model for 5- and 6- substituted isatins described above, the position 6 on the benzene ring can be considered as the para position with reference to the coupled α-dicarbonyl moiety, while the position 5 corresponds to the meta position with regard to this system. Using such a V-C model the arithmetic means of the wave numbers of symmetric and asymmetric vibrations $\overline{(v(C = O))}$ rather than those of the individual bands as suggested by the O'Sullivan - Sadler Model (O'S-S – model,) can be correlated with Hammett σ_P and σ_m substituent constants. The above correlation shows good statistical results (see Table 2), the correlation coefficient being 0.948 and F-test 88. Thus, the vibrational behaviour of these compounds is analogous to that of other cyclic β- and α- dicarbonyl compounds (12 - 15). The wave number separation of the absorption bands of symmetric and asymmetric C=O stretching vibrations, $\Delta v(C=O)$ = 21 cm^{-1} for unsubstituted isatin **1** in CCl_4 is by 6 cm^{-1} higher than that for saturated five - membered α- diketones (16,17), but is very close to the $\Delta v(C=O)$ values reported recently for unsaturated four - membered α-diketones (13).

Table 1. Infrared Spectral Data for Substituted Indole-2,3-diones

Compound	ν (cm^{-1})					
	CHCl$_3$				CCl$_4$	
	ν_s(C=O)	(ν(C$_2$=O))[a]	ν_{as}(C=O)	(ν(C$_3$=O))[b]	ν_s(C=O)	ν_{as}(C=O)
1	1761.6	(1755)	1744.0	(1740)	1769.6	1748.4
2	1760.0	(1758)	1740.1	(1738)	1769.6	1748.0
3	1761.2	(1757)	1744.0	(1739)	1769.6	1748.0
4	1763.6	(1755)	1744.8	(1744)	—[c]	—[c]
5	1763.0	—	1750.8	—	—[c]	—[c]
6	1767.0	—	1750.4	—	—[c]	—[c]
7	1763.0	—	1749.0	—	—[c]	—[c]
8	1765.0	—	1753.6	—	—[c]	—[c]
9	1761.8	(1755)	1740.0	(1738)	1769.6	1745.6
10	1760.1	(1756)	1734.5	(1744)	—[c]	1740.4
11	1768.0	(1765)	1744.0	(1734)	—[c]	—[c]
12	1766.0	(1765)	1746.0	(1743)	1769.6	—[c]

[a] Taken from ref. (8). [b] Taken from ref. (7). [c] Insoluble.

Table 2. Correlations between the carbonyl stretching Wave Numbers for Substituted Indole-2,3-diones

Model	y	Ref	n[a]	r[b]	s[c]	F[d]	p[e]	q[h]
V – C[g]	$\overline{\nu(C=O)}$[h]	[i]	12	0.948	1.38	88	13.97±1.48	1752.0
O´S-S[h]	ν(C$_2$=O)	[i]	12	0.866	2.01	30	11.08±2.02	1762.0
O´S-S[h]	ν(C$_3$=O)	[i]	12	0.854	2.93	27	16.40±3.16	1742.0
O´S-S[h]	ν(C$_2$=O)	(8)	14	0.848	2.43	31	15.66±2.82	1757.9
O´S-S[h]	ν(C$_3$=O)	(7)	15	0.948	1.41	125	16.19±1.45	1738.0

[a] Number of points used in the correlation. [b] Correlation coefficient. [c] Standard deviation. [d] F-test. [e] Slope and its accuracy (in cm^{-1}). [h] Intercept (in cm^{-1}). [g] Vibrational coupling (V-C) model: for substituents 6-X^2, σ_p constants and for 5-X^1 substituents σ_m constants were employed (see also Scheme 1). [h] $\overline{\nu(C=O)}$ =[ν_s(C=O) - ν_{as}(C=O)/2]. [i] This work (see Table 1). [h] O´Sullivan-Sadler (O´S-S) model for ν(C$_2$=O) : 5-X^1 - σ_p and 6-X^2 - σ_m ; for ν(C$_3$=O) : 5-X^1 - σ_m and 6-X^2 – σ_p were used (see also **Scheme 1**).

Table 3. ^{1}H NMR Chemical Shifts for Substituted Indole-2,3-diones in DMSO-d_6

Compound	$\delta(^{1}H)$/ppm				
	H_4	H_5	H_6	H_7	N_1H
1	7.48	7.05	7.57	6.90	11.00
2[a]	7.26	—	7.37	6.79	10.89
4	7.32	—	7.40	6.90	11.00
5	7.52	—	7.59	6.91	11.11
6	7.64	—	7.73	6.87	11.11
7	8.22	—	8.45	7.09	11.64
9[b]	7.30	6.80	—	6.66	10.93
10[c]	7.46	6.57	—	6.41	10.94
11	7.49	7.08	—	6.96	11.30
12	7.33	7.16	—	7.06	11.07

[a] $\delta(^{1}H)$ for CH_3, 2.23 pm. [b] $\delta(^{1}H)$ for CH_3, 2.30 ppm [c] $\delta(^{1}H)$ for CH_3, 3.86 ppm.

