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Article

Electrophilic Aromatic Substitution on Benzofuran and Indole: Possible Explanation through Wheland Intermediates, Frontier Orbitals Control, and Charges Control

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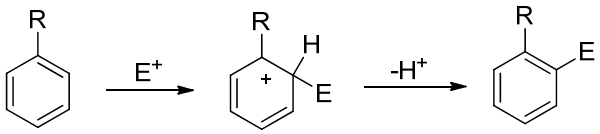
Abstract

Benzofuran and indole are structurally similar compounds, but they show different reactivity patterns. Benzofuran can undergo electrophilic substitution at either the α or β position depending on the electrophile, whereas indole reacts preferentially at the β position. Density functional theory (DFT) calculations of the Wheland intermediates in the Vilsmeier-Haack formylation and nitration reactions are consistent with the experimental results for formylation, but cannot explain the regioselectivity observed in the nitration of of benzofuran. A frontier orbital approach successfully explains the regiochemistry of Vilsmeier-Haack reaction: electron density favors substitution at the α position in benzofuran and at the β position in indole. In contrast, nitration at the β position in both benzofuran and indole can be explained by assuming charge control as the dominant factor governing the reaction.

Keywords: electrophilic aromatic substitution; benzofuran; indole; regioselectivity; wheland intermediate; frontier orbitals; hirshfeld charges; DFT

1. Introduction

Electrophilic aromatic substitution (EAS) is a fundamental reaction in organic chemistry and the orienting effects of substituents have been known since the end of the nineteenth century [1,2]. In this way, some substituents (such as -OH) direct the reaction to the *ortho* and *para* positions of the aromatic ring, while others (such as -NO_2) direct the electrophilic substitution to the *meta* position. However, the reasons for this behavior were not initially understood and early studies were limited to describing these patterns without attempting to rationalize it. The orienting effects of the substituents in EAS were initially interpreted using the alternating polarity theory [3], until Wheland proposed the formation of arenium ion intermediate [4]. This approach allowed the explanation of the mechanism of EAS (Scheme 1) [5].



Scheme 1. The mechanism of electrophilic aromatic substitution.

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Based on the proposed mechanism, substituents that can stabilize the resonant positive charge in the ring also stabilize the intermediate and, consequently, the transition state of the first step in Scheme 1. On the contrary, substituents that do not stabilize the positive charge lead to destabilization of both the intermediate and the corresponding transition state. The observed orienting effects are due to kinetic control. Substituents that stabilize the σ-complex formed upon ortho/para attack are able to lower the activation barrier for these pathways, while in the absence of such kind of stabilization, meta substitution becomes kinetically favored. Several studies have been conducted on this mechanism in order to explain the observed regioselectivity [6-14].

A possible involvement of frontier orbitals in the determination of regioselectivity in the EAS has been proposed by Fukui [15,16], while Klopman and Salem proposed a general approach to the reactivity of a compound where both frontier orbitals and charges interactions were considered (eq. 1 is a simplified version of the Klopman–Salem equation) [17-19].

$$\Delta E = \frac{Q_{nucl}Q_{electr}}{\varepsilon R} + \frac{2(c_{nucl}c_{electr}\beta)^2}{E_{HOMO}-E_{LUMO}} \quad (1)$$

Recently, we reported the results of DFT calculations (B3LYP/aug-cc-pVDZ level of approximation) on the electrophilic aromatic substitution. Our analysis shows that the frontier orbital control and/or the charge control can be applied to explain the reactivity of activated *ortho*/*para* orienting compounds, depending on the nature of the electrophile. On the contrary, both approaches failed in the description of the reactivity of deactivated *meta* orienting substrates [20]. In the case of benzaldehyde, *meta* orientation in nitration reaction can be explained by using Hirshfeld charges, while both frontier orbitals and Hirshfeld charges approaches failed to explain the observed orientation in chlorination reaction [21].

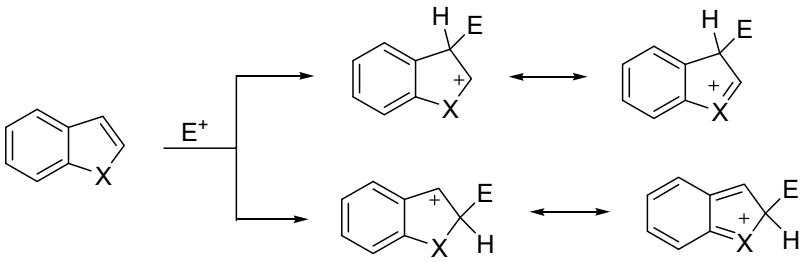

Figure 1. Resonance structures of possible intermediates in electrophilic aromatic substitution of benzofuran (X = O) and indole (X = NH).

