

EXPERIMENTAL AND AB INITIO STUDY OF THE VIBRATIONAL SPECTRA AND THE STRUCTURES OF ISATIN AND ITS 5-(F, Cl) ANALOGUES

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Abstract: In order to investigate the inferences of 5-halogenosubstitution on the structural and spectroscopic properties of isatin, its FT IR spectrum was studied together with those of its 5-(F, Cl) analogues. The isatin analogues were synthesized from the respective 4-(F, Cl) anilines utilizing the Sandmeyer method. The vibrational spectra of all species were calculated for their HF/6-31G** optimized geometries and the $\nu(\text{CO})$ regions were compared with the corresponding experimental solid-state FT IR spectra.

The comparison of the optimized geometries implies that the geometrical changes accompanying the 5-halogenosubstitution of isatin should spread over the whole parent molecule. Both C–O bonds and the C–N bond are expected to shorten slightly. Simultaneously, the two carbonyl groups should become more coplanar, while the dihedral angle of the amido group should be enlarged.

Key words: Ab initio, FT IR spectra, halogenation, isatin, molecular geometry

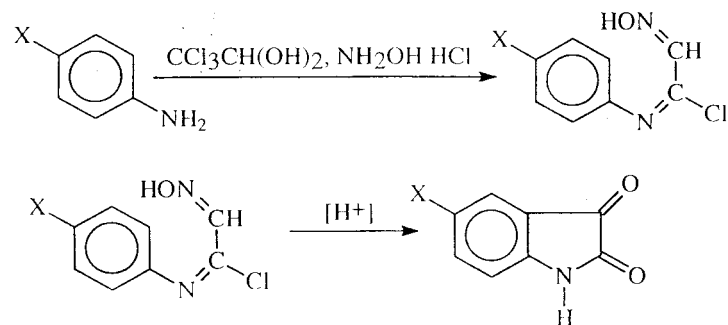
1. Introduction

Recent QSAR study of several 5- and N-substituted derivatives of isatin (2,3-indolindione) has clearly shown that the anticarcinogenic activity exhibited by these compounds is dependent on the substituent [1]. Since that the biological activity could be correlated with the electron affinities of the substituent groups, it is of interest to investigate the structurally significant perturbations of the structure of the isatin molecule that accompany its 5-substitution with various groups (F, Cl, Br, I, NO_2 , CH_3 , OCH_3).

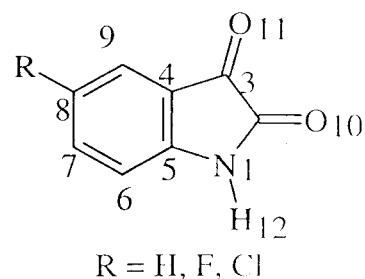
Another reason that led us to treat isatin was that it might serve as a model for small-sized cyclic dicarbonyl systems. It is well known that the two adjacent carbonyl groups, namely, a lactam and a ketone one, show distinctively different chemical properties. Contrary to the simplest single-ring aromatics, moreover, no systematic study was undertaken to characterize the influence of substitution on the geometry of condensed heterocycles. Our interest in the vibrational spectra of isatin and its derivatives, on the other hand, arises mainly from the known fact that the proximity of the CO groups troubles the interpretation of the carbonyl stretching region in its spectrum. In this paper we report on the results from the theoretical and experimental study of isatin and its 5-(F, Cl) substituted analogues.

2. Experimental

Isatin was twice recrystallized from EtOH. Its 5-(F, Cl) substituted analogues were synthesized from the corresponding 4-substituted anilines according to the Sandmeyer method (Scheme 1), using H_2SO_4 as a medium to perform the cyclization of the intermediary compounds. The products were thoroughly washed and recrystallized to obtain crystal solids. The FT IR spectra were recorded with Perkin-Elmer System 2000 interferometer in the $4000\text{--}370\text{ cm}^{-1}$ region recorded from Nujol muller suspensions) in a Graseby Specac variable



Scheme 1



Scheme 2

temperature cell. The molecular geometries of all studied compounds were optimized and their vibrational spectra were calculated at the HF/6-31G** level. All theoretical calculations were performed with *Gaussian94* series of computer programs.

