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The molecular structure of 5-X-isatines where (X = F, Cl, and Br) determined by gas-phase electron diffraction with theoretical calculations

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ABSTRACT

The molecular structures of 5-X-isatines where X = F (**1**), Cl (**2**), and Br (**3**) were studied by gas-phase electron diffraction (GED) and theoretical calculations at M062X/aug-cc-pVTZ and MP2/aug-cc-pVTZ levels. The best fit of the experimental scattering intensities was obtained for a molecular model of C_s symmetry. The small differences between similar geometric parameters were constrained at the values calculated at the M062X level. The bond distances in the benzene ring are in agreement with their standard values. The (O=)C–C(=O) carbon-carbon bonds of the pyrrole moiety in title compounds (1.581(11), 1.578(8), 1.574(12) Å, respectively) are remarkably lengthened in comparison with standard $C(sp^2)$–$C(sp^2)$ value, 1.425(11) Å for *N*-methylpyrrole. According to NBO analysis this lengthening cannot be attributed to the electrostatic repulsion of oxygen lone pairs alone and is, mainly, due to the hyperconjugation, that is delocalization of oxygen lone pairs of π-type into the corresponding carbon-carbon antibonding orbital, $n_\pi(O)\rightarrow\sigma^*(C-C)$. Deletion of $\sigma^*(C-C)$ orbital followed by subsequent geometry optimization led to shortening of the corresponding C–C bond by 0.05 –0.06 Å. Electronegative halogen atoms led to increase of $C-C_X-C$ endocyclic bond angles at *ipso* carbon atom as compared with the value of 120° in regular hexagon. According to different aromaticity descriptors, aromaticity of benzene moiety of title compounds is smaller in comparison with benzene molecule. External magnetic field induces diatropic ring current in benzene moiety. Local reactivity descriptors that indicate sites in a molecule that are susceptible to nucleophilic, electrophilic and radical attack are calculated.

1. Introduction

Isatin core is widely used scaffold by medicinal chemist [1], substitution in isatin aromatic moiety with non-charged groups majorly affects the sterical properties of molecules and can affect the target binding affinity, as well as solubility and other ADMET properties (Absorption, Distribution, Metabolism, and Excretion - Toxicity in pharmacokinetics). From the other hand substitution in isatin scaffold may non-obviously change the electronic properties of the molecule and contribute potency of the isatin derivatives acting as a ligands coordinating to metal centers. It is worth noticing that the field of inorganic chemistry of isatin derivatives remains poorly examined [2]. Being homologues to non-innocent quinone molecules, isatin derivatives in combination with d-metals can result formation of complexes with interesting spectro-electrochemical properties. In this context studies that aim to understand the influence of substitutions in the core of isatin can be helpful in future design of complex with tunable properties. Isatin and its derivatives are involved in many pharmacological activities like antiallergic, antimalarial, antiviral and antimicrobial. They have been found to show promising results against various cancer cell lines and are precursors for many bioactive molecules and their diversified nature makes them a versatile substrates for further modifications [3–8].

The aim of the present study is to determine the molecular structures of free 5-X-isatines where X = F (**1**), Cl (**2**), and Br (**3**) by

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electron diffraction method supported by theoretical calculations. The crystal structures of **1**–**3** were determined in Refs. [9–11]. It was found that most remarkable feature of this molecules is very long (O=)C–C(=O) carbon–carbon bonds (1.581(11), 1.578(8), 1.574(12) Å for **1**–**3**, respectively). This bonds are also significantly longer than 1.48 Å expected for a C(sp^2)–C(sp^2) single bond. The C(sp^2)–C(sp^2) single bond for *N*-methylpyrrole is 1.425(11) Å [12]. Moreover, any reasonable resonance structure would be expected to increase the double bond character of this bond and even shorter carbon–carbon bond distance would be predicted. The authors of [13] attributed this carbon–carbon bond lengthening to nonbonded oxygen lone pair repulsions. A survey of *cis*-diketones found in the Cambridge Structural Database [14] indicates that a long carbon–carbon bond distance with an average of 1.542(17) Å is common feature of these molecules. In contrast the *trans*-diketones have an average carbon–carbon bond distance of 1.476(24) Å. This also was attributed to nonbonded oxygen lone pair repulsions, which are present in *cis*- and absent in *trans*-diketones. The concept of nonbonded lone pair repulsions is used to explain bond lengthening in other model molecules [15–17]. In addition, the easy decarboxylation of α-keto acids [18] can also be explained on the basis of a weakening of the carbon–carbon bond due to lone pair–lone pair repulsion. However, the influence of nonbonded interactions, either repulsive or attractive, on geometrical parameters is not well understood. In order to elucidate peculiar features of molecular structures of the titled compounds we performed NBO (Natural Bond Orbitals) analysis [19,20]. Experimental and theoretical vibrational analysis of isatin, its 5-(NO_2, F, Cl, Br, I, CH_3) analogues and the isatinato anion was performed in Ref. [21]. In this work effects of 5-X substitution and *N*-deprotonation on the 4000–400 cm^{-1} region of the low temperature FT IR spectrum and the molecular structure of solid isatin were investigated. It was found that substitution at 5-X position has relatively greater influence on the electron density and the force constant of the amide than on the ketone carbonyl group. Strong electron-donors shorten and stabilize the unusually long α-dicarbonyl C–C bond, while electron-accepting groups tend to stretch this bond further. *N*-Deprotonation brings to elongation of the five membered-ring along the N–$C_{CO(ketone)}$ vector and expansion of the bonds within the α-dicarbonyl part [21]. To elucidate local reactivity of the molecules under study the preferred sites for nucleophilic, electrophilic and radical attack are revealed on the basis of condensed Fukui functions and dual descriptors.