This article explains the observed reactivity of benzofuran and indole. Based on resonance-stabilized intermediates (Fig. 1), no particular orientation is expected to be favored, and the observed reactivity of these two compounds shows a complex behavior.

2. Materials and Methods

Gaussian09 was used to optimize all geometries discussed in this work [22]. All the computations were based on the Density Functional Theory (DFT) by using the B3LYP hybrid xc functional [23], B3PW91 [24], BPV86 [25], CAM-B3LYP [26], HCTH [27], HSEH1PBE [28-34], LSDA [35], MPW1PW91 [36], PBEPBE [37], TPSSTPSS [38,39], and WB97XD [40]. Geometry optimizations from the Gaussian09 program have been obtained at aug-cc-pVDZ [41] level of approximation. Geometry optimizations were performed with default settings on geometry convergence (gradients and displacements), integration grid and electronic density (SCF) convergence. Redundant coordinates were used for geometry optimization as produced by the Gaussian09 program. Analytical evaluation of the energy second derivative matrix ~~w.r.t.~~ with respect to Cartesian coordinates (Hessian matrix) confirmed the nature of minima on the energy surface points associated with the optimized structures.

3. Results and Discussion

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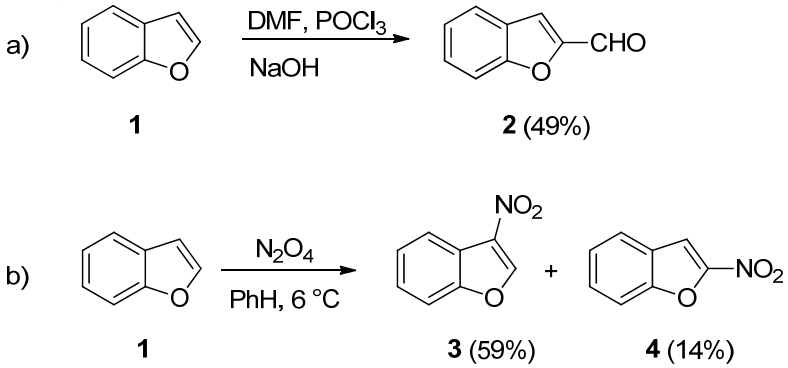
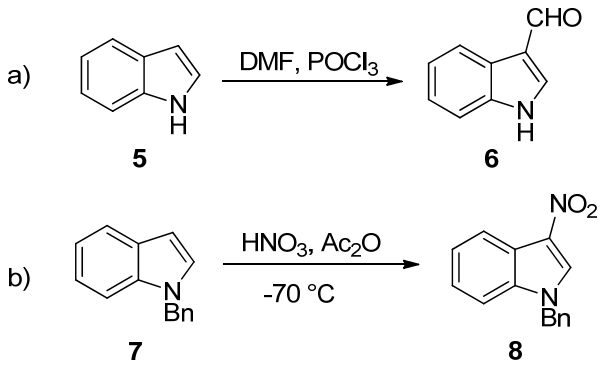
Benzofuran showed an unusual reactivity towards electrophiles. The reaction of benzofuran (**1**) with dimethylformamide and phosphorus oxychloride gave benzofuran-2-carbaldehyde (**2**) (Scheme 2a) [42,43]. The same substrate reacted with dinitrogen tetroxide to give 3-nitrobenzofuran (**3**) as the main product, along with a small amount of of 2-nitrobenzofuran (Scheme 2b) [44].



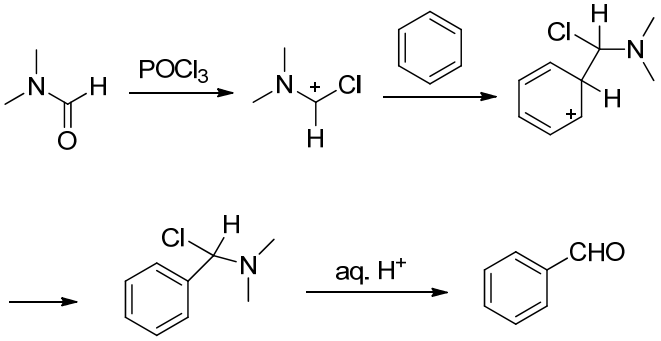
Scheme 2. *(a)* Formylation of benzofuran; *(b)* nitration of benzofuran.



Scheme 3. *(a)* Formylation of indole; *(b)* nitration of *N*-benzylindole.