3. Results and Discussion

3.1. Geometries of Isatin and its 5-(F, Cl) Analogues

The values of the relevant geometrical parameters for the HF/6-31G** optimized geometries of the studied species are presented in Table 1.¹

Table 1. Selected Geometrical Parameters for the HF/6-31G** Optimized Molecular Geometries of Isatin and its 5-(F, Cl) Analogues (the distances are in Ångströms, angles in degrees; labels refer to Scheme 2)

Parameter	Isatin	5-Cl-isatin	5-F-isatin
N(1)–H(12)	0.9935	0.9937	0.9935
N(1)–C(2)	1.3898	1.3720	1.3695
C(2)–C(3)	1.5548	1.5542	1.5542
C(3)–C(4)	1.4725	1.4748	1.4758
C(2)–C(10)	1.1836	1.1825	1.1825
C(3)–C(11)	1.1835	1.1824	1.1824
C(4)–C(5)	1.3928	1.3917	1.3907
C(5)–C(6)	1.3791	1.3793	1.3794
C(6)–C(7)	1.3899	1.3883	1.3889
C(7)–C(8)	1.3898	1.3877	1.3819
C(8)–C(9)	1.3861	1.3832	1.3776
C(4)–C(9)	1.3811	1.3799	1.3812
C(5)–N(1)–C(2)	112.1571	112.1285	112.1163
N(1)–C(2)–C(3)	105.1747	105.1854	105.2068
C(2)–C(3)–C(4)	104.6820	104.6266	104.7171
C(3)–C(4)–C(5)	107.6434	107.5991	107.5319
C(4)–C(5)–N(1)	110.3429	110.4604	110.4279
C(7)–C(8)–C(9)	119.7544	120.8711	122.1165

The structural perturbations that accompany the introduction of electron-withdrawing groups (–F, –Cl) in the isatin molecule can be briefly summed up as follows: *a.* the C–N bond is significantly *shortened*, the effect being more pronounced in 5-F-isatin; *b.* both carbonyl groups are *shortened*, but there should not be any significant difference in the extent of this effect between the 5-F and 5-Cl substitution; *c.* almost all bonds within the phenylene ring are also *shortened* (understandably, mostly influenced are the bonds adjacent to the

¹ Important note: the labels throughout the text **do not** follow the systematic numeration of the isatin molecule except the one shown in Scheme 2 [e.g., 5-substitution would mean substitution at C(8)].

substitution center); *d.* the largest deformation of the system geometry is the *enlargement* of the internal angle at C(5); *e.* the internal angle at the nitrogen atom is *bent* on account of the *expansion* of the internal angle at C(2); *f.* the carbonyl groups in the substituted analogues are *more coplanar* than in the isatin itself, and *g.* the dihedral angle of the amide group is *enlarged* upon substitution.

3.2. Vibrational Spectra of Isatin and its 5-(F, Cl) Analogues

Selected results from the harmonic vibrational analyses on the optimized geometries of the studied systems are presented in Table 2.

Table 2. Selected Spectroscopic Data for Isatin and its 5-(F, Cl) Analogues

Frequency/cm ⁻¹						IR Intensity**			Raman Activity**			Approx. Assignment
Unscaled			Scaled*			I	5-Cl	5-F	I	5-Cl	5-F	
I	5-Cl	5-F	I	5-Cl	5-F							
3905	3903	3905	3510	3508	3510	90	101	92	91	100	88	$\nu(\text{NH})$
2069	2074	2073	1860	1864	1863	651	665	591	94	97	101	$\nu_{\text{as}}(\text{CO})$
2060	2064	2063	1851	1855	1854	174	171	222	36	35	28	$\nu_{\text{s}}(\text{CO})$
1821	1821	1837	1637	1637	1651	348	252	104	56	53	37	$\nu(\text{CC}), \delta(\text{CNC})$
1635	1639	1663	1469	1473	1495	130	211	415	3	5	1	$\nu(\text{CC}), \nu(\text{CN})$
1456	1418	1426	1309	1274	1282	160	157	169	7	6	19	$\nu(\text{CN}), \delta(\text{NCC})$

* Empirical scaling factor 0.89876.