The ^{1}H and ^{13}C NMR chemical shifts for substituted isatins were assigned using DQF COSY, PFG, ^{1}H, ^{13}C HMQC and HMBC experiments and together with the so far unreported ^{15}N NMR chemical shifts are listed in Tables 3 and 4. The present ^{13}C NMR assignments based on modern 2D NMR techniques differ significantly from those reported previously (11).

Table 4. ^{13}C and ^{15}N NMR Chemical shifts for Substituted Indole-2,3-diones in DMSO-d_6

	$\delta(^{13}C)$/ppm								$\delta(^{15}N)$/ppm
Compound	C_2	C_3	C_4	C_5	C_6	C_7	C_{7a}	C_{3a}	N_1H
1	159.29	184.33	124.61	122.71	138.32	112.17	150.68	117.74	-247.8
2[a]	159.43	184.56	124.74	132.02	138.81	112.07	148.56	117.71	-249.6
4[b]	159.46	184.92	111.30	157.56	124.55	113.54	147.01	118.42	-249.8
5	159.08	183.29	124.06	126.79	137.22	113.81	149.18	119.05	-248.7
6	158.89	183.12	126.82	114.24	140.00	114.24	149.52	119.48	-248.4
7	159.80	182.31	119.52	142.58	133.01	112.45	155.14	118.08	—[d]
9[c]	159.87	183.58	124.67	123.54	150.24	112.70	151.14	115.50	-248-7
10	160.55	181.48	127.24	108.80	167.73	97.81	153.54	111.13	-248.7
11	159.17	182.92	126.08	122.61	142.27	112.21	151.84	116.54	-248.6
12[e]	159.46	183.47	126.36	126.01	132.14	115.53	151.87	117.02	-248.1

[a] $\delta(^{13}C)$ for OCH_3, 20.07 ppm. [b] $J(C_4,F) = 24.4$ Hz, $J(C_5,F) = -236,7$ Hz, $J(C_6,F) = 24.0$ Hz, $J(C_7,F) = 7.2$ Hz . [c] $\delta(^{13}C)$ for CH_3, 22.24 ppm. [d] Not observed. [e] $\delta(^{13}C)$ for OCH_3, 56.10 ppm.

In all cases satisfactory statistical results have been obtained for mutual correlations of arithmetic means of experimental (ν(C=O)) and calculated (ν_c(C=O)) C=O stretching vibrational wave numbers , AM1 C=O bond orders (p(C=O), ^{13}C NMR chemical shifts (δ) and AM1 charge densities (q):

$$\overline{\nu(C=O)} = 792.1\ p\overline{(C=O)} + 248.1$$

r = 0.941, s = 1.34, F = 69 (in cm^{-1})

$$\overline{\nu(C=O)} = 2.7\ \overline{\nu_c(C=O)} - 3958.6$$

r = 0.898, s = 1.74, F = 37 (in cm $^{-1}$)

$$\overline{\delta(C_2,C_3)} = 800.7\ \overline{q(C_2,C_3)} + 384.6$$

r = -0.806, s = 0.48, F = 11 (in ppm)

This can be regarded as a further support of the validity of the V-C model discussed and suggested above.

Experimental

The 5- and 6- substituted indole-2,3-diones **1** - **12** were prepared by known methods and their m.ps, physical and analytical data were in good agreement with the reported values (18 - 22).

The Infrared spectra were measured at room temperature in the region of 1800 - 1600 cm^{-1} using a Zeiss Specord M80 spectrometer. The measurements were carried out in $CHCl_3$ and CCl_4 employing NaCl cells of 1.0 and 5.0 mm thickness. $CHCl_3$ and CCl_4 were of spectral purity (Uvasol, Merck). The concentrations of the solutions were chosen to reach a maximum of absorption of 75 - 80%. Peak positions were determined with accuracy of ±0.2cm^{-1} after deconvolution and separation of the overlapping bands in the region of 1770 - 1730 cm $^{-1}$.

All NMR measurements were run for 0.1 M DMSO-d_6 solutions at 30° C with a Bruker Avance DRX 500 FT NMR spectrometer equipped with an inverse detection probehead and z-gradient accessory working at 500.13 MHz in ^{1}H, 125.67 MHz in ^{13}C and 50.68 MHz in ^{15}N experiments, respectively. In order to ascertain ^{1}H and ^{13}C NMR chemical shift assignments also Double Quantum Filtered (DQF) Correlation Spectroscopy (COSY) (23,24) as well as Pulsed Field Gradient (PFG) ^{1}H, ^{13}C Heteronuclear Multiple Quantum Coherence (HMQC) (25,26) and PFG ^{1}H,^{13}C Heteronuclear Multiple Bond Correlation (HMBC) (27) maps have been recorded. In PFG ^{1}H, ^{13}C HMBC experiments a 50 msec delay for evolutions of multiple bond correlations was inserted in the pulse sequence. For determination of ^{15}NMR chemical shifts PFG ^{1}H, ^{15}N HMBC maps have been recorded. The ^{15}N NMR chemical shifts are referenced to the signal of an external nitromethane (δ=0.0 ppm) in a 1 mm diameter capillary tube inserted coaxially inside the 5 mm NMR tube.

Semiempirical calculations were done by the AM1 (28) Hamiltonian using the AMPAC program package (29).

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