PHOTOCHEMICAL BEHAVIOUR OF HALOGENOHETEROCYCLIC DERIVATIVES. THE ALTERNATIVE BETWEEN ARYLATION AND DEHALOGENATION REACTIONS

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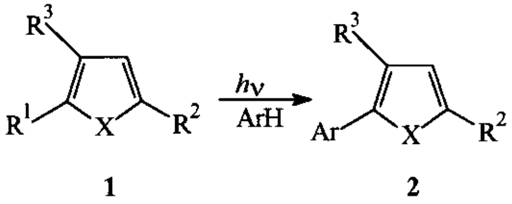
Abstract - Semiempirical calculations on the transient intermediates involved in the irradiation of halogenoheterocyclic derivatives showed that the difference between the heat of formation of the substrates and the heat of formation of the radical intermediates derived from the cleavage of the C-X bond can be a useful parameter to justify the observed chemical behaviour towards the arylation reaction or the dehalogenation reaction.

The photosubstitution reactions on haloheterocyclic derivatives[1] have been the subject of our research interests from a long time. In fact, we reported that both 5-bromo and 5-iodofuran derivatives can be arylated if irradiated in the presence of aromatic compounds.[2-4] Successively, this type of reaction has been extensively used on the thiophene derivatives.[5-8] Recently, we reported that some pyrrole derivatives can be arylated with aromatic or heteroaromatic compounds under irradiation (Scheme 1). However, we found that the irradiation of 5-iodo-2-cyanothiophene (**3**) gave 2-cyanothiophene (**4**) as the only product.[7] Furthermore, while the irradiation of 5-iodo- and 5-bromothiophene-2-carboxaldehyde gave the expected arylation product when irradiated in benzene, the same reaction attempted on 5-chlorothiophene-2-carboxaldehyde (**5**) gave only the dehalogenation product (**7**). This result was unexpected because, if the arylation reaction occurs *via* a homolytic cleavage of the C-X bond on the substrate (see below),[9] the compound **5**, the 5-iodo-, and the 5-bromo- derivatives give the same thienyl radical. Finally, the irradiation of the pyrrole derivative (**7**) gave a 1:1 mixture of the arylated **8** and the dehalogenated product (**9**), when it was irradiated in benzene (Scheme 2).

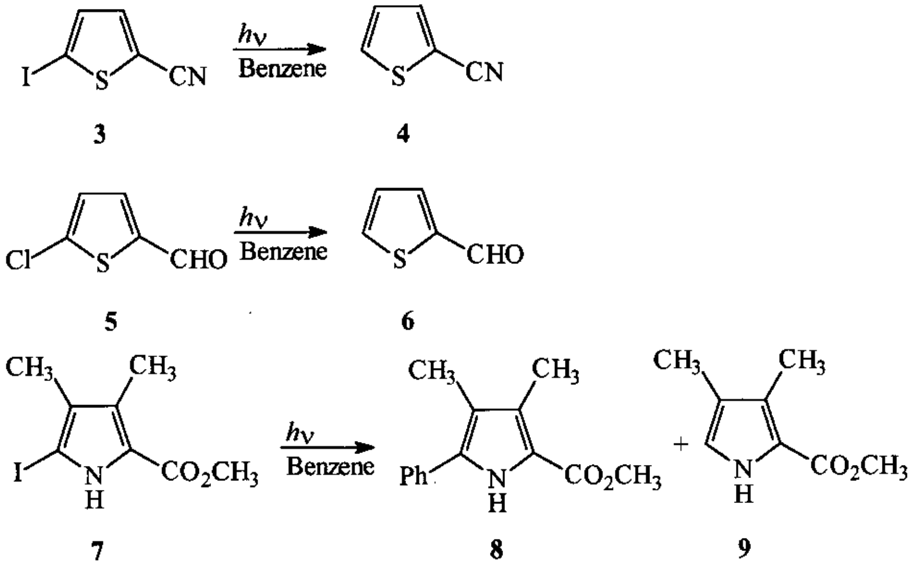
In this paper we describe an explanation of this behaviour on the basis of semiempirical calculations.