** Only the numeric values are shown.

In summary, the vibrational analysis has shown that: *a.* the stretching vibration of the *keto* carbonyl group [(C(3)–O(11))] contributes largely to the *higher*-frequency $\nu(\text{CO})$ mode, while the *lower*-frequency $\nu(\text{CO})$ mode mainly results from the vibration of the *amide* carbonyl group [(C(2)–O(10))]; *b.* both carbonyl stretchings of the 5-(F, Cl) substituted isatin analogues should appear at higher frequencies than the corresponding modes of the isatin itself; *c.* the frequency split between the two carbonyl stretchings in isatin and its 5-halogenated analogues should be practically equal and amounts around 9 cm⁻¹ (in case of isolated gas-phase molecules, within the harmonic approximation); *d.* both in the infrared and Raman, the higher-frequency $\nu(\text{CO})$ band should feature a higher intensity than the lower-frequency one (the similarity of their intensities in the IR spectrum of the 5-F analogue, however, should be more pronounced), and *e.* certain vibrations localized mainly in the benzene ring should be halogen-sensitive, e.g., the isatin mode at 1617 cm⁻¹ (theoretical value – 1651 cm⁻¹) should be practically unshifted upon 5-chlorination, but should be shifted to higher wavenumbers upon 5-fluorination, as it can be indeed observed from Fig. 1.

At least three prominent and overlapped bands are present in the 1775-1685 cm⁻¹ region of the spectra of the studied compounds (Fig. 1). Beyond any doubt, such a complex picture largely results from the solid-state effects on the spectra. However, along with the expectations from the ab initio results, the centroids of the complex $\nu(\text{CO})$ bands in the spectra of the halogenated isatin derivatives are found at *higher* frequencies than the corresponding bands of isatin. One of the bands in the case of 5-Cl-isatin, however, is split, bringing one of the resulting $\nu(\text{CO})$ bands to lower frequency than the corresponding isatin band.

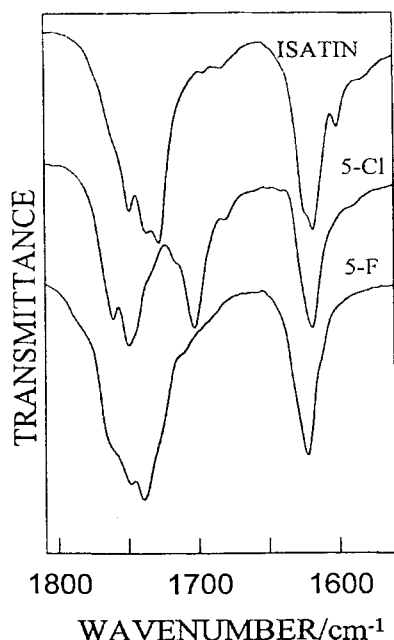


Fig. 1. The $\nu(\text{CO})$ Region in the FT IR Spectra of Isatin and its 5-(F, Cl) Analogues Recorded at Liquid-nitrogen Boiling Temperature

4. Conclusions

The geometrical changes accompanying the 5-halogenation of isatin are expected to spread over the whole molecular system. Besides the expected deformations within the benzene ring, the geometry of the amide group should be also perturbed. Future studies on a larger series of isatin analogues might shed some light on the eventual correlation between these structural changes, on the one hand, and the resulting biological activity, on the other.

5. Reference

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ЕКСПЕРИМЕНТАЛНО И АВ ИНИТИО ИЗУЧУВАЊЕ НА ВИБРАЦИОНИТЕ СПЕКТРИ И СТРУКТУРИТЕ НА ИЗАТИНОТ И НЕГОВИТЕ 5-(F, Cl) АНАЛОЗИ

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Апстракт: Со цел да се испита влијанието на 5-халогеносупституцијата на структурните и спектроскопските својства на изатинот, изучен е неговиот Фурие-трансформен инфрацрвен спектар заедно со тие на неговиот 5-(F, Cl) супституирани аналози. Анализите на изатинот се синтетизирани од соодветните 4-(F, Cl) анилини според методата на Сандмеер. Геометриите на сите испитувани соединенија се оптимизирани на нивото HF/6-31G**, пресметани се нивните вибрациони спектри, а областите на $\nu(\text{CO})$ модовите се споредени со експерименталните спектри снимени во цврста состојба. Споредбата на оптимизираните геометрии покажува дека 5-халогеносупституцијата на изатинот е проследена со структурни промени низ целата молекула. Притоа, се очекува да дојде до мало сусување на двете C-O врски, како и на C-N врската. Истовремено, двете карбонилни групи стануваат попланарни, додека диедарскиот агол на амидната група би требало да се зголеми.