Indole showed a completely different behavior, reacting only at the β position. Indole (**5**) reacted with dimethylformamide in the presence of condensing agents similar to phosphorus oxychloride to give indole-3-carbaldehyde (**6**) (Scheme 3a) [45,46]. In contrast, *N*-benzylindole (**7**) reacted with nitric acid in acetic anhydride at -70 °C to produce *N*-benzyl-3-nitroindole (**8**) (Scheme 3b) [47].

To rationalize the differing behaviors observed in the formylation and nitration of benzofuran and indole, calculations were performed to evaluate the stability of the possible intermediates. As mentioned above, the greater the stability of an intermediate, the more stable the corresponding transition state, and thus the faster the reaction. For the identification of intermediates in the formylation reaction, the mechanism shown in Scheme 4 was used. [48,49].



Scheme 4. Mechanism of Vilsmeier-Haack reaction.

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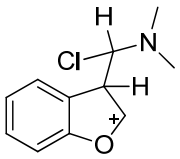
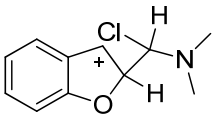
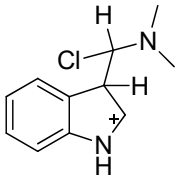
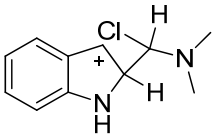
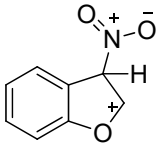
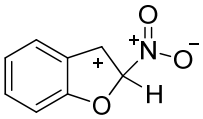
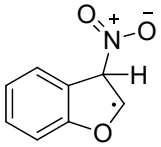
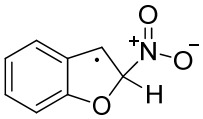
DFT calculations were performed at B3LYP/aug-cc-pVDZ level of theory using Gaussian09 and the results are reported in Table 1. The energies of the intermediates agree with the observed behavior in the Vilsmeier-Haack reaction. For benzofuran, attack at the α position is favored, while, for indole, electrophilic substitution is favored at the β position. However, the energies of the intermediates do not explain the observed behavior of nitration on benzofuran. Calculations assuming the formation of the Wheland intermediate from the attack of the nitronium ion agree for a reaction at the α position, while contrasts with the experimental results. Nitration performed with dinitrogen tetroxide can occur through the formation of a radical intermediate (due to the formation of $\cdot NO_2$) [50]; therefore, calculations were also performed on the possible radical intermediate (Table 1). However, in this case as well, calculations favor the formation of the intermediate at the α position and do not agree with the experimental results.

The differences in stability between the intermediates can be explained by the varying distribution of positive charge in these compounds. Fig. 2 collects the Hirshfeld charges on the formylation intermediates of benzofuran and indole. Notably, for benzofuran derivatives, the intermediate deriving from attack at the β position shows a localized charge at C-2, while the intermediate from attack at the α position shows a more delocalized charge. In contrast, for the intermediates derived from indole, the one formed by the attack at the β position shows a significant contribution from the nitrogen atom, while this effect is less pronounced in the other intermediate.

Table 1. Energy of some intermediates in electrophilic aromatic substitutions on benzofuran and indole.

Compound	ΔE [kJ mol^{-1}]	Compound	ΔE [kJ mol^{-1}]
	35.58		0
	0		18.26
	39.80		0
	39.76		0

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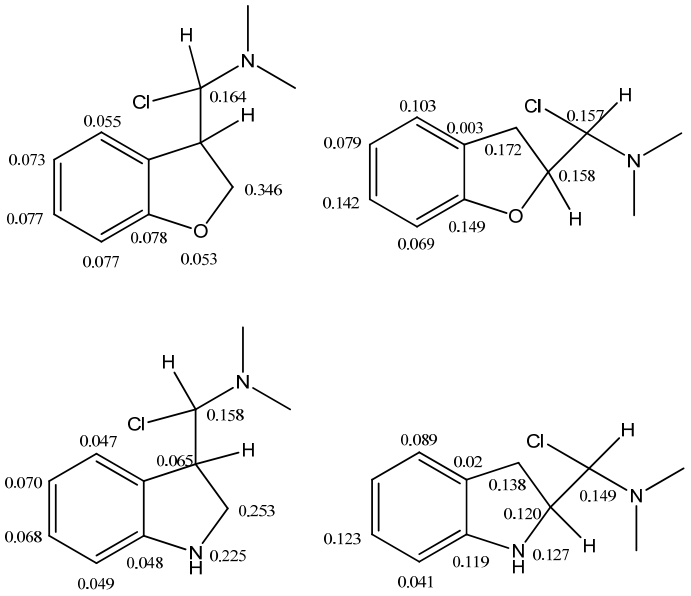
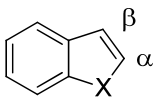


Figure 2. Hirshfeld charges in formylation intermediates

Table 2. Atomic coefficients in the HOMO, electron density, and Hirshfeld charges in benzofuran. and indole.