Scheme 1



a: X = O, R^1 = Br, R^2 = CHO, R^3 = H
b: X = O, R^1 = I, R^2 = $COCH_3$, R^3 = H
c: X = S, R^1 = Br, R^2 = CHO, R^3 = H
d: X = S, R^1 = I, R^2 = $COCH_3$, R^3 = H
e: X = S, R^1 = I, R^2 = CO_2CH_3, R^3 = H
f: X = S, R^1 = I, R^2 = NO_2, R^3 = H
g: X = NH, R^1 = I, R^2 = CHO, R^3 = I

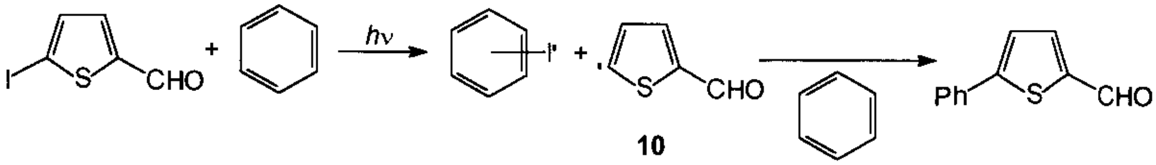
Scheme 2



RESULTS AND DISCUSSION

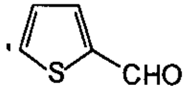
Recently we reported a careful study on the mechanism of this reaction.[9] Our studies showed that the excitation of the substrate leads to a n,π* triplet state, but this excited state is unable to undergo the dissociation of the carbon-iodine bond. This assertion could be demonstrated considering that, if the n,π* triplet state was generated by the sensitisation with chrysene, this triplet state did not produce any coupling products. Thus, probably the reaction occurs in a higher excited (π,σ^*, n,σ^*, or σ,σ^*) triplet state localised mainly on the carbon-iodine bond. Furthermore, the interaction between the triplet states of the substrate and aromatic compounds leads to the homolytic cleavage of the carbon-iodine bond with the formation of both the radical (**10**) and a complex between the aromatic compound and the halogen atom. The formation of this complex was demonstrated by the presence of a short-lived transient species with λ_{max} = 510 nm showing second-order decay kinetics and a half-life of *ca.* 0.4 μs in laser flash photolysis. The thienyl radical thus formed reacts rapidly with the aromatic compound to form the corresponding arylation product (Scheme 3). The same results were obtained by using bromo-[9] and chloro-substituted thienyl derivatives in the presence of carbonyl, cyano, and nitro substituents (work in progress).

Scheme 3



On the basis of these results we decided to study the possible behaviour of the radical intermediates derived from the homolytic cleavage of the C-X bond. Obviously, this radical intermediates react rapidly with the reagent (benzene) to give either the arylation product or the dehalogenation product. We studied the reaction of these radical intermediates with benzene by using PM3 semiempirical method for the arylation and the reaction of the same intermediates with benzene for the hydrogen abstraction. We found that the first reaction does not show any appreciable transition state while the second reaction showed a transition state with an energy of 2-3 kcal mol^{-1}. The reaction with benzene forming the arylation product is very fast while the hydrogen abstraction reaction required more energy to be carried out.

Difference in the reactivities between **1d**, **3**, and **7** could be explained by assuming that the electrophilic radical derived from the homolytic cleavage of the C-X bond reacts with the aromatic compound to give the substitution product *via* the interaction of its SOMO with the HOMO of the aromatic compound in a frontier orbital-controlled fashion. Furthermore, if the energy gap between the SOMO and the HOMO was large, the reaction could be charge-controlled on the basis of the Klopman - Salem equation,[10] and then could give the hydrogen abstraction product. It is known, in fact, that the transition state of the hydrogen abstraction reaction is polar.[11] To test this hypothesis we calculated the energy of the SOMO of the radicals (**10**) and (**11**). The first gave the substitution reaction, the second gave only the hydrogen abstraction. The calculated values were -7.45 and -7.35 eV, respectively. The difference between the energies of these two orbitals does not account for the different reactivity observed. In any case, this hypothesis did not account for the different behaviour observed by using 5-iodothiophene-2-carboxaldehyde and 5-chlorothiophene-2-carboxaldehyde, which give the same radical but different reactions.