2. Quantum chemical calculations

Quantum chemical calculations were performed with Gaussian 09 program package [22] at M062X/aug-cc-pVTZ and MP2/aug-cc-pVTZ levels of theory. Theoretical Cartesian coordinates are presented in Supplementary data. NBO analysis of the SCF wave function [19,20] was performed using the NBO 6.0 computer program [23]. Topological analysis of electron density were performed with the use of AIM method [24]. Aromaticity descriptors such as harmonic oscillator model of aromaticity (HOMA) [25,26], isochemical shielding surface (ICSS), which exhibits the distribution of nuclear independent chemical shift (NICS) in 3D space with reverse sign [27], anisotropy of current induced density (ACID) [28–30] were calculated with the use of Multiwfn [31] and AICD [28] computer programs. Theoretical study of local electronic reactivity properties is performed with the use of condensed Fukui functions and condensed dual descriptors [32,33]. The definition of the condensed Fukui functions, associated with nucleophilic (+), electrophilic (−) and radical (0) attacks, for the atom *X*, f_X^α ($\alpha = +, -, 0$), can be written as:

$$f_X^+ = [q_X(N+1) - q_X(N)]$$
$$f_X^- = [q_X(N) - q_X(N-1)]$$
$$f_X^0 = [q_X(N+1) - q_X(N-1)]/2$$

where $q_X(i)$ with $i = N-1,\ N,\ N+1$, denotes the electronic population of atom *X* in the molecule with *i* electrons [32]. It is to be noted that, to calculate Fukui functions, when going from *N* to *N*–1 state, one has only to change the charge and multiplicity to +1 and 2 from 0 to 1, respectively, and does not reoptimize molecule structure for *N*–1 state, because nuclear coordinate is defined as constant in the partial derivative of Fukui function. From Fukui functions Morell et al. [33] obtained a new local reactivity index defined by a function $f_k^{(2)}$, called the condensed dual descriptor:

$$f_k^{(2)} = f_k^+ - f_k^-$$

It is a descriptor that indicates sites in a molecule that are susceptible to nucleophilic, $f_k^{(2)} > 0$, or electrophilic, $f_k^{(2)} < 0$, attacks. Thus using these descriptors one can make predictions about local reactivity in a molecule. As recommended in Ref. [34], to calculate condensed Fukui functions we used Hirshfeld charges and natural population analysis (NPA) as calculated by Mutiwfn computer program [31]. In Table 4 the local reactivity indexes according to the type of attack are given.

3. Electron diffraction analysis

3.1. Experimental

The commercial samples of **1**, **2** and **3** were purified by recrystallization from ethanol. Purity of the samples were not worse than 99.5%. The electron diffraction patterns were recorded in the Moscow State University on the EG-100 M apparatus using the R^3 sector from brass. The electron wavelength was calibrated against gaseous CCl_4. The structural parameters of the CCl4 molecule were taken from Ref. [35]. Information about the experimental conditions for all datasets used in the present investigation is given in Table 1.

Photo films (TASMA FT-41P) were scanned with the use of Epson Perfection Photo 4870 commercial scanner in the16-bit/4800-dpi gray scale scanning mode and with the use of VueScan computer program [36]. This program permits to obtain data directly from detector without any modifications. The data were processed using a computer program written by AV.B. as in Refs. [37,38]. Preliminary, high resolution was reduced by averaging square regions of pixels as described in Ref. [36]. With this method mean transmittances and its standard deviations were collected. The latter were used as weights for smoothing of transmittance surface using 2D cubic splines [39]. The calibration of the scanner was carried out against MD100 microdensitometer with the use of 24 gray scale optical wedge of IT8 transmissive target on Kodak Ektachrome Professional E100G film [40]. Displacements of the scanner were corrected against a special ruler manufactured by LOMO. After refinement of the center of electron diffraction pattern by the least squares method the data of scanning were transformed into total intensity curve taking into account 2D background. The atomic scattering factors were taken from Ref. [41].

3.2. Structural refinements

To calculate Cartesian coordinates of atoms we used algorithm described in Ref. [42]. For the ring closure the calculation of the coordinates is not terminated at the last atom in the ring, but is