Compound	Functional	HOMO Atomic coefficient (electron density)		Hirshfeld charges	
		α	β	α	β
Benzofuran	B3LYP	0.32 (0.10)	0.28 (0.08)	0.037	-0.072
	B3PW91	0.31 (0.10)	0.27 (0.07)	0.037	-0.080
	BPV86	0.31 (0.10)	0.29 (0.08)	0.027	-0.075
	CAM-B3LYP	0.31 (0.10)	0.27 (0.07)	0.038	-0.075
	HCTH	0.30 (0.09)	0.28 (0.08)	0.028	-0.074
	HSEH1PBE	0.31 (0.10)	0.28 (0.08)	0.035	-0.077
	LSDA	0.32 (0.10)	0.28 (0.08)	0.013	-0.081
	MPW1PW91	0.31 (0.10)	0.28 (0.08)	0.036	-0.077
	PBEPBE	0.30 (0.09)	0.28 (0.08)	0.023	-0.074
	TPSSTPSS	0.30 (0.09)	0.27 (0.07)	0.031	-0.069
	WB97XD	0.31 (0.10)	0.27 (0.07)	0.038	-0.077

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Indole	B3LYP	0.26 (0.07)	0.31 (0.10)	-0.033	-0.090
	B3PW91	0.26 (0.07)	0.31 (0.10)	-0.006	-0.093
	BPV86	0.25 (0.06)	0.32 (0.10)	-0.012	-0.091
	CAM-B3LYP	0.26 (0.07)	0.31 (0.10)	-0.003	-0.093
	HCTH	0.24 (0.06)	0.31 (0.10	-0.010	-0.091
	HSEH1PBE	0.25 (0.06)	0.31 (0.10)	-0.006	-0.094
	LSDA	0.23 (0.05)	0.32 (0.10)	-0.022	-0.098
	MPW1PW91	0.26 (0.07)	0.31 (0.10)	-0.006	-0.094
	PBEPBE	0.23 (0.05)	0.30 (0.09)	-0.013	-0.092
	TPSSTPSS	0.23 (0.05)	0.30 (0.09)	-0.005	-0.087
	WB97XD	0.25 (0.06)	0.31 (0.10)	-0.004	-0.094

Considering the limitations observed in the nitration of benzofuran, where the energies of the intermediates do not explain the observed regioselectivity, the possible influence of frontier orbitals or charge control has been tested. Calculations were performed at the DFT/aug-cc-pVDZ level of theory using different functionals. The results are reported in Table 2 and refer to the α and β positions in benzofuran and indole. The table includes the atomic coefficients and electron density in the HOMO (highest occupied molecular orbital), as well as the Hirshfeld charges at these positions.

These results require careful discussion. In the case of benzofuran, calculations using different functionals yield very similar trends. In all cases, the HOMO exhibits the highest electron density at the α position, in agreement with the experimental results for the Vilsmeier-Haack reaction . We can suppose that the reagent $(Me_2N{=}CHCl)^+$ in which the positive charge il delocalized over both carbon and nitrogen, can be considered a soft electrophile. In contrast, the β position is favored when the charge distribution plays a dominant role in the determining the regiochemistry of electrophilic substitution. This is observed in nitration, where a hard electrophile is used and the reaction predominantly occurs at the β position.

This ~~different~~t behavior is not observed for indole . Both the HOMO electron density and the Hirshfeld charges favor the electrophilic attack at the β position. For all functionals employed, the highest electron density is located on the β carbon atom, promoting reaction at this position. A similar trend is observed when charges are considered: although both the α and β carbons carry a negative charge, all functionals assign the highest negative charge to the β carbon, in agreement with the experimental results.

5. Conclusions

In this article, we examined the electrophilic aromatic substitution~~s~~ of benzofuran and indole. These compounds are particularly interesting because, despite their similar structures, they show different reactivity: benzofuran can undergo α or β substitution depending on the reaction conditions, whereas indole displays complete β-selectivity. DFT calculations of the Wheland intermediates for the Vilsmeier-Haack and nitration reactions are generally consistent with the observed reactivity. However, the relative stability of the possible intermediates in benzofuran

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nitration does not full explain the experimental outcome. The frontier molecular orbital approach successfully rationalizes the regioselectivity observed in the formylation reaction. Additionally, the concept of charge control in electrophilic aromatic accounts for the for the β-selectivity observed in the nitration reaction.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Z matrix of calculated compounds.

Author Contributions: Conceptualization, M.D. and L.E..; validation, R.R.; investigation, L.E. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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