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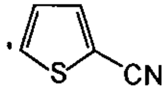

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In Table 1 we summarised the calculated heat of formation ΔH_f of some substrates used in the above reactions, the energy of the singlet state (S_1) estimated on the basis of their UV absorptions, and the experimental absorptions observed in some substrates. We used these absorptions to calibrate our calculations. We calculated the UV absorptions of all the other substrates described in Table 1. We can calculate the energy of the first excited singlet state S_1 (Table 1). This represents all the energy involved in the process. The excited singlet state generates the excited triplet state which gives the cleavage of the C-X bond on the basis of the Scheme 3. We do not know the energy level of this triplet state. However, we can calculate the heat of formation of all the radical intermediates.

Table 1 - Physical properties of suitable haloheterocyclic compounds.

Substrate	ΔH_f [kcal mol^{-1}]	λ_{max} [nm]	S_1 [kcal mol^{-1}]	$\Delta\Delta H_f$ ($S_0 \rightarrow D_0$) [kcal mol^{-1}]
2-Cyano-5-iodothiophene	155.0	278	103	57
Methyl 5-iodothuiphene-2-carboxylate	40.6	285	100	33
5-Iodothiophene-2-carboxaldehyde	79.8	306	93	35
5-Bromofuran-2-carboxaldehyde	90.3	341	100	50
5-Nitro-2-iodothiophene	103.8	284	84	53
4,5-Diiodopyrrole-2-carboxaldehyde	89.5	299	95	45
Methyl 5-iodo-3,4-dimethylpyrrole-2-carboxylate	-2.5		94	55
5-Chlorothiophene-2-carboxaldehyde	52.9		92	62
5-Iodofuran-2-carboxaldehyde	43.3		93	43
3-Iodothiophene-2-carboxaldehyde	91.1		93	35
3,5-Diiodothiophene-2-carboxaldehyde	118.4		86	39
2-Acetyl-4,5-diiodothiophene	112.7		94	52
5-Bromothiophene-2-carboxaldehyde	64.2		100	51

In Table 1 we reported the difference $\Delta\Delta H_f$ between this heat of formation and the heat of formation of the substrates. This difference represents the fraction of the adsorbed photochemical energy ($S_0 \rightarrow S_1$) that was not dissipated during the process. Then, it represents the real energy of the intermediates.

On the basis of the data reported in Table 1 we can see that when $\Delta\Delta H_f$ is low the only allowed reaction is arylation. The borderline for this reaction can be estimated at an energy of 53 - 54 kcal mol^{-1}. In fact, methyl 3, 4-dimethyl-5-iodothiophene-2-carboxylate, a compound that gives a 1:1 mixture of arylation and dehalogenation product, shows a $\Delta\Delta H_f$ value of 55 kcal mol^{-1}. Furthermore, 5-iodothiophene-2-carbonitrile and 5-chlorothiophene-2-carboxaldehyde, compounds that give only the dehalogenation product, show $\Delta\Delta H_f$ values of 57 and 62 kcal mol^{-1}, respectively.

In conclusion the photochemical behaviour of haloheterocyclic compounds can be explained considering the energy that the radical derived from the homolytic cleavage of the C-X bond has. If this energy is low the only reaction allowed is the photoarylation, while, if the energy is higher than 55 kcal mol^{-1}, the dehalogenation reaction, that involves a higher transition state energy than the photoarylation, becomes predominant